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COMBINING SCIENTIFIC RESEARCH AND CLINICAL EXPERIENCE:

A NEW APPROACH TO PSYCHOLOGICAL SUPPORT

OF ADOLESCENTS WITH CANCER

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STRUCTURED ABSTRACT

Background

The treatment of cancer in adolescents and young adults is still challenging nowadays, presenting, in addition to the biological complexity of the disease and its treatment, special psychosocial needs of this subset of patients. This type of patient lies in a “no man's land”, between pediatric and adult oncology, too often without an adequate care. Moreover, suffering for cancer during adolescence, could hinder or delay the normal construction of a personal identity; therefore, these patients require more specific tools aimed at their protection and support. Due to the specific Italian historical background and scientific culture, to the complexity of psychosocial needs and to the multidisciplinary approach accomplished, the development of medical and psychological cancer treatment in children, adolescents and young adults represents a productive context for experimenting new approaches to psychological care, with each path of care tailored on the specific needs of a particular patient. This dissertation collects the studies conducted at the Pediatric Oncology Unit of Istituto Nazionale Tumori di Milano (INT), where a model for the best care of adolescent is being defined. These studies concern the critical aspects of the Adolescent and Young Adult Oncology, i.e. medical and psychological aspects, the primary role of communication, the use of new media, and the definition of an appropriate intervention strategy.

Aim of the project

The aim of this work is to describe the major concerns of cancer treatment in adolescents, reporting my scientific research and clinical experience at the Pediatric Oncology Unit of Istituto Nazionale dei Tumori of Milan, in which a multidisciplinary team is seeking a new psychological approach.

Results

In the present dissertation I present the results of the work carried out in the last three years. These results can be divided in four major categories, which are described in the different chapters.

For each chapter, a brief summary is followed by a complete version of the single studies, most of which have been already published, or are in press or submitted to international scientific journals.

Chapter 1: Medical problems. In recent years, pediatric oncologists reported that the survival trend for adolescents with cancer is disappointingly lower when compared with the improvements seen in children in the last few decades. I report two studies in which this is particularly evident.

- Study 1.1. The situation in Italy is described, along with the current efforts made in order to bridge the gap in the curve of survival rates and implement specific programs for patients suffering of synovial sarcoma and rhabdomyosarcoma, two high-grade soft tissue sarcoma subtypes that occur in adolescents and young adults.

- Study 1.2. It appears that adolescents often arrive to qualified cancer institutions with a considerable delay, and this is likely to affect their chances of being healed. We conducted a prospective investigation on patients with different types of solid tumors with the aim of establishing whether the diagnostic delay observed for soft tissue sarcomas, is confirmed in case of other malignancies. The data we collected suggest that this is the case.

Chapter 2: Psychological aspects. Dealing with patients' psychosocial needs has become an increasingly fundamental goal of care institutions. This is true, in particular, for adolescent patients. They develop the disease when are experiencing major psychological and physical changes, establishing their self-image, structuring their identity, their personality and their relationships with their peers. This makes especially important the presence of an adequate psychological care, that takes into account the relationship they are establishing with their social world. Medical care system must take responsibility for the person as a whole, and has to combine traditional therapy with new methods specifically designed for each individual patient.

- Study 2.1 This study reviews the international literature from 1980 to present, with considerations on the perspectives for integrating the clinical, psychological, and psychopharmacological interventions. I discuss the specific issues relating to the psychopathological diagnosis in the course of organic disease, and behavioral aspects determined by the biological mechanisms directly related to the disease and their treatment.

- Study 2.2. The organic components of psychic and behavioral alterations occurring during the disease are illustrated, considering the symptoms, the causes, and the possible remedies in the light of the most recent interdisciplinary viewpoints. The main mechanisms connected with the oncologic treatments - chemotherapy, surgery, radiotherapy - and responsible for psycho-organic alterations in children and adolescent with cancer are described. Within the Pediatric Oncology centres, the psychological intervention and the psychotherapy are generally offered to children and adolescents in order to support their adjustment to disease and treatment. The clinical practice, however, points out that the cognitive and emotional symptoms are sustained by biological mechanisms connected with disease and treatment, and that do not respond to psychological consultation and to other psychosocial resources. These manifestations could interfere with the treatment or with the long-term adjustment, and sometimes it is necessary to use also pharmacological supports to face them, but precise guidelines are needed .

- Study 2.3. The use of the mirror therapy to treat phantom limb syndrome in a 39-year-old patient, whose right lower limb had been amputated at the age of 17 for an osteosarcoma is described. The patient suffered from frequent episodes of pain, with severe negative consequences on the quality of

his life. In particular, the advantages of using an unconventional rehabilitation technique, and the recently developed mirror therapy are discussed.

- Study 2.4. Cancer patients may have particular and clinically unconventional needs that are often unnoticed. It is a characteristic of adolescents to wonder about the meaning of life: who am I? Where am I going? What is the meaning of life? Disease and suffering unavoidably interfere with such processes (which are already critical *per se*). With the idea that spirituality is a relevant aspect for adolescents suffering from cancer, a ‘spiritual assistant’ should be included in the multidisciplinary team, whose aim is to adequately deal with patients’ needs, in order for them to have faith, trust and hope. This study explains what exactly the role of the spiritual assistant is within our group/department.

- Study 2.5. Oncological diseases may demand long treatments, and the emotional attachment between care providers and patients might become intense. This especially happens when the patient is a child or an adolescent. This work reports the procedure devised and adopted for the immediate support of grief in use at the Istituto Nazionale Tumori in Milan when a patient dies. Clinicians should possess the necessary tools in order to cope with these emotional issues, as integral part of their responsibilities.

- Study 2.6. Even when the therapy is capable of treating the disease, after the completion of the treatment, returning to normal life can be dramatically difficult. In this study I describe the case of a 17-year-old girl cured of Burkitt lymphoma, that committed suicide after completing her treatment. The complex needs of adolescent patients require a multidisciplinary team comprising different specialists, all involved in providing a more global treatment. It is essential for all the personnel to be alert in order to perceive any sign of psychic and social discomfort; this should be a constitutive part of the long-term follow-up program for childhood cancer survivors.

- Study 2.7. This letter to Editor comments the editorial by Masera et al.¹ that discusses the extraordinary adaptation processes implemented by young individuals who experience neoplastic disease. In the letter we clarify the idea that resilience may be the result of patient’s adaptation. On one side, cancer in developmental age can have severe permanent consequences, that can interfere with the adaptation process; on the other side, we believe that it is important to note that psychopathological criteria are not enough to assess patient’s quality of life.

Chapter 3: Translating Scientific knowledge into an improved doctor-to-patient communication.

Video sharing websites have become increasingly important in recent years in providing information and orienting people’s decisions relevant for their health.

¹ Masera G, Chesler M, Zebrack B, et al. Cure is not enough: One slogan, two paradigms for pediatric oncology. *Pediatr Blood Cancer* 2013;60(7):1069-1070

New technologies are nowadays an innovative form of worldwide communication. Unlike traditional videos, these resources stimulate the interaction among users; therefore they have become a sort of hybrid between public and personal tools. Especially adolescents use Internet to obtain information on pediatric oncological diseases. The potential of these new tools, however, implies that all the traditional institutions dedicated to the research and education acquire the skill to use them. The aim of this chapter is presenting my research activity in this area.

- Study 3.1. This work describes the availability and the type of video content on YouTube concerning a particular set of pediatric neoplastic diseases, i.e. rhabdomyosarcoma and soft tissue sarcoma. These observations indicate that video sharing websites— like blogs and social media - constitute an easier way for the patients to describe their impressions and experiences of the disease. Moreover, this could help other patients to figure out new strategies to coop with the disease, and provide them with a further support, and opportunities of information and resources sharing.

- Study 3.2. This study review the literature on the use of online videos in the health field. In Italy, like in other countries, Internet is an increasingly used source of diseases-related informations, used both by health professionals and patients. In recent years, besides the most common search engines, sanitary information explained in video sharing sites have gained an increased influence.

- Study 3.3. Internet and social networks, such as Facebook, have changed the way people communicate, especially young people. They may be extremely useful for adolescent cancer patients. Disease severely limits adolescents' school attendance and time spent with peers, leading to the risks of a social isolation. Facebook can help young diseased people to keep in touch with their friends. In addition, Facebook makes possible for such adolescents to become friends of other patients, and to stay in touch with people outside the hospital. This is a positive aspect, but it also carries inherent risks. This study emphasizes the importance for patients with cancer of using Facebook, in particular for adolescents.

- Study 3.4. The innovative and recently developed experience at the INT, of using on line videos to inform the patients about the pathologies and their treatments is reported..

Chapter 4: The Youth Project.

This chapter presents two studies that describe the key aspects of the Youth Project launched in 2011 at the INT pediatric oncology unit and focusing on adolescents and young adult with pediatric tumors. One of the main aims of the Youth Project is to help the older patients to feel more as if they were at home, by providing a dedicated and adequately equipped multifunctional room, together with various activities and events. Patients may also have access to particular services, for their psychosocial support, fertility preserving measures, and the access to care after completing their cancer therapy. This project may become a possible new clinical and organizational model,

capable to address the unique needs of adolescent and young adult patients, also in order to bridge the existing lack of their treatment accessibility, their recruitment in clinical trials and in clinical and psycho-social management.

Conclusion

Overall the work presented in the current thesis represents an attempt to bridge together biological, psychological and social aspects of cancer disease in adolescents adopting a psychosocial approach to provide an integrated support to this special subset of patient. This thesis reveals the complexity of psychological research in a hospital setting, where the constraints imposed by the clinic practice cannot be ignored and it is necessary to take into account issues that affect the real needs of the department in which research is conducted. The psychological intervention in serious organic disease can not be centred only on traditional models of support and psychotherapy, based on a rigorous setting and on treatment of symptoms. We need new models that support the resources of the patients during treatments and even later, with preventive interventions and with different type of helps (psychological support, socialization, entertainment, school in hospital). We also need new languages that are close to the changed ways of communicating and relating of the new generations (Internet, YouTube, Facebook, social network). This work is a starting point for the elaboration of a new model of psychological support in hospital. Studies that composed this thesis also shows that the method and the demands of medical care can be harmonized with psychological methods and intervention through a close working relationship between psychologists and medical doctors.

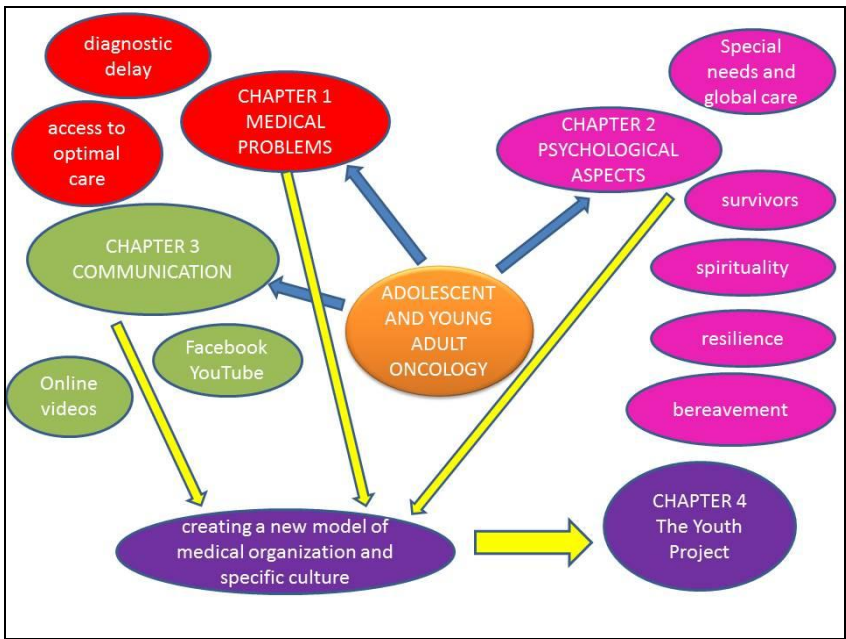


Figure 1. Graphical abstract: the four different thematic fields are represented in different colors. Blue arrows indicate the three aspects investigated in the current work, and yellow arrows point to the approach used to combine and unify them, described in chapter 4.

Key words: adolescents, young adults, cancer, psychosocial, clinical psychology, pediatric oncology

INTRODUCTION

The last few decades witnessed a growing success of healing developmental-age and adult oncologic disease cases. However, adolescent and young adult patients (from 15 to 29 years of age), do not still find an appropriate environment in neither the pediatric nor the adult oncology (Bleyer 2007; Ferrari 2007, 2010).

Adolescents and young adults cancer patients have often serious difficulties in accessing the excellence health care system and in being enrolled within clinical trials. This is especially evident when their situation is compared with the healthcare optimization already existing for pediatric oncology (i.e. when patients are below the age of 15), thanks to highly efficient cooperative networks (e.g. the Italian Association of pediatric Hematology and Oncology, AIEOP, <http://www.aieop.org>).

Several recent studies, among them the survival study EURO CARE 1995-2002 (Gatta, 2009), have clearly shown that adolescents and young adults display a decreased healing probability when compared with children with a similar clinical condition.

In other words, the recent positive survival trend of cured children and adults, has not been observed for adolescents and young adults.

Adolescents have special and complex needs, due to the special developmental phase they are crossing and to the characteristics of the biology of cancer. The organization of the medical and psychological support has to take in count these peculiarities.

From many years the Pediatric Oncology has recognized the complexity of the management of the adolescents with cancer and the need of a global care of the adolescent patient - and his/her family - with a multidisciplinary team in which near the oncologist, daily work surgeon, radiotherapist, radiologist, pathologist, endocrinologist, neurologist, but also clinical psychologist, the social assistant, teacher, entertainer. Nevertheless not every center has the same resources and competences for the adolescents care, and some boys and girls don't reach the best place for the best care.

Also Psychology in the last decades has reached a deeper understanding and has defined new approaches in this context. For many years Psychology focused on the clinical symptoms of the psychological suffering, like anxiety or depression detectable during illness or in the immediately period after it.

More recent research directions underline instead the need of a new diagnostic criteria that consider the impact of the serious illness on the personality and the consequences on the long term adjustment. In this perspective the psychological intervention does not occur only in case of acute

crisis, but concerns also a preventive and continuative support of the individual resources. Also after the cure.

Coping with the disease and its treatment in the most crucial time for the formation of one's identity is a complicated challenge, which can sometimes result in problematic or in some cases arrested evolutionary paths. An issue of great relevance to the quality of life of patients healed. Thanks to medical care more and more young patients can heal from cancer.

An issue of great relevance to the quality of life of patients healed. Thanks to medical care more and more young patients can heal from cancer. The return to normal life can be problematic, however, and some studies show that the evolutionary path after the disease is not always straightforward.

Over the past twenty years psychology has adopted the term resilience to denote the set of phenomena that characterize a satisfactory fit to the environment, even under adverse or risk conditions (Masten and Reed, 2002).

Resilience is a term that originates from physics, and indicates the capacity of a body to cushion the blows by elastic deformations, through which it absorbs energy which then gives back when it regains its original structure.

In a general sense the resilience indicates the inherent capacity of some people to react in a positive way in hardship situations, including serious physical illness, becoming even stronger as a result of what they have experienced.

According to recent theoretical perspectives, resilience is not derived from innate predispositions, it is not synonymous with intrinsic invulnerability, but emerges from basic processes common to all human beings, as the interest toward the acquisition of new information and the motivation towards competence. However, a key element of resilience is the availability of personal and environment resources and social support (Delle Fave, 2013).

Clinical experience shows that generally the patients who undergo a successful adjustment to the disease and treatment are in fact the result of a multidisciplinary approach and a synergistic effect of interventions on different levels of care (medical, social, psychological, relational).

The cure is thus understood as a holistic approach to the person who has as the ideal target the best possible adjustment by actively promoting all the resources available.

Also the communication between patients and patients has changed. Young people today communicate through mobile phones and social networks, get informed through Internet and YouTube.

So, another burning point is that the medical world has to adjust its language to the one by which the new generations communicate, for spreading important messages of prevention, information and hope for a cure.

A new model of care in the treatment of adolescents with cancer and new ways of communication with patients is therefore needed.

At the pediatric oncology unit at the Institute of Cancer Institute of Milan (INT) there is a productive laboratory of scientific research and clinical experiences with the aim of improving the treatment and the quality of life of the teen patients. The Pediatrics of the INT is in fact the most advanced center in Italy both for the oncological management and the psychosocial support offered to patients and families.

The University of Milan has been supporting this activity from years and has collaborated to innovative programs such as the Youth Project, launched in 2011 with the aim to create a new model of medical organization and specialized culture with the challenge of taking care not only of the disease, but of the global lives of young patients.

For these reasons it is a very lively and dynamic context in order to develop a biopsychosocial approach and to pursue innovative pathways of integrating psychology and medical practice.

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AIM OF THE RESEARCH AND DISSERTATION STRUCTURE

The aim of this work is to describe the major concerns of cancer treatment in adolescents, reporting my scientific research and clinical experience at the Pediatric Oncology Unit of Istituto Nazionale dei Tumori of Milan, in which a multidisciplinary team is seeking a new psychological approach.

All the studies reported in this work were possible thanks to the daily presence on the ward with oncologists and other operators with the aim to find common languages and common objectives on which working together and with the need to flexibly adapt to them working in a team. So this work collects very different studies that are linked together by a common theme: the care of adolescent or young adult patients with tumor.

The treatment of cancer in children, adolescents and young adults, for its historical background, scientific culture, complexity of psychosocial needs and level of the multidisciplinary integration reached, represents a productive context for experimenting new approaches to psychological care, tailored on the special needs of patients.

RESULTS

In the present dissertation I present the results of the work carried out in the last three years especially in collaboration with Dr.ssa Maura Massimino, head physician of the pediatric oncology unit, Dr. Andrea Ferrari, pediatric oncologist, Dr. Carlo Alfredo Clerici, physician specialized in clinical psychology. These results can be divided in in four major interrelated categories, which are described in the different chapters (Fig. 1). For each chapter, a brief summary is followed by a complete version of the studies conducted on the topic, most of which have been already published, or are in press or submitted to international scientific journals.

In **Chapter 1** I report 2 studies dealing with *Medical Problems*. In recent years, pediatric oncologists reported that the survival trend for adolescents with cancer is disappointingly lower when compared with the improvements seen in children in the last few decades. I report two studies in which this is particularly evident.

In **Chapter 2** I present my work on *Psychological aspects*, reporting 7 studies. Adolescentst patients develop the disease when are experiencing major psychological and physical changes, establishing their self-image, structuring their identity, their personality, and their relationships with their peers. This makes especially important the presence of an adequate psychological care.

Chapter 3 deals with the issue of *Translating Scientific knowledge into an improved doctors-to-patient communication*, reporting 4 studies carried out on the communicative tools as videos,

internet and social network as Facebook. These new way to search and share medical information have become increasingly important in recent years. Especially adolescents use Internet to obtain information on pediatric oncological diseases. The potential of these new tools, however, implies that all the traditional institutions dedicated to the research and education acquire the skill to use them. The aim of this chapter is presenting my research activity in this area

Finally **Chapter 4** presents two studies that describe the key aspects of the *Youth Project* launched in 2011 at the INT pediatric oncology unit and focusing on adolescents and young adult with pediatric tumors.

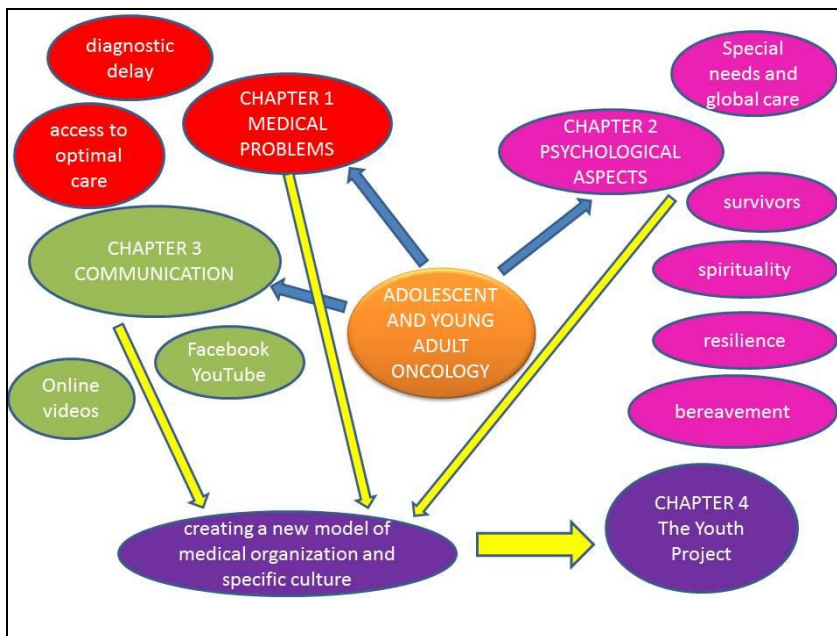


Figure 1. Graphical abstract: the four different thematic fields are represented in different colours. Blue arrows indicate the three aspects investigated in the current work, and yellow arrows point to the approach used to combine and unify them, described in chapter 4.

Patients and background

The whole research presented in these studies took place at the Pediatric oncology unit of the Istituto Nazionale Tumori (INT) in Milan. With 23 inpatient and 12 outpatient beds, the unit has always been tailored to the treatment of children with solid tumors (927 patients treated in 2013 with 167 newly diagnosed patients), while it has been cooperating closely with the pediatric hemato-oncology center at San Gerardo Hospital in Monza since the 1980s, where it refers children with leukemia. The INT pediatric oncology unit includes a pediatric surgery subunit. The unit is

part of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), the network of Italian pediatric oncology centers founded in the late 1970s to promote multicenter clinical trials and research. Unlike other Italian pediatric oncology centers at children's hospitals or being part of pediatric departments in general hospitals, our unit is the only pediatric oncology unit in Italy within a large cancer hospital. As well as attracting large numbers of patients over the years, this has facilitated close cooperation with the INT divisions dedicated to adult cancers, enabling us to gain particular experience of certain tumor types (e.g., bone and soft tissue sarcomas) across the pediatric and adult age groups, and of adult-type tumors occurring in children (melanoma, carcinomas). In addition, special attention has been paid to patients with pediatric-type tumors (e.g., rhabdomyosarcoma, medulloblastoma) who are no longer of pediatric age. For many years now there has been no upper age limit for admitting patients with pediatric cancers to our pediatric unit: a large number of adolescents, and also patients up to 25 or even 30 years old with pediatric tumors, have consequently been referred to our unit.

CHAPTER 1

MEDICAL PROBLEMS

In recent years, the oncology community has become aware that, in the past, the needs of this group of patients have sometimes been inadequately addressed by health care systems. In particular, pediatric oncologists have seen that survival trends for adolescents with cancer have been disappointing by comparison with improvements seen in children in the last few decades. Limited access to the most expert care and the considerable delay in diagnosis have been suggested as two possible reasons for this difference, since several studies have shown that adolescents are under-represented in clinical trials on therapies that might improve their outcome. In this chapter two studies concerning this problem are described:

- **Study 1.1:** *The challenge of access to care for soft tissue sarcomas bridging pediatric and adult age: the Italian pediatric oncology view* (2012). Synovial sarcoma and rhabdomyosarcoma, two high-grade soft tissue sarcoma subtypes that occur in adolescents and young adults. Managing these malignancies in patients in this agebracket poses various clinical problems, partly because different therapeutic approaches are sometimes adopted by pediatric and adult oncologists, even though they are dealing with the same condition. In this review, the doubts concerning how best to manage soft tissue sarcomas in patients between pediatric and adult ages lead up to a more general discussion of the issue of access to optimal cancer services for adolescents and young adults – a subset of patients acknowledged as being under-represented in clinical trials on therapies that may improve their outcome. The situation in Italy is described, along with action taken in an effort to bridge the gap and implement specific programs tailored to these patients.

- **Study 1.2:** *Symptom interval in pediatric patients with solid tumors: adolescents are at greater risk of late diagnosis* (2013). It also seems that adolescents are often referred to qualified cancer centers only after a considerable delay, and this is likely to affect their chances of cure. To further clarify this issue, we conducted a prospective investigation on patients with solid tumors of any type with a view to establishing whether the diagnostic delay seen for adolescent patients with soft tissue sarcomas was confirmed in other malignancies. Our aim was also to characterize the separate contributions to the symptom interval, distinguishing between the time after the onset of symptoms to the first contact with a doctor, and from then to referral to an oncologist, and to a final diagnosis.

The challenge of access to care for soft tissue sarcomas bridging pediatric and adult age: the Italian pediatric oncology view

Expert Rev. Anticancer Ther. 12(2), 243–254 (2012)

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Synovial sarcoma and rhabdomyosarcoma are two high-grade soft tissue sarcoma subtypes that occur in adolescents and young adults. Managing these malignancies in patients in this age bracket poses various clinical problems, partly because different therapeutic approaches are sometimes adopted by pediatric and adult oncologists, even though they are dealing with the same condition. In this review, the doubts concerning how best to manage soft tissue sarcomas in patients between pediatric and adult ages lead up to a more general discussion of the issue of access to optimal cancer services for adolescents and young adults – a subset of patients acknowledged as being under-represented in clinical trials on therapies that may improve their outcome. The situation in Italy is described, along with action taken in an effort to bridge the gap and implement specific programs tailored to these patients.

KEYWORDS: access to care • adolescents • age • clinical trials • rhabdomyosarcoma • soft tissue sarcomas • synovial sarcoma • young adults

Soft tissue sarcomas (STS) form a set of different mesenchymal extraskelatal malignant tumors that may occur at any age. They are rare tumors, with a reported annual incidence of 5.9 per 100,000 population, but this figure increases with age, rising from 0.9 per 100,000 in children <10 years to 18.2 per 100,000 in individuals > 70 years old, with the most dramatic rise in incidence occurring beyond 30 years of age [1]. Although the number of cases seen in pediatric ages is much lower than in adults, STS account for a fair proportion – that is, up to 8% of all cancers in children and adolescents (as opposed to 1.5% of all malignant tumors in adults).

STS are different tumor entities with a different biology, clinical behavior and response to treatment. While all the histotypes can occur at any age, some are particularly rare in pediatric ages (i.e., liposarcoma, leiomyosarcoma and fibrohistiocytic tumors), while others are unusual in young children (infantile fibrosarcoma) or occur mainly in childhood (rhabdomyosarcoma) (TABLE 1 & FIGURE 1). As a result, when pediatric and medical oncologists talk about STS, they may

mean different things. Moreover, whether the biology and clinical behavior of a given histotype is the same in patients of different ages remains to be seen. In fact, different therapeutic approaches are sometimes adopted by pediatric and adult oncologists treating the same tumor (as regards the use of chemotherapy, for instance) [2], and different overall outcomes have been reported in pediatric and adult series (FIGURE 2). It is still not clear whether the less satisfactory global results documented in many adult series relate only to differences in the tumor's biology and a different incidence of adverse prognostic features or also, to some degree at least, to the different strategies used to treat them.

Adolescent and young adult (AYA) patients (from 15–24 or 15–29 years old, respectively, depending on the various definitions adopted) belong to neither the pediatric nor the adult worlds of oncology. This is an age group in which the STS family represents a subgroup of relatively frequent tumors: while other histotypes (e.g., malignant peripheral nerve sheath tumor or alveolar soft part sarcoma) may have a

Table 1. Annual incidence (per million population) of soft tissue sarcoma histotypes in the Surveillance, Epidemiology and End Results 17 database (1973–2008, with 87,909 cases registered), excluded Kaposi sarcoma.

Histotype	Incidence by age (years)		
	0–14	15–29	30+
RMS	4.8	2.1	1.5
Synovial sarcoma	0.6	1.8	1.5
Alveolar soft-parts sarcoma	0.1	0.3	0.1
Blood vessel tumors	0.1	0.6	4
Extrarenal rhabdoid tumor	0.1	0	0.1
Fibroblastic and myofibroblastic tumors	0.8	1.2	4.1
Fibrohistiocytic tumors	1.1	5.4	19.3
Leiomyosarcoma	0.2	1.3	20.3
Liposarcoma	0.1	1	10.6
MPNST	0.4	1.5	2.7
Extrasosseous ESFT	0.4	0.7	0.3
Chondromatous tumors	0	0.2	0.8
Miscellaneous tumors	1.2	2.5	11.7

ESFT: Ewing's sarcoma family of tumors; MPNST: Malignant peripheral nerve sheath tumor; RMS: Rhabdomyosarcoma.
Data taken from [101].

predilection for this age group, synovial sarcoma is a particular example of a tumor bridging the pediatric and adult settings. Just

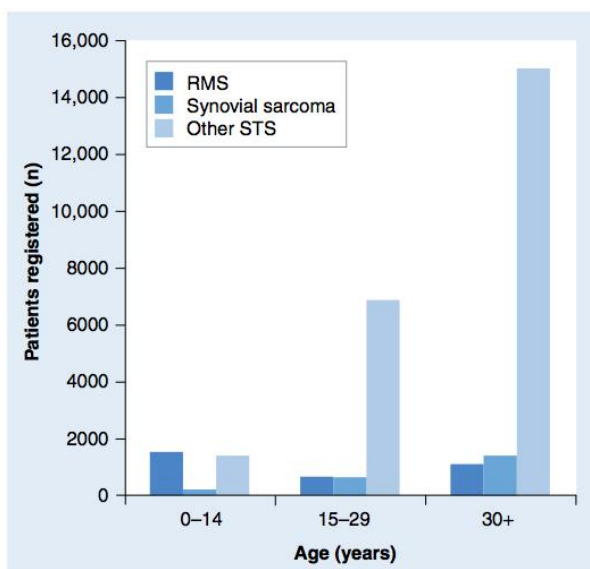


Figure 1. Number of cases registered in the Surveillance, Epidemiology and End Results 17 database (1973–2008), with 87,909 soft tissue sarcomas registered by age group. RMS: Rhabdomyosarcoma; STS: Soft tissue sarcomas. Data taken from [101].

as adolescence and young adulthood is an age of transition, synovial sarcomas encompass two different worlds, and this may well have its drawbacks – there sometimes seems to be a sort of uncertainty regarding the ‘intellectual property’ of synovial sarcoma, which ‘belongs’ to both pediatric and medical oncologists, or to neither, and AYAs with STS (and also other diseases) seem to inhabit a sort of ‘no man’s land’.

Synovial sarcoma

The specific t(X;18)(p11.2;q11.2) chromosomal translocation and the SYT–SSX transcript (in its various forms) are the hallmark of the three synovial sarcoma subtypes (monophasic, biphasic and poorly differentiated). Synovial sarcoma is generally considered a high-grade sarcoma that is locally invasive and has a propensity to metastasize, regardless of how it is graded in terms of tumor differentiation, mitosis and necrosis. The prognosis for synovial sarcoma patients depends mainly on the feasibility of surgical resection and the tumor’s size and site, and any presence of metastases, but the optimal treatment

remains to be determined. The role of chemotherapy, in particular, is still debated, partly due to the rarity of the disease and the difficulty of conducting clinical trials large enough to arrive at evidence-based, or at least shared, treatment guidelines [3,4].

Historically, relatively high rates of response to chemotherapy have been documented in pediatric synovial sarcoma series (i.e., 60%, which is higher than is usually reported for adult STS) [5]. Consequently, pediatricians tended to assume that synovial sarcoma was chemosensitive [3,4] – a sort of ‘rhabdomyosarcoma-like’ tumor (in Europe at least) – and so children were enrolled in rhabdomyosarcoma protocols and given the same chemotherapy as for rhabdomyosarcoma patients – even in cases of completely-resected small tumors [2,5–9]. The treatment strategy was substantially different for adult patients, that is, synovial sarcoma was treated like the other adult STS (generally thought to be poorly chemosensitive) and the treatment focused on local control [10]. Whether these different strategies produced differences in patient survival remains to be established. As shown in Figure 2, data from the Surveillance, Epidemiology and End Results (SEER) epidemiological database indicated a progressively worsening outcome with age. A recent SEER study on 1268 synovial sarcoma cases reported cancer-specific mortality rates of 34 and 16% in adults and children, respectively [11]. It is noteworthy that the adults’ outcome remained consistently worse than the children, even after adjusting for the different prognostic variables (tumor size, site and stage), suggesting that factors other than a difference in the incidence of unfavorable clinical variables may be involved in this unsatisfactory outcome. The hypothesis that the different

treatment outcomes correlate, to some degree at least, with the different usage of chemotherapy would be supported by a retrospective study by the Istituto Nazionale Tumori (Milan, Italy), which compared pediatric and adult cases (for a total of 271 cases), and found that adjuvant chemotherapy (administered to 80% of the children but only to 20% of the older patients) improved patient outcome (the metastases-free survival was 60% in patients given chemotherapy and 48% in those who were not) [2]. However, in the most recent adult series published by major referral institutions or cooperative groups (e.g., the MD Anderson Cancer Center [TX, USA], the Memorial Sloan–Kettering Cancer Center [NY, USA] and the French Sarcoma Group), the survival rates of adult patients did not differ substantially from those reported by pediatric groups, although chemotherapy was used in a lower proportion of cases [12–20]. It remains to be demonstrated whether the worse outcome of adult synovial sarcoma reported in epidemiological analyses relates to a different access to care, since it has been variously reported that adults with cancer may have fewer chances of being enrolled in clinical trials and, more in general, of being treated at referral centers than children [21–23]. In other words, it seems that adults with synovial sarcoma do not seem to have a worse chance of survival than children if they are treated at referral institutions or within clinical protocols (with 5-year disease-specific survival rates in the range of 60–80%) [5–9,14–20], but how many of them have this opportunity?

A review of the literature on adult synovial sarcoma shows a lack of consensus on the role of chemotherapy; while some studies concluded that chemotherapy failed to produce a significant improvement in patient outcome [12,13,17–19], others judged that synovial sarcoma should be considered a chemosensitive tumor [14] and recommended chemotherapy, particularly in cases with high-risk features [15,16]. Nowadays, many adult oncologists generally recommend chemotherapy for synovial sarcoma patients – not only in cases with advanced disease, but also as an adjuvant treatment after primary resection – even though its efficacy has yet to be demonstrated. While it is true to say that, until recently, 18 year olds with synovial sarcoma would probably be treated differently if they were referred to a pediatric or adult oncologist, even within the same experienced institution (e.g., the study by the Istituto Nazionale Tumori [2]), the situation has now changed to some degree, and clinical protocols have tended to converge towards a common strategy. Adult oncologists seem to be recognizing that synovial sarcoma may be quite different from other adult STS (with a younger age at onset, greater metastatic potential and greater chemosensitivity) [14–16]. Pediatric oncologists have drawn from adult experiences and shifted from a ‘rhabdomyosarcoma-like’ strategy in favor of a treatment approach that suggests the use of chemotherapy (ifosfamide–doxorubicin chemotherapy remaining the standard regimen) according to the patient’s risk stratification, based on tumor size, site and stage [3,4]; while a low-risk group of patients (with completely-resected tumors under 5 cm in size) [6] has recently been identified, for which chemotherapy is currently omitted [3].

FIGURE 3 shows the current risk-adapted treatment recommended by the European pediatric Soft Tissue Sarcoma Study Group

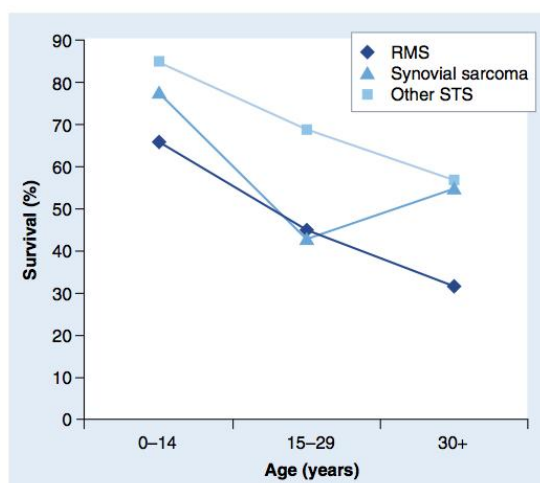


Figure 2. Five-year relative overall survival rates for rhabdomyosarcoma, synovial sarcoma and all other soft tissue sarcomas, by age group, in the Surveillance, Epidemiology and End Results 17 database (1973–2008). RMS: Rhabdomyosarcoma; STS: Soft tissue sarcomas. Data taken from [101].

(EpSSG) [101]. A similar approach has also been proposed for the other less frequent, less chemosensitive, adult-type STS [24].

Another STS histotype with a significant incidence in AYAs and which, like synovial sarcoma, often raises important clinical questions, is rhabdomyosarcoma. Pediatric oncologists have become quite expert in managing rhabdomyosarcoma, but various data raise the suspicion that the treatment of AYAs with rhabdomyosarcoma is still a major problem [25,26].

Rhabdomyosarcoma

Rhabdomyosarcoma accounts for more than 50% of STS cases of childhood and adolescence, and is a typical pediatric cancer. Although it can occur at any age, its incidence decreases significantly with increasing age: about three in four cases occur in children under 10 years of age, with a peak incidence between 3 and 5 years of age and a second smaller peak in adolescence [102]. Rhabdomyosarcoma must be distinguished accurately from other STS, mainly because it has two particular characteristics: first it is always highly aggressive and tends to spread along hematogenous routes, so it should always be assumed that micrometastatic disease exists right from the tumor’s onset; second it is chemosensitive, with more than 80% of newly diagnosed cases responding to current multiagent chemotherapy regimens [27].

Between two-thirds and three-quarters of children with rhabdomyosarcoma can currently be cured thanks to the systematic use of multidisciplinary, risk-adapted treatment programs developed over the years by cooperative international pediatric groups [28–31]. The backbone of treatment is intensive alkylating-based multidrug chemotherapy – the gold standard is the vincristine, actinomycin-D and cyclophosphamide combination, or the

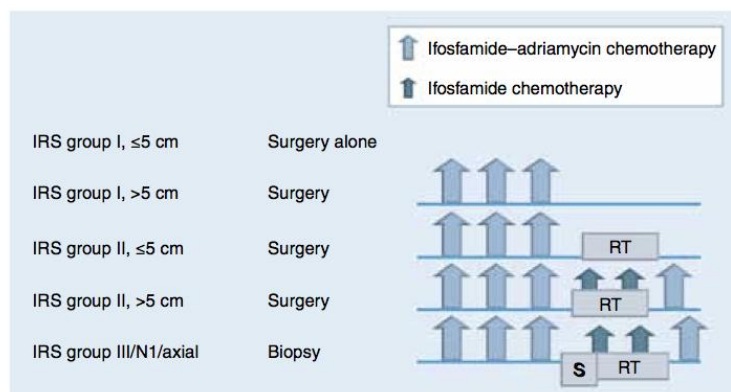


Figure 3. Treatment program for synovial sarcoma, as required by the Non-Rhabdomyosarcoma Soft Tissue Sarcomas 2005 protocol of the European pediatric Soft Tissue Sarcoma Study Group.

IRS: Intergroup Rhabdomyosarcoma Study; N: Nodal; RT: Radiotherapy; S: Surgery.

combination with ifosfamide instead of cyclophosphamide – for at least 6–9 months, combined with surgery and/or radiotherapy. Patient outcome is influenced by certain prognostic variables (i.e., histology, local and distant invasiveness, tumor site, and size) identified over the years, and is currently considered for stratifying patients and deciding the treatment's intensity [32,33]. The patient's age has also emerged as a factor significantly influencing survival: in various pediatric series, patients over 10 years of age have been reported to have a worse prognosis than younger children [34,35].

A recent study by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Soft Tissue Sarcoma Committee (STSC) investigated the clinical features and outcome of adolescents (76 patients aged 15–19 years old) treated in pediatric trials from 1988 to 2005, in comparison with children (567 patients aged 0–14 years old) [36]. Age is considered a risk variable in the ongoing EpSSG protocol, but it was not considered a factor for stratifying treatment in previous Italian protocols, therefore adolescents received the same treatment as children, making them an ideal population for evaluating any differences in outcome.

The study found that an age of below 15 years correlated with a better survival: the 5-year overall survival (OS) rate was 68.9% in children and 57.2% in adolescents ($p = 0.006$). The adolescent subgroup had a significantly higher prevalence of unfavorable features, however, including alveolar subtype (47 vs 33%), nodal infiltration (39 vs 23%) and metastases at diagnosis (31 vs 18%). When the analysis focused only on patients with localized disease, treatment outcomes in adolescents did not differ from the situation in children (5-year OS: 78.6 vs 76.6%, respectively). The outcome was also very similar between 10–14 and 15–19-year-olds, suggesting that a 10-year-old patient cutoff may be more appropriate than distinguishing between children and adolescents (i.e., using a cutoff of approximately 14–15 years of age) for the purpose of attributing different risk factors (the 5-year OS for 1–10-year-olds was 72 vs 56.8% for the older cases; $p < 0.0001$). It remains to be seen whether the different survival results relate to a more aggressive

disease in older patients, or to age-related differences in the host – that is, differences in body composition, hormonal status, organ maturity and function (enzyme system), psychosocial or behavioral attitudes that may influence treatment compliance, may change, for example, drug disposition and efficacy [37]. Nonetheless, the Italian study suggests that, when adolescents are treated according to the same approach as children with the same stage of disease, no observed difference in cure rates emerged.

Can the same be said for adult patients? Rhabdomyosarcoma can also occur in adults, albeit rarely, but published series on adult cases seem to describe a different disease from the one seen in pediatric age, with a 5-year OS reportedly in the range of 20–50% [26,38–41]. As in the case of synovial sarcoma, epidemiological data have

highlighted declining survival rates with increasing age (FIGURE 2). This finding may be related to the occurrence of the pleomorphic variants in adults, which is generally characterized by an adverse prognosis (although this subtype should probably be considered more close to an adult STS, such as malignant fibrous histiocytoma, than to other rhabdomyosarcoma subtypes). However, the worse outcome of adult patients also remained when pleomorphic cases were excluded from the analysis. A recent study compared the clinical features and outcome of more than 1000 adult rhabdomyosarcoma cases registered in the SEER database with corresponding pediatric cases. Not only did it confirm the far worse prognosis for adult rhabdomyosarcoma (5-year OS: 26.6 vs 60.5% in children), it also showed that adults fare poorly regardless of the histological and clinical variables known to influence survival [26]. Despite the obvious limits of such an analysis (e.g., no major data on treatment were available), these findings give the impression that the unsatisfactory survival rates seen in adults with rhabdomyosarcoma may relate to factors other than the disease's clinical presentation, such as the delivered treatment. A role for treatment in explaining the different outcomes is supported by a retrospective study by the Istituto Nazionale Tumori, in which 171 adult patients with embryonal and alveolar rhabdomyosarcoma were stratified according to how appropriately they had been treated from the point of view of current pediatric treatment guidelines [25]. The study showed that only 39% of adult patients had been treated in line with the pediatric protocols, although they had turned to a referral cancer center. However when the adults had, in fact, received the same treatment as was used in children, their outcome closely resembled the figures for pediatric series (that is, they had a 5-year OS higher than 60%). These findings prompt two main considerations: first, adults with rhabdomyosarcoma would fare better if they were treated like pediatric patients; second, adults with rhabdomyosarcoma are sometimes not treated adequately. What is it that prevents most adult patients from receiving proper treatment? For a start, there is

the challenge presented to the adult oncologist regarding managing a disease that is very rarely encountered in their daily activity. Then there is the shortage of dedicated trials. However, it is possible that intensive treatment programs originally developed for children may be easily applied to adolescents but not to adults (e.g., the neurotoxicity associated with vincristine may be more frequent and more severe in adult patients). In any case, new strategies are needed, based on a better cooperation between pediatric and adult oncologists, to enable adult rhabdomyosarcoma patients to access the best quality of care and assure the best prognosis possible.

Access to care

In recent years it has become clear that AYAs with cancer should be considered a separate group whose needs have been inadequately addressed by healthcare systems in the past. In particular, it has been recognized that this age group is under-represented in clinical trials on therapies that may improve their outcome. At the same time, the survival and mortality rates for these patients have reflected their clinical trial accrual pattern, suggesting that their limited access to optimal cancer services and limited involvement in clinical trials have lowered their chances of an outcome as good as the one patients in other age groups enjoy [21–23,42–45]. In the USA, a population-based analysis reported that 71% of patients <15 years of age were formally registered in cooperative group studies from 1992 to 1997, but this was true of only 24% of 15–19-year-olds [46]. The participation of 15–19-year-olds in protocols sponsored by the National Cancer Institute (NCI) from 1997 to 2003 was approximately 10–15%: only a quarter of the corresponding proportion of younger children. The picture was even worse for 20–29-year-old patients, who had the lowest rate of participation in clinical trials (under 2%) [42–45]. When it came to survival rates, the SEER data showed that the 15–34-year-old patients had the lowest average annual improvement in their survival rate (0–0.5 vs 1.5% a year for children <15 years and older adults, respectively) [21].

A similar picture has been seen in other countries. For example, inclusion rates into National Cancer Research Network Phase III clinical trials in England were 43, 25 and 13%, respectively, for patients aged 10–14, 15–19 and 20–24 years of age in the 2005–2007 period [47]. A French study reported that only 9% of their 15–19-year-old patients were entered into a clinical trial (6 and 3%, respectively, into adult and pediatric clinical trials) in the 1988–1997 period [48].

In Italy, a recent AIEOP study reported on a comparison between the number of 15–19-year-old cancer patients treated at AIEOP-affiliated pediatric oncology centers (as recorded in their hospital-based registries) and the number of cases expected to occur in Italy judging from incidence rates obtained from population-based cancer registries of Associazione Italiana Registro Tumori [49]. The ratio of observed to expected (O/E) adolescent cases was only 0.10, as opposed to the 0.77 for children up to 14 years old. There was evidence of a gradual overall improvement in adolescent accrual rates in recent years, and the O/E ratio was higher for certain tumor types (e.g., sarcomas). Nevertheless, the study emphasized that the AIEOP network was far less effective in enrolling adolescents than children in its trials, and the situation was far from satisfactory, since around two in three cancers occurring in adolescence are ‘pediatric-type’ tumors.

The problem of referral also emerged in the abovementioned AIEOP-STSC study on rhabdomyosarcoma [36]: adolescent

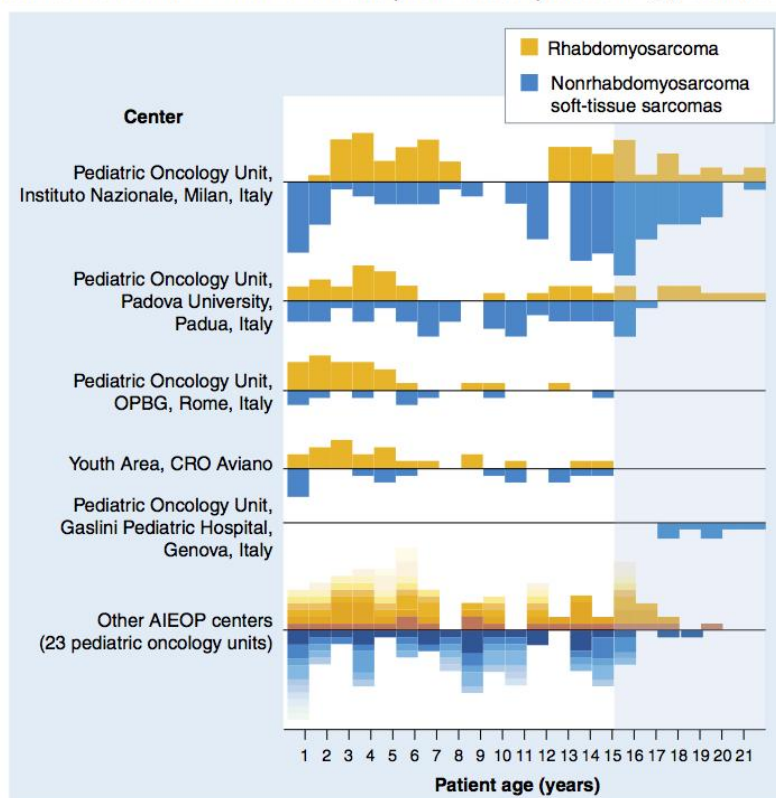


Figure 4. Cases enrolled by Italian Associazione Italiana Ematologia Oncologia Pediatrica centers in the European pediatric Soft Tissue Sarcoma database from 2005 to June 2011. Order by patients' age (above the x-axis [orange]: rhabdomyosarcoma; below the x-axis [blue]: nonrhabdomyosarcoma soft tissue sarcoma). The pattern of cases registered by patient age changes with the 'type' of center. AIEOP: Associazione Italiana Ematologia Oncologia Pediatrica; OPBG: Ospedale Pediatrico Bambino Gesù. Redrawn courtesy of Chiara Secco (Pediatric Oncology Unit of the Istituto Nazionale Tumori, Milan, Italy) and Ilaria Zanetti (EpSSG International Data Centre). Data taken from [101].

Table 2. Italian cases registered in the European pediatric Soft Tissue Sarcoma database (2005–2011): geographical pattern of access to care.

Place of residence	Place where treatment was provided			Total
	Southern regions	Central regions	Northern regions	
0–14 year olds				
Southern regions	71	1	42	114
Central regions	18	17	11	46
Northern regions	1	1	138	140
Total	91	19	190	300
15–21 year olds				
Southern regions	5	0	12	17
Central regions	1	1	6	8
Northern regions	0	0	38	38
Total	6	1	56	63

The table matches the patients' place of residence (by macro-area) with the place where they were treated. The concordance between residence and treatment place was moderate according to the κ Cohen's test ($\kappa = 0.57$) for children aged 0–14 years and only fair for older children aged 15–21 ($\kappa = 0.31$). Data taken from [101].

patients were not usually referred to pediatric oncology units; and, even when they were, they often arrived after a considerable delay, which probably affected their chances of a cure. Given that 15.4 cases of adolescent rhabdomyosarcoma were expected each year in Italy (based on epidemiological data), the median number of four adolescents registered in AIEOP protocols gave an O/E ratio of 0.27, compared with 0.9 observed in children. The number of adolescents registered in the Italian STSC trials gradually rose from 3.6 (in 1988–1993) to 5.5 (in 2000–2005) cases per year [36], but the percentage remained unsatisfactory. Although no data are available on where and how adolescents not seen at AIEOP centers were treated (any number of these patients may feasibly have been treated with adequate therapies), the AIEOP network includes all Italian pediatric oncology centers and the protocols coordinated by the STSC are the only national multicenter protocols available for children with rhabdomyosarcoma in Italy. In other words, there is good reason to worry about the quality of care for adolescents with rhabdomyosarcoma treated elsewhere, who run the risk of being treated according not to current pediatric guidelines, but to the approach adopted for adult STS, which is a very different matter. Patient referral for adolescents with pediatric cancers remains an unsolved problem. Sometimes, the reason why, for example, a 16-year-old boy, who is diagnosed with rhabdomyosarcoma, may be referred to adult instead of pediatric oncology facilities, is that the first physician seeing the patient, who may be an internist, a family doctor, an emergency room physician, or another specialist, lacks the necessary awareness of the nature of the problem [50]. In other cases, their referral to pediatric oncology facilities may be prevented by inflexible upper-age limits for admitting patients to pediatric units. Even when adolescents are referred to pediatric oncology centers, they are often diagnosed and treated too late. In the AIEOP-STSC rhabdomyosarcoma series, the median latency period for adolescents was twice as long as for children

(8 vs 4 weeks; $p < 0.0001$) [51–53]. A series of 575 STS patients <21 years of age seen at the Istituto Nazionale Tumori confirmed the association between diagnostic delay and patient's age: the geometric mean interval since symptom onset was 1.54 months for STS patients <10 years old, 2.69 months for those 10–14 years old, and 2.72 months for patients >15 ($p = 0.006$) [51]. The same study also found diagnostic delay to be independent factor affecting patient survival. There may be many reasons for such a diagnostic delay in adolescents; including families' and the community's limited awareness that adolescents can develop cancer, the relative lack of parental control, and teenagers' particular psychological features that makes them tend to have a strong sense of independence and be reluctant to ask for help or see a doctor [44,54–56].

FIGURE 4 shows the STS cases enrolled in the EpSSG database from 2005 to June 2011 by Italian AIEOP centers, and by patient age: it shows how the pattern of registered cases changed according to the 'type' of center:

- The Gaslini Hospital (Genova, Italy) and the Ospedale Pediatrico Bambino Gesù (Rome, Italy) are two large pediatric oncology units forming part of children's hospitals, where upper-age limits for patient admission are fixed by the hospital administration; the median age of treated patients is 4 years, and far more rhabdomyosarcomas (tumors typical of childhood) are seen than nonrhabdomyosarcoma STS (more typical of adolescents and adults);
- At Padova University (Padova, Italy), the pediatric oncology unit is part of a large comprehensive general hospital, and there is a flexible upper-age limit for patient admission of 18 years; the median age of registered cases is 10 years and the sarcoma types are seen in equal proportions;
- The pediatric oncology unit at the Istituto Nazionale Tumori is the only Italian pediatric oncology unit forming part of a large referral cancer hospital. This has facilitated a close cooperation with other hospital departments dedicated to adult cancers, and particularly with the adult STS division [57]; there are no fixed upper-age limits for admitting patients to the pediatric unit (who may generally be up to 25–30 years old), particularly when they have pediatric cancers. FIGURE 4 shows that a third of all Italian STS cases registered in the EpSSG database are treated in Milan: the median age of recruited cases is 14.5 years (vs 6 years for the other Italian centers as a whole) and there is a higher proportion of tumor types that are more typical of adolescents (100 nonrhabdomyosarcoma STS vs 73 rhabdomyosarcomas);

- The Youth Area Project run by the Centro di Riferimento Oncologico (Pordenone, Italy) in Aviano is not a pediatric unit, but is affiliated to the AIEOP as it has all the facilities for treating adolescents; the center is dedicated to 14–24 year-olds and it has registered nine patients in the EpSSG database.

TABLE 2 refers to the Italian cases registered in the EpSSG database (from 2005 to June 2011) and describes the geographical pattern of access to care. When we matched the patient's place of residence (by macro-areas) and the place where they were treated, it was clear that the central and southern Italian regions had a low capacity for patients at AIEOP clinical units, and that centers in northern Italy attract patients from outside their macro-area. The migration rate differed according to the patient's age, however; among the 0–14-year-olds, 63 and 38% of cases from central and southern Italy, respectively, were treated outside their area of residence and they opted mainly for centers in northern Italy (73%). For 15–21-year-olds, the migration rate from the central and southern regions was 88 and 70%, respectively (95% of cases going to northern centers). Patterns of migration between 0–14-year-olds and older children were significantly different (χ^2 test for equal κ coefficients; $p = 0.0116$).

These findings again suggest that the AIEOP network has been more effective in serving children than adolescents, with the exception of the Istituto Nazionale Tumori who particularly focused on this subset of patients.

The above data give an outline of access to care for adolescents and their inclusion in clinical trials as seen from the pediatric oncology point of view. But how does the situation look from the other side? Can we estimate how many adolescent STS cases are included in adult clinical trials? Can we tell where and how adolescents not referred to pediatric oncology centers are treated? Less information is available, to our knowledge at least, on adult STS. Epidemiological data suggest that the annual number of STS cases in Italy (calculated on the population in 2008) is 55, 67 and 143 cases for the 0–9, 10–19 and 20–29 year-old age groups, respectively, and 4025 cases for people over 30 years of age [PASTORE G, PERS. COMM.]. The Italian Sarcoma Group (ISG), to which all the major referral centers for adult STS belong, recently concluded a multicenter Phase III randomized trial (testing three vs five cycles of anthracycline and ifosfamide chemotherapy) on localized, high-risk STS

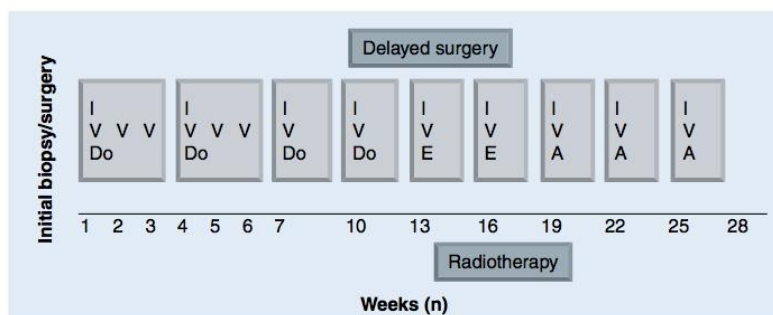


Figure 5. Treatment program for adult rhabdomyosarcoma in the protocol developed by the Italian Sarcoma Group and the Italian Rare Tumor Network, in cooperation with pediatric oncologists.

of the extremities and trunk wall: 328 patients were recruited from 2002 to 2007 [58]. Some additional cases have been included in upfront therapy adult clinical trials on particular histotypes (e.g., retroperitoneal STS, angiosarcoma and mixoid liposarcoma). On the other hand, a large number of Phase I–II studies on relapsing/refractory STS (and particularly on new target agents) have been conducted – or are underway – coordinated by the ISG or by single Italian institutions [59,60]; reflecting the great deal of effort put into Phase I–II trials and research on novel treatments (an imperative goal given the lower chemosensitivity of adult STS compared with rhabdomyosarcoma). However, as a matter of fact, only a minority of adult STS cases are included in clinical protocols (~1% as a rough estimate). Whether or not they are included in clinical trials, it remains to be seen how many

Table 3. Associazione Italiana Ematologia Oncologia Committee on Adolescents: action to deal with low rates of adolescent enrollment in Associazione Italiana Ematologia Oncologia trials.

Aims	Actions
Improve awareness	A press release has been launched on adolescent access to care A brief documentary video has been prepared and uploaded on [102] Various conferences have been organized A document has been prepared to send to the Ministry of Health, universities and hospitals Partnerships with charities and testimonials have been planned
Increase the number of adolescents referred to pediatric oncology centers	Upper-age limits at pediatric oncology centers should be raised (a survey on AIEOP centers has been published; an official document has been prepared to overcome administrative barriers)
Address specific issues	Links with other AIEOP working groups have been established to define adolescent-specific aims in their protocols Adolescent-focused biological studies have been planned Cooperative schemes have been developed with other International groups working on AYA
Cooperate with adult medical oncologists	Cooperative schemes have been implemented with adult organizations A protocol has been prepared for adult rhabdomyosarcoma in cooperation with the ISG

AIEOP: Associazione Italiana Ematologia Oncologia Pediatrica; AYA: Adolescents and young adults; ISG: Italian Sarcoma Group.

adult STS patients are treated at cancer referral centers (e.g., the Istituto Nazionale Tumori or the Rizzoli Institute).

Bridging the gap

Assuring AYAs with STS access to the most qualified cancer centers and to clinical trials remains a major challenge. Improving their chances is no easy task and requires broad-based schemes involving the public and its awareness, healthcare providers, cooperative groups running clinical trials, and national and local governments [23,61].

Various attempts at comprehensive programs dedicated to AYAs have been developed around the world [62]. The UK pioneered the movement in the 1990s by founding a national charity, the Teenage Cancer Trust; substantial progress was made in the UK when the National Cancer Research Institute subsequently established its Teenage and Young Adult Clinical Studies Group and began to support the development of hospital units dedicated to AYAs [63–65]. In North America, AYA oncology programs started at a national level, not at local level, but mainly under the initiative of pediatric oncologists. The Children's Oncology Group funded by the NCI formed an AYA Committee in 2000, focusing on improving adolescent and young adult access to care and accrual for clinical trials (starting with sarcoma patients, developing intergroup sarcoma committees and clinical protocols, including both pediatric and adult cases) [21,66]. The Lance Armstrong Foundation and, later on, the LIVESTRONG Young Adult Alliance have supported the project and promoted research [67]. As a direct effect of these schemes, the rate of AYA accrual in NCI-sponsored national trials has improved, especially for sarcoma patients (the proportion of sarcoma patients under 40-year-old enlisted has risen from 5% in 1998–1999 to 19% in 2004–2005) [44–46].

On an international cooperative level, the International Working Group on Adolescent/Teenage and Young Adult Oncology, presented at the International Society of Pediatric Oncology (SIOP) held in Geneva, Switzerland, in September 2006, and is an organization that will hopefully organize and coordinate new collaborative initiatives [68].

Up until recently, a few places in continental Europe have attempted to start specific programs tailored to AYAs with cancer. In Italy, the pioneering initiative of the Youth Area Project at the Centro di Riferimento Oncologico, dedicated to 14–24 year olds, began in January 2007 [62], but remains a small unit only able to treat a few cases.

The recently-published evidence of the AIEOP's failure to enroll adolescents in its trials [49] prompted the creation of an AIEOP Committee on Adolescents. Since referral to pediatric oncology facilities in many cases may be restricted by inflexible upper-age limits for patient admission or enrollment in clinical trials, the AIEOP Committee launched a survey to assess the Italian pediatric oncology centers' use of upper-age limits [69], discovering that many of them set upper limits at 16, 15, or even 14 years of age (46%), while others place a rigid limit at 18 years of age (39%). In principle, therefore, these pediatric oncology units reject patients over their upper-age limit, even if they suffer from

tumors typical of pediatric ages, such as rhabdomyosarcoma, or acute lymphoblastic leukemia. The report also documented a correlation between upper age limits and the numbers of adolescents treated at pediatric centers, suggesting that raising these age limits may make pediatric oncology centers more readily accessible to adolescents.

TABLE 3 shows the steps taken by the AIEOP Committee on Adolescents to deal with the low rates of adolescent enrollment in AIEOP trials. Major efforts have been directed to establish forms of collaboration with adult medical oncologists. In fact, raising the upper-age limits for pediatric centers and protocols will only really help if adult patient groups can also be included in the project. Most AIEOP protocols are currently open to patients up to 18 or 21 years of age, but adult physicians may not hear of such trials, or may be reluctant to enroll their patients in trials in which they themselves have no part. The goal of developing a protocol for adult rhabdomyosarcoma has recently been achieved by the ISG and the Italian Rare Tumor Network (mainly concerned with adult oncology), in cooperation with the AIEOP: a cooperative network has been formalized with the view to referring patients up to 21 or 25 years of age to pediatric oncology centers. While older patients would be treated by medical oncologists according to a program based on a pediatric-like strategy (FIGURE 5).

Discussions are also underway to try and develop a common protocol on synovial sarcoma that would integrate the same treatment concepts regardless of age, and thus, provide numbers large enough to answer some important questions based on results obtained in randomized samples.

Meanwhile, the AIEOP Committee has been prompting the activation of local programs. In particular, a youth project has been launched by the Pediatric Oncology Unit at the Istituto Nazionale Tumori: the close cooperation of pediatric oncologists with the divisions dedicated to adult cancers in the same hospital have prompted a peculiar focus on particular subsets of patients over the years – that is, adolescents, especially those affected by tumor types crossing the pediatric and the adult age groups (e.g., sarcomas), and young adult patients affected by pediatric tumors (e.g., rhabdomyosarcoma). To enable young adults with pediatric tumors to be treated by physicians with the greatest experience of their disease, it was decided some years ago to not consider any upper-age limits for admitting patients with pediatric cancers to the pediatric unit, and this has meant that a large number of adolescents, as well as patients up to 25 or even 30 years of age with pediatric tumors, have been referred to the Istituto Nazionale Tumori in Milan's pediatric unit. For example, among 4110 newly-diagnosed patients treated between 1985 and 2010, there were 880 who were 15–19 years old and 206 were more than 20 years old (26% of all treated cases were over 15 years old). Among all the Italian pediatric centers [49], 40% of all patients >15 years old with solid tumors registered in the AIEOP database (1989–2006) were treated at the Istituto Nazionale Tumori (nearly one in two cases of brain tumor or soft tissue and bone sarcoma; FIGURE 4). The Youth Project has provided suitably equipped, multifunctional dedicated rooms where AYAs can socialize and occupy their time in recreational activities (including a gym), or study, or take part

in various activities and events. The project has also implemented new programs for accessing care after patients have completed their hospital treatments (including psychosocial support and fertility preservation) [70].

Expert commentary

We believe that to take a step towards really improving AYA patients' access to health services and clinical trials demands a multilevel comprehensive effort based on a new form of collaboration between pediatric and medical oncologists dealing with the same diseases. We wish to underscore this issue as in the past (in Italy at least), the two worlds of pediatric and adult oncology have sometimes seemed to be streets apart. Getting pediatric and medical oncologists to cooperate fruitfully in the same trials potentially poses several cultural and logistical problems deriving from their different backgrounds, different priorities and different goals. The two groups may sometimes even speak different languages (e.g., adult oncologists' surgical stages R0, R1 or R2 are what pediatric oncologists call IRS group I, II or III) and use different methods for data collection (which could make it difficult to share data), as well as different healthcare delivery models – that is, the pediatric model is 'family focused' and relies on multidisciplinary teams with a high staff-to-patient ratio, while the adult model is more 'disease focused', with programs for dealing with specific types of tumors [62]. The target of pediatric oncology has often been to promote national or international multicenter networks focusing on Phase III (randomized or risk-based) trials, while adult oncologists have generally given priority to Phase I–II trials and research on new treatments, especially in recent years. However, in our opinion, in the past there has also been some reluctance on the part of physicians on both sides to cooperate: they have been more inclined to defend their own background and strategies [71]. Times are changing, however, in the field of STS and researchers are realizing the importance of cooperating, particularly for tumor types spanning pediatric and adult ages. For synovial sarcoma, for instance, effective cooperation may lead to a standardized treatment of AYAs, as well as enabling enough cases to be pooled to permit randomized studies and, thus, answer important questions on the disease's therapy. In fact, although the EpSSG covers most of the pediatric oncology centers in Europe, the protocol for synovial sarcoma is still unable to reach the numbers needed for randomized therapeutic arms. Greater collaboration may mean the availability of enough tumor samples to be able to study age-related biological changes that could shed light on biological differences between a given disease in different age groups, possibly accelerating the identification of molecular targets for novel therapeutic approaches. In particular, the experience of adult oncologists with novel therapies may help pediatric oncologists to gain access to new drugs. In the near future, histology-driven therapies will probably be available for single STS histotypes [3], which are very rare in children, and this is another reason why pediatric oncologists must recognize the need for close cooperation with adult medical oncology groups if they want to manage their patients with the most up-to-date approach [71].

Five-year view

Enabling AYAs with cancer, and with STS in particular, to access proper care has become a major goal of health systems around the world in recent years [44,72]. Increasing, a number of health services have developed age-specific schemes, with different formats and varying degrees of success [62]. These programs were prompted by pediatric oncologists, adult medical oncologists, or both. The previously-described Italian scheme, proposed by the national committee on AYA and based on the experience of the Istituto Nazionale Tumori, was developed to focus more on adolescents than on young adults, in the conviction that adolescent patients may benefit more from the multidisciplinary team typical of pediatric oncology units, where pediatric oncologists work closely not only with surgeons, radiotherapists, nutritionists, infectious disease experts, neurologists, and endocrinologists, but also with psychologists and social workers. Studies on pediatric neoplasms other than STS (e.g., acute lymphoblastic leukemia) have also reported significantly better outcomes for adolescents treated at pediatric cancer centers than for those admitted to adult facilities [73–78].

Adolescents are neither children nor adults, however (although they share many characteristics of both), and several authors have written that their particular needs cannot be met by either pediatric or adult models of care: they need adequately trained and supported, dedicated professionals. It is hard to say whether this is really feasible, but it seems probable that the real, ultimate goal would be to develop a new discipline, 'AYA oncology', with tailored units and dedicated research strategies unavailable through either pediatric or adult care programs [62]. Profound cultural changes need to be made by oncology communities and health systems and, although they are already underway in many countries, they seem to be far from occurring in Italy. What we may expect in Italy in the next 5 years is that newly developed programs will succeed in increasing the proportion of adolescents able to access the best possible care. Nonetheless, we also hope to get our adult oncologist colleagues involved, not only at single centers, but on a nationwide level: this may broaden our horizons and pave the way to the development of shared national AYA programs.

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Key issues

- Synovial sarcoma and rhabdomyosarcoma are tumor types that can occur in children, adolescents and adults. Various data indicate that adolescents and young adults with these tumors are sometimes treated very differently, depending on whether they are referred to adult or pediatric cancer centers.
- Adolescent and young adult cancer patients are sometimes midway between the two different worlds of pediatric oncology and adult medical oncology, and they may pay a high price in terms of the quality of the care they receive due to shortcomings in the cooperation between pediatric and adult oncologists. Several publications have emphasized that these patients have clearly been under-represented in clinical trials, and this situation has coincided with this particular age group's survival rates failing to improve over the last few years.
- The Associazione Italiana Ematologia Oncologia Pediatrica has recently looked into how many patients over 15 years of age access their centers and trials: while the figures were satisfactory in children, the situation was significantly worse for adolescent accrual. Adopting inflexible upper-age limits for admitting patients to Italian pediatric units or enrolling them in clinical trials emerged as a potential barrier.
- A broad initiative involving the public and its awareness, healthcare providers, cooperative groups running clinical trials, and national and local governments is needed to ensure that adolescents and young adults with soft tissue sarcomas access the most qualified cancer centers and clinical trials.
- New forms of cooperation between pediatric and medical oncologists dealing with the same diseases remain a fundamental step: in Italy, this may enable us to turn a project started in the pediatric oncology setting into a broader scheme to create a new discipline, 'adolescent/teenage and young adult oncology', with tailored units and dedicated research strategies.

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Symptom Interval in Pediatric Patients With Solid Tumors: Adolescents Are at Greater Risk of Late Diagnosis

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Background. The awareness that adolescents can have cancer is probably insufficient, not only among teenagers and their families, but also among physicians, and adolescent patients are reportedly often referred to qualified cancer institutes after a considerable delay. **Procedure.** A prospective series of 425 patients (28% of them adolescents) with solid tumors was analyzed to investigate the correlation between symptom interval and age, and the different contributions to symptom interval in terms of the time from symptom onset to the first contact with a doctor (patient delay), referral to the oncologist (referral delay), and final diagnosis (oncologist delay). **Results.** The median symptom interval was 47 days for 0 to 14-

year-old patients and 137 for those ≥ 15 years ($P < 0.001$). The greatest delay in the adolescent group related to the patient delay (63.3% of the total symptom interval). **Conclusion.** Adolescents are often diagnosed with longer delay as compared to children. The main contribution to symptom interval in adolescents appears to be due to the time they first go to a doctor; however, also the time taken by the physician to the patient to a specialist (oncologist or surgeon) able to define the diagnosis of cancer was longer for adolescents than for younger patients. *Pediatr Blood Cancer*
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Key words: adolescents; cancer; diagnostic delay; pediatric oncology; symptom interval

INTRODUCTION

Adolescents with cancer represent a subset of patients with particular psychosocial and clinical characteristics. In recent years, the oncology community has become aware that the needs of this group of patients have sometimes been inadequately addressed by health care systems in the past [1]. In particular, pediatric oncologists have seen that survival trends for adolescents with cancer have been disappointing by comparison with improvements seen in children in the last few decades. Limited access to the most expert care has been suggested as one possible reason for this difference, since several studies have shown that adolescents are under-represented in clinical trials on therapies that might improve their outcome [2–6]. It also seems that adolescents are often referred to qualified cancer centers only after a considerable delay, and this is likely to affect their chances of cure [7–9].

In a previous study [10], our group focused on symptom interval, defined as the time elapsing between the onset of the first signs or symptoms of the disease and its definitive diagnosis. That study investigated the association between symptom interval and clinical variables in a retrospective series of children and adolescents with soft tissue sarcomas, showing that a higher mortality rate was associated with longer symptom interval, and that this interval was longer in adolescents than in children [10].

To further clarify this issue, we conducted a prospective investigation of patients with solid tumors of any type in order to establish whether the diagnostic delay seen for adolescent patients with soft tissue sarcomas was confirmed in other malignancies. Our aim was also to characterize the separate contributions of the symptom interval, distinguishing between the time after the onset of symptoms to the first contact with a doctor, to referral to an oncologist, and to a final diagnosis.

METHODS

Our series included 425 consecutive patients with solid tumors admitted to the Pediatric Oncology Unit of the Istituto Nazionale Tumori, Milan, Italy, between September 2007 and March 2011. On the first admission, to either at the inpatient or outpatient units,

the physician in charge recorded the patient's clinical history and also obtained information on the symptom interval with the aid of an *ad hoc* form. Patients or their guardians had to provide their informed consent to enter the study.

The time elapsing from the initial onset of symptoms to the final diagnosis was defined as the "symptom interval," which was split into three components: (1) "patient delay"—the time from the initial presentation of symptoms to the first contact with a doctor. The physicians who first examined the patient were classified as: general practitioners/pediatricians, emergency doctors, specialists other than oncologists (e.g., orthopedics specialists, ophthalmologists, urologists, and neurologists), or radiologists; (2) "referral delay" – the time from the first doctor's visit to assessment by an oncologist. For the purposes of our analysis, oncological surgeons and neurosurgeons were considered as oncologists; (3) "oncologist delay"—the time taken after the oncological examination to arrive at a final diagnosis, intended as the time of the surgical procedure (resection or biopsy) that led to a final histological diagnosis.

The types of disease were classified as: central nervous system (CNS) tumors, soft tissue sarcomas (STS), bone sarcomas (including osteosarcoma and Ewing sarcoma), rare pediatric tumors (e.g., germ cell tumors, carcinomas, and melanomas), non-Hodgkin lymphomas (NHL), neuroblastomas, Wilms tumors and Hodgkin disease (HD). Additional details considered in the analysis included: the patient's age and gender; the family's place of residence, defined by macro-area (northern, central, and southern Italy); the

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family's socio-economic status, classified as high, medium, or low class, according to the ISTAT [11]; and the type of initial sign/symptom, classified in three categories as growing swelling/mass, pain, or specific symptoms relating to the effect of the tumor mass on adjacent structures, for example, proptosis, ascites, vomiting, gastrointestinal or urinary tract obstruction, hemorrhage, and neurological dysfunctions. Analysis was done according to four age groups (0–4, 5–9, 10–14, and 15+ years old), and patients ≥ 15 years were defined as “adolescents.”

Statistical Analysis

The characteristics of the sample of patients were described using standard descriptive statistics, that is, absolute and relative frequencies for categorical data, medians, and interquartile (IQ) ranges for continuous variables. Associations regarding the overall symptom interval and its components (patient, referral and oncologist delays, as defined above) were investigated with the non-parametric Kruskal–Wallis test in univariate analyses. Multivariate analyses were performed according to the Iman and Conover approach [12], which is based on using linear multiple regression models after transforming the dependent variable (the delays in the case in point) into natural ranks. In addition to age (as a four-class variable), the covariates entered in the multivariate models were gender, geographical area, socio-economic status, type of initial sign/symptom, type of disease, and first contact with a doctor. A non-parametric approach was used in the univariate and multivariate analyses after finding that symptom intervals and delays were not normally distributed. The statistical analyses were completed with the SAS (SAS Institute Inc., Cary, NC), and *P* values below 0.05 (two-tailed) were considered statistically significant.

RESULTS

The main patient and disease characteristics are shown in Table I. The median age was 10 years (IQ range: 4.0–15.0 years). Adolescents accounted for 28% of the sample (120 cases, 24 of them over 20 years). CNS tumors (29%) and soft tissue sarcomas (25%) were the most frequent tumor types. The frequency of the different malignancies differed by age. For example, CNS tumors represented 35% of the cases among the 0–14 year olds, but only 11% in the older group (over 15 year olds). Soft tissue and bone sarcomas together accounted for 33% of the cases among the children and 58% among the adolescents. Neuroblastomas and Wilms tumors together accounted for 15% and 2% in children and adolescents, respectively.

The distributions of the delays by patient and disease features are summarized in Tables II–IV. The median symptom interval was 65 days altogether, but differed significantly ($P < 0.001$ at both univariate and multivariate analysis) according to the patient's age (Table II): it was 47 days for the 0–14 year olds and 137 for the patients over 15 years old.

A detailed description of the pattern of the association between the delay in its various components and age is given in Figures 1 and 2. Notably, there was a marked increase in the delay, and particularly in the patient delay, in terms of both the absolute number of days (Fig. 1) and the number of days relative to the overall symptom interval (Fig. 2), for the patients over 15 years of age. On average, for cases below and above the age cut-off of

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TABLE I. Main Characteristics of Patients and Their Disease

	No.	%
Overall	425	—
Gender		
Female	167	39.3
Male	258	60.7
Age group (years)		
0–4	112	26.4
5–9	92	21.6
10–14	101	23.8
15+	120	28.2
Geographical area		
Northern Italy	314	73.9
Central Italy	21	4.9
Southern Italy	90	21.2
Socio-economic status		
Low	152	35.8
Medium	216	50.8
High	57	13.4
Initial sign/symptom		
Pain	119	28.0
Growing swelling/mass	107	25.2
Specific symptoms	199	46.8
Disease		
CNS tumors	121	28.5
Soft tissue sarcomas	105	24.7
Bone sarcomas	65	15.3
Rare tumors	44	10.4
Non-Hodgkin lymphoma	30	7.1
Neuroblastoma	25	5.9
Wilms tumor	23	5.4
Hodgkin lymphoma	12	2.8
First doctor contacted		
GP/pediatrician	138	32.5
Emergency room doctor	136	32.0
Non-oncological specialist	114	26.8
Radiologist	37	8.7

IQ, interquartile; CNS, central nervous system; GP, general practitioners.

15 years, the median patient delay was 8 and 72 days, while the median referral delay was 18 and 34 days, respectively. In relative terms, the patient delay accounted for 36.4% of the total time elapsing for the children, as opposed to 63.3% for the adolescents ($P < 0.0001$ at Kruskal–Wallis test), while for the referral delay the figures were 56.1% and 34.7%, respectively ($P < 0.0001$). Univariate and multivariate analyses consistently showed a significant association between the patient's age and their patient (Table III) and referral delay (Table IV).

The oncologist delay was a smaller component of the symptom interval, ranging from 0 to 136 days (median 0), and accounting overall for 6% of the symptom interval. In 76% of cases, the final diagnosis was established at the time of the oncological assessment, and no significant age-related difference was observed.

As for the other parameters analyzed for their association with the delays, significant results, confirmed by univariate and multivariate analyses, were obtained for the overall symptom interval vis-à-vis the type of disease and the first contact with a doctor (Table II). The type of disease was particularly associated with the patient delay, with sarcomas and rare tumors showing the longest

TABLE II. Median (IQ Range) of Symptom Interval

	No. of pts	Median	IQ range	P-value	
				Univar.	Multivar.
Overall	425	65.0	28.0–127.0		
Factor					
Gender				0.742	0.173
Female	167	68.0	26.0–128.0		
Male	258	63.0	29.0–125.0		
Age (years)				<0.001	<0.001
0–4	112	37.0	15.5–70.5		
5–9	92	51.5	23.0–98.5		
10–14	101	47.0	24.0–110.0		
15+	120	137.0	84.0–217.0		
Geographical area				0.025	0.153
Northern Italy	309	56.0	24.0–120.0		
Central Italy	21	96.0	63.0–143.0		
Southern Italy	90	72.5	44.0–159.0		
Socio-economic status				0.071	0.225
Low	152	73.5	36.0–154.5		
Medium	216	58.5	24.0–113.5		
High	57	66.0	31.0–117.0		
Initial sign/symptom				0.039	0.708
Pain	119	70.0	31.0–165.0		
Growing swelling/mass	107	82.0	23.0–159.0		
Specific symptoms	199	56.0	26.0–103.0		
Disease				<0.001	0.002
CNS tumors	121	47.0	23.0–101.0		
Soft tissue sarcomas	105	97.0	53.0–186.0		
Bone sarcomas	65	84.0	35.0–165.0		
Rare tumors	44	86.5	49.5–171.0		
Non-Hodgkin lymphoma	30	37.0	23.0–52.0		
Neuroblastoma	25	54.0	15.0–108.0		
Wilms tumor	23	24.0	13.0–64.0		
Hodgkin lymphoma	12	69.0	37.5–98.5		
First doctor contacted				<0.001	<0.001
GP/pediatrician	138	68.0	32.0–121.0		
Emergency room doctor	136	38.5	13.5–77.0		
Non-oncological specialist	114	106.5	52.0–209.0		
Radiologist	37	96.0	33.0–170.0		

IQ, interquartile; CNS, central nervous system; GP, general practitioners.

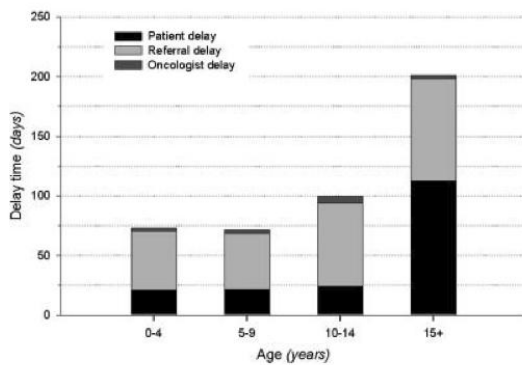


Fig. 1. A marked increase in the delay, and, particularly in the patient delay in terms of the absolute number of days for the patients over 15 years of age.

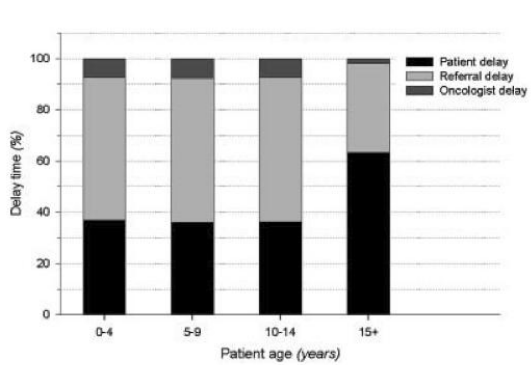


Fig. 2. A marked increase in the patient delay in terms of days relative to the overall symptom interval for the patients over 15 years of age.

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TABLE III. Median (IQ Range) of Patient Delay

	No. pts	Median	IQ range	P-value	
				Univar.	Multivar.
Overall	425	19.0	4.0–58.0		
Factor					
Gender				0.178	0.932
Female	167	14.0	4.0–49.0		
Male	258	28.5	4.0–61.0		
Age (years)				<0.001	<0.001
0–4	112	7.5	1.0–23.0		
5–9	92	7.0	2.0–31.0		
10–14	101	10.0	3.0–31.0		
15+	120	72.0	39.0–123.0		
Geographical area				0.025	0.410
Northern Italy	309	16.0	3.0–46.0		
Central Italy	21	36.0	14.0–74.0		
Southern Italy	90	33.0	5.0–75.0		
Socio-economic status				0.080	0.577
Low	152	30.0	5.0–68.0		
Medium	216	15.0	3.0–46.5		
High	57	17.0	6.0–59.0		
Initial sign/symptom				0.158	0.426
Pain	119	32.0	5.0–71.0		
Growing swelling/mass	107	28.0	3.0–74.0		
Specific symptoms	199	15.0	4.0–43.0		
Disease				<0.001	0.002
CNS tumors	121	15.0	4.0–37.0		
Soft tissue sarcomas	105	36.0	14.0–81.0		
Bone sarcomas	65	30.0	5.0–80.0		
Rare tumors	44	40.5	5.0–81.5		
Non-Hodgkin lymphoma	30	6.5	3.0–36.0		
Neuroblastoma	25	5.0	1.0–10.0		
Wilms tumor	23	2.0	0.0–13.0		
Hodgkin lymphoma	12	22.5	4.5–32.5		
First doctor contacted				<0.001	0.026
GP/pediatrician	138	14.0	3.0–41.0		
Emergency room doctor	136	14.5	2.0–36.5		
Non-oncol. specialist	114	35.0	7.0–78.0		
Radiologist	37	51.0	8.0–107.0		

IQ, interquartile; CNS, central nervous system; GP, general practitioners.

intervals (Table III). Regarding the first contact with a doctor, both the patient and the referral delay were shorter when the doctor involved was an emergency room physician, and longer in the case of radiologists or other non-oncological specialists (Tables III and IV).

Concerning geographical area and socio-economic status, patient delay was shorter for cases from northern Italy (median of 16 days, as compared to 36 and 33 days in cases from Central and Southern Italy, $P = 0.025$), and longer for cases with a low socio-economic status (median of 30 days, as compared to 15 and 17 days in cases with medium and high socio-economic status, $P = 0.080$).

DISCUSSION

This study investigated the symptom interval in a prospective single-institutional series of children and adolescents with solid tumors. The main finding of our analysis is a strong relationship between symptom interval and patient's age, consistent with what others have reported [7–10,13–19]. The median time between the

onset of the first symptom and the final diagnosis was 47 days for 0 to 14-year-old patients and 137 days for older patients.

As new finding, the study investigated the role of the different component parts of symptom interval in determining the longest diagnostic delay of adolescents. In principle, there may be two major contributions to the time delays observed [7,13]: (1) patient delay, the time from the onset of the first symptom to the first visit to the doctor, which depends on how quickly patients and their families report their signs and symptoms to a physician; and (2) referral delay, the time between the first contact with a doctor and examination by an oncologist, which depends on how doctors who first see a patient interpret their symptoms, and how they manage the clinical problem referral to a specialist (oncologist or surgeon) capable of determining a diagnosis. Our findings suggest that these two contributions generally have a similar impact on the total symptom interval (in the series as a whole, the median times were 19 and 22 days, respectively), while the time elapsing between the oncological examination and the procedure leading to the final diagnosis (oncologist delay) is less influential. In our series, the intervals were longer for adolescents than for children

TABLE IV. Median (IQ Range) of Referral Delay

	No. of pts	Median	IQ range	P-value	
				Univar.	Multivar.
Overall	425	22.0	6.0–62.0		
Factor					
Gender				0.263	0.143
Female	167	22.0	7.0–81.0		
Male	258	20.5	5.0–60.0		
Age (years)				0.001	0.024
0–4	112	11.5	3.0–50.5		
5–9	92	21.0	5.0–68.5		
10–14	101	21.0	7.0–57.0		
15+	120	33.5	10.0–85.5		
Geographical area				0.192	0.600
Northern Italy	309	20.0	5.0–60.0		
Central Italy	21	37.0	11.0–69.0		
Southern Italy	90	28.5	9.0–63.0		
Socio-economic status				0.061	0.073
Low	152	28.0	9.0–72.0		
Medium	216	18.0	5.0–57.0		
High	57	28.0	6.0–51.0		
Initial sign/symptom				0.176	0.994
Pain	119	24.0	8.0–73.0		
Growing swelling/mass	107	28.0	7.0–70.0		
Specific symptoms	199	20.0	5.0–56.0		
Disease				0.018	0.084
CNS tumors	121	13.0	4.0–52.0		
Soft tissue sarcomas	105	32.0	10.0–87.0		
Bone sarcomas	65	24.0	9.0–85.0		
Rare tumors	44	27.5	7.5–63.0		
Non-Hodgkin lymphoma	30	17.5	4.0–35.0		
Neuroblastoma	25	29.0	4.0–98.0		
Wilms tumor	23	7.0	5.0–24.0		
Hodgkin lymphoma	12	15.5	10.0–46.0		
First doctor contacted				<0.001	<0.001
GP/pediatrician	138	29.5	10.0–76.0		
Emergency room doctor	136	7.5	2.0–23.5		
Non-oncol. specialist	114	44.0	13.0–98.0		
Radiologist	37	23.0	9.0–63.0		

IQ, interquartile; CNS, central nervous system; GP, general practitioners.

for both patient and referral delays. However, patient delay had the major effect in determining the increased symptom interval of adolescents as compared to younger patients. Patient delay was 8 and 72 days, respectively, for cases below and above 15 years, and represented around one third of the symptom interval in children and two-third of the symptom interval in adolescents (Fig. 2).

Some peculiar psychosocial features of teenagers may partially explain the longer patient delay observed for patients ≥ 15 years. In teenagers, the detection of symptomatic disease relies largely on self-reporting (parents are probably more aware of their son's or daughter's physical condition when they are younger). Adolescents are still not fully independent, but they generally have a strong sense of independence, they often refuse their parents' attentions and mistrust adults generally, leading sometimes to a reluctance to see a doctor [20,21].

Our study suggested that also referral delay was longer for adolescents than for children. The problem of the appropriate referral of adolescent patients to comprehensive cancer centers, and their consequent inclusion in clinical trials, has emerged from various studies [2–6,22–26], suggesting that this may be one of

the main reasons why there has been little improvement in the survival trends for adolescents by comparison with the advances seen in children in recent decades [2–6,22–26].

The time it takes for referral to an oncologist and an institution with sufficient experience can vary depending on the type of physician to first see the patient. In our sample, patient delay was shorter when the first doctor to be contacted was in the Emergency Room setting (possibly because patients generally go there with more severe and acute symptoms), and it was longer when the first doctor was a radiologist or non-oncological specialist (possibly related to the waiting times for booking an appointment with a specialist). It is noteworthy that the percentage of children seen first by Emergency Room doctors was higher than among adolescents (35% vs. 24%). Referral delay resulted shorter after initially seeing an Emergency Room doctor or a radiologist, probably for their possibility to easily complete various examinations as blood tests or radiological imaging.

There may be a confounding effect in our study deriving from the different tumors observed in the two age groups. Different tumor types were associated with different symptom intervals.

Sarcomas are more common in older patients, and, at the same time, are neoplasms with the longest symptom interval, possibly because they are sometimes indolent with non-specific symptoms; CNS tumors are more frequent in younger patients, and emerged as those with the shortest symptom interval. The analysis was nonetheless controlled for tumor type: multivariate analysis confirmed that the patient's age was the main variable influencing the symptom interval.

In conclusion, the present article asserts that adolescents often arrive at a diagnosis of cancer after an unacceptably long delay as compared to younger patients. Our analysis showed that the main contribution to this interval in adolescents appears to be due to the time they first go to a doctor, probably influenced by teenagers' (and their families') limited awareness that they might have cancer. The time taken by the physician to interpret their symptoms and refer them to a specialist (oncologist or surgeon) was also longer for adolescents than for younger patients.

Corrective actions to reduce the diagnostic delay at all levels are needed, with educational measures designed for teenagers and their families, and other members of the community (e.g., school staff), as well as schemes in the public health care system, including training programs for healthcare operators, university courses, and refresher courses for general practitioners.

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CHAPTER 2

PSYCHOLOGICAL ASPECTS

Managing psychosocial needs has become an increasingly fundamental goal of care providers, and this is particularly true when it comes to patients in adolescence. Dealing adequately with the psychological and social issues of patients in their teens is especially important because they become ill at a time when they are experiencing major psychological and physical changes, establishing their self-image, structuring their identity, their personality, and their relationships with their peers. Medical care has to take charge of the whole person of the patient and has to combine traditional therapy with new methods tailored to the patients.

In this chapter studies concerning psychosocial issues are described.

- **Study 2.1:** *Psychopharmacology and psychotherapy in pediatric oncology. Update and perspectives of integration* (2011). This study shows a review of international literature from 1980 to present and considerations on the perspectives for the integration of clinical psychological and psychopharmacological interventions. The specific issues relating to the psychopathological diagnosis in the course of organic disease are discussed and aspects of behavior determined by biological mechanisms directly related to the disease and care.

- In **Study 2.2:** *Psycho-organic diseases in children and adolescents affected by pediatric neoplasms* (2013). Organic components of psychic and behavioral alterations in the course of disease are illustrated, considering the symptoms, causes and possible remedies in the light of the most recent interdisciplinary views. The main mechanism connected with oncologic treatments - chemotherapy, surgery, radiotherapy - and responsible for psycho-organic alterations in children and adolescent with cancer are also described. At Pediatric Oncology centres, psychological intervention and psychotherapy are generally offered to children and adolescents for supporting their adjustment to disease and treatment.. The clinical practice, however, point out that cognitive and emotional symptoms are sustained by biological mechanisms connected with disease and treatment and not respondent to psychological consultation and to other psychosocial resources. These manifestations could interfere with treatment or with the long-term adjustment.

- **Study 2.3:** *Mirror therapy for phantom limb pain in an adolescent cancer survivor* (2012). This work describes the use of the mirror therapy to treat phantom limb syndrome in a 39-year-old patient, whose right lower limb had been amputated at the age of 17 for an osteosarcoma. The patient suffered from frequent episodes of pain, with severe negative consequences on the quality of his life. The advantages of using an unconventional rehabilitation technique, the recently reported mirror therapy are discussed.

- **Study 2.4:** *Spiritual aspects of care for adolescents with cancer* (in press). Cancer patients may have particular, not strictly clinical needs that often go unnoticed. It is characteristic of adolescents to wonder about the meaning of life: Who am I? Where am I going? What is the meaning of life? Disease and suffering unavoidably interfere with such processes (which are already critical in themselves). In the conviction that spirituality is an aspect of interest to adolescents suffering from cancer, also a 'spiritual assistant' could be in the multidisciplinary team, whose aim is to deal adequately with patients' need to have faith, trust and hope. Study 2.4 explains what the spiritual assistant does at our Unit.

- **Study 2.5:** *At least we can send some flowers...*(2012) The study reports the procedure in use at the Istituto Nazionale Tumori in Milan, in the unlucky event that the patient dies. Oncological diseases may demand lengthy treatment and the emotional attachment between care providers and patients may become intense, especially when the latter is a child or adolescent. Clinicians should be provided with the tools they need to cope with these emotional issues as part of their patient care responsibilities.

- **Study 2.6:** *Dying after cure: a case of suicide in an adolescent treated for cancer* (submitted) Even when the outcome of the therapies is the best possible, after completion of the treatment the return to normal life can be dramatically difficult. In this study is described the case of a 17-year-old girl cured of Burkitt lymphoma committed suicide after completing her treatment. The complex needs of adolescent patients demand a multidisciplinary team comprising different specialists, all involved in providing a global patient care. Is essential for all the personnel to be constantly on the lookout for any signs of psychic and social discomfort in young patients as part of long-term follow-up programs for childhood cancer survivors.

- **Study 2.7:** *"What does not kill me makes me stronger": is it always true?* (2014) This study reports the letter to Editor commenting the editorial by Masera et al. [Masera G, Chesler M, Zebrack B, et al. Cure is not enough: One slogan, two paradigms for pediatric oncology. *Pediatr Blood Cancer* 2013;60(7):1069-1070] that discusses the extraordinary adaptation processes implemented by young individuals who experience neoplastic disease. The aim of the letter is to express the idea that resilience may be the result of patient's adaptation in some cases and not in many others. On one side, cancer in developmental age can have severe permanent consequences that can interfere with the adaptation process; on the other side, we believe that it is important to note that psycho-pathological criteria are not enough to assess patient's quality of life.

Psicofarmaci e psicoterapia in oncologia pediatrica. Stato dell'arte e prospettive di integrazione

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Riassunto. Le malattie oncologiche dell'età pediatrica sono state oggetto, negli ultimi decenni, di trattamenti integrati multidisciplinari che ne hanno notevolmente migliorato la prognosi. La sofferenza psichica dei bambini e degli adolescenti affetti da queste patologie è generalmente affrontata con interventi di psicologia clinica e psicoterapia; restano tuttavia situazioni che richiedono interventi psicofarmacologici aggiuntivi o in alternativa a quelli psicologici. I criteri di intervento psicofarmacologico sono ancora scarsamente codificati. In questa rassegna vengono presentate una revisione della letteratura internazionale dal 1980 ad oggi ed alcune considerazioni sulle prospettive d'integrazione degli interventi psicologici e psicofarmacologici. Sono illustrate le problematiche specifiche relative alla diagnosi psicopatologica in corso di una malattia organica, e vengono discussi gli aspetti del comportamento causati da meccanismi biologici direttamente legati alla malattia e alle cure.

Parole chiave. Ansia, depressione, disturbi dell'umore, oncologia pediatrica, psicofarmacologia, psicoterapia, suicidio.

Introduzione

Farmacoterapia e psicoterapia possono essere alleate a beneficio di pazienti con malattie organiche? I progressi della terapia medica e quelli sul fronte psicologico possono migliorare la loro qualità di vita? Esiste oggi un forte interesse a perfezionare la collaborazione fra diverse modalità di trattamento delle sofferenze mentali di soggetti con malattie organiche; questa rassegna intende fornire alcune risposte a tali interrogativi, partendo dal particolare contesto dell'oncologia pediatrica, che – grazie alla attenzione prestata alle dimensioni biologiche, psicologiche ed umane della cura – può offrire spunti utili anche alla medicina dell'adulto.

Le malattie oncologiche dell'età pediatrica sono state infatti oggetto, negli ultimi decenni, di trattamenti integrati multidisciplinari che ne hanno notevolmente migliorato la prognosi. La maggiore possibilità di guarigione e il maggior tempo di sopravvivenza hanno evidenziato il problema della qualità di vita durante e dopo i trattamenti. La sofferenza psichica dei bambini e degli adolescenti af-

Summary. *Psychopharmacology and psychotherapy in pediatric oncology. Update and perspectives of integration.*

In recent decades, integrated multidisciplinary treatments have greatly improved the prognosis of oncological diseases of childhood. The psychological suffering of children and adolescents with these conditions is generally dealt with interventions of clinical psychology and psychotherapy. However, remain clinical situations that require psychopharmacological interventions beside, or alternatively, to the psychological. Criteria for psychopharmacological intervention in this context are poorly defined. This paper shows a review of international literature from 1980 to present and considerations on the perspectives for the integration of clinical psychological and psychopharmacological interventions. The specific issues relating to the psychopathological diagnosis in the course of organic disease are discussed and aspects of behavior determined by biological mechanisms directly related to the disease and care.

Key words. Anxiety, depression, mood disorders, pediatric oncology, psychooncology, psychopharmacology, psychotherapy, suicide.

fetti da neoplasie è generalmente affrontata con interventi di psicologia clinica e psicoterapia, con l'obiettivo di sostenere l'adattamento ad una situazione traumatica, che pone sfide continue nel percorso di crescita. L'integrazione della cura medica da parte del supporto psicologico, sociale, scolastico ed educativo ha favorito nel corso del tempo un miglioramento delle condizioni di vita; restano tuttavia situazioni che richiedono interventi psicofarmacologici aggiuntivi o alternativi a quelli psicologici.

Sintomi ansiosi e depressivi (anche secondari ai trattamenti chemioterapici), agitazione (anche conseguente a terapia con steroidi), aggressività e apatia sono fra le manifestazioni che possono richiedere una consultazione psicofarmacologica. I testi di psicofarmacologia e le linee guida (dell'adulto) indirizzano però solo in parte le scelte terapeutiche adottate. Sono infatti ancora scarsamente codificati i criteri di intervento psicofarmacologico in oncologia pediatrica, dal punto di vista sia metodologico che clinico, nonostante esso sia frequentemente riportato in letteratura^{1,2}.

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È stata eseguita una revisione della letteratura scientifica in lingua inglese, dal 1980 ad oggi, sull'impiego di psicofarmaci in oncologia pediatrica, attraverso le banche dati on-line Medline, PsychINFO e Cochrane Library. La ricerca è stata integrata dalla consultazione di libri, articoli e repertori bibliografici.

Sono stati reperiti 31 lavori pubblicati su riviste internazionali. I dati sono riassunti per categoria di farmaci: neurolettici, antidepressivi, ansiolitici, anticonvulsivanti ed antistaminici (tabella 1 a pagina seguente).

Neurolettici

La letteratura riporta dati sull'uso di aloperidolo per il trattamento di sintomi emotivi e comportamentali nel corso di malattie organiche gravi: l'impiego è tanto empiricamente diffuso nella pratica clinica quanto scarsamente indagato dalla letteratura sulle malattie organiche di bambini e adolescenti³. Obiettivo di questo neurolettico, anche per il suo effetto antiemetico, è il trattamento di ansia, agitazione, aggressività, confusione e disorientamento.

I neurolettici (clorpromazina) risultano impiegati anche nel trattamento dell'ansia nel corso di terapia steroidea, con maggiore efficacia rispetto alle benzodiazepine⁴, e nella sedazione terminale⁵. Fenotiazine e butirrofenoni sono stati largamente impiegati sui pazienti in trattamento chemioterapico per i loro effetti ansiolitici e antiemetici, fino all'introduzione di farmaci più specifici ed efficaci sull'emesi da chemioterapia. I neurolettici di vecchia generazione richiedono cautela a causa di effetti collaterali, fra cui, quantunque molto rari, le discinesie tardive e la sindrome neurolettica maligna. Altri effetti avversi, più frequenti, comprendono sintomi extrapiramidali, sedazione, iperprolattinemia. Sono pure descritti effetti aritmogeni, con allungamento dell'onda QT.

Di recente è stato illustrato l'impiego di risperidone per il trattamento del disturbo dell'umore in età evolutiva (disturbo caratterizzato da irritabilità, agitazione, diminuzione del sonno e ridotte interazioni sociali), secondario ad una malattia organica grave, anche di tipo oncologico⁶.

Antidepressivi

Prima applicazione hanno trovato i farmaci antidepressivi triciclici⁷. Il loro uso era già noto nell'adulto dagli anni sessanta per il trattamento del dolore oncologico e successivamente si è diffuso come trattamento adiuvante analgesico in oncologia pediatrica⁸. I triciclici sono impiegati anche nel trattamento dell'insonnia conseguente a dolore, ad ansia, ad alterazione dei cicli circadiani ed alla depressione⁹. Più di recente hanno trovato impiego in oncologia pediatrica gli antidepressivi serotoninergici. In particolare sono riportati studi su fluvoxamina^{10,11} e citalopram¹². Una rassegna sull'uso degli SSRI¹¹ sottolinea come il loro utilizzo debba

essere prudente ed effettuato in stretta collaborazione con il team psicosociale. Uno studio multicentrico statunitense più recente riporta che il 71% degli oncologi pediatri consultati ha utilizzato SSRI².

Antidepressivi sono saltuariamente impiegati in pazienti oncologici pediatrici con un disturbo ossessivo-compulsivo¹³ primitivo o con sintomi ossessivi e compulsivi reattivi alla condizione di malattia, così come nelle alterazioni dell'umore (caratterizzate da irritabilità e deflessione del tono) conseguenti all'uso di steroidi¹⁴, considerata l'osservazione di una diminuzione dei livelli di serotonina (in particolare nell'ippocampo) per effetto dei corticosteroidi¹⁵.

L'impiego di antidepressivi è descritto infine per il trattamento dell'angoscia in fase terminale⁵.

La letteratura riporta che alcuni problemi in merito alla prescrizione di antidepressivi e in particolare di SSRI in oncologia pediatrica ne hanno probabilmente limitato l'uso. Si rileva come l'uso di alcuni serotoninergici (fluoxetina) possa diminuire l'efficacia degli antiemetici 5-HT₃ antagonisti e come il loro impiego estemporaneo richieda particolare attenzione per il rischio di sindrome serotoninergica.

Il maggiore allarme correlato a rischio suicidario, ha fatto seguito a segnalazioni di alcuni anni fa da parte dell'FDA negli USA. L'agenzia Europea dei Medicinali (EMA) ha introdotto nel 2005 l'obbligo di riportare nel foglietto illustrativo degli antidepressivi SSRI e SNRI un'avvertenza sull'aumentato rischio di comportamento suicidario e di aggressività in pazienti al di sotto dei 18 anni.

Gran parte di questi farmaci è approvata nell'Unione Europea per il trattamento della depressione e dell'ansia negli adulti, ma nessuno di essi è stato durevolmente autorizzato negli Stati membri per il trattamento della depressione di bambini e adolescenti. Oggi, solo sertralina e fluvoxamina sono approvati per il trattamento del disturbo ossessivo compulsivo in età pediatrica, mentre la fluoxetina è l'unico farmaco serotoninergico ammesso per il trattamento dei disturbi depressivi in pazienti di minore età. Nel caso di impiego di antidepressivi di nuova generazione per il trattamento di sintomi depressivi si pone quindi il problema di uso off-label con specifico consenso informato da parte dei genitori.

Non vi sono invece restrizioni all'impiego di altri antidepressivi che sono, tuttavia, gravati da maggiori effetti collaterali (cardiologici, abbassamento della soglia convulsiva). Come ricordato da vari autori, esiste la necessità di limitare l'impiego indiscriminato di farmaci per alterazioni comportamentali, disturbi che possono trovare nella psicoterapia un più adeguato trattamento. I bambini e gli adolescenti affetti da malattie organiche gravi possono presentare disagi emotivi e alterazioni comportamentali quali ad esempio i disturbi dell'adattamento e il disturbo post traumatico da stress, la cui diagnosi differenziale è delicata, ma il cui trattamento è prevalentemente di tipo psicologico.

Tabella 1. Psicofarmaci utilizzati in oncologia pediatrica		
Categoria di farmaco	Impiego	Principali effetti collaterali
Neurolettici		
		Comuni: sintomi extrapiramidali, sedazione, iperprolattinemia. Sono descritti effetti aritmogeni. Rari: discinesie tardive, sindrome neurolettica maligna.
Aloperidolo	Effetto antiemetico; trattamento di ansia, agitazione, aggressività, confusione e disorientamento	
Clorpromazina	Trattamento dell'ansia nel corso di terapia steroidea; sedazione in fase terminale.	
Fenotiazine e butirofenoni	Effetti ansiolitici e antiemetici	
Risperidone		Trattamento di pazienti con disturbo dell'umore caratterizzato da irritabilità, agitazione, diminuzione del sonno e ridotte interazioni sociali.
Antidepressivi		
Triciclici	Sintomi depressivi; adiuvanti analgesici; trattamento del dolore neuropatico	
Serotoninergici (fluvoxamina e citalopram)	Sintomi depressivi (irritabilità e deflessione del tono dell'umore) anche conseguenti all'uso di steroidi; trattamento dell'angoscia in fase terminale; trattamento del disturbo ossessivo-compulsivo	Diminuzione dell'efficacia antiemetica; aumento dell'aggressività e del rischio suicidario; sindrome serotoninergica (rara).
Ansiolitici		
Midazolam	Riduzione dello stress e della paura nelle procedure con ago; sedazione durante la radioterapia	
Benzodiazepine	Trattamento di ansia anticipatoria e disturbi del comportamento (oppositività e aggressività); ansia durante terapia steroidea; sedazione in fase terminale; trattamento del dolore neuropatico (sindrome dell'arto fantasma).	
Anticonvulsivanti		
Carmabazepina, fenitoina, clonazepam, valproato	Dolore neuropatico; stabilizzazione dell'umore; trattamento di condotte aggressive	
Gabapentin	Effetto anticonvulsivante, trattamento del dolore neuropatico (arto fantasma)	
Antistaminici		
Miaprazina	Trattamento dell'insonnia e delle condotte aggressive	Stipsi; confusione e anomalie della conduzione cardiaca.

Ansiolitici

Benzodiazepine sono utilizzate per ridurre lo stress legato a procedure diagnostiche o terapeutiche, ad esempio basse dosi di midazolam per ridurre lo stress e la paura rispetto alle procedure con ago¹⁶ e come sedazione durante la radioterapia¹⁷.

Il ricorso ad un trattamento farmacologico è generalmente preferito a tecniche comportamentali per la maggiore rapidità d'azione e riproducibilità rispetto a trattamenti non farmacologici (come, ad esempio, l'ipnosi).

Ansiolitici benzodiazepinici trovano impiego nelle situazioni di ansia anticipatoria, ad esempio prima dell'accesso in ospedale¹⁸ e sono impiegati per il trattamento di disturbi del comportamento, in situazioni di oppositività e aggressività.

Le benzodiazepine risultano impiegate anche nel trattamento dell'ansia nel corso di terapia steroidea, quantunque in letteratura siano descritti maggiori effetti collaterali e minore efficacia rispetto al trattamento con neurolettici (clorpromazina)⁴, così come nel trattamento dell'angoscia in fase terminale di malattia ed infine (a basse dosi) nel trattamento del dolore neuropatico, come, ad esempio, nella sindrome da arto fantasma.

Se i benefici di queste molecole per la terapia dell'adulto sono noti da tempo, risulta minore la loro efficacia in ambito pediatrico.

Anticonvulsivanti

I farmaci anticonvulsivi (carbamazepina, fenitoina, clonazepam e valproato) trovano impiego, oltre che per le loro indicazioni specifiche, anche per il controllo del dolore neuropatico. Negli anni novanta si è diffuso l'impiego clinico del gabapentin, un anticonvulsivante con minori rischi di effetti collaterali, prevalentemente ematologici ed epatici. Questo farmaco ha trovato applicazione nelle neoplasie dell'infanzia e dell'adolescenza^{19,20} insieme a trattamenti complementari non farmacologici come la mirror therapy. Anticonvulsivanti vengono utilizzati per la stabilizzazione dell'umore e per il trattamento di condotte aggressive¹⁹.

Antistaminici

Derivati antistaminici sono impiegati dai pediatri per il trattamento dell'insonnia; soprattutto nei lattanti e nei bambini in età prescolare essi vengono usati anche nell'ambito dell'oncologia pediatrica. Sono descritti nel trattamento delle condotte aggressive, anche se è necessaria cautela per gli effetti anticolinergici fra cui stipsi, confusione e anomalie della conduzione cardiaca²¹.

Problematiche diagnostico-terapeutiche

Nei pazienti con neoplasie pediatriche, un problema rilevante riguarda la scelta se intervenire con mezzi psicologici oppure farmacologici e in quest'ultimo caso con quale farmaco. Il problema della prescrizione psicofarmacologica in età evolutiva è annoso e gravato anche da pregiudizi ideologici.

Le teorie psichiatriche e psicologiche rappresentano una diversa prospettiva di lettura dei disturbi somatici e psicologici in età evolutiva, nella quale gli interventi richiedono una armonica integrazione. Benché, oggi, non esista più alcuna contrapposizione fra farmaci e psicoterapia, ma anzi la necessità di un impiego sinergico²², una pratica

clinica realmente integrata spesso non è attuata o attuabile. Esiste scarsa letteratura per orientare la scelta degli interventi in quelle situazioni particolari ove disturbi emotivi o del comportamento si presentano in pazienti affetti da neoplasia^{1,21,23,24}.

E ancor prima di tale problematica, si pone quella di formulare una corretta diagnosi differenziale.

È, infatti, peculiarità degli interventi psicologici in oncologia pediatrica ricorrere raramente a diagnosi secondo DSM-IV; ci si limita preferibilmente all'ambito dei disturbi reattivi; e ciò per vari motivi: per la caratteristica del breve periodo di osservazione, per la natura spesso acuta e transitoria dei sintomi e per la difficoltà di più ampie valutazioni della personalità. Sono ancora poco utilizzati nuovi sistemi classificatori che consentirebbero di includere nella diagnosi una considerazione più integrata della personalità: è il caso del Manuale Diagnostico Psicodinamico (PDM)²⁵, le cui promettenti potenzialità sono ancora limitate dalla carenza di strumenti applicativi: in particolare nelle situazioni di malattia organica.

Le condizioni più frequentemente descritte nei pazienti pediatriche in trattamento per neoplasie riguardano quindi per lo più aspetti sintomatici; fra questi: agitazione, ansia, disturbo post-traumatico da stress, disturbi dell'adattamento, demoralizzazione²⁶, sintomi depressivi^{23,27,28}, disturbo ossessivo-compulsivo¹³. Sono frequenti manifestazioni ansiose reattive alla condizione di malattia e di cura, il palesarsi di manifestazioni situazionali (fobie per aghi/siringhe) o il riacutizzarsi di preesistenti problemi ansiosi (es. disturbi ossessivi compulsivi). Fra i fattori psicologici che possono generare disturbi psichici o del comportamento nel corso di una malattia oncologica sono da annoverare: il trauma causato da insorgenza improvvisa di patologia potenzialmente fatale che richiede cure impegnative, il distress legato alla condizione di malattia grave, i cambiamenti dell'immagine corporea, le limitazioni nella vita di relazione, la necessità di un rapporto di più frequente intimità.

QUALI INTERVENTI?

Benché vi sia una preferenza per gestire con strumenti psicologici e relazionali la maggior parte dei disturbi identificati, l'esperienza suggerisce la necessità di affrontare alcune situazioni con l'ausilio di terapia psicofarmacologica. Secondo alcuni studi su pazienti adulti, i sintomi ansiosi risulterebbero più responsivi ad un trattamento psicologico rispetto a quelli depressivi²⁹ e queste considerazioni possono applicarsi anche ai pazienti in età evolutiva (seppure sintomi ansiosi di grado marcato necessitano di un trattamento farmacologico perché refrattari ad un conforto e sostegno verbale).

Alcune riserve tradizionali sull'uso degli psicofarmaci associato ad terapia psicologica derivano dalla preoccupazione che questi deprimano la

manifestazione di stati d'animo importanti, impedendone una piena consapevolezza. Un'altra riserva consiste nel timore che una terapia farmacologica indebolisca le risorse dell'Io ostacolando il lavoro psicoterapeutico. Già dagli anni settanta, però, l'associazione tra farmaci e psicoterapia è stata accreditata³⁰ e, negli ultimi tre lustri, importanti studi ne hanno sottolineato i benefici²².

Sintomi ansiosi, di agitazione e irrequietezza richiedono comunque un'accurata diagnosi differenziale e la valutazione di trattamenti fisici in grado di eliminarne le cause. È il caso del dolore che, soprattutto nei pazienti più piccoli, si accompagna a manifestazioni comportamentali. Rispetto alle manifestazioni depressive, è stata evidenziata una minore prevalenza di depressione rispetto ai controlli sani, ma ciò pone problemi in merito alla possibilità di una corretta diagnosi³¹. Nei pazienti affetti da neoplasie la diagnosi differenziale fra condizioni depressive e demoralizzazione reattiva alla malattia non è agevole²⁶. Scale e reattivi sviluppati in ambito psichiatrico sono di limitata utilità per la presenza di sintomi fisici simili a quelli depressivi (astenia, anedonia, ecc...) legati alla malattia e ai trattamenti³².

Tutto ciò induce a riconsiderare i criteri con i quali solitamente sono interpretati e codificati i disturbi psichici dell'età evolutiva. Comportamenti verbalmente o fisicamente violenti autodiretti o eterodiretti possono essere conseguenti a trattamenti, a difficoltà di comunicazione, oppure possono dipendere da preesistenti disturbi mentali (ADHD, condotte oppostive, disturbi dell'umore, disturbi psicotici, disturbi pervasivi dello sviluppo). L'approccio a queste situazioni deve presupporre un'efficace relazione fra sanitari e paziente e necessità di interventi ambientali, psicoterapia e farmacoterapia (figura 1). La letteratura riporta l'uso di stabilizzatori dell'umore, beta-bloccanti (propranololo), alfa-agonisti, antistaminici, benzodiazepine o neurolettici, ma mancano dati sulla diffusione del loro impiego nello specifico contesto di patologia pediatrica oncologica²¹.

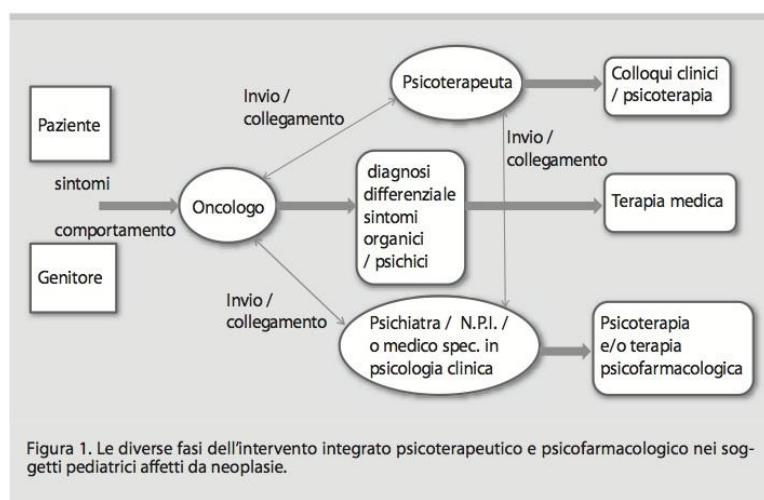
Preesistenti condizioni psicopatologiche possono compromettere il necessario processo di adattamento alla malattia oncologica e anche la compliance alle cure mediche. Sono queste le condizioni in cui l'intervento psicologico e psicoterapeutico (con i limiti dell'intervento in ospedale compresi quelli di tempo, setting e di risorse) può essere messo in scacco dalla severità del disturbo mentale,

cui si aggiunge la malattia oncologica. Il disturbo peraltro può non essere stato diagnosticato in precedenza ed essere identificato solo nel corso dell'iter di cura in oncologia. In condizioni di psicopatologia si pone il problema di come aiutare il paziente ad accettare le terapie oncologiche, visto che gli interventi psicologici e psicoterapeutici possono non produrre modificazioni comportamentali nel troppo breve tempo disponibile.

SOFFERENZA PSICOLOGICA E DISTURBI ORGANICI

I disturbi psico-organici osservati con maggiore frequenza sono conseguenti a encefalopatie metaboliche, tossiche, infettive, o più raramente, a localizzazione intracranica della malattia. La somministrazione di chemioterapici antitumorali può accompagnarsi ad alterazioni dello stato mentale, a sintomi comportamentali e ad alterazioni del tono dell'umore³³. Fra i farmaci gravati da maggiore tossicità neurocomportamentale sono glucocorticoidi, interferone e interleukina-2, acyclovir, oppioidi, barbiturati e altri agenti anticonvulsivanti, propranololo, alcuni antibiotici, vincristina, cisplatino, procarbazine, ifosfamide, L-asparaginasi e tiotepa ad alte dosi. Manifestazioni neurotossiche possono essere frequenti, anche se, per lo più, a carico del sistema nervoso periferico, dato che questi farmaci attraversano solo in una misura ridotta la membrana ematoencefalica.

Un'entità sintomatologica riscontrabile nei pazienti affetti da neoplasie è la fatigue, che ha elementi di sovrapposizione ma anche di distinzione rispetto alla depressione. Al suo determinarsi concorrono, secondo alcune prospettive di ricerca, meccanismi immunitari che mediano il comportamento di malattia con un quadro caratterizzato da astenia, diminuita attività, ridotta concentrazione e attenzione, perdita d'interesse, tristezza, ansia e tensione³⁴.



Poiché tali disturbi sono simili a quelli osservati nell'adulto, possiamo ipotizzare che siano compromessi i medesimi sistemi neurochimici e le stesse strutture anatomiche. Non sono ancora ben conosciute le interferenze dei trattamenti oncologici con i neurotrasmettitori; tuttavia, dato che questi disturbi hanno effetti rilevanti sulla qualità di vita, può rendersi necessario un trattamento talvolta con farmaci al di fuori delle precise indicazioni cliniche per cui essi sono autorizzati.

VERSO UN'INTEGRAZIONE DEGLI INTERVENTI

Nell'ambito dell'oncologia pediatrica è necessario disporre di criteri per utilizzare psicofarmaci con minori effetti collaterali. Un limite nell'impiego di psicofarmaci è stato correlato ad un possibile aumento di rischio suicidario; tuttavia non è stata rilevata una incidenza significativa³⁵. Ciò è stato interpretato da alcuni autori come risultato della elevata qualità dell'assistenza, da parte sia dell'équipe curante sia dei genitori.

Nel caso di pazienti con disturbi psicotici, di ansia e dell'umore preesistenti alla neoplasia, si pone il problema della interazione tra la terapia oncologica e quella psichiatrica.

Conclusioni

Esistono crescenti evidenze a favore di un trattamento multimodale delle problematiche emotive e comportamentali dei pazienti pediatrici affetti da neoplasie.

È auspicabile che gli sviluppi delle ricerche possano approfondire i legami fra sintomi depressivi, fatigue, neurotossicità da chemioterapia e aspetti immunitari.

Altra finalità della ricerca e della clinica è l'integrazione fra trattamenti. Quantunque non si veda più contrapposizione fra farmaci e psicoterapia, tale prospettiva integrata non è sempre oggetto d'insegnamento nel corso degli studi universitari e della formazione professionale degli operatori²². È necessario un maggiore dialogo fra l'agire psicologico e quello biologico riguardo al significato ed alla necessità di trattamento di manifestazioni che pur presentando aspetto sintomatico, possono avere valore di adattamento: fra tutte, la deflessione del tono dell'umore nel corso di una malattia grave, interpretato in una prospettiva di psicologia dinamica come fase irrinunciabile di adattamento. Il percorso di una patologia severa è caratterizzato infatti da una molteplicità di risorse, vissuti, relazioni, ove i sintomi psichici non costituiscono di per sé un'entità da eliminare; al contrario, il "compenso patologico" ha molto spesso necessità di essere rispettato e sostenuto.

Alcuni fattori hanno limitato un'integrazione terapeutica ottimale in oncologia pediatrica. La consultazione sulla salute mentale nel corso di

malattie organiche appare frequentemente condotta e orientata in base alle prassi ed alle tradizioni dei diversi ospedali e l'intervento è oggi estremamente variegato per formazione degli operatori, teorie di riferimento, obiettivi, durata e tecniche. Anche la ricerca ha sofferto di numerose limitazioni; la scarsità di studi sui trattamenti psicosociali nelle malattie gravi dell'età evolutiva ne è un esempio³⁶. Nei malati organici gravi non esiste una demarcazione netta fra patologia psichica e sofferenza emotiva: essi possono oscillare, nelle diverse fasi della malattia, lungo l'intero arco di questo *continuum*³⁷.

Il tema non è trascurabile perché prevede una non sempre agevole attribuzione di compiti terapeutici (tra psicologi e farmacologi) e al contempo la indispensabile loro integrazione. È sicuramente tempo di affrontare anche su questo fronte i problemi di integrazione fra diverse discipline³⁸.

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Disturbi psico-organici in bambini e adolescenti affetti da neoplasie pediatriche

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PSYCHO-ORGANIC DISEASES IN CHILDREN AND ADOLESCENTS AFFECTED BY PEDIATRIC NEOPLASMS

At Pediatric Oncology Centers, psychological intervention and psychotherapy are generally offered to children and adolescents for supporting their adjustment to disease and treatment. The clinical practice, however, point out that cognitive and emotional symptoms, such as psychic distortions, fatigue, anxiety, irritability and depression, are sustained by biological mechanisms connected with disease and treatment and not respondent to psychological consultation and to other psychosocial resources. These manifestations could interfere with treatment or with the long-term adjustment and call for psychopharmacological treatments. Biological factors able to cause these alterations are not yet studied in depth in clinical tradition and scientific literature on the integration of psychological and psychopharmacological intervention in pediatric oncology is still poor. In this paper organic components of psychic and behavioral alterations in the course of disease are illustrated, considering the symptoms, causes and possible remedies in the light of the most recent interdisciplinary views. The main mechanism connected with oncologic treatments – chemotherapy, surgery, radiotherapy – and responsible for psycho-organic alterations in children and adolescent with cancer are also described.

KEY WORDS: Medical oncology - Psychology, clinical - Physiological effects of drugs - Child.

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Interventi di psicologia clinica e psicoterapia sono i supporti generalmente offerti presso i centri di oncologia pediatrica ai bambini e agli adolescenti affetti da neoplasie per sostenere l'adattamento alla malattia e alle cure. In oncologia pediatrica vi è, infatti, la consuetudine di gestire mediante strumenti psicologici e relazionali la maggior parte delle condizioni di disagio emotivo e comportamentali. Le esperienze cliniche mostrano però alterazioni cognitive, *fatigue*, ansia, irritabilità e depressione insieme ad altri sintomi cognitivi, emotivi e alterazioni del comportamento, in tutto o in parte legati alla patologia o alle cure, non responsivi al colloquio e alle altre risorse di supporto psicosociale. Tutto ciò può portare a marcato distress, che può necessitare di una consultazione psicofarmacologica, anche se i trattamenti psichiatrici possono non essere specifici per queste condizioni legate alla malattia organica.

Qui di seguito saranno illustrate le com-

ponenti organiche alla base delle alterazioni psichiche e comportamentali in oncologia pediatrica, considerando i sintomi, le cause e i possibili meccanismi fisiopatologici alla luce delle recenti prospettive di ricerca interdisciplinari.

I sintomi

La pratica clinica con pazienti affetti da neoplasie pediatriche evidenzia disturbi psichici e del comportamento alimentati da meccanismi biologici legati alla malattia e alle cure:

Depressione e ansia

La comorbilità fra sintomi depressivi e neoplasie è stimata nell'adulto con un'incidenza variabile fra l'1,5% e il 50%¹. In oncologia pediatrica mancano stime attendibili sulla reale prevalenza dei sintomi ansiosi e depressivi. I dati della letteratura sono discordanti, in particolare per la difficoltà di identificare e definire univocamente queste condizioni in età evolutiva. La prevalenza di sintomi ansiosi e depressivi varia fra il 17% e il 41% in studi su piccole serie di pazienti². Gli strumenti di valutazione più utilizzati in queste ricerche, come le scale di valutazione di provenienza psichiatrica, non sembrano del tutto adeguati a rilevare la complessità dei processi emotivi e di adattamento di questi pazienti. Un ulteriore limite di queste ricerche è dato da campioni numericamente troppo limitati e non omogenei per età. Dati della letteratura riportano come l'impiego di antidepressivi avvenga di frequente anche in oncologia pediatrica (con una prevalenza stimata attorno al 10%) e suggeriscono un rischio aumentato di depressione maggiore in questi pazienti, rispetto alla popolazione pediatrica generale².

Un problema classico riguarda la distinzione fra i sintomi neurovegetativi della depressione e i sintomi direttamente legati alla patologia medica. La distinzione è difficile, anche per la sovrapposizione degli effetti collaterali dei trattamenti.

Un problema di diagnosi differenziale, non sempre possibile, si ha con la *fatigue*³. L'astenia appartenente al quadro della depressione maggiore presenta componenti emotive, che sono assenti invece nella *fatigue*, anche se i pazienti che la sperimentano possono sviluppare successivamente demoralizzazione.

La demoralizzazione, caratterizzata da senso di disperazione e isolamento (*hopelessness, helplessness*), confusione e riduzione dell'autostima, costituisce un'esperienza umana universale, fisiologica, che prelude o accompagna la messa in atto di meccanismi di adattamento emotivo e comportamentale alla malattia; è responsiva al trattamento con tecniche di psicoterapia di supporto⁴ e deve essere distinta dai quadri clinici di depressione maggiore.

Nonostante l'incidenza di depressione sia rilevante nelle neoplasie rispetto alle altre malattie mediche, solo una parte limitata dei pazienti sviluppa sintomi depressivi. Questo fatto indica come una neoplasia costituisca un fattore di rischio ma non una causa invariabile di depressione. Sintomi depressivi acuti possono inoltre essere un effetto diretto delle neoplasie sul cervello. È ancora poco noto, e meritevole di approfondimento, il ruolo delle terapie oncologiche rispetto all'insorgenza di sintomi depressivi tardivi. Sintomi ansiosi di grado marcato, caratterizzati da irrequietezza, paura, manifestazioni fisiche di aumentato *arousal* e sintomi acuti tipo attacchi di panico possono richiedere un trattamento farmacologico in casi selezionati, quando refrattari a una possibilità di conforto e sostegno verbale o mediante tecniche non farmacologiche. La prevalenza dei disturbi d'ansia nei pazienti in età evolutiva con malattie organiche è maggiore rispetto ai coetanei sani, variando fra il 7% e il 40%⁵.

Disturbi ansiosi possono essere la risposta alla condizione di malattia e all'ospedalizzazione, in un contesto percepito come minaccioso, o essere legati a meccanismi biologici, anche dipendenti dalla patologia neoplastica.

Alcune condizioni organiche possono necessitare una diagnosi differenziale. Pa-

tologie neurologiche, endocrine, cardiache, respiratorie e metaboliche possono comportare infatti sintomi ansiosi. In pazienti con disturbi convulsivi la ripetuta stimolazione dell'amigdala può predisporre ad ansia interictale. L'esperienza clinica suggerisce di procedere sempre con un'accurata rivalutazione del quadro organico in presenza di dispnea, tachicardia e tremori che compaiono all'improvviso.

In alcuni pazienti affetti da neoplasie pediatriche possono presentarsi sintomi ossessivi caratterizzati da pensieri, impulsi o immagini ricorrenti e persistenti, vissuti come intrusivi o inappropriati e che causano ansia o disagio marcati, accompagnati in alcuni casi da comportamenti ripetitivi o azioni mentali. Rari casi di sintomatologia ossessiva sono descritti come effetto della terapia con steroidi⁶. Alcune manifestazioni ossessive possono essere legate a neoplasie del SNC, secondo la letteratura di tradizione neuropsicologica e neurochirurgica sul tema. In altri casi, invece, i sintomi ossessivi si manifestano in pazienti affetti da neoplasie localizzate in distretti diversi. Nei casi in cui non dipendano da localizzazioni nel SNC la psicologia clinica e la psichiatria dinamica attribuiscono a queste manifestazioni un significato di difesa psichica contro l'angoscia (in alcuni casi i sintomi sono attribuiti alla slatentizzazione di condizioni pre-esistenti).

Una parte delle manifestazioni ansiose rilevate in oncologia pediatrica è attribuita all'elaborazione di tipo traumatico della malattia, con analogie con il disturbo post-traumatico da stress (PTSD)⁷.

Alcuni disturbi ansiosi devono comunque essere interpretati anche considerando le interazioni genitore-bambino in quella cornice definita "sindrome del bambino vulnerabile" e caratterizzata da: difficoltà patologiche della separazione dai genitori, infantilizzazione, preoccupazioni per la vulnerabilità del corpo eccessive anche considerando le condizioni di patologia, rendimento scolastico al di sotto delle possibilità intellettuali. Il trattamento di prima scelta indicato è sempre di tipo psicologico o psicoterapeutico.

Agitazione e aggressività

Talvolta si osservano nella pratica clinica in oncologia pediatrica casi rari, ma problematici, di agitazione psicomotoria, caratterizzati da irrequietezza o aggressività. La letteratura sull'argomento è scarsa e sono poche le indicazioni di trattamento⁸ per queste condizioni nel contesto pediatrico. Alcune condizioni più frequenti si verificano in pazienti con una pre-esistente storia psichiatrica o di disadattamento psicosociale, mentre altre più rare sono legate a concause metaboliche o ad effetti diretti della patologia organica sul SNC. Altre condizioni, infine, soprattutto nei pazienti più piccoli, sono interpretabili come la somma di angoscia del paziente e la difficoltà di contenimento emotivo da parte dei genitori.

Fatigue

Un'entità sintomatologica riscontrabile nei pazienti affetti da neoplasie è la *fatigue*, che ha elementi di sovrapposizione, ma anche di distinzione, rispetto alla depressione⁹. Si tratta di una condizione caratterizzata da astenia, diminuita attività, ridotta concentrazione e attenzione, perdita d'interesse, tristezza, ansia, tensione, con difficoltà a svolgere le attività quotidiane; al suo determinarsi concorrono dolore, disturbi del sonno e anemia, oltre a meccanismi immunitari. Vari studi hanno descritto, nell'oncologia dell'adulto, l'associazione della *fatigue* con un appiattimento della curva del cortisolo, che potrebbe essere indice di alterazioni dell'asse ipotalamo-ipofisi-surrene (HPA)¹⁰. Sintomi di *fatigue* possono comparire in associazione con disturbi del sonno già nelle prime fasi dei trattamenti¹¹.

Nell'esperienza dell'oncologia pediatrica sono descritti casi poco frequenti, ma non rarissimi, di pazienti guariti la cui qualità di vita è ridotta da sintomi di stanchezza cronica¹². In particolare l'incidenza di *fatigue* nei pazienti guariti è più elevata in soggetti di genere femminile, con sintomi dolorosi e depressivi, disoccupati e fumatori^{13, 14}.

Insomnia

Disturbi del sonno, caratterizzati da ridotta efficacia del sonno, prolungata latenza all'addormentamento e risvegli notturni sono un'evenienza frequente nel corso delle cure di un malattia neoplastica. Sintomi di insomnia sono descritti variabili fra il 30 e il 50% su dei pazienti adulti affetti da neoplasie¹⁵ e disturbi del sonno sono riportati nel 60% dei pazienti con neoplasie pediatriche¹⁶ in uno studio recente). L'esperienza clinica riporta casi con ampio spettro di manifestazioni¹⁷ dei disturbi del sonno, ipersonnia, insomnia, parasonnie e disturbi del ritmo sonno-veglia che possono essere presenti in combinazione fra loro. A questi disturbi concorrono fattori eterogenei come la preoccupazione e il dolore, aspetti ambientali legati alla degenza ospedaliera, minzioni frequenti per l'idratazione parenterale in corso di chemioterapia, terapie mediche (fra cui gli steroidi) o elementi biologici legati alla malattia. Fra le cause dei disturbi del sonno possono avere un ruolo combinato la *fatigue*¹¹, dovuta all'attivazione immunitaria, per l'attivazione immune legata alla malattia e ai trattamenti, l'inattività diurna e l'influenza dello stress sui ritmi del sonno, con una desincronizzazione dei ritmi circadiani, per azione del cortisolo^{18, 19}. Il legame fra sistema immunitario e sonno attende ancora approfondimenti, anche se almeno tre decenni di studi e esperienze cliniche suggeriscono importanti collegamenti.

Anoressia, nausea, emesi anticipatoria

Nei pazienti con neoplasie sono di frequente riscontro i disturbi dell'alimentazione. Queste manifestazioni sono prevalentemente secondarie e legate ai trattamenti (che causano alterazioni gustative, nausea, emesi e mucosite). Tuttavia, esistono anche quadri eterogenei che vanno dalla transitoria anoressia psicogena legata allo stress fino a quadri di cachessia neoplastica nelle fasi terminali di malattia. Il rifiuto di alimentarsi, in particolare se ostinato e debilitante, deve essere posto in diagnosi differenziale

con l'anoressia nervosa, anche se difficilmente possono essere applicati i criteri diagnostici del DSM-IV. La letteratura su quadri di anoressia nervosa in corso di neoplasie è scarsa e le cure sono basate sull'impiego di tecniche di psicoterapia individuale e familiare.

Il rifiuto del cibo può avere il significato di una ribellione alle regole, alle limitazioni imposte dalla malattia e dalle cure senza comprometterne l'identità e può essere suscettibile di miglioramento attraverso interventi psicologici sul contesto di cura e la relazione.

Nei pazienti in corso di chemioterapia possono verificarsi manifestazioni di nausea e di emesi anticipatoria. Questi fenomeni sono interpretati come una risposta comportamentale appresa. Una risposta condizionata di tipo pavloviano si verifica, per effetto di stimoli visivi e olfattivi, prima della somministrazione di chemioterapia, in pazienti con precedente esperienza di emesi acuta e ritardata da chemioterapia²⁰. Anche l'ansia può concorrere alla sintomatologia, così come le alterazioni di gusto e olfatto in corso di terapia; alcuni pazienti riferiscono che il disagio si manifesta percependo odori caratteristici dell'ospedale o addirittura mentre si recano in ospedale. I sintomi possono persistere anche a lungo dopo la conclusione delle terapie. Il Sistema Nervoso Centrale media la comparsa di nausea e vomito e rileva gli stimoli condizionati e incondizionati l'associazione tra di essi. L'esperienza clinica e la letteratura evidenziano una risposta alla terapia con benzodiazepine in aggiunta agli antiemetici²¹, eventualmente con l'impiego associato di tecniche comportamentali²².

Deficit memoria, difficoltà di apprendimento e altri disturbi del SNC

Sono tutt'altro che rari in oncologia pediatrica e se ne riconoscono cause diverse, quali interessamento metastatico del SNC, compromissioni del SNC, disturbi metabolici, effetti iatrogeni (chemio-radioterapia, farmaci per il controllo dei sintomi o delle complicanze stesse), infezioni, vasculopatie,

disturbi della circolazione liquorale (idrocefalo) e sindromi paraneoplastiche²³, che possono portare a encefalopatie caratterizzate da alterazioni della coscienza, anomalie comportamentali, convulsioni o deficit neurologici focali. La letteratura riporta come anche alcuni bambini trattati per neoplasie con la sola chemioterapia possano presentare deficit cognitivi²⁴.

Le terapie oncologiche possono associarsi, in pazienti adulti e in età evolutiva, a deficit delle funzioni esecutive, delle funzioni visuo-motorie e dei processi visivi²⁵⁻²⁸. Anche se alcuni danni possono essere legati a effetti negativi su neuroni maturi e strutture vascolari, in gran parte dei disturbi cognitivi moderati sono presenti lesioni evidenziabili dagli esami di imaging a carico del SNC.

Disturbi somatoformi

Nella pratica clinica dell'oncologia è in alcuni casi difficile distinguere le preoccupazioni per la salute da franche manifestazioni ipocondriache.

Alcune osservazioni suggeriscono una maggiore incidenza di disturbi somatoformi in pazienti guariti da neoplasie pediatriche³¹.

È impossibile distinguere con certezza la sovrapposizione fra motivata preoccupazione verso i segnali del proprio corpo dopo una malattia grave, rispetto a un quadro di amplificazione somatosensoriale caratterizzata da ipervigilanza somatica e dalla tendenza a percepire sensazioni corporee normali come allarmanti, intense e moleste²⁹. Alcune ricerche hanno ipotizzato un ruolo delle citochine proinfiammatorie nei disturbi da somatizzazione³⁰ e approfondimenti in questo senso, anche rispetto ai pazienti guariti, potrebbero essere una futura evoluzione delle ricerche.

I meccanismi

Vari disturbi psico-organici sono osservati nel corso di encefalopatie metaboliche, tossiche, infettive, o per localizzazione intracranica della malattia. La neurotossicità

può essere un effetto diretto di farmaci o radiazioni sul SNC o indiretto per danno vascolare, processi infiammatori, o alterazioni metaboliche.

Nella letteratura scientifica recente emergono anche alcune interpretazioni neuroendocrine e immunitarie in grado di spiegare sindromi psico-comportamentali a carico dei pazienti in trattamento.

Trattamenti farmacologici

CHEMIOTERAPICI

I trattamenti chemioterapici hanno permesso negli ultimi decenni di migliorare notevolmente la prognosi delle neoplasie pediatriche, consentendo le attuali riflessioni sulla qualità di vita dei pazienti in trattamento e guariti. Le terapie possiedono, tuttavia, un effetto citotossico *non targeted* su molteplici organi e apparati, compreso il SNC.

La somministrazione di vari chemioterapici antitumorali (fra cui metotrexato, vinblastina, vincristina, cisplatino, procarbazina, ifosfamida, L-asparaginasi e thiotepa) può accompagnarsi ad alterazioni dello stato mentale, sintomi comportamentali e alterazioni del tono dell'umore³².

Gli effetti sono generalmente acuti, anche se alcune ricerche hanno ipotizzato un collegamento fra chemioterapia e sviluppo di depressione in alcuni adulti curati per neoplasie dell'età pediatrica³³. Va considerato tuttavia che l'entità del disturbo dipende da variabilità genetica e tipo e dosi del farmaco utilizzato.

Tradizionalmente gli effetti cognitivi e comportamentali acuti sono stati attribuiti a un generico effetto neurotossico; la neurotossicità più frequente è a carico del sistema nervoso periferico, per il ridotto passaggio attraverso la membrana ematoencefalica (che spesso però è alterata nelle malattie oncologiche). Se la neurotossicità centrale è stata tradizionalmente attribuita a un danno corticale e sottocorticale, per un effetto diretto sulle cellule a rapida replicazione, in particolare quelle gliali ed endoteliali, prospettive recenti propongono meccani-

smi più complessi rispetto all'effetto diretto sulle cellule in proliferazione.

In anni recenti emergono maggiori dati sugli effetti neurobiologici della chemioterapia su psiche e comportamento e iniziano a essere identificati i meccanismi neurotossici di alcuni farmaci chemioterapici qui di seguito riassunti:

Metotrexato. — È un chemioterapico antagonista della sintesi dell'acido folico. Il suo impiego può accompagnarsi a una sindrome neurologica acuta transitoria che comprende anomalie comportamentali³⁴. L'azione neurotossica di questo farmaco si esplica inibendo la rimetilazione folato-dipendente dell'omocisteina-metionina che aumenta la concentrazione di omocisteina nel plasma³⁵ e nel liquor³⁶. L'omocisteina è tossica per l'endotelio vascolare e sull'ippocampo, causando atrofia neuronale e blocco del metabolismo energetico³⁷. L'omocisteina e i suoi metaboliti sono analoghi strutturali del glutammato e sono agonisti dei recettori NMDA³⁸ potendo concorrere a convulsioni³⁹ e alla morte neuronale^{38, 40}. Ad alte dosi l'omocisteina combinata con l'adenosina forma l'S-adenosilomocisteina, che ha effetti inibitori sulle reazioni di metilazione necessaria per l'integrità della guaina mieliniche.

Ifosfamide. — È un derivato delle mostarde azotate. La sua tossicità neuropsichiatrica insorge durante l'infusione o subito dopo il termine della somministrazione ed è caratterizzata da sonnolenza, confusione, agitazione, afasia, convulsioni, sintomi extrapiramidali, allucinazioni, coma, raramente con esito fatale. Talora sono presenti sintomi dispercettivi in assenza di alterazioni del sensorio.

L'azione neurotossica è svolta attraverso vari meccanismi. La cloroetilamina prodotta dal metabolismo dell'ifosfamide altera la catena respiratoria mitocondriale, portando all'accumulo di NADH, che impedisce la deidrogenazione della cloroacetaldeide. Quest'ultima è un metabolita neurotossico, con effetto deprimente sul SNC, che porta alla deplezione di glutatione intracellulare con l'effetto di impedire la disintossicazio-

ne da sostanze tossiche. La relativa carenza di NAD ostacola anche la gluconeogenesi epatica. Alla produzione di cloroacetaldeide concorrono anche i tessuti extraepatici e il plasma.

Le manifestazioni tossiche da ifosfamide sono trattate, anche preventivamente, con la somministrazione di blu di metilene, che ripristina la catena respiratoria mitocondriale, servendo da accettore di elettroni alternativo, ripristina la gluconeogenesi epatica riducendo l'inibizione di NADH e previene la trasformazione di cloroetilamina in cloroacetaldeide⁴¹. Il trattamento prevede anche la somministrazione di glucosio, che compensa l'inibizione della gluconeogenesi, e la somministrazione di benzodiazepine.

Altri chemioterapici. — È esiste un legame dimostrato fra *fatigue* e carnitina in bambini e adolescenti affetti da neoplasie trattati con cisplatino, doxorubicina o ifosfamide⁴². Questi chemioterapici interferirebbero specificamente con la disponibilità nell'organismo di carnitina, micronutriente essenziale per la sintesi di adenosin-trifosfato, con un ruolo importante nel metabolismo energetico muscolare⁴². Nausea, vomito e anoressia concorrerebbero a ridurre l'introito alimentare di questa sostanza. Tentativi terapeutici con somministrazione di carnitina, avviati sperimentalmente, dovrebbero dimostrare anche nell'uomo l'effetto mostrato nell'animale di modulare i recettori glucocorticoidi e dovrebbero essere quindi approfondite le interazioni con i corticosteroidi impiegati nei trattamenti.

Tutti i trattamenti chemioterapici possono avere teoricamente neurotossicità. Gli effetti sono variabili a seconda dell'età del paziente, delle modalità e del timing dei trattamenti, dell'integrità della barriera emato-encefalica e in base ad eventuali concomitanti alterazioni endocrine, metaboliche e funzionali a carico dei diversi organi. Le manifestazioni sono inoltre legate al livello di funzionamento premorboso e ai meccanismi psichici di adattamento, compresi meccanismi di difesa, stili di personalità, meccanismi di coping e risorse del contesto familiare e socioeconomico.

Un fattore che media la dose di chemioterapici che raggiunge il SNC è la variabilità genetica dei trasportatori di membrana⁴³. Altri aspetti considerati nello studio sperimentale dei danni cognitivi da chemioterapia riguardano i fattori genetici responsabili della riparazione del DNA⁴³.

GLUCOCORTICOIDI

È ben noto il legame fra le terapie steroidee e l'insorgenza di sintomi psichiatrici quali ansia, psicosi, alterazioni del tono dell'umore (mania e depressione), oltre che effetti negativi sulla memoria dichiarativa e di lavoro e alterazioni della coscienza fino a psicosi o delirium⁴⁴. In letteratura sono riportati alcuni casi di ossessioni e compulsioni indotte da steroidi, generalmente risolte dopo lo scalaggio del farmaco⁶.

I sintomi psichiatrici legati all'impiego di steroidi sono dose-dipendenti e si risolvono generalmente con la riduzione del dosaggio o la loro sospensione.

Vari lavori hanno descritto disturbi psichiatrici legati alle terapie steroidee^{45, 46}. La maggior parte degli effetti negativi insorge nelle prime due settimane di trattamento, anche se sono stati descritti andamenti bimodali, con sintomi psichiatrici acuti e subacuti⁴⁵.

Per la cura delle leucemie si ricorre a una somministrazione prolungata di steroidi nella fase d'induzione e durante la cura intensiva. Steroidi sono impiegati anche nella fase d'induzione della chemioterapia nel trattamento dei linfomi e per il loro effetto antiedemigeno in vari tumori solidi che presentano un effetto massa, fra cui le neoplasie cerebrali, in particolare nel corso dei trattamenti radioterapici. Esistono varie evidenze di una maggiore tossicità neurocomportamentale del desametasone rispetto al prednisone⁴⁷.

La terapia steroidea ha effetti sul comportamento e sullo stato emotivo dei pazienti. Fra i meccanismi invocati per le alterazioni neuropsichiatriche da steroidi vi è la loro azione sull'ippocampo²⁸. L'ippocampo è l'area cerebrale con la maggiore concentrazione di recettori per i glucocorticoidi⁴⁸ e

presenta alterazioni strutturali in presenza di livelli elevati di steroidi⁴⁹. Nella regione subgranulare del giro dentato dell'ippocampo continua la neurogenesi anche in età adulta e questa attività è legata al consolidamento dei ricordi e alla memoria spaziale.

La neurogenesi attiva nell'ippocampo appare legata alle funzioni mnesiche. Una riduzione della dimensione dell'ippocampo è stata descritta in diverse condizioni psichiatriche quali la depressione e il PTSD⁵⁰ e i danni ippocampali sono identificati come il substrato biologico degli effetti dei glucocorticoidi sulla memoria⁵¹.

Il danno ippocampale avviene attraverso molteplici vie. Gli steroidi agiscono attraverso effetti diretti sull'ippocampo attraverso un potenziamento dei danni da parte degli agonisti NMDA e di altri agenti³⁴, inibendo la neurogenesi ippocampale⁵², interrompendo il ciclo energetico neuronale e alterando l'espressione ippocampale dei recettori N-metil-D-aspartato (NMDA). Alcuni studi sottolineano la relazione fra glucocorticoidi e glutammato; gli steroidi possono diminuire la disponibilità di glucosio a livello ippocampale, aumentando la concentrazione di glutammato nella sinapsi ippocampale⁵³ portando a un'eccessiva stimolazione dei recettori post-sinaptici fino all'apoptosi⁵⁴. I sintomi psicotici sarebbero da attribuire⁵⁵ alle alterazioni di trasmissione a livello dei recettori NMDA della regione ippocampale CA3.

È stato inoltre descritto come la somministrazione di prednisone si associ a diminuzione di livelli di corticotropina, norepinefrina, beta-endorfine e beta-lipotropina nel liquido cerebrospinale.

ANALGESICI

Farmaci oppioidi sono impiegati di frequente in oncologia e possono produrre sintomi psichici (per gli oppioidi sedazione e allucinazioni) che necessitano di scalaggio, sospensione o impegno di terapie psicofarmacologiche per mitigarne gli effetti collaterali. La morfina si lega ai recettori presenti a livello delle corna dorsali del midollo spinale, del sistema limbico (corteccia

frontale e temporale, amigdala e ippocampo), di talamo, ipotalamo e corpo striato, provocando un innalzamento della soglia percettiva del dolore e attenuando la componente emotiva del dolore. L'attività agonista sui recettori $\delta 1$ e $\delta 2$ si associa euforia, mentre ai recettori σ sono legati gli effetti psicomimetici (disforia e allucinazioni).

Gli oppioidi infine aumentano il livello di serotonina, e, in concomitanza con altri farmaci, possono causare una sindrome serotoninergica, condizione potenzialmente fatale, di riscontro estremamente raro in oncologia pediatrica, che consegue all'uso terapeutico, o a scopo autolesionistico, o per una inattesa interazione farmacologica, di farmaci serotoninergici.

RETINOIDI

Gli isotretinoidi, analoghi di sintesi della vitamina A, impiegati per il trattamento di alcune neoplasie (come il neuroblastoma) si sono mostrati nel loro impiego in altri ambiti clinici (es. trattamento dell'acne nodulo-cistica), gravati non solo di effetti collaterali fisici, ma anche psicopatologici (depressione, ideazione suicidaria e psicosi) meritevoli di considerazione⁵⁶. Il meccanismo d'azione alla base degli effetti psichici di queste sostanze liposolubili è sconosciuto, anche se esistono evidenze di come i retinoidi possano influenzare lo sviluppo neuronale e vari sistemi neurotrasmettitoriali. In particolare è stata ipotizzata un'azione sulla neurogenesi a livello dell'ippocampo che avrebbe l'effetto di diminuire le funzioni orbitofrontali⁵⁷.

TERAPIE IMMUNITARIE

Alcuni farmaci attivi sul sistema immunitario impiegati correntemente per il trattamento di malattie virali come l'epatite C e alcune neoplasie sono legati allo sviluppo di sintomi neuropsichiatrici come depressione, ansia, psicosi, ideazione suicidaria, ipomania e alterazioni cognitive⁵⁸. Fra i farmaci gravati di maggiore tossicità neurocomportamentale vi sono in particolare le citochine come l'interferone-alfa-2-beta

(IFN-alfa) e l'interleuchina-2^{59, 60}. L'incidenza di depressione maggiore nel corso di trattamenti con IFN-alfa è variabile a seconda delle patologie. Negli adulti è stimata dal 30% nei pazienti affetti da HCV⁶¹, al 45-50% nei pazienti affetti da melanoma⁶⁰. Nel caso dell'IFN-alfa sono descritti sintomi precoci neurovegetativi e somatici (anoressia, *fatigue*, disturbi del sonno, dolore e febbre), mentre depressione e disfunzioni cognitive si presentano più tardivamente⁵⁹. Gli effetti generalmente si interrompono con l'interruzione del trattamenti, anche se in alcuni pazienti possono persistere per alcuni mesi sintomi residui. I meccanismi fisiopatologici, fra cui come le alterazioni del metabolismo del triptofano, saranno esposti più in dettaglio nel paragrafo dedicato alle alterazioni immunitarie.

La letteratura riporta come i soggetti che hanno sviluppato depressione maggiore durante i trattamenti con interferone abbiano mostrato un'aumentata produzione di ACTH e di cortisolo in risposta alla dose iniziale di IFN-alfa⁶². L'aumento di ACTH e cortisolo indotto da interferone si correla con la presenza di moderati sintomi depressivi prima della terapia con interferone⁵⁹. Ciò potrebbe indicare una pre-esistente iperattività dei sistemi di risposta allo stress, che potrebbero predisporre allo sviluppo di sintomi depressivi nel corso di trattamenti con interferone.

Anche se vari studi hanno evidenziato un effetto positivo dell'impiego di antidepressivi sui sintomi depressivi legati all'immunoterapia in alcuni gruppi di pazienti, mancano elementi per attuare una sistematica prevenzione psicofarmacologica⁶³. Le alterazioni neuropsichiatriche da IFN dipendono da molteplici meccanismi fra cui induzione di citochine proinfiammatorie, deplezione di triptofano, attivazione dell'asse ipotalamo-ipofisi-surrene (*hypothalamus-pituitary-adrenal*, HPA) attraverso l'azione di CRH (*corticotropin-releasing hormone*) e la riduzione della disponibilità di ormone tiroideo⁵⁹.

In oncologia pediatrica sono impiegate terapie immunitarie; da alcuni anni è stato introdotto nell'uso clinico per il trattamento

del neuroblastoma l'anticorpo ch14.18, anticorpo monoclonale anti GD2, su cui mancano studi sugli effetti neuropsichiatrici.

Alterazioni immunitarie e sickness behavior

Da alcuni anni è descritta la capacità delle citochine proinfiammatorie, fra cui la tumor necrosis factor (TNF)-alfa, IL-1 e IL-6 di indurre una "cytokine-induced sickness syndrome" o "sickness behavior syndrome" (SBS) ⁶⁴. Originariamente descritta come parte di una sindrome che si verifica nel corso di un'infezione ⁶⁵, la SBS comporta sintomi emotivi e comportamentali. Diversi sintomi manifestati dai pazienti adulti con neoplasie hanno analogie con la SBS, parte di una sindrome che si manifesta nel corso di sollecitazioni del sistema immunitario. Analisi dei cluster hanno mostrato la coerenza di questo costrutto anche in oncologia pediatrica ⁶⁶.

Le citochine sono prodotte dalle cellule neoplastiche, dalle cellule del sistema immunitario (neutrofili, macrofagi, linfociti) e dalle cellule del sistema nervoso (cellule gliali, paragangliari e di Schwann).

I sintomi somatici della SBS comprendono risposte della fase acuta (febbre, riduzione sistemica di minerali), dolore (iperalgia) e aumento dell'attività dell'asse ipotalamo-ipofisi-surrene e del sistema nervoso periferico. Le manifestazioni comportamentali comprendono anedonia, isolamento sociale, *fatigue*, alterazioni dell'appetito come anoressia, perdita di peso, disturbi del sonno, disturbi cognitivi (difficoltà nell'apprendimento), diminuzione della libido, ritardo psicomotorio, iperalgia e riduzione delle interazioni sociali; tutte queste manifestazioni sono comuni al mondo animale ⁶⁷.

Lo scatenamento della SBS richiede una comunicazione fra cervello e sistema immunitario. Anche se per molti anni si è presunto che il SNC fosse scarsamente influenzato dalle reazioni immunitarie periferiche e nonostante le citochine siano troppo grandi per passare liberamente attraverso la barriera emato-encefalica, sono state descritte varie modalità di trasmissio-

ne del segnale al cervello. Una via lenta è legata alla produzione di citochine da parte dei macrofagi che può agire sugli organi circumventricolari e sui plessi coroidei che circondano i ventricoli cerebrali. Fra i meccanismi coinvolti è compreso anche il passaggio delle citochine attraverso le zone danneggiate della barriera, il trasporto attivo e la trasmissione del segnale delle citochine attraverso fibre nervose afferenti (come il nervo vago) ⁶⁸. Nel cervello è stata inoltre descritta la presenza di cellule che producono citochine (glia/neuroni) e ricevono i loro segnali attraverso recettori ⁶⁹. Benché non indagate sistematicamente, esistono evidenze di un aumento delle citochine durante i trattamenti chemioterapici ⁴³ e in ambito oncologico pediatrico il legame fra aspetti psicologici e cambiamenti delle citochine è clinicamente stato descritto nel corso di trapianto di cellule staminali emopoietiche ⁷⁰. Alterazioni immunitarie sono inoltre descritte ancora a lungo termine dopo la conclusione delle cure oncologiche in bambini con neoplasie.

Sono stati ipotizzati vari meccanismi con cui le citochine proinfiammatorie interagiscono con la regolazione dell'umore:

— un primo meccanismo sarebbe un'alterazione del metabolismo delle monoamine nel sistema nervoso centrale;

— un secondo meccanismo ipotizzato sarebbe la stimolazione da parte delle citochine dell'asse ipotalamo-ipofisi-surrene, prevalentemente attraverso l'attivazione dell'ormone CRH; questo ha effetti di indurre nell'animale risposte analoghe a quelle dei pazienti depressi con riduzione dell'attività, dell'appetito e del sonno ⁷¹. Osservazioni *in vivo* e *in vitro* mostrano come le citochine proinfiammatorie possano indurre resistenza ai glucocorticoidi circolanti nel sistema nervoso, endocrino e immunitario, attraverso l'inibizione diretta dell'espressione o della funzione dei recettori per i glucocorticoidi ⁷². Si è riscontrato un aumento del CRH in molti pazienti con disturbi comportamentali, inclusa la depressione maggiore ⁷¹;

— dati recenti mostrano come le alterazioni del metabolismo del triptofano siano

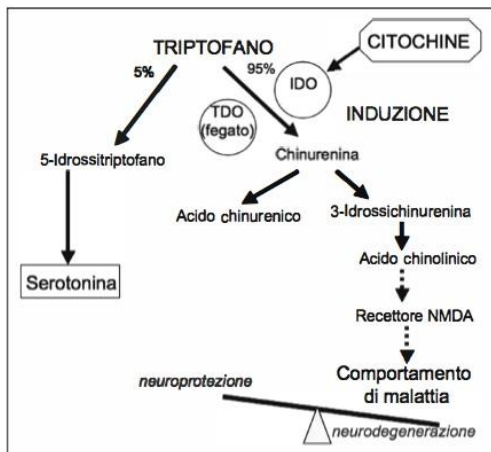


Figura 1. — Azione delle citochine sul metabolismo del triptofano.

coinvolte nello sviluppo di depressione. Le citochine inducono alterazioni del metabolismo del triptofano⁷³ (Figura 1) che, oltre a essere legate a una riduzione dell'introito alimentare, (a causa dell'anoressia), si lega anche all'induzione dell'enzima indoleammina 2,3-diossigenasi (IDO) nel corso della risposta immunitaria tipo Th-1. Il triptofano è un aminoacido essenziale, precursore della serotonina; è degradato per la maggior parte in sede epatica attraverso la triptofano-2,3-diossigenasi che genera NAD (presente in sede epatica). Una via alternativa è l'IDO (in sede extraepatica) la cui attività è normalmente trascurabile ma inducibile dalle catecolamine, che porta alla degradazione del triptofano a cataboliti come la chinurenina. Astroцитi, micrighia e macrofagi perivascolari metabolizzano la chinurenina in metaboliti neurotossici. La carenza di triptofano prodotta dalla reazione immunitaria sarebbe anche coinvolta nella riduzione della sintesi di serotonina, di cui il triptofano costituisce il precursore. La chinurenina inoltre è degradata a 3-idrossichinurenina (3OHK) che ha azione neurotossica interessando i recettore NMDA⁵⁸;

— si è evidenziato che le citochine TNF-alfa e IL-1, attraverso l'attivazione della p38 MAPK (proteina chinasi attivata da mitogeni), incrementano la funzione e l'espressio-

ne sinaptica della pompa per il re-uptake della serotonina e della norepinefrina;

— un altro meccanismo con cui le citochine possono produrre alterazioni comportamentali è legato ad effetti sull'attività cerebrale regionale. Ad esempio, la somministrazione di IFN-alfa si associa a un aumentato flusso sanguigno nella parte dorsale della corteccia cingolata anteriore⁵⁹ che risulta coinvolta nell'individuazione di pericoli ambientali e sociali e quindi anche nelle risorse di adattamento alla malattia (*coping*).

I dati della letteratura recente invitano a considerare alcuni cambiamenti cognitivi e comportamentali nel corso delle neoplasie che impegnano il sistema immunitario come effetti in parte dovuti a alterazioni neuroendocrine⁴³. Le citochine proinfiammatorie prodotte dalle cellule immuni periferiche sarebbero da considerare un segnale motivazionale che trasmette al cervello la necessità di cambiare le priorità dell'organismo di fronte a un pericolo, con effetti di riorganizzazione fisiologica, comportamentale e soggettiva⁷⁴.

La sickness behavior negli esseri umani assume probabilmente aspetti multiformi, che comprendono sia sintomi depressivi, sia neurovegetativi, accompagnati da *fatigue* e anoressia⁵⁹. La SBS e la depressione maggiore avrebbero in comune i sintomi di apatia, ritiro sociale, disturbi del sonno, *fatigue*, anoressia, perdita di peso, disturbi cognitivi, diminuzione della libido e ritardo psicomotorio, mentre nella depressione maggiore sarebbero più frequenti umore depresso, sentimenti di colpa e vergogna e ideazione suicidaria.

È probabilmente importante riconsiderare gli aspetti depressivi o i sintomi psichici nel corso di una malattia grave all'interno di una concezione più ampia che integri gli aspetti psicologici e biologici, presupposto per una maggiore efficacia dei trattamenti. In particolare alla base della *fatigue* sono state proposte alterazioni della coordinazione fra sistemi corticali e sottocorticali attraverso alterazioni a livello dei nuclei della base e talamico che deprimono l'attività corticale prefrontale. Per il trattamento del-

la *fatigue* in pazienti adulti in corso di trattamento per neoplasie o guariti da tumore sono state impiegate terapie con tutte le categorie di antidepressivi inibitori specifici della ricaptazione della serotonina (SSRI), antidepressivi serotoninergici specifici e noradrenergici (NaSSA), antidepressivi triciclici (TCA), stimolanti e corticosteroidi.

Aspetti comportamentali

In alcune risposte ai trattamenti quali l'emesi e la nausea sono coinvolti meccanismi complessi con componenti psico-organiche. Le strutture del S.N.C. coinvolte comprendono il centro di regolazione della nausea nel tronco cerebrale⁷⁵ che riceve afferenze dalla zona trigger dei chemorecettori (chemoreceptor trigger zone - CTZ) nell'area postrema (struttura al limite infero-posteriore del quarto ventricolo), la corteccia cerebrale e il sistema limbico, il sistema vestibolare e il tratto gastroenterico.

Di conseguenza, gli stimoli incondizionati sono gli effetti rilevabili a livello centrale di quegli stimoli biologicamente attivi (cioè gli effetti centrali dei farmaci citotossici, una discrepanza motoria o sensoriale e/o una stimolazione gastrointestinale), che raggiungono in modo afferente il centro dell'emesi che porta alla nausea. Lo stesso sintomo può essere poi evocato e ai sintomi relativi e ai cambiamenti endocrinologici e immunologici incondizionati; queste componenti possono poi essere evocate attraverso gli stimoli condizionati e le risposte condizionate.

Neuroncologia

Aspetti anatomici e chirurgici

Nella cura delle neoplasie del SNC la comprensione del danno biologico si accompagna in modo particolare al tentativo di dare supporto alla condizione dei pazienti che si trovano a funzionare con un cervello "diverso e unico". I bambini con neoplasie cerebrali costituiscono una popolazione con aumentato rischio di proble-

matiche psicosociali. L'incontro fra diversi ambiti della neuroscienze e delle scienze del comportamento da anni in corso può forse anche in questo ambito trovare applicazione. Dal punto di vista clinico alcune manifestazioni psichiche e comportamentali sono legate alla localizzazione della neoplasia cerebrale. Lesioni a livello di alcuni distretti sono soggette a maggiore rischio di danni neuropsicologici, in particolare le strutture sottocorticali, le aree temporo-mesiali, specialmente l'ippocampo, le aree peri-ippocampali e la sostanza bianca⁷⁶, anche se il cervello in corso di sviluppo presenta rilevanti capacità di riadattamento.

La presenza di idrocefalo ostruttivo produce ipertensione intracranica; l'effetto della pressione sulle fibre della sostanza bianca e sui lobi frontali causa sintomi neuropsichici.

Gli interventi chirurgici possono produrre lesioni se le vie d'accesso comportano la produzione di danni ulteriori rispetto a quelle esistenti o se comportano la prolungata dislocazione dei lobi frontali per consentire l'accesso chirurgico a zone più profonde, comportando danni a causa della particolare complessità interna di queste strutture⁷⁶.

Neoplasie cerebellari o della fossa posteriore si accompagnano a deficit nella regolazione emotiva, impulsività, ritiro e agitazione.

Danni particolari sono legati a trattamenti chirurgici dei tumori della fossa posteriore, dato che lesioni del verme cerebellare si accompagnano ad alterazioni sociali e della comunicazione⁷⁷. Un caso particolare è la sindrome della fossa posteriore (PFS). Conosciuta anche come mutismo cerebellare, descritta da Hirsch nel 1979, è caratterizzata da anartria, riso e pianto spastico, irritabilità, deficit motori anche severi. Si verifica in circa il 20% dei pazienti sottoposti in età pediatrica a resezioni di neoplasie della fossa posteriore. Generalmente questa sindrome è transitoria: varie osservazioni indicano come la componente del mutismo possa può risolversi mentre possono persistere complicanze neuropsicologiche

a lungo termine come aumentata irritabilità e labilità emotiva durante la convalescenza⁷⁸. Bambini con PFS hanno maggiore probabilità di evidenziare problemi internalizzanti, sociali e attentivi.

L'insorgenza di sintomi ossessivi e compulsivi in pazienti adulti operati per neoplasie cerebrali mostra un'incidenza frequente nel periodo perioperatorio e a ciò sembrano concorrere simultaneamente disfunzioni cerebrali causate dalla neoplasia, gli effetti dell'intervento, paura e preoccupazione. La fisiopatologia del disturbo ossessivo e compulsivo è oggi attribuita ad alterazioni del metabolismo della serotonina e dei neuropeptidi coinvolti nella reazione di stress⁷⁹, e anatomicamente da alterazioni dei circuiti prefrontali-nuclei della base⁸⁰. Sintomi ossessivo-compulsivi secondari sono descritti associarsi a lesioni della regione fronto-orbito-striatale e nei pazienti con neoplasie si è evidenziata un'associazione con lesioni nelle regioni frontali dell'encefalo⁸¹. Le alterazioni di neurotrasmettitori e neuropeptidi nei pazienti con neoplasie cerebrali e in particolare in oncologia pediatrica sono meritevoli di maggiori studi.

Effetti dei trattamenti radioterapici

Dal punto di vista neurobiologico negli ultimi anni le concezioni sul cervello sono molto evolute. Negli ultimi due decenni quest'organo è descritto non più come una struttura statica ma sono oggi riconosciute cellule staminali e progenitori cellulari in proliferazione nell'ippocampo e nel sistema ventricolare⁸². Precursori degli oligodendrociti sono presenti nella sostanza bianca sottocorticale²⁶.

Gli effetti neuropsichici della radioterapia sono oggi interpretati con maggiore dettaglio distinguendo reazioni acute, early-delayed e late-delayed⁸³:

— le reazioni acute sono attribuite a edema cerebrale radio-indotto. Sono caratterizzate da cefalea, nausea, sonnolenza e vomito;

— le reazioni early-delayed, caratterizzate da sonnolenza e peggioramento dei

deficit neurologici, sono ritenute effetto dell'interruzione della sintesi di mielina conseguente al danno prodotto dalla radioterapia sugli oligodendrociti. Queste reazioni sono di solito transitorie e possono essere mitigata dalla somministrazione di steroidi;

— le reazioni late-delayed insorgono a distanza di mesi/anni dalla conclusione della radioterapia e possono comprendere necrosi e danni a carico dei piccoli vasi. A carico della sostanza bianca può verificarsi una leucoencefalopatia radio-indotta. Le disfunzioni cognitive correlate possono variare da minimi deficit cognitivi (deficit attentivi, deficit memoria a breve termine, bradifrenia) fino a danni severi. Il trattamento costituisce una sfida aperta e sono stati sperimentati vari trattamenti come steroidi, anticoagulanti, terapia iperbarica, vitamine ad alte dosi e inibitori dell'angiogenesi come il bevacizumab.

La neurogenesi ippocampale è influenzata negativamente da chemioterapia, radioterapia, glucocorticoidi coinvolti nelle reazioni da stress e da stati infiammatori. Dosi di radioterapia relativamente basse possono interferire con la proliferazione dei precursori cellulari nel giro dentato⁸⁴. La radioterapia sembra bloccare la neurogenesi ippocampale, attivando la microglia e stimolando la produzione di citochine proinfiammatorie come l'interleuchina-6 modulabili mediante terapie con FANS⁸⁵.

Negli animali è stata evidenziata una riduzione della neurogenesi ippocampale anche causata da trattamenti chemioterapici⁸⁶. L'effetto degli agenti citotossici sulla neurogenesi ippocampale è descritto come il principale meccanismo che giustifica delle difficoltà cognitive in corso di chemioterapia⁸⁷. Agenti come il metotrexato svolgono però azione tossica su diverse altre popolazioni cellulari, come i progenitori delle cellule gliali, che formano oligodendrociti e astrociti con funzioni mielinizzanti.

I disturbi cognitivi che seguono la radioterapia e la chemioterapia sarebbero quindi nel complesso dipendenti da alterazioni della neurogenesi postnatale e della gliogenesi.

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Discussione

In questa revisione è stato presentato l'articolato panorama eziologico di alterazioni psichiche e comportamentali basate, oltre che su difetti della trasmissione neurotrasmettitoriale, anche su repertori comportamentali con significato evolutivistico e con effetto su dimensioni psicologiche quali le relazioni e l'adattamento. La maggior parte dei pazienti non producono effetti negativi sulla qualità di vita di tutti i pazienti, ma una grande percentuale riesce ad ottenere una qualità di vita adeguata con soddisfacente funzionamento sociale e scolastico. Ciò è probabilmente da attribuirsi anche all'investimento di attenzione e risorse di cui questi pazienti sono oggetto da parte delle famiglie e dal contesto delle cure in oncologia pediatrica.

Esiste in ogni caso ancora scarsa letteratura per orientare i trattamenti a sostegno della salute mentale, ove disturbi emotivi o del comportamento⁸ si presentino in pazienti affetti da una neoplasia.

Migliorare le conoscenze sulla complessità psicobiologica dei pazienti affetti da neoplasie pediatriche è una base di partenza per nuove strategie d'intervento.

Per attuare trattamenti preventivi o precoci è necessario approfondire lo studio dei fattori di vulnerabilità dei pazienti rispetto ai disturbi cognitivi, emotivi o comportamentali.

Ad esempio, i pazienti che presentano già sintomi ansiosi o depressivi prima dell'impegno del sistema immunitario potrebbero essere considerati soggetti a rischio e meritevoli di un trattamento precoce o profilattico con antidepressivi. È da indagare se il trattamento preventivo delle convulsioni da busulfano o dell'encefalopatia da ifosfamide con benzodiazepine possa avere effetti preventivi anche sugli aspetti cognitivi, emotivi e comportamentali. È meritevole di approfondimento anche il trattamento mediante l'impiego di farmaci con azione diversa dagli antidepressivi, come i cannabinoidi⁸⁸. Alcuni dati della letteratura suggeriscono, infatti, come gli steroidi inducano una rapida risposta anti-infiammatoria, deviando il

metabolismo delle membrane lipidiche dalla produzione di acido arachidonico verso la sintesi di endocannabinoidi, in particolare l'anandamide (AEA) e il 2-arachidonoilglicerolo (2-AG), per effetto dell'inibizione della ciclossigenasi-2 (Cox2)⁸⁹. Esiste l'ipotesi che questo meccanismo possa rappresentare un primario elemento neuroprotettivo, e in collegamento con il sistema della leptina a livello ipotalamico, contribuire a coordinare l'omeostasi energetica e la risposta infiammatoria⁹⁰.

Nonostante i trattamenti psicofarmacologici siano utilizzati in oncologia pediatrica⁹¹, esiste ancora una scarsità di trial di antidepressivi con questi pazienti.

Uno sforzo centrale per i clinici è oggi l'integrazione di diagnosi cliniche descrittive della sofferenza emotiva e dei disturbi comportamentali con una comprensione in termini dinamici dei disturbi del paziente, utilizzando tutte le prospettive offerte dalle diverse tradizioni e pratiche cliniche. Recenti prospettive neurobiologiche vedono importanti convergenze fra l'azione degli psicofarmaci e della psicoterapia attraverso la modulazione dell'attività delle strutture cerebrali, rispettivamente con un meccanismo bottom-up e top-down⁹². Devono però essere ancora precisati gli effetti biologici della psicoterapia, in particolare nell'ambito del suo impiego con pazienti con patologie organiche, spesso usata nelle due forme più comuni (supportiva psicodinamica e cognitivo-comportamentale). Benché una prospettiva moderna non veda più alcuna contrapposizione fra farmaci e psicoterapia⁹³, una pratica clinica realmente integrata spesso non è attuata o attuabile.

Alcuni ambiti clinici e di ricerca nell'ambito della salute mentale, come quelli sul trauma, dove l'integrazione fra orientamenti psicodinamici, cognitivi e biologici ha maggiore tradizione, possono offrire un utile riferimento. Questa tradizione suggerisce la presenza di tre aree critiche costituite da processi emozionali, risposte cognitive e rappresentazione di sé. Le risposte emozionali e sono legate sia ai meccanismi psicodinamici sia all'attivazione delle sottostanti strutture anatomo-fisiologiche. Le risposte

emotive possono consistere in sensazioni di torpore e ottundimento emotivo, a cui concorre il repertorio sintomatologico del comportamento di malattia. Cognitivamente la gamma dei pensieri può essere limitata. I pazienti possono sperimentare l'assoluta assenza di emozioni positive a causa dei meccanismi biologici depressivi.

Se il corpo è sofferente e mal funzionante per la patologia organica o per aspetti legati alle cure, il paziente può sperimentare un conflitto fra i propri schemi interni e la nuova realtà, avvertendo sensazioni caotiche, di depersonalizzazione e di derealizzazione accentuate dagli effetti cognitivi delle alterazioni biologiche legate alla malattia e ai trattamenti. Sono frequenti sensazioni d'isolamento; a questi processi contribuiscono sia fattori ambientali (l'isolamento può essere reale) sia fisici (diminuisce la forza per rompere l'isolamento e coltivare le relazioni).

Obiettivo di un trattamento integrato nelle fasi precoci dell'esordio della malattia e in tutto il suo decorso è il raggiungimento e il mantenimento di un sufficiente equilibrio emotivo per mantenere un'adeguata rappresentazione di sé e delle proprie relazioni. Tale intervento mira anche a ridurre la confusione per consentire al paziente di relazionarsi efficacemente con i curanti e partecipare validamente alla gestione delle proprie cure e costruire un rapporto di fiducia. Il trattamento ha anche il fine di proteggere il paziente dall'isolamento sociale, e dai danni derivanti da decisioni inappropriate (come l'abbandono delle terapie).

I cambiamenti dell'immagine corporea, con effetti negativi sull'autostima e l'adattamento, possono essere moderati dal supporto sociale.

Un supporto integrato dovrebbe quindi articolarsi in tre aree fondamentali: il supporto psicologico, il supporto sociale e il supporto biologico. A interventi per mantenere la continuità scolastica e delle relazioni di amicizia deve affiancarsi la comprensione degli stati emotivi e l'uso di metodi di controllo delle emozioni mediante tecniche di psicoterapia di supporto e terapie farmacologiche. Le psicoterapie compren-

dono tecniche cognitive, comportamentali, supportive, orientate all'insight per favorire l'adattamento emotivo, il coping e la riduzione dello stress.

Conclusioni

Le malattie gravi in età pediatrica rappresentano un'interferenza rispetto alle capacità mentali integrative e al percorso evolutivo, legata alla stretta interazione di fattori biologici, cognitivi, emotivi, relazionali e sociali. È auspicabile che gli sviluppi delle ricerche possano approfondire i legami fra lesioni anatomiche, alterazioni neurochimiche e meccanismi immunitari, sviluppando anche trattamenti per diminuire la neurotossicità con effetti più specifici rispetto agli attuali trattamenti psicofarmacologici. Grazie ai progressi dell'oncologia si fa strada la speranza che una parte delle sofferenze emotive e delle sequele cognitive e comportamentali legate alla malattia possano in futuro trovare strumenti di ancor più efficace contenimento. Comprendere le componenti biologiche delle alterazioni del comportamento è importante anche per il paziente e i familiari che se informati possono meglio tollerarlo.

Una sfida che già oggi impegna i clinici è di armonizzare in un piano d'intervento integrato le diverse prospettive per leggere la sofferenza dei pazienti e poter attuare sempre più efficacemente interventi preventivi e di trattamento precoce.

Riassunto

Presso i centri di oncologia pediatrica è generalmente offerto ai bambini e agli adolescenti il supporto di interventi di psicologia clinica e psicoterapia per sostenere l'adattamento alla malattia e alle cure. La pratica clinica evidenzia però anche sintomi cognitivi, emotivi e alterazioni del comportamento, quali alterazioni cognitive, fatigue, ansia, irritabilità e depressione, alimentati da meccanismi biologici legati alla malattia e alle cure e non responsivi al colloquio e alle altre risorse di supporto psicosociale. Queste manifestazioni possono ostacolare i trattamenti o la riabilitazione e la vita a lungo termine, causando marcato distress, e richiedere trattamenti

ti psicofarmacologici. I fattori organici in grado di produrre queste alterazioni hanno trovato ancora scarso approfondimento nella tradizione clinica ed esiste ancora scarsa letteratura sugli interventi integrati psicologici e psicofarmacologici in pazienti affetti da neoplasie dell'età evolutiva. In questo articolo sono illustrate le componenti organiche alla base delle alterazioni psichiche e comportamentali nel corso delle patologie, considerando i sintomi, le cause e i possibili meccanismi fisiopatologici alla luce delle recenti prospettive di ricerca interdisciplinari. Sono inoltre analizzati i principali meccanismi legati ai trattamenti oncologici chemioterapici, chirurgici e radioterapici, responsabili di alterazioni psico-organiche in bambini e adolescenti affetti da neoplasie.

PAROLE CHIAVE: Oncologia medica - Psicologia clinica - Farmaci, effetti psicologici - Età pediatrica.

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Study 2.3

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Mirror therapy for phantom limb pain in an adolescent cancer survivor

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ABSTRACT

Aims and background. Several pediatric tumors require mutilating procedures in order to be treated effectively. Although the pain caused by the surgery is usually of a transient nature, the perception of pain in the amputated limb may persist. This prolonged pain, which is often refractory to pain-killing medication, may severely affect the patient's quality of life. The phenomenon of phantom limb pain (or phantom limb syndrome) has been investigated using neurological, neurophysiological and psychopathological approaches. Here we discuss the advantages of an unconventional rehabilitation technique, the recently reported mirror therapy, whose positive effects might be due, according to some researchers, to neuronal plasticity mechanisms.

Case report. We describe the use of mirror therapy to treat phantom limb syndrome in a 39-year-old patient whose right leg had been amputated at the age of 17 because of an osteosarcoma. The patient suffered from frequent episodes of pain, with severely negative effects on his quality of life.

Results. We obtained positive subjective feedback from the patient, who reported having benefited significantly from using the mirror. The beneficial effect was still present six months after the start of mirror therapy.

Conclusions. The reported case highlights the value of an integrated multidisciplinary approach including neurological/physiatric assessment, clinical psychological support, physiotherapy and other, unconventional treatment modalities. This report should guide future studies towards the application of mirror therapy in order to elucidate its effects and efficacy.

Introduction

Over the last 20 years, multidisciplinary integrated therapies and the use of preoperative chemotherapy have considerably reduced the rate of limb amputation as primary treatment for bone tumors. However, several pediatric tumors (namely osteosarcoma, Ewing's sarcoma and soft tissue sarcoma) often still require such mutilating procedures. Although the pain caused by the surgery is usually of a transient nature, the perception of pain in the amputated limb can persist. Whenever the patient feels that (i) the pain originates from the missing limb, (ii) begins and ends in a vacuum, and (iii) its localization does not correspond to a remaining anatomical part of the arm or leg, we name it phantom limb pain. Moreover, in those cases where pain had never been a symptom (often the disease is diagnosed incidentally, for example after a sports injury), any contribution to the phantom pain by the preexisting tumor is clearly to be excluded. This prolonged pain, which is often refractory to pain-killing medication, may severely affect the patient's quality of life and interfere with his or her psychosocial adjustment to the amputation. The phenomenon has already been investigated by several neurological, neurophysiological and psychopathological approaches.

Key words: pain, quality of life, late effects, psychological support, psychology, pediatric oncology.

All authors declare they have no conflict of interests and no competing financial interests.

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Here we discuss the advantages of using an unconventional rehabilitation technique, the recently reported mirror therapy¹⁻³, whose positive effects might be due, according to some researchers, to neuronal plasticity mechanisms⁴.

Case report

The patient, now a 41-year-old man, was admitted to our pediatric oncology center in July 1988 at the age of 17. He was diagnosed with osteosarcoma in the right femur and received several cycles of preoperative chemotherapy in the following 4 months.

In October 1988 the patient underwent surgery for amputation of the right leg in a center specialized in orthopedic oncology surgery. During the postoperative period, he suffered from pain in the amputated limb, which was refractory to analgesics. At that time, he described with precision (and can remember it after many years) temporary relief from the postoperative pain when his mother massaged his bed in the area overlapping with the amputated limb.

The patient was subsequently transferred to a rehabilitation center in Budrio (Italy) focused on patients post-amputation. There he learned to walk with a prosthesis that he decided to abandon 1 year later, when, in June 1990, he started using only elbow crutches.

In the same year the patient was diagnosed with lung metastases and underwent a right lower lobectomy, followed by radiotherapy and chemotherapy. In 1993 he was operated on for a retrosternal metastasis and 3 years later, in 1996, further left lung metastases were removed through thoracotomy followed by local radiotherapy. In 1998, another metastasis within the fourth lumbar vertebra was identified and treated immediately with radiotherapy to the L4-L5 region. After this episode he was also assisted by a clinical psychologist, who established a weekly clinical support session for a period of 2 years and less frequent but periodic check-ups thereafter. In August 2003 he moved with his girlfriend to a new house, purchased with a 15-year loan. Over the years, the patient subjectively enjoyed a good quality of life and remained able to keep his job.

Interestingly, for a long time he did not experience any phantom limb pain but reported being in a constant state of restlessness ("I was always expecting a storm."). It was only after his last cancer treatment, in 1998, that he started to suffer from phantom limb pain again, characterized by recurrent episodes that he described as unendurable. This elicited further oncological, psychiatric and neurological assessments almost on a weekly basis.

A radiotherapy-related axonal lesion due to L5-S1 radiculopathy was diagnosed, with damage to the left sciatic nerve that was making it difficult for the patient to walk. The consultant physiatrist recommended the

use of a Codivilla spring, which improved the patient's autonomy. He was able to walk again with the aid of elbow crutches.

The phantom limb pain occurred almost daily; the patient referred to it as "detaching me from the world." It called for the frequent use of analgesics, which did not, however, bring symptom relief. Diazepam was prescribed in the evening, but its use was immediately interrupted because of the excessively sedative effect. The patient was given a tricyclic antidepressant for several months, with modest effect. However, the episodes of acute pain persisted.

The fortnightly physiotherapeutic sessions, though generally well tolerated, produced only transient benefit. The patient described experiencing a certain relief: "When my foot, and, the day after, my back were treated, relief was immediate." In particular, he reported feeling "lighter" the following 2-3 days.

When reports describing the use of mirror therapy for the rehabilitation of war amputees were published in the literature, the patient was invited to test this method. He was to be treated at the same pediatric oncology center where he was still undergoing periodic follow-up.

The patient was tested for his capacity to recognize his body schema and for his mental representations of movement. These functions were found to be delayed, apparently due to peripheral factors common in cases of amputation or chronic pain⁵.

Based on the suggestions of the patient's personal physiotherapist, a protocol was devised including several exercises with the use of a mirror. The patient purchased a glass mirror of 108 × 37.5 cm and began daily mirror therapy in October 2009. Each session lasted 30 minutes and was done during the evening after working hours.

The exercises consisted of looking at, touching, caressing, scratching and moving his leg. The mirror was tilted in order to prevent him from seeing his stump, giving the illusion of perfect symmetry between the limbs. While touching, scratching and gently caressing his remaining leg with his left arm and hand, the patient had the impression of doing this to the missing right leg; he even reported experiencing muscle contractions in the missing limb. One requirement was that the right hand should not be reflected in the mirror because it could damage the fiction of the perfect symmetry obtained by the mirror image of the left hand and leg alone. For this purpose, the use of a large mirror was recommended.

He kept a diary to record information and feelings and used the Zung test for depression symptoms⁶. He wrote, "It seemed as if I was on the beach, a feeling I had not experienced for years."

The intensity of the pain was measured before the start of mirror therapy and periodically thereafter by asking the patient to fill in a visual analogue scale (VAS).

The self-testing showed that the intensity of the pain decreased and gradually became stable and tolerable (Figure 1). The Zung test indicated no evidence of significant depression (Figure 2).

We also obtained positive subjective feedback from the patient, who reported he had derived significant benefit from using the mirror and had suffered in the last few months only very short episodes of acute pain

(never while using the mirror), during which he relied on antiinflammatory medication (ketoprofen). These painful episodes were not found in correlation with any peak of depression scores recorded by the patient.

Six months after starting the mirror therapy, the patient was still enjoying the sessions, which he experienced as a daily routine that “made him feel lighter” and “helped to get rid of the stress at the end of the day.” He

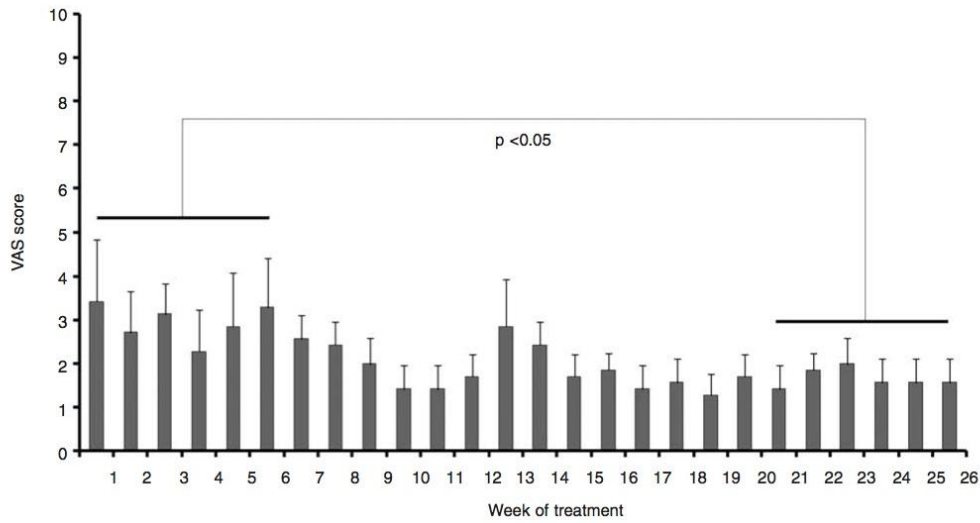


Figure 1 - Scores on the VAS scale. The difference in the perception of pain within the last period proved to be statistically significant (the p value between two groups of 6 weeks is indicated above the figure).

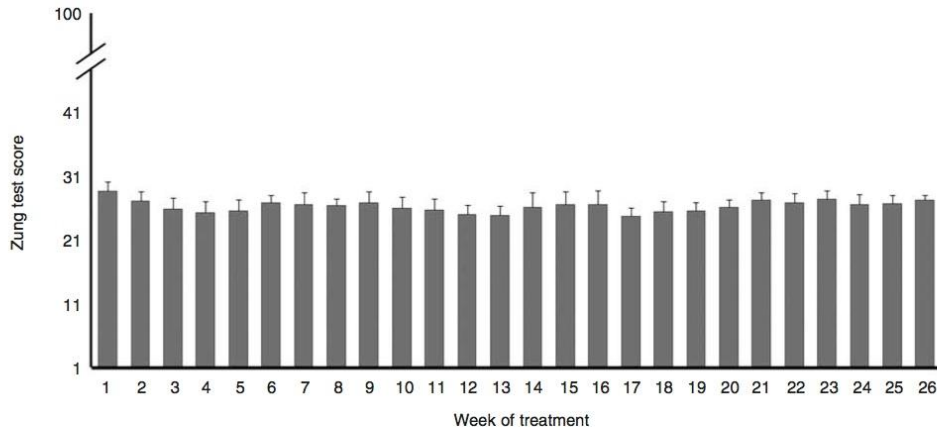


Figure 2 - Scores on the Zung test. No statistically significant differences were observed.

also described as beneficial the experience of having the illusion of massaging the missing limb. The beneficial effect was still present after 6 months and the patient performed a half-hour session almost daily, usually in the evening after work.

Ever since his amputation, the patient had never considered taking up any form of sport. This was due, at least in part, to the persistent phantom limb syndrome. (The patient was an assiduous tennis player before the amputation.) During a regular follow-up visit, the oncologist convinced him to take part in a hand-biking marathon that was to take place in the patient's hometown.

A tailored training schedule based on his baseline cardiorespiratory capability and response to physical stress (also considering the multiple thoracic surgeries and the lung radiotherapy) was designed by a medical doctor in a center specialized in sports medicine. The patient trained for 2 months before attending the competition, which he completed with a final time of about 2 hours and 30 minutes: he was able to reach the target he had set for himself.

Discussion

Several approaches to treating phantom limb pain have been developed, including physical and pharmacological therapies, but the results have generally been unsatisfactory⁷. Among the pharmacological options are painkillers, tranquilizers, antidepressants and anti-convulsants. Patients frequently abandon such therapies because they can have disturbing side effects such as sedation, drowsiness and depression.

This case report highlights the value of an integrated multidisciplinary approach including neurological/physiatric assessment, clinical psychological support, physiotherapy, and other, unconventional treatment modalities. We cannot exactly quantify the relative effect of the mirror therapy within the multifaceted approach used for this case; however, when drug therapy was used alone, no significant positive effect was reported.

It is worth emphasizing what we consider an important and remarkable choice made by the patient: when his pain decreased, possibly in response to the mirror therapy, he decided to take part in a hand-bike marathon race. In order to be successfully completed, this kind of long-lasting sports competition requires strong motivation as well as marked psychophysical well-being. We interpreted it as a benefit derived from the mirror therapy that he started intensive training de-

spite his functional impairment and the very long period of inactivity.

A positive effect of the hand-biking was related to the patient's posture on the bike and the symmetric hand movement during pedaling, which might have recalled the mirror therapy. Together with the patient we interpret this effect as a result of his focusing on the strong symmetry of the upper limbs' continuous rotation, which made him look at his legs as if they were both pedaling and enabled him to shut off the asymmetry resulting from the amputation.

Moreover, the patient himself reported that the mirror therapy, followed by training for a sports competition, had a strong positive effect on his psychophysical health. Both mirror therapy and sports require attention to movement, which helps to shift the patient's focus from the missing limb to the still existing and moving limbs. We cannot exclude that the endorphins released during sport activities might have substantially contributed to the final result⁸.

In conclusion, this report should guide future studies towards the application of mirror therapy in order to elucidate its effects and efficacy. We believe that its use might be extended also to pediatric patients with phantom limb syndrome, though under the supervision of a team of experts in the disciplines involved.

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Study 2.4 (*Submitted to Tumori journal*)

SPIRITUAL ASPECTS OF CARE FOR ADOLESCENTS WITH CANCER

Running title:SPIRITUAL ASSISTANCE IN ADOLESCENTS WITH CANCER

Tullio Proserpio, Andrea Ferrari, Laura Veneroni, Barbara Giacon, Maura Massimino, Carlo Alfredo Clerici

Abstract

Aims and background. Adolescents with cancer have psychosocial issues that need to be adequately addressed. Spirituality is a fundamental aspect of their psychological well being.

Methods. A ‘spiritual assistant’ is daily present in the ward of the Youth Project of the Pediatric Oncology Unit of the Istituto Nazionale Tumori, Milan. The routine spiritual assistant’s work includes: a) daily visits to the ward and the outpatient/day hospital; b) daily meetings with the psychologists on the staff; c) biweekly meetings with doctors and/or nurses. The numbers of cases referred for spiritual assistance between January and December 2012 were analyzed, according to patient’s age and the reasons for the consultation, and compared to the cases referred for psychological consultation.

Results. Psychological consultation was offered to 84% of patients/families; further support was needed for 23% of children and 45% of teenagers. Spiritual support was provided for 2 children and 20 adolescents (24% of this group).

Conclusions. Acknowledging patients’ spiritual needs helps patients to battle with their disease. The reasons why patients/parents ask for spiritual assistance only partially overlap with the motives behind requests to see a psychologist. The care of adolescents with cancer should include meeting spiritual needs by assuring the constant presence of a spiritual assistant in hospital wards.

Keywords: cancer, adolescent, spiritual assistance, psychosocial

Introduction

Cancer patients may have particular, not strictly clinical needs that often go unnoticed. Managing these needs has become an increasingly fundamental goal of care providers, and this is particularly true when it comes to patients in adolescence.^{1,2} Dealing adequately with the psychological and social issues of patients in their teens is especially important because they become ill at a time when they are experiencing major psychological and physical changes, establishing their self-image, structuring their identity, their personality, and their relationships with their peers.^{3,4} It is characteristic of adolescents to wonder about the meaning of life: who am I? where am I going? what is the meaning of life? Disease and suffering unavoidably interfere with such processes (which are already critical in themselves).^{5,1}

Together with the family or peer groups, the medical staff may have an important role in coping with the complex psychological world of teenagers and the dramatic psychological impact of a diagnosis of cancer at this age, but this demands the support of a specialist. The Youth Project for adolescent patients developed at the Pediatric Oncology Unit of the Istituto Nazionale Tumori in Milan provides for three specialists in clinical psychology and one social worker to routinely guarantee a daily presence in the ward. In the conviction that spirituality is an aspect of interest to adolescents suffering from cancer,^{6,7} there is also a 'spiritual assistant' on the multidisciplinary team, whose aim is to deal adequately with patients' need to have faith (for those people who are believer), trust and hope.^{3,8}

All persons have spiritual needs. Some persons have religious needs.

Specific religious beliefs and practices should be distinguished from the idea of a universal capacity for spiritual and religious experiences. This distinction is important conceptually for understanding various aspects of evaluation and the role of different beliefs, practices, and experiences in coping with cancer.

The most useful general distinction to make in this context is between religion and spirituality. There is no general agreement on definitions of either term, but a number of reviews address matters of definition.^{9,10,11} Religion can be viewed as a specific set of beliefs and practices associated with a recognized religion or denomination. Spirituality is generally recognized as encompassing experiential aspects, whether related to engaging in religious practices or to acknowledging a general sense of peace and connectedness. The concept of spirituality is found in all cultures and is often considered to encompass a search for ultimate meaning through religion or other paths.¹² Most individuals consider themselves both spiritual and religious; some may consider themselves religious but not spiritual. Others, including some atheists (people who do not believe in

the existence of God) or agnostics (people who believe that God cannot be shown to exist), may consider themselves spiritual but not religious.¹³

The spiritual care works to help patients, family members and staff address both spiritual and religious needs. (Source: What is Spiritual Care? | University of Maryland Medical Center <http://umm.edu/patients/pastoral/what-is-spiritual-care#>).

This paper explains what the spiritual assistant does at our Unit.

Matherial and methods

The Youth Project is a specific, comprehensive project launched at our Unit in 2011, and dedicated to adolescents (over 15 years old), and young adults (up to 25 years old) suffering from pediatric tumors.¹⁹ The project covers various aspects, ranging from the inclusion of these patients in appropriate clinical trials to offering them psycho-social support, preserving their fertility, providing multifunctional rooms and equipment and organizing activities and events suited to their developmental age, to help these older pediatric patients feel more at home in the hospital.

Psychological support is provided on different levels. The first focuses on the patient-physician relationship, seeking to identify any premonitory signs of psychological issues by investigating areas such as family, friends, school or work, boyfriends/girlfriends, and spare time activities. Basic emotional support is provided. The unit's staff receives specific training on these issues at meetings and courses.

Clinical psychology specialists represent the second level of intervention, and three such specialists are permanent staff members¹⁵.

As of 2011 also the activities of the spiritual assistant have been reorganized and better structured and this figure is now acknowledged as a permanent staff member. The spiritual assistant is a Catholic priest with a degree at the Psychology Institute of the Pontificia Universita' Gregoriana, Rome, and a further qualification in Pastoral Health, Pontificia Universita' Lateranense, Rome, requiring training in counseling and in hospital-based work. He is member of the National Council for Pastoral Health of the Conferenza Episcopale Italiana.

Some of his time is spent on religious procedures, such as celebrating Mass, giving blessings, saying prayers, administering the sacraments (Sacrament of the sick, Baptism, Reconciliation, Eucharist and Confirmation) at the request of patients and families; moreover, he is involved in organizing religious experiences (such as pilgrimages) and cooperating with local religious communities.

In addition to these general practices, the spiritual assistant's work includes:

- a) daily visits to the ward and the outpatient/day hospital;

- b) daily meetings with the psychologists on the staff;
- c) biweekly meetings with doctors and/or nurses.

Daily talks with patients, relatives and staff members enable the spiritual assistant to assess patients' and their relatives' spiritual needs, identifying special cases that need particular attention and counseling, and discussing the management of cases. A typical scenario is when the spiritual assistant supports terminal patients and their families, providing individual support during the process of grief. This spiritual support is not only offered at the end of the patient's life, it is also available as a resource throughout the period of patient care.

Pastoral counseling and spiritual support are offered also to non-Catholic patients/families. In case of non-Catholic believers, the spiritual assistant helps in contacting the local representative for their specific religion, when required. Talks concerning spiritual needs are generally carried out also with non-believer families.

The spiritual assistant also periodically attends meetings and events organized for adolescents involved in the Youth Project (taking an active part in sporting activities, for instance), acts as supervisor for the volunteers who work at the hospital and in social housing, and is involved in research work (relating to spiritual issues and patient care).

To better elucidate the type of spiritual support provided at the Unit, we retrospectively analyzed the number of patients referred for psychological consultation and for spiritual assistance, focusing on new cases diagnosed between January and December 2012, describing what motivated the chaplain's intervention, and comparing the pattern of referral seen in children (0-14 year-olds) or their parents, and in adolescents (over 15 years old).

Results

From 1 January to 31 December 2012, there were 274 patients with a new diagnosis of solid tumor treated at our Pediatric Oncology Unit: 191 of them (70%) were between 0 and 14 years old ('children'), the other 83 (30%) were over 15 ('adolescents').

Specific support was provided by our spiritual assistant for 2 children (11 and 12 years old) and 20 adolescents (24% of this group). All but one patient were Catholic. The number of appointments was usually from 3 to 5, sometimes more. In some cases, this spiritual assistance needed to be protracted, with several appointments also after completing the patient's treatment. It is noteworthy that 11 of the adolescents took an active part in the events and activities organized as part of the Youth Project. Spiritual assistance was also provided for 29 parents of children (15%) and 9 parents of older patients (11%). In 3 cases, parents were non-Catholic.

The reasons prompting a spiritual consultation with patients are schematically described in table 1. In many cases, patients asked the spiritual assistant about the meaning of their illness: “Why me? Why now?” “What did I do wrong?”(6 cases). Sometimes patients asked the spiritual assistant for advice because they felt the burden of still having to depend on their parents (5 cases). Other commonly-encountered issues related to patients’ own religious communities (e.g. patients asked the spiritual assistant to contact their priest) (5 cases). More rarely, patients needed to talk to the spiritual assistant about their religious doubts (2 cases) (“If God exists, why did he let me become ill?”), guilty feelings about having mistreated their parents when their illness and treatment made them irritable (2 cases), or concerns about death (2 cases).

As for the parents seeking spiritual support, their motives and needs varied (and there were sometimes more than one). The more common issues related to: a sense of guilt deriving from imagined failings that might have caused their child’s disease (14 cases); behavioral or relational problems with their son or daughter (14 cases) (including the perceived risk of treating them like a child still needing to be looked after and protected at a time when adolescents also needed to grow up and detach themselves from their parents); doubts about whether they were doing enough for their child (“Are we doing all we can?”); a sense of anger with their child’s disease (11 cases), sometimes focused on a superior being (God). The spiritual consultations occasionally involved parents asking the Chaplain to pray for them (8 cases), or talking about their fear of death (4 cases), or about conflicts arising between the two parents (2 cases) .

Discussion

The aim of this work was to illustrate how important the role of Chaplain can be as part of the psycho-social follow-up of oncological patients, and adolescents in particular.⁸ Adolescence is a special time of life, when an individual’s approach to spiritual matters and religion (and their relationship with God in the case of believers) often changes.^{16,17} Another characteristic aspect of this stage of development concerns the crucial changes taking place in an adolescent’s relationships with adults, which are a fundamental part of the process of constructing their individuality. Paradoxically, their disease and its treatment oblige adolescent cancer patients to stay close to their parents and depend on adult figures (including their doctors).

We are convinced that acknowledging patients’ spiritual needs helps them to battle with their disease.

There is a widespread diffidence in relation to the figure of the Chaplain, often associated with the idea that “there is nothing more to be done”. This misconception makes it more difficult for people to contact the Chaplain and ask for help. There are also other reasons why it may be difficult to see

the hospital Chaplain,¹⁸ one of which – to our mind - is an inadequate awareness that Chaplains receive specific training to work with patients^{19, 20}. We feel that the spiritual assistant should be seen as an integral part of the hospital staff, with particular responsibilities.

The role of spiritual assistants is important not only when it comes to administering the traditional sacraments, assisting the terminally ill or the bereaving, and they should not be considered as a resource to call to a patient's bedside on request to deal with a spiritual emergency. The Chaplain's role should be seen as an accompaniment throughout the various phases of a patient's disease and its treatment, a constant and active comforting presence in the hospital ward, right from the start of a patient's journey with cancer. It is also important to remember that patients' and their families' emotional states can have a direct impact not only on the clinical picture, but also on the tenor of communications between the medical staff and the patients and their relatives.²¹

Our analysis goes to show that the reasons why patients or members of their families ask for Chaplain only partially overlap with the motives behind requests to see a psychologist. For some concerns, the psychologist may not be the most appropriate option, and spiritual support may be essential.

The spiritual assistant should be a constant presence at the department. Our experience indicates that the Chaplain's informal involvement at the time of Youth Project meetings was important for the purposes of establishing a relationship with our patients, and was likewise important for the young people to be used to seeing the Chaplain coming and going in the ward every day so that they would have made his acquaintance before they considered asking for his professional help. It soon became evident that most of the adolescents who received spiritual support had also taken an active part in our Youth Project activities.

It is also indispensable to ensure a continuous exchange of impressions and opinions between the spiritual assistant and the other staff to bring out any problems that need to be dealt with, patients who need extra support, the methods for referring patients to the Chaplain to discuss their spiritual needs. These exchanges might also lead to the preparation of protocols for referring patients to the Chaplain, and a fine tuning of the way in which the spiritual assistant is introduced to patients.

Parents have their spiritual issues too. When their children become ill, they often experience a heavy sense of guilt. Sometimes their child's disease feels like a sort of punishment inflicted on them by some superior being because they have failed in some way. Some parents report feeling responsible for giving their child a severe disease instead of life and good health. Such ideas can be a cause of anxiety and interfere with the parents' faith in the future. Parents may also become confused, experiencing contrasting feelings that difficult to reconcile: one moment they may be hopeful and optimistic, the next they may be angry with God for their child's plight, despite their

faith. The spiritual assistant can help them deal with these issues and general regain a sense of confidence.²²

It is worth mentioning that the Joint Commission International Accreditation Standards for Hospitals has stated that, given the need to safeguard patients' rights in the broadest possible sense, a modern hospital should have in place "a process to respond to patient and family requests for pastoral services or similar requests related to the patient's spiritual and religious beliefs".²³ The purpose of such Chaplain should be not to convert anyone to a given cult, but to respond to spiritual appeals and provide comfort so as to facilitate communications, relationships and future projects (thereby sustaining patients' and their family's confidence and hope). Ideally, attention should be paid to a patient's spiritual history right from the moment when their disease is diagnosed. Spiritual assistants are therefore being asked increasingly by public health institutions to witness and vouch for the spiritual needs of patients,¹⁹ believer, whatever their faith, or not believer. New spiritual perspectives focus on human beings who are suffering with a view to supporting them in their personal journey through life, irrespective of their chosen religion. This topic is probably one of the challenges for multidisciplinary care-providing teams that have to combine different forms of expertise and different approaches (which need not be in opposition) in an effort to benefit patients and their families.²¹

Based on these considerations, we would suggest that the constant and active presence of a spiritual assistant in hospital wards as part of a multidisciplinary care-providing team, might be proposed as a possible model to address the specific emotional and spiritual needs of cancer patients, and adolescents in particular.

No large data are currently available on the efficacy of this model (e.g. patients' satisfaction questionnaire). However, far to represent a scientific conclusion, the percentage of adolescents involved in the talks with the spiritual assistant should be considered satisfactory.

It is likewise essential to train such spiritual assistants specifically to cope with hospital work and the type of patient they will need to deal with. The figure of the spiritual assistant absolutely must come to be seen as an indispensable resource at the service not only of adolescent patients and their parents, but also of the medical teams, acting as a guarantor of all their spiritual (not only religious) needs.²⁴

Table 1. Reasons for requesting spiritual support

Motives prompting spiritual consultations		No. of cases	Reports of the consultations
Patients			
	The meaning of illness	6	Why am I sick? Why me? I'm still young... I have not yet begun to live...
	Dejection due to persistent dependence on parents	5	"Now that I begin to be independent, that I was happy to grow and to liberate myself from my parents ... Now I feel forced to have to depend from them again, and this thing makes me angry "
	Issues relating to their religious communities	5	"I'm lucky, because with Skype, even when I'm here in the hospital, I can attend the meetings that are occurring in the parish and I join to my friends "I am glad, however, that the Father comes to visit me here in the hospital and as soon as I get home he comes to me"
	Sense of guilt for mistreating parents	2	"When I bad stretch my father and my mother, then I feel guilty; they go on telling me that I should not do this or that other thing, that I should not go out, that I have to stay indoors, I have to stay away from crowded places ...and these things make me angry and I answer in wrong way , then I'm sorry "
	Doubts about the existence of God	2	"If God exists, why am I sick? I continue to pray, but my situation gets worse, so I get many doubts, I do not know what to believe, the first time it was easier, but now ..."
	Concerns about death	2	"I am thinking about death because the more time passes and more and more I see that my cancer got worse. I try not to think about it but I know that you can also die from this disease, since I heard that Andrea died... I had a huge fear of thinking about this "
Parents			
	Behavioral or relational difficulties with their child	14	"Since he has got sick, I do not know any more how to relate to him, he has completely changed, I do not recognize him anymore... I try to tell him that, however, there are also his brothers at home and he can not claim to have all my attention at every time...I can not to understand what sense can have all this mess, why does God allow all this pain, this suffering... "
	Sense of guilt	14	"I would have to give my life for my son and instead I gave him the death ...why have not I noticed before that he was ill? Maybe, he told me that he had hurt but I did not believe it, I thought it was an excuse not to go to school... I am not a good dad, I could not avoid this situation to my son, I do not go well, where did I go wrong? "
	Anger	11	"I am angry with those doctors who did not

			<p>understand what my daughter had, I took her to many specialists who didn't understand anything, we walked around for more than six months without coming to a conclusion..."</p> <p>"When I see classmates Federica who are healthy, while she is still in hospital and she is always hurt, I get angry...Why my own daughter ?"</p>
	Requests that others pray for them	8	"Please pray for my son, pray also for us, many people are praying for us. That is a great help and support for us"
	Fear of death	4	"I'm afraid that my son will not face, I try not to think about it but the thought always goes to death, especially during the night"
	Conflict between the parents	2	<p>"My husband does not understand and he can never say no to our son, always making him do whatever he wants"</p> <p>"Because now my daughter is sick, but I can not bear my wife any longer, there is never anything good about what I do... I try not to see me by my daughter but I would cast her out "</p>

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Study 2.5

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Tumori, 98: e146-e148, 2012

At least we can send some flowers...

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ABSTRACT

Aims and background. Cancer may demand lengthy treatment and the emotional attachment between care providers and the patient may become intense, especially when the latter is a child. If patients die, their families and the care-providing staff need help to cope with the loss.

Short communication. We describe a procedure in use at the Istituto Nazionale Tumori in Milan for taking leave of families whose children die. This practice is based on simply sending flowers to families who have lost their child, and was started after an emotionally very demanding case.

Conclusion. Our sending flowers with a handwritten condolence letter is a simple gesture that seems to have helped both the patients' families and the members of our care-providing team in the process of mourning.

Introduction

Patient-doctor relationships are to do with trust and have profound emotional implications, especially in such delicate settings as pediatric oncology. When treatments fail and patients die after a more or less lengthy period of care during which families and staff members share difficult experiences, the tragedy of death imposes the need to deal with two processes, namely the family's mourning and the defeated doctor's leave-taking^{1,2}. For clinicians, the failure of a number of treatments in which they had invested intellectually and emotionally risks having the effect of belittling their efforts and interfering with an effective mourning process, preventing them from distinguishing between what has been lost with the child's death and what remains in their memories and in the experience they have gained. At the same time, it is the medical team's duty to help families cope with the terrible burden of a child's death³ and to provide emotional support for the bereaved⁴⁻⁶. Pediatric oncology departments all have their own customs and rituals, which are not based on protocols and procedures⁷⁻⁹. Clinicians should be provided with the tools they need to cope with these emotional issues as part of their patient care responsibilities. We report on our experience, based simply on sending flowers to families who have lost their child.

Short communication

A 7-year-old boy called G was diagnosed with non-Hodgkin lymphoma (NHL) in 1986. He had encountered a number of problems in his early childhood: his father had died and G had since lived in very modest economic conditions with his mother and 2 brothers, one of whom had become a heroin addict.

When the child started receiving medical treatment for his cancer, the family also became the object of intensive support efforts by the social workers on our team at the pediatric department. After 2 years of treatment, the child was followed up as an outpatient and his routine checkups gradually became less frequent, but we were still

Key words: grief, bereavement, psychological support, psychology, pediatric oncology, condolence letter.

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able to monitor G as he grew up and, where necessary, help him deal with the problems of his fragile family.

Ten years after completing his treatment for NHL, the boy was diagnosed with a new neoplastic disease, T-cell leukemia. Chemotherapy was successful in obtaining disease remission and treatment continued with conventional doses until the boy could be given an umbilical cord stem cell transplant. During this time, his mother also became ill with breast cancer. Although G's cancer remained in remission, he developed an arthritis-related cerebral vasculopathy with invalidating peripheral polyneuropathy that ultimately proved fatal, probably due to diffuse brain hemorrhage.

Our care-providing group was struck by something that one of our physicians said with a heavy heart when told that G had died, "If there's nothing more we can do, at least we can send some flowers." Ever since, whenever a young patient treated at our pediatric oncology department dies, we send the family a bunch of flowers.

All the staff on our interdisciplinary team (physicians, nurses, social workers, secretaries, teachers, youth workers and volunteers) may be involved in reporting a patient's death if this happens at home or at another public health facility. When the department secretary is notified, a flower delivery service is contacted (because 40% of our patients come from outside our region and a large percentage of these deaths take place at home) and a bunch of flowers is delivered to the family with a ribbon bearing the words "*The Pediatric Department of the Istituto dei Tumori in Milan*" and a handwritten letter from one of the doctors most involved in caring for the patient.

The cost of the flowers is covered by department funds.

Discussion

From our experience with G and other patients, we have the impression that showing some sign of sharing in the family's bereavement also helps the medical team members cope with their own mourning and take their leave of the patient.

Flowers were sent to 366 families from 1999 to 2008. This gesture can serve to express a genuine interest in the person who died, to emphasize the value of the relationship that developed between the care-providing team and the patient's family. Flowers can be a very tangible sign of this involvement because of their acknowledged emotional charge.

We cannot say whether all families appreciated the flowers, but many were in touch with us afterwards. Some came to the hospital for a formal discussion of the psychological aspects of their experience, or to meet the staff again; others phoned or wrote to staff members. Most of them said explicitly that they appreciated the gesture and that the flowers made them feel that the medical team shared their pain.

The medical staff saw sending the flowers and writing the letter, and the opportunity to contact the family again, as a structured way to deal with their mourning. All the clinicians on our staff agreed to the procedure; they said that the opportunity to write to the family and express their sympathy was very helpful to them. Transferring experiences into words enables thoughts and feelings to be combined, generating a sense of resolution and reducing the negative feelings associated with the experience^{10,11}.

Various authors have suggested that highly scientific and technological treatments may lead to a more limited involvement or even a substantial disinterest of physicians when their patient dies¹²⁻¹⁵. In addition, health-care providers generally receive little or no training in how to cope with bereavement and doctors are rarely in the habit of writing letters of condolence^{16,17} or showing mourning families their sympathy by other means^{18,19}. Nurses and/or social workers provide families with some form of support^{20,21}, but no standardized and shared methods have been devised as yet for physicians coping with the loss of a patient.

Far from suggesting a scientific solution to the problem, this paper aims to draw attention to a complex problem and describe a simple idea that we use, hopefully contributing a little to improving the methods employed to deal with mourning the death of a patient, given that (at least in our opinion) this is hardly a problem to approach by conducting randomized tests on different ways to express sympathy.

Sending flowers is naturally not meant to be in lieu of individual physicians contacting families personally, wherever possible, to express their condolences with a telephone call, by writing a letter or attending the funeral – though sending flowers may be a better way to respect the wishes of families who prefer not to have any further direct contact with the doctors. Flowers can express a sense of emotional involvement without any need for direct contact, which may be painful in some cases.

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Study 2.6

Dying after cure: a case of suicide in an adolescent treated for cancer (*Submitted to Journal of Cancer Research and Therapeutic*)

Laura Veneroni, Andrea Ferrari, Maura Massimino, Carlo A. Clerici

Abstract

Although suicide among childhood cancer survivors is rare, there is still a significantly higher risk in this population than in healthy adolescents.

A 17-year-old girl cured of Burkitt lymphoma committed suicide after completing her treatment. She had never previously shown signs of psychological suffering and was in good general health.

This case made the operators wonder how this tragic possibility might be prevented. It is essential for the ongoing monitoring of the psychological and social suffering of young people during follow-up programs to be assured by a multidisciplinary team involved in the patient's global care.

Key words: suicide, adolescent, survivors, global care, psychosocial, prevention

Introduction

The care of adolescents with neoplastic diseases has to meet particular, not only medical, but also psychosocial needs.^[1] It is essential to provide support to helping them to adapt to disease and treatment without interfering with the development of an identity and independence.

Among the psychosocial risks to consider when it comes to adolescents with cancer there is the rare but dramatic risk of self-destructive behavior. This study reports the case of a 17-year-old Chinese girl committed suicide after the end of the treatment. Suicides and suicide attempts in adolescence have particular features that must be known to the medical, psychiatric and social support personnel so that they can take preventive action or provide early treatment wherever possible.

Case History

A 17-year-old Chinese girl committed suicide 5 months after successfully completing chemotherapy for Burkitt lymphoma at the Pediatric Oncology Department.

Between September 2011 and February 2012 received intravenous and intrathecal chemotherapy for four months, achieving the complete remission of the disease (initially localized only in the abdominal cavity). During the treatment period, the girl had never shown any signs of psychological suffering. Her family was nonetheless followed up by the psychosocial staff at our department, given the patient's particular social situation (her mother spoke no Italian and did not have a secure job; her father had died 3 years earlier). Economic support was provided and the territorial services took other action to help the mother find work, and support the girl's education.

In May 2012 (after completing her treatment), the girl was worried about the likelihood of her disease recurring, but these concerns were soon overcome. During the spring of 2012, she had enthusiastically attended various meetings as part of a project for adolescents implemented at our INT Pediatric Department (dedicated particularly to fashion).^[2]

In September, new problems relating to the renewal of the girl's residence permit (as she was about to turn 18) were overcome with the active involvement of our social workers in cooperation with the territorial services. The mother found a regular job and the girl enrolled at a hospitality management school and began working in a bar, with much personal satisfaction. The decision to commit suicide seems to have developed suddenly during this apparently happy period. The girl threw herself under a train.

After the suicide, the psychosocial staff tried to reconstruct the last days of the girl's life and seek possible reasons for her action by means of interviews (psychological autopsy).^[3] The girl's mother and cousin mentioned that the girl had a sentimental relationship with a Chinese boy, accessing her profile in QQ (an instant messaging program commonly used by the Chinese community), it

emerged that she had discovered a few days earlier that he was going out with another girl. A few hours before committing suicide she had written, “*I think about you but you wouldn’t want me if you knew about me*”. She had also written on the computer, “*My father called me last night and said he will accompany me*”.

Discussion

Although suicide is the third leading cause of death among teenagers, after accidents and neoplastic disease, little is known about the prevalence, correlates, or treatment of its immediate behavioral precursors (suicide ideation, plans, and attempts). An Italian study conducted on secondary school students reported that at least 20% of adolescents have suicidal fantasies. ^[4] A recent North American study on 6,483 healthy adolescents reported an estimated prevalence of suicide ideation, plans, and attempts of 12.1%, 4.0%, and 4.1%, respectively. ^[5] Adolescent suicide is only weakly linked to psychopathological conditions. Psychoanalytical tradition explains that suicidal fantasies can develop in the adolescent’s mind as part of the process that leads them to discover their own mortality. The decision to commit suicide is almost never sudden and it is not generally prompted by a traumatic event or depression. The suicide plan more frequently involves the adolescents’ relationships with themselves, when their sense of identity is jeopardized by perceived failures they consider intolerable (a bad mark at school, sentimental rejection, feeling ugly). Core elements in adolescent suicide are: secrecy; a lack of self-confidence and independence (from families or peers); and a sense of personal falsity. The decision to die may paradoxically be a way to put an end to the feeling of not existing, to draw attention to themselves, and also to punish others.

Although suicide among childhood cancer survivors is rare, there is still a significantly higher risk in this population than in healthy adolescents. ^{[6],[7],[8]} Suicide ideation has been associated with a diagnosis of primary brain cancer, depression, and poor health outcomes, including chronic conditions, pain, and poor global health ratings. ^[9]

Our patient’s suicide seems unrelated to physical problems (she was in good general health and she had no painful symptoms or neurological impairment). From the psychopathological standpoint, the only trait that had been identified concerned this young girl’s relational attitude, characterized by a constant demand for affection revealing almost regressive features. This form of adaptation is not unusual and was even functional while the girl was receiving treatment, since she had to place her trust in the medical staff. But when the girl was no longer in our care (and was left without the daily reassurance assured by the hospital environment), she should have returned to a normal life and regained her sense of independence, but may have been unable to do so, and this probably added to her uncertainty about the future.

In this particular case, some other issues may have contributed to the onset of her suicidal ideation, including: the fragility of her social and family support network; her father's death; cultural aspects relating to the young patient's ethnic origin. ^[10]

This story reinforces our conviction that it is essential for all the multidisciplinary team to be constantly on the lookout for any signs of psychic and social discomfort in our young patients as part of long-term follow-up programs for childhood cancer survivors. ^[11]

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LETTER TO THE EDITOR

“What Does Not Kill Me Makes Me Stronger”: Is it Always True?

To the Editor: The aim of our letter is to comment that resilience may be the result of patient's adaptation in some cases and not in many others. On one side, cancer in developmental age can have severe permanent consequences that can interfere with the adaptation process; on the other side, we believe that it is important to note that psycho-pathological criteria are not enough to assess patient's quality of life.

In his *Twilight of the Idols* Friedrich Nietzsche wrote, “What does not kill me makes me stronger,” meaning that individuals adapt to, and even benefit from, potentially harmful situations. The editorial by Masera et al. [1] discusses how remarkably young people adapt when they experience (and survive) neoplastic disease. The authors' comments help clinicians, patients and families to be optimistic about the chances of the disease not just being destructive, but also making patients go through a mental process that makes them stronger and more mature.

In some cases, patients do adapt amazingly well and become resilient, but there is no escaping the fact that treatments for cancer (especially solid tumors) in developmental age can have even severe permanent consequences (e.g., cognitive impairments in very young children given radiotherapy to the brain, major demolitive surgery involving the loss of a limb) that may make adaptation very difficult indeed.

Given the variety of possible outcomes for patients having to adapt to such a traumatic experience as cancer [2], assessing their quality of life on the strength of psychopathological criteria alone is not enough. The literature on severe psychological trauma, such as child abuse [3], shows that effects on the child's mind may go undetected (a “hidden epidemic [4]) if we are only looking for symptoms. Clinicians working with traumatized patients have pointed out the inadequacy of the Diagnostic and Statistical Manual (DSM)-IV criteria for diagnosing mental trauma in developmental age, partly because the most insidious effects may trigger dissociative behavior impossible to assign to clear-cut diagnostic categories. Clinical experience in pediatric oncology shows that trauma can cause psychopathological conditions in survivors, as well as affecting their neurobiological systems, and leading to biomedical diseases and social malfunctioning.

For psychological trauma to be treated adequately, it must first be diagnosed. Young survivors of cancer need to be assessed in terms of their vulnerability and mental resources. The recently published DSM-V [5] acknowledges the need for broader criteria for defining psychopathology: it attempts to absorb the complexity of the processes involved in adapting to trauma by focusing on defense mechanisms, changing the criteria for assessing personality disorders, combining a categorical model with a dimensional model for assessing pathological traits and levels of functional impairment as a continuum with various levels of severity, and classifying “Trauma- and stressor-related disorders” separately from anxiety disorders. How this effort by the American Psychiatric Association [5] can be applied to pediatric oncology remains to be seen, however.

Modern approaches to trauma show that special treatment methods are needed, including psychotherapy (or psychopharma-

logical solutions), but also helping patients to plan for the future. In pediatric oncology, attention has always been paid to the patient's overall care and the relatively low incidence of psychopathologies in young cancer survivors is probably thanks partly to their natural resilience, and partly to the extensive efforts made to provide these patients with both top-quality health care and psychological support, though there is never any guarantee of such efforts proving successful.

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CHAPTER 3

TRANSLATING SCIENTIFIC KNOWLEDGE INTO AN IMPROVED DOCTOR-TO-PATIENT COMMUNICATION

Video sharing sites have become increasingly important in recent years in providing information and orienting people's decisions relating to their health.

New technologies are nowadays an innovative form of worldwide communication. Unlike traditional videos, these resources stimulate the interaction among users and so they have become a sort of a hybrid between public and personal tools. Especially adolescents use Internet to obtain information on pediatric oncological diseases. The potential of these new tools, however, implies that all the traditional institutions dedicated to the research and education acquire the skill to use them. The aim of this chapter is presenting the researches in this area. In particular:

- In **Study 3.1** *Videos on rhabdomyosarcoma on YouTube: an example of the availability of information on pediatric tumors on the web* (2012). The availability and type of video content on YouTube relating to a particular set of pediatric neoplastic diseases, i.e. rhabdomyosarcoma and soft tissue sarcoma is described. The observations indicate that video sharing sites have become tools – like blogs and social media - that make it easier for patients to describe their impressions and experiences of the disease and this could help other patients devise strategies for coping with the disease, providing them with support and opportunities for sharing information and resources.
- **Study 3.2:** *Online videos in the health field. Novel technologies for physicians and patients* (2012). The aim of this study is to review the literature on the use of online videos in the health field. Like in other parts of the world, in Italy internet is an increasingly used source of diseases-related informations, used both by health professionals and by the patients. In recent years, besides the most common search engines, sanitary informations contained in video sharing sites have gained an increased influence, either in the search and in the choice phases.
- **Study 3.3:** *Pros and cons of using facebook in pediatric oncology* (submitted). Internet and social networks like Facebook have changed the way people communicate, especially young people. They may be hugely useful for adolescent cancer patients, for instance. Disease severely limits adolescents' school attendance and time spent with peers, and risks isolating them socially. Facebook can help young people who are ill to keep in touch with friends. Facebook makes it easier for such adolescents to make friends with other patients and to stay in touch with people outside the hospital. This is a good thing, but carries inherent risks too. This study emphasizes the importance of the use of Facebook in patients with cancer, and in adolescents in particular.

- **Study 3.4** The innovative experience ongoing at the INT of using on line videos to inform the patient about the pathologies and their treatments is described.

Videos on Rhabdomyosarcoma on YouTube: an Example of the Availability of Information on Pediatric Tumors on the Web

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Purpose: Video-sharing sites have become increasingly important in recent years in providing information and orienting people's decisions relating to their health. Adolescents and their families use internet to obtain information on pediatric oncological diseases.

Methods: We describe the availability and type of video content and origin on YouTube relating to a particular set of pediatric neoplastic diseases, that is, rhabdomyosarcoma and soft-tissue sarcoma.

Results: A total of 149 videos were analyzed: 25 were considered as useful; only 1 video was produced by a doctor, whereas 82.5% were produced by patients or their families, in many cases for commemorating the death of a child.

Conclusions: Our observations indicate that video-sharing sites have become tools, such as blogs and social media, that make it easier for patients to describe their impressions and experiences of the disease, and this could help other patients devise strategies for coping with the disease, providing them with support and opportunities for sharing information and resources.

Key Words: rhabdomyosarcoma, video sharing, internet, YouTube, health information

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Pediatric tumors are uncommon events. The rarity of childhood cancer, the variability of their nature, their location, and their manifestations may induce, in parents and people caring for children and adolescents, a state of alarmed surprise and deep anguish. This state can push parents, but also young patients themselves, in search of information about the disease, the treatment options, and prognosis. How adolescents and their families use internet specifically to obtain information on pediatric oncological diseases and their treatment has recently been the object of investigation.^{1,2} In addition to the usual search engines, video-sharing sites have also become increasingly important in recent years in providing information and orienting people's decisions relating to their health. The best-known site in this category is YouTube, which is dedicated to

circulating videos on the web: created in 2005, the site hosts amateur videos recorded by users, and musical and television video clips. Forty-eight hours of video footage are uploaded every minute, and the site is visited by 3 million people every day. For the adolescent age bracket, this site has come to occupy a space alongside television, partially replacing the latter. The purpose of the present study was to investigate the availability and type of video content on YouTube relating to a particular set of pediatric neoplastic diseases, that is, rhabdomyosarcoma and soft-tissue sarcoma. Rhabdomyosarcoma and soft-tissue sarcomas have been chosen as the subject of our research for the special expertise in this field by the authors, but also because it represents a good example of a rare neoplastic disease that can also affect adolescents,³ an age-group representing one of the major users of the internet.

MATERIALS AND METHODS

The keywords "pediatric soft-tissue sarcomas," "rhabdomyosarcoma," and "soft-tissue sarcoma in children" were input on the site <http://www.youtube.com>. Our search, conducted on August 12, 2011, resulted in the identification of 352 video clips on YouTube. In the first phase, the videos were viewed and selected by 2 independent researchers, who arbitrarily classified them according to their origin and the reliability of their content. We initially excluded those videos judged as nonpertinent by both the researchers on the basis of the content of the commentary text, because it was not clearly related to oncologic subjects. In case of a disagreement (not occurred), the evaluation of a third researcher was foreseen. Those videos that were online from > 1 month and had received < 100 visits were arbitrarily excluded because of their potential low impact. After this first selection, 149 video clips were considered by the researchers for further analysis.

The videos were classified for their origin as follows: (1) patients or relatives; (2) television; (3) government agencies; (4) physicians; (5) universities; (6) not-for-profit organizations; (7) advertising; and (8) public-health websites. Fourteen types of content were expected: (a) general information on the disease; (b) risk factors; (c) prevention; (d) diagnosis; (e) conventional therapies; (f) complementary and alternative therapies; (g) psychological aspects; (h) prognosis; (i) sequelae; (j) bereavement; (k) research; (l) appeals for economic aid; (m) information on associations; and (n) health-related advertising. A video could refer to > 1 content. Videos were classified as "useful" (if the video contained accurate medical information on the disease and its treatment), "misleading" (if it contained erroneous or unscientific information on the disease and its treatment),

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“personal experience” (if it described individual experiences relating to rhabdomyosarcoma patients or members of their families), and “not pertinent” (if no information on rhabdomyosarcoma or soft-tissue sarcomas was provided). Details were recorded on the total number of visits, the duration of the footage, the professional or amateur nature of the video, and uploading data. This information was input in a spreadsheet for analysis.

RESULTS

Of the 149 videos included in the study, 138 were in English, 5 in Spanish, 3 in Italian, and 3 in other languages. The resulting set of video clips had been viewed 4,067,101 times in all.

The table shows the data obtained on the origin of the video, the nature of the production, and its content (Table 1).

With respect to the reliability of the content, the 2 independent researchers defined 25 videos as useful, but only 1 as really complete and adequate (ie, the one produced by a physician); 1 was considered misleading (ie, a video focusing on acne, where the subject of rhabdomyosarcoma and soft-tissue sarcomas was considered just for the differential diagnosis with dermatological diseases), and none was considered as not pertinent; 123 videos were personal experiences.

Of the 149 videos, 103 related mainly or only to rhabdomyosarcoma, 18 to soft-tissue sarcomas other than rhabdomyosarcoma, and 28 to both.

With respect to the origin, the majority of the videos (82.5%) were produced by patients or members of their families (123). The target of most of them was the general public; there was only 1 video produced by a physician and intended for other physicians. Most of the videos (129; 86.5%) were amateur productions; only 20 had been prepared using professional criteria (12 of these were clips from television programs). The videos lasted a mean 4'16" (range, 16" to 14'28"). The videos had been viewed from 100 to 3,506,460 times, but it is worth noting that the most often viewed video was that on the topic of acne, in which the term rhabdomyosarcoma had been included together

with a large number of other keywords. The second most often seen video was an amateur clip in memory of a patient who had died (141,953 views). Only 10 videos provided general information about the disease concerned (which was accurate in 9 of them, although somewhat superficial), and only 11 dealt with its treatment (9 of them accurately). None of the videos discussed complementary therapies. Three contained appeals for economic support for a given patient, and 23 urged viewers to support an association. As many as 94 of the videos were dedicated to commemorating ≥ 1 patients who had died of rhabdomyosarcoma.

DISCUSSION

Although the situation may be different for other pediatric tumors, we believe that rhabdomyosarcoma represents a good example to analyze the status and the potentiality of YouTube.

Generally, online videos can be a more effective form of communication than written texts, thanks also to the immediacy of the spoken language. In addition, video-sharing sites have become tools, such as blogs and social media, that make it easier for patients to describe their impressions and experiences of the disease.⁴ If patients cured of neoplastic diseases tell their stories,⁵ this could help other patients devise strategies for coping with the disease from the practical and emotional standpoints, providing them with support and opportunities for sharing information and resources.

Although several studies have emphasized the risk of antiscientific information being circulated in such videos and misleading patients, none of the videos examined contained important elements recommending against medical treatment or in favor of alternative therapies. Instead, our search identified a relative shortage of video footage on YouTube containing information about the medical aspects of these diseases and their treatment. The videos considered “useful” that dealt with medical issues had been viewed 18,442 times altogether, as opposed to 531,587 views of videos telling a patient’s story or commemorating a patient’s death. The first useful video came in

TABLE 1. Characteristics of Videos Identified

Origin of Clips	Patients or Relatives (n = 123)*	Television (n = 13)*	Physician (n = 4)*	Universities (n = 1)*	No Profit (n = 5)*	Public-Health Websites (n = 3)*	Total (n = 149)*
Information	2	4	3	0	0	1	10
Risk factors	0	2	0	0	0	0	2
Prevention	0	0	0	0	0	0	0
Diagnosis	2	3	2	1	0	1	9
Conventional therapy	3	3	3	1	0	1	11
Psychological aspects	0	0	0	0	0	0	0
Complementary and alternative treatments	0	0	0	0	0	0	0
Prognosis	0	1	1	1	0	0	3
Bereavement	92	1	0	0	1	0	94
Research	4	3	1	0	0	0	8
Appeal for economic aid	3	0	0	0	0	0	3
Associations	17	0	0	0	6	0	23
Sequelae	1	0	0	0	0	0	1
Health-related advertising	1	0	0	0	0	0	1

*Number of clips uploaded.

18th place in terms of the number of views, preceded by 17 videos dedicated to commemorating patients. In the case of rhabdomyosarcoma, it would therefore be useful for clinicians to know what impact distributing this type of content might have on patients, and particularly on adolescents seeking information about the disease by surfing the web and YouTube. The term “rhabdomyosarcoma” was associated with more videos about patients who died than about cases who were cured. Among the aspects that are probably worth supporting and facilitating, it would consequently seem useful to produce informative videos that explain the various issues relating to these diseases.

Using modern communication technologies is no longer just a game. Online video sites such as YouTube are innovative forms of mass communication. Unlike conventional videos, these resources stimulate an interaction between users, thanks to the opportunity to vote a video for instance, to add comments, and to point out interesting videos using social media (Facebook, Twitter, Blogger, etc.). They thus become hybrid means of communication, between public channels and personal tools. However, the potential of these new instruments is such that the agencies conventionally dedicated to research and education needs to learn to use these new media to best effect. It is important

to update the traditional concepts of communication and information design in order not to neglect the opportunities afforded by these new technologies.

ACKNOWLEDGMENT

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Video online e medicina: nuove tecnologie per i clinici e i pazienti

Carlo Alfredo Clerici^{1,2}, Laura Veneroni¹, Andrea Ferrari², Marco Carraro³

Riassunto. Internet è una fonte utilizzata sempre più spesso, anche in Italia, sia dai professionisti della salute, sia dai pazienti, per ottenere informazioni sanitarie. Accanto ai comuni motori di ricerca, i siti di video sharing hanno acquisito da qualche anno un crescente rilievo nell'orientare l'informazione e le scelte in materia di salute. Obiettivo di questo lavoro è la revisione della letteratura dedicata all'impiego di video online in ambito sanitario. Sono stati inclusi studi sperimentali, rassegne e report sull'argomento pubblicati da riviste in lingua inglese dal 2000 ad oggi. Dalla ricerca sono stati identificati 179 articoli di cui 43 ritenuti pertinenti. È possibile suddividere schematicamente gli articoli considerati sulla base del tema trattato: video per informazione sanitaria/patient education e video per uso didattico; altri usi del video. Possibilità di impiego e aspetti critici sono descritti e sono formulate alcune indicazioni e raccomandazioni per la preparazione di materiali informativi sanitari in formato video, progettati per la diffusione via web. L'impiego di alcune tecnologie di comunicazione è oggi una forma innovativa di comunicazione di massa. A differenza dei video tradizionali queste risorse stimolano l'interazione fra utenti e costituiscono così strumenti di comunicazione ibridi fra canali pubblici e strumenti personali. La potenzialità di questi nuovi strumenti richiede però che le tradizionali agenzie dedicate alla ricerca e all'istruzione acquisiscano la capacità di utilizzarli.

Parole chiave. Internet, online, patient education, video, YouTube.

Introduzione

Non so una cosa; cerchiamola su Internet. Questa è una frase ricorrente. Ma quali sono i problemi se la "cosa" è un argomento che riguarda la salute o le cure?

Internet è una fonte utilizzata in modo crescente, anche in Italia sia dai professionisti della salute¹, sia dai pazienti², per ottenere informazioni sanitarie. Accanto ai comuni motori di ricerca, hanno acquisito da qualche anno un crescente rilievo nel-

Online videos in the health field. Novel technologies for physicians and patients.

Summary. Like in other parts of the world, in Italy internet is an increasingly used source of diseases-related informations, used both by health professionals and by the patients. In recent years, besides the most common search engines, sanitary informations contained in video sharing sites have gained an increased influence, either in the search and in the choice phases. The aim of the present paper is to review the literature on the use of online videos in the health field. Experimental studies, reviews, and reports published by English magazines and scientific journals on this subject since the year 2000 have been included. 179 articles were identified, but only 43 were considered as relevant.

The articles are schematically divided into three major categories according to their subject: videos for health information/patient education, videos for educational use and other uses of the video. We describe the critical aspects of the different video types and suggestions for their use, as well as some guidelines and hints for the preparation of new health information material in video format, specifically designed for spreading via the web.

New technologies are nowadays an innovative form of worldwide communication. Unlike traditional videos, these resources stimulate the interaction among users and so they have become a sort of a hybrid between public and personal tools. The potential of these new tools, however, implies that all the traditional institutions dedicated to the research and education acquire the skill to use them.

Key words. Internet, online, patient education, video, YouTube.

l'orientare l'informazione e le scelte in materia di salute, i siti di video sharing. Il più noto in questa categoria è YouTube, dedicato alla diffusione di video via web. Creato nel 2005, ospita video amatoriali realizzati dagli utenti, oltre a video clip musicali e video televisivi. Ogni minuto sono caricati in questo sito 48 ore di video che ogni giorno è visitato da 3 milioni di persone; numeri più contenuti ma comunque non trascurabili riguardano altri siti di video sharing come Vimeo, Metacafe, Dailymotion e numerosi altri. Questa revisione della letteratura

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è dedicata all'impiego di video online in ambito sanitario, con l'obiettivo di identificare aspetti critici e possibilità di impiego da parte dei clinici.

Materiali e metodi

La letteratura è stata raccolta mediante le banche dati online Medline, Embase, Cochrane Library e PsychINFO. Sono stati utilizzati i seguenti termini di ricerca variamente combinati: video online, Internet, YouTube, Vimeo, Metacafe, social network, movie. Sono stati incluse studi sperimentali, rassegne, e report pubblicati da riviste in lingua inglese dal 2000 ad oggi. Sono state escluse dallo studio articoli duplicati, lettere e contributi narrativi che non riportano esperienze sperimentali.

Analisi dei dati

Dalla ricerca sono stati identificati 179 articoli di cui 43 ritenuti pertinenti. È possibile suddividere schematicamente gli articoli considerati nei seguenti temi: video per informazione sanitaria/patient education; video per uso didattico; altri usi del video (per es., per divulgazione dei risultati della ricerca scientifica).

Discussione

VIDEO PER INFORMAZIONE SANITARIA E PATIENT EDUCATION

Studi sulla ricerca via web mostrano come siti a carattere enciclopedico o comunque connotati da un approccio non specifico siano preferiti anche a siti tematici o a portali esplicitamente dedicati all'informazione sanitaria³. Tra l'altro, i motori di ricerca generalisti sono lo strumento principale che in molti casi media l'accesso alle riviste scientifiche peer-reviewed da parte dei medici⁴.

Mancano studi specifici sulla fruizione di video online su temi sanitari; in particolare mancano studi su come le persone formulino le ricerche, come selezionino i risultati e come li considerino attendibili.

In ogni caso l'impiego dei video via web per l'educazione di pazienti è stato di recente sperimentato in diversi ambiti⁵⁻⁷. In alcuni contesti è riferito come il video abbia un valore istruttivo superiore a spiegazioni solo verbali. Un esempio riguarda il riconoscimento di alcune condizioni patologiche come gli spasmi infantili⁵. Rispetto a questo disturbo è stato evidenziato come i video possano facilitare la diagnosi, educare i genitori a ricorrere ad un aiuto medico e identificare i progressi dei pazienti. Analoga utilità rispetto alla diagnosi precoce è stata rilevata per i video online sul melanoma⁸⁻¹⁰. Altre ricerche hanno mostrato il valore dei video come fonte di informazioni in malattie croniche come l'epilessia¹¹ e la sclerosi multipla¹², nella calcolosi renale¹³ o nelle malattie infettive^{7,14}.

La possibilità di accesso anonimo alle risorse offerte dalla rete può facilitare l'informazione di quei pazienti che sarebbero riluttanti ad accedere di persona ai servizi sanitari per la delicatezza di alcune

tematiche, come nel caso del counselling preventivo per l'HIV^{15,16}. Sono in crescita i contenuti realizzati dai pazienti¹². I siti di video sharing costituiscono insieme ai blog e ai social media, strumenti che facilitano la trasmissione delle testimonianze dei pazienti rispetto alla propria esperienza di malattia. Un fenomeno di particolare interesse riguarda ad esempio la testimonianza dei pazienti guariti da neoplasie¹⁷. Video di questo genere possono offrire agli altri pazienti esempi di strategie per affrontare la malattia dal punto di vista pratico ed emotivo, fornendo supporto e possibilità di condivisione di informazioni e risorse (tabella 1).

Tabella 1. Siti di video sharing.

	Data di creazione	N° video	Video visti al giorno
Dailymotion	2005	> 10.000.000	> 60.000.000
Metacafe	2003	17.000.000	> 17.000.000
Vimeo	2004	> 1.000.000	1.000.000
Youtube	2005	> 64.000.000	1.200.000.000

Una caratteristica peculiare di Internet è la velocità di diffusione delle notizie rispetto a problemi emergenti, come è stato nel caso dell'epidemia di influenza H1N1⁷.

È rilevato come i video abbiano particolare impatto su quelle fasce di popolazione che utilizzano intensivamente la rete, non abituati tuttavia a consultare risorse specificamente concepite per il personale sanitario come PubMed. È il caso ad esempio degli adolescenti abituati a ricorrere ai social media per ottenere informazioni, ad esempio in merito alle cure ortodontiche¹⁸.

I video in rete permettono di fornire informazioni ai pazienti^{19,20} e di attuare educazione fra pari^{21,22}.

L'educazione dei pazienti è un fattore importante correlato alla loro soddisfazione che richiede però ampia disponibilità di tempo da parte dei clinici. L'impiego di video a cui rimandare durante brevi interventi di counseling permetterebbe un risparmio di tempo sia per i clinici sia per i pazienti²³.

Esperienze favorevoli sull'uso di video preparati da clinici o organizzazioni sanitarie sono state condotte su alcuni ambiti tematici, ad esempio per motivare all'uso di protezioni solari²⁴, a gestire la dermatite atopica²⁵. Anche se l'uso dei video è in crescita, si registra ancora una carenza di video appositamente predisposti, con criteri scientifici, da enti accreditati per entrare nel circuito dei siti di video sharing utilizzati dalla popolazione generale. Le informazioni che la popolazione generale può ottenere dai video ospitati dai siti di video sharing presentano quindi vari limiti. Il primo riguarda l'attendibilità delle informazioni disponibili in generale sul web. Alcune ricerche hanno indagato la

validità dei video informativi su YouTube riferiti ad alcuni contesti di patologia, come le neoplasie della prostata²⁶, alla calcolosi renale²⁷ e alla disassuefazione da fumo²⁸, evidenziando, salvo eccezioni, una generale inadeguatezza.

La qualità delle informazioni fornite da YouTube, anche in contesti preventivi, è stata descritta come problematica, ad esempio rispetto all'impiego dei lettini abbronzanti²⁹. Uno studio ha descritto la qualità migliorabile dei video in rete dedicati alla rianimazione cardiopolmonare³⁰.

I siti web non sono generalmente peer-reviewed, citano raramente una bibliografia³¹ e possono presentare opinioni come se fossero dati scientifici. Gli autori e le loro qualifiche possono non essere ben riconoscibili. Alcuni argomenti presentano una elevata presenza di video caratterizzati da parte di tesi antiscientifiche e disinformative, come ad esempio posizioni contrarie alle vaccinazioni^{14,20} a cui i clinici devono essere pronti a rispondere.

Un esempio particolarmente evidente riguardo all'attendibilità delle informazioni in rete e al rischio di diffusione di messaggi distorti riguarda la psichiatria. A titolo aneddotico riportiamo come una ricognizione su YouTube condotta dagli autori usando la parola chiave "psichiatria" (8 agosto 2011) abbia ottenuto come risultato, sui 10 video nella prima pagina, 8 video con contenuti allarmistici o contrari ai metodi scientifici di cura (per lo più traduzioni di video statunitensi).

Internet è stata segnalata in più ambiti come fonte di informazioni potenzialmente pericolose. La divulgazione senza filtri critici di istruzioni su tecniche diagnostiche e terapeutiche può essere pericolosa. È ad esempio segnalata la diffusione di video su tecniche di auto chirurgia³² che trovano applicazione in particolare in quei contesti in cui non esiste un Servizio Sanitario pubblico³³.

È stato segnalato in più contesti come l'accesso a informazioni online da parte dei pazienti si accompagni ad una maggiore informazione e ad un incremento delle aspettative, mutando il ruolo di questi da riceventi passivi a consumatori attivi di informazioni³⁴.

Anche per questo è richiesto oggi ai medici il compito di orientare i propri pazienti al corretto e selettivo uso della rete.

I programmi di videosharing hanno affiancato, e in parte sostituito, la fruizione della televisione tradizionale, creando peraltro una sorta di zona franca rispetto ai controlli, tanto che YouTube è stato utilizzato come veicolo per messaggi pubblicitari di generi strettamente regolamentati come il tabacco³⁵. Anche in conseguenza di ciò è in crescita il numero di riviste scientifiche e di istituzioni, che hanno propri canali YouTube³⁶.

VIDEO PER LA DIDATTICA

I video hanno da tempo trovato impiego in ambito didattico anche per un importante mutamento che ha portato a considerare gli studenti consuma-

tori di prodotti educativi, con una forte domanda di modelli d'insegnamento più interattivi e stimolanti rispetto a quelli tradizionali. La tradizione del documentario didattico risale ai primi impieghi della pellicola cinematografica e ha avuto una fase di sviluppo con i programmi teledidattici costituiti da lezioni frontali, fruibili per mezzo dei canali televisivi mediante videoregistrazione. L'impiego del web consente oggi di fruire dei video in qualsiasi momento, con maggiore semplicità.

Ricerche sperimentali sull'efficacia degli strumenti di insegnamento hanno da anni evidenziato come l'utilizzo di strumenti multimediali porti ad un apprendimento più efficace rispetto alle lezioni tradizionali³⁷.

Il valore delle tecnologie multimediali per la formazione degli studenti di discipline sanitarie è stato più volte segnalato nella letteratura scientifica³⁸⁻⁴¹, anche per l'insegnamento delle discipline chirurgiche^{42,43}.

Occorre anche ricordare come la preparazione dei video possa costituire per la sua stessa natura di lavoro di équipe, un addestramento al lavoro in gruppo multidisciplinare, tipico di numerose professioni sanitarie.

È stato anche segnalato come l'impiego didattico di video online si accompagni a un incremento della sensazione di autoefficacia³⁸. In particolare è riportato come l'uso di YouTube nell'insegnamento delle materie infermieristiche favorisca l'attenzione degli studenti, stimoli la partecipazione critica e ne faciliti l'apprendimento profondo⁴⁴.

Anche se l'ultima generazione di studenti è "nativa digitale" e circondata di strumenti per la navigazione nel web, è necessario che gli studenti siano formati a interagire con questi media con senso critico⁴⁵ e preparati all'uso che ne faranno i loro pazienti.

ALTRI USI DEI VIDEO ONLINE

Un ultimo ambito di applicazioni sanitarie dei video online riguarda la comunicazione scientifica. Il video offre la possibilità di condividere rapidamente aggiornamenti sulle ricerche in corso, può facilitare la costituzione di team di ricerca virtuali e multidisciplinari tra ricercatori con sedi geograficamente lontane e permette di mantenere un aggiornamento dell'opinione pubblica e delle comunità di finanziatori sull'andamento delle attività di ricerca.

Un numero crescente di pubblicazioni scientifiche, fra cui JAMA e il New England Journal of Medicine, prevede il link a contenuti multimediali che possono offrire la possibilità di illustrare in video procedure complesse clinico-diagnostiche⁴⁶. Fra le esperienze più significative va ricordata quella nata nel 2006 del Journal of Visualized Experiments" (www.jove.com), in cui i ricercatori illustrano gli esperimenti tramite video, offrendo una più chiara fruibilità ai lettori e al grande pubblico.

Fra i siti da segnalare per l'impiego di video online per la didattica al personale sanitario ricordiamo www.PathLab.org, dedicato all'anatomia patologica e www.WebSurg.com alle tecniche chirurgiche (a pagamento).

Un video permette anche di dare visibilità e circolazione a lavori scientifici pubblicati in formato tradizionale, aumentando le possibilità di citazione, un parametro oggi spesso usato a fini concorsuali per stabilire il valore della produzione scientifica di un clinico. Un esempio di questo impiego sono i video-abstract pubblicati sul www.scivee.tv.

Un ultimo ambito in cui si segnalano esperienze innovative riguarda l'uso di video su YouTube come fonte di materiale osservativo e sperimentale. Un lavoro dedicato alle fratture delle arti inferiori è stato ad esempio basato sullo studio di video di incidenti reperiti in rete⁴⁷.

CARATTERISTICHE DI UN VIDEO SU TEMI SANITARI

Questa rassegna della letteratura permette di formulare alcune indicazioni e raccomandazioni per la preparazione di video sanitari da divulgare in rete (tabella 2). Le esperienze e i modelli di audiovisivi impiegati in passato, per lo più di provenienza televisiva, sono utili solo in parte. Innanzitutto alcuni aspetti sono di carattere etico e rientrano nelle generali regole a cui deve uniformarsi la comunicazione sanitaria.

Nel caso di video destinati all'informazione dei pazienti è opportuno che sia specificato che in nessun caso i video possono sostituire la consultazione di un medico.

Deve sempre essere rispettata la riservatezza come previsto dal codice deontologico e dalla normativa sulla privacy. Va inserito un richiamo alla necessità di firmare i video e di corredare le firme con le qualifiche degli autori (affiliazioni ed e-mail).

Tabella 2. Criteri per la realizzazione di un video sanitario online.

Rispetto privacy e consenso
Evitare l'uso di sequenze recitate se non si dispone di attori professionisti
Brevità (durata preferibilmente minore di 3 minuti)
Semplicità visiva
Variabilità visiva
Monitorare periodicamente la validità del video e, se necessario, aggiornarlo o rimuoverlo
Inserire indicazione degli autori, con qualifiche, affiliazioni ed e-mail per contatti
Classificare il contenuto con tag univoche e precise per un migliore reperimento tramite i motori di ricerca

Si pone il problema se per i video didattici sia più opportuno usare riprese di scene reali in cui compaiono pazienti o usare ricostruzioni con attori. Il tema ha importanti indicazioni e controindicazioni che meritano approfondimenti deontologici e tecnici, anche rispetto a come ricostruire la realtà e quale realtà si debba ricostruire, ad esempio nel contesto della psicoterapia.

Altre considerazioni sono tecniche e riguardano le peculiarità dei video destinati a essere fruiti online, spesso su monitor di dimensioni più limitate rispetto a quelli televisivi, se non addirittura nei display degli smartphone.

Il tempo medio dell'attenzione per un contenuto online è molto breve prima di cliccare un contenuto successivo. Esperienze di impiego commerciale dei video invitano a utilizzare video di durata non superiore ai tre minuti⁴⁸.

Per le caratteristiche di fruizione, spesso mediante piccoli schermi, è opportuno evitare immagini complesse, assicurando mediante ripresa e montaggio di ottenere immagini non monotone, con una buona variabilità visiva. Esiste la necessità di monitorare periodicamente l'aggiornamento e la validità dei contenuti video pubblicati, procedendo se necessario ad un loro aggiornamento o rimozione.

Video appositamente realizzati e ospitati, se opportuno, in sezioni ad accesso riservato ai sanitari possono costituire un utile materiale didattico su procedure mediche o chirurgiche, sull'esempio di quanto in uso crescente in alcune riviste scientifiche internazionali.

È importante che i video, in particolare se destinati a una fruizione attraverso i motori di ricerca convenzionali, siano adeguatamente classificati tramite tag univoche e precise, descrittive del contenuto.

Conclusioni

L'impiego di alcune tecnologie di comunicazione è oggi qualcosa di più di un "gioco da ragazzi". I siti di video online, fra cui YouTube, costituiscono una forma innovativa di comunicazione di massa. A differenza dei video tradizionali queste risorse stimolano l'interazione fra utenti, grazie ad esempio alla possibilità di votare i video visti, inserire commenti, segnalare i video interessanti tramite i social media (Facebook, Twitter, Blogger, ecc.), costituendo così strumenti di comunicazione ibridi fra canali pubblici e strumenti personali. Le potenzialità di questi nuovi strumenti richiede però che le tradizionali agenzie dedicate alla clinica, alla ricerca e all'istruzione universitaria acquisiscano capacità di utilizzare questi nuovi mezzi.

È importante che la concezione tradizionale (e datata) di progettare la comunicazione e l'informazione non trascuri la sperimentazione di queste nuove tecnologie, con il rischio di lasciare la loro gestione soltanto a singoli, più o meno informati, e ad enti a fini di lucro.

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Study 3.3

Letter to Editor

PROS AND CONS OF USING FACEBOOK IN PEDIATRIC ONCOLOGY (*submitted to Pediatric Hematology Oncology Journal*)

Carlo Alfredo Clerici, Maura Massimino, Laura Veneroni, Andrea Ferrari

Keywords: Facebook, social networks, adolescents, cancer, pediatric oncology

Internet and social networks like Facebook have changed the way people communicate, especially young people. They may also change relations between health professionals and users, possibly making it difficult to keep private and professional lives separate, but they may be hugely useful for adolescent cancer patients, for instance. Facebook is a powerful tool and we should learn how best to exploit it. Disease severely limits adolescents' school attendance and time spent with peers, and risks isolating them socially. Facebook can help young people who are ill to keep in touch with friends and schoolmates, talk about their life (and maybe about their health), and hear about life outside the hospital. Ensuring this continuity with their own social world is crucially important, given the huge psychological and developmental significance of social relations at this age.

Facebook makes it easier for such adolescents to make friends with other patients and to stay in touch with people outside the hospital. This is a good thing, but carries inherent risks too: our patients may exchange information about the (possibly unfavorable) clinical course of a disease, also misunderstanding about therapies effects programs, or announce a patient's death. Disease and death are no longer private, but public events, and there is generally no way to filter such information, which is often shared virtually in real time amongst more or less interested parties. News circulated in this way may contrast with the legitimate need for some patients not to know about the unfavorable others' outcomes - also to avoid the risk of identification ("I'll be next"). Then there is the risk of patients or families using Facebook to obtain clinical opinions or treatment recommendations outside the appropriate institutional setting. Then there is the issue of clinicians' privacy: having a window open onto health operators' private worlds can create a false sense of intimacy and weaken their role.

As part of our *Youth Project* (scheme for adolescent patients with projects relating to fashion, music and sports, activities designed to help patients adapt to their disease and treatment) [1], we also have a Facebook platform for exchanges between adolescent patients and dedicated operators (physicians, social workers, psychologists, teachers, activity organizers). Facebook has proved a useful practical tool in some projects, as well as helping patients feel they are part of a group of

young people with similar problems. The operators have found the experience interesting, but not easy to manage. In addition to facilitating communications and participation in our projects, Facebook has been useful in understanding the circulation of misleading or inappropriate information, or identifying adolescents' psychological issues, enabling clinicians to take corrective action (e.g. personal interviews or discussion groups). In short, despite the related risks and lack of rules to help us manage it, we feel that Facebook could be a valuable asset in pediatric oncology. Operators should learn to use their patients' communication systems and languages, though always bearing in mind that virtual media should be used to sustain, not to supplant face-to-face personal interactions.

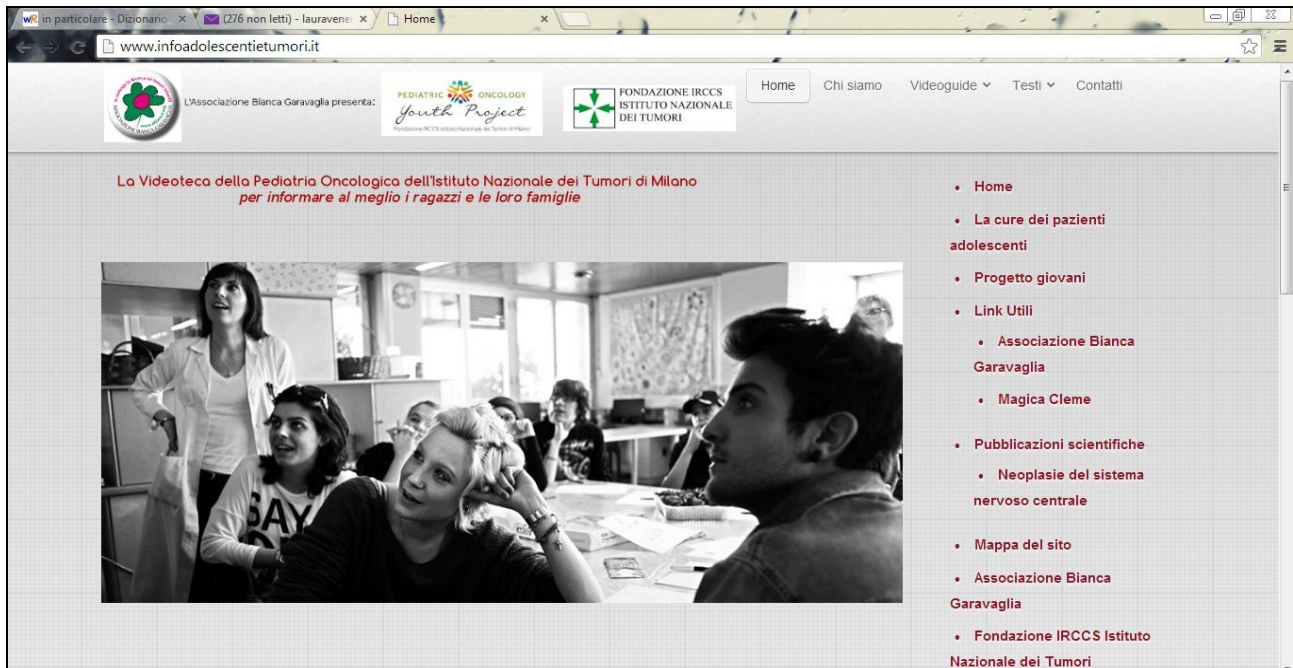
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Study 3.4

Provide better information to promote better healing: innovative experiences of communications at the Istituto Nazionale Tumori of Milan: the online video library and the web site of the Youth Project

Figure 3.1. Mainscreen of the website www.infoadolescentietumori.it



The website www.infoadolescentietumori.it (Fig. 3.1) created by the Pediatrics Oncology National Cancer Institute of Milan, contains an informational series of videos about the diagnosis and the treatment of developmental-age cancers. These videos have been generated by the medical specialists who devote their professional lives for the treatment of this type of disease. The aim is to benefit, in particular, adolescent or very young patients, their family, and everybody else seeking simple, clear, and reliable informations. The need for a widespread website arises from an insufficient awareness, existing not only among common people but also in the medical world, of cancers in adolescents, and of pathways leading to a correct and timely diagnosis, which constitutes the best possible care. Teenagers often reach hospital Institutions being already sick, and with consistent diagnostic delays, even higher than the one occurring for children. The ability to communicate with adolescents, by using familiar information technologies, is the actual purpose of this video library. In fact we believe that, in addition to providing the patients with the best available treatments, the physicians must improve a consistent flow of information, in order to raise awareness of the importance of early diagnosis, thereby facilitating the use itself of a suitable

treatment. Moreover, the necessity to generate this website also arises from evidence indicating that the majority of internet content, concerning the pediatric oncology, leads to great misunderstanding and confusion. The video library currently includes 12 tutorial videos (Fig. 3.2-4) , concerning some disease and important aspects of their treatment, such as clinical or spiritual support. All these short movies have been directed in person by medical specialist deriving from that particular field. The aim of the whole project is to create at least one video for each of the different disease currently treated within our Pediatric Institution.

The website www.ilprogettogiovani.it (figure 3.5) contains instead the information about the Young Project (see chapter IV).

Figure 3.2 Drop-down menù of the website: www.infoadolescentietumori.it

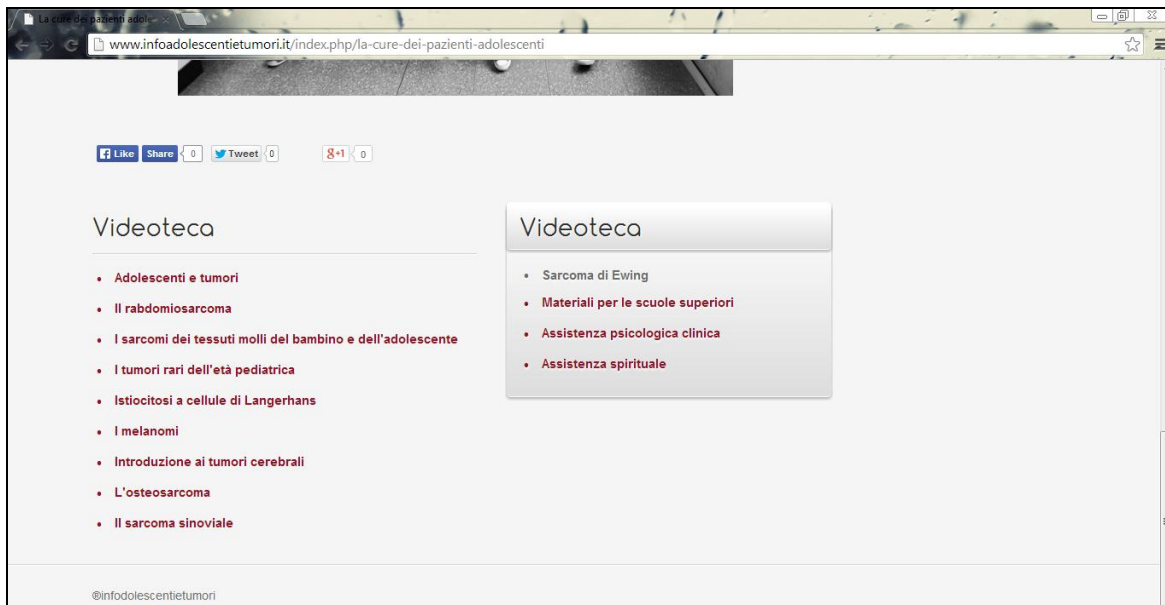


Figure 3.3 Some examples of the informative pages of the site

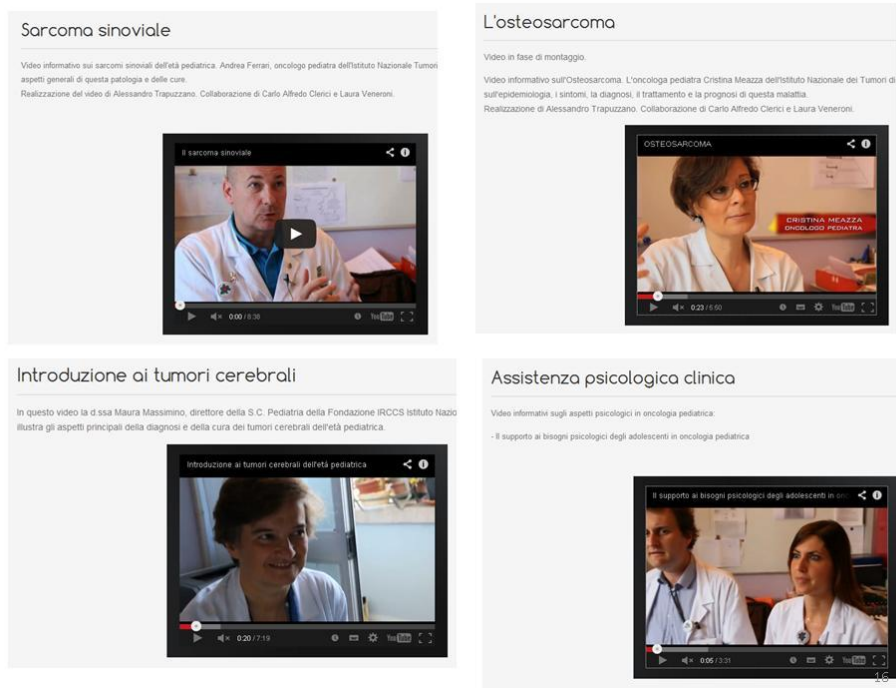


Figure 3.4 Healed patients talks about their experiences of disease and treatment

La voce dei ragazzi

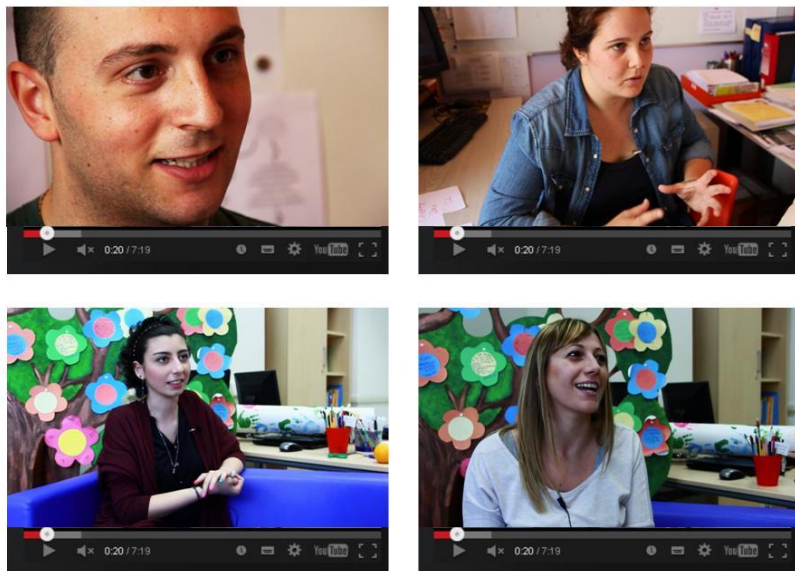


Fig. 3.4 Main page from www.ilprogettogiovani.it



L'Associazione Bianca Garavaglia presenta:



PEDIATRIC ONCOLOGY
Youth Project
Fondazione IRCCS Istituto Nazionale dei Tumori di Milano



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Il Tempo meglio

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Rassegna Stampa

Progetto Giovani

Il Progetto Giovani della Pediatria Oncologia della Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, nasce nel 2011, dedicato ai pazienti adolescenti malati di tumore, con l'obiettivo di creare un nuovo modello di organizzazione medica e di cultura specifica, con la sfida di occuparsi non solo della malattia, ma della vita dei ragazzi, facendo entrare in ospedale la loro normalità, la loro creatività, la loro forza, la loro bellezza.

Il Progetto Giovani vuole dare vita ad un momento che affondi in modo ampio e determinato il fatto che i pazienti adolescenti hanno minori possibilità di accedere ai centri di eccellenza e, come risultato, hanno minori probabilità di guarire dai tumori, e periti di abbandono clinico.

Il Progetto Giovani vuole migliorare e standardizzare particolari aspetti clinici come l'accesso ai protocolli di cura, il supporto psicologico, la misura di consapevolezza della famiglia, la gestione dei genitori dopo la conclusione delle terapie. Ha vuole anche creare - in un reparto *invalentato nato per curare i bambini* - specifici progetti dedicati per rendere il luogo di cura un posto un po' "speciale" per gli adolescenti malati.

Adolescenti e tumore



Video introduttivo al problema delle cure degli adolescenti malati di tumore


 PEDIATRIC ONCOLOGY
Youth Project
 Fondazione IRCCS Istituto Nazionale dei Tumori di Milano

The Pediatric Oncology unit of Istituto Nazionale Tumori Milan

The Pediatric Oncology unit of Istituto Nazionale Tumori (INT) in Milan conducts clinical and research projects on pediatric oncology with 23 inpatients and 12 outpatients beds. The unit has always been tailored to the treatment of children with solid tumors (SE) newly diagnosed patients treated in 2010, while it has been cooperating closely with the pediatric hemato-oncology center at San Gerardo Hospital in Monza since the 1980s, where it refers children with leukemia and includes a pediatric surgery subunit.

[Read more...](#)



Takeda Italia

Progetto realizzato grazie al contributo non condizionato di Takeda Italia

CHAPTER 4

THE YOUTH PROJECT

In this chapter I present two studies that describe the key issues of the Youth Project.

The INT pediatric oncology unit thus officially launched its Youth Project in 2011, focusing on adolescents (over 15 years old) and young adults (up to 25 years old) with pediatric tumors. Patients in this age range are admitted to our inpatient and outpatient wards and managed by the same staff as our children, though they may also have access to particular services (regarding their psychosocial support, fertility preserving measures, and access to care after completing their cancer therapy). Since our unit was originally designed for children (with cartoons on the walls and the involvement of clowns on the ward), one of the main aims of the Youth Project is to help the older patients feel more at home in the hospital by providing dedicated, adequately equipped multifunctional rooms and various activities and events (Fig. 4.1-3).

This project is a possible clinical and organizational model to address the unique needs of patients in this age group and for bridge the gap in access to care and in recruitment in clinical trials, in clinical and psycho-social management and in curves of healing.

- **Study 4.1:** *The Youth Project at the Istituto Nazionale Tumori in Milan* (2012).

- **Study 4.2:** *Adolescents with cancer: the "Youth Project" at the Istituto Nazionale Tumori in Milan* (2013).

Study 4.1

Tumori, 98: 399-407, 2012

The Youth Project at the Istituto Nazionale Tumori in Milan

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ABSTRACT

The paper describes the key issues of the Youth Project launched in 2011 at the pediatric oncology unit of the Istituto Nazionale Tumori in Milan dedicated to adolescents (over 15 years old) and young adults (up to 25 years old) with solid tumors. The Youth Project was developed within the pediatric oncology unit in the conviction that adolescent patients may benefit from the multidisciplinary team typical of the pediatric oncology setting, as well as the expertise in treating pediatric-type malignancies and enrolling patients in clinical trials. The project was an offshoot of existing activities, making no major changes to the hospital's organization and posing no major demands on the institution's administration and board. Patients are managed by the pediatric oncology staff, but they have access to particular services (e.g., regarding their psychosocial support, fertility preserving measures, access to care after completing therapy); dedicated, adequately equipped multifunctional rooms have been provided. The location of the pediatric unit within a cancer referral center and the cooperation with divisions dedicated to adults have played an important role in the project's creation.

Introduction

The pediatric oncology unit of the Istituto Nazionale Tumori (INT) in Milan conducts clinical and research projects on pediatric cancers. With 23 inpatient and 12 outpatient beds, the unit has always been tailored to the treatment of children with solid tumors (265 newly diagnosed patients treated in 2010), while it has been cooperating closely with the pediatric hemato-oncology center at San Gerardo Hospital in Monza since the 1980s, where it refers children with leukemia. The INT pediatric oncology unit includes a pediatric surgery subunit. The unit is part of the *Associazione Italiana Ematologia Oncologia Pediatrica* (AIEOP), the network of Italian pediatric oncology centers founded in the late 1970s to promote multicenter clinical trials and research.

Unlike other Italian pediatric oncology centers at children's hospitals or being part of pediatric departments in general hospitals, our unit is the only pediatric oncology unit in Italy within a large cancer hospital. As well as attracting large numbers of patients over the years, this has facilitated close cooperation with the INT divisions dedicated to adult cancers, enabling us to gain particular experience of certain tumor types (e.g., bone and soft tissue sarcomas)¹ across the pediatric and adult age groups, and of adult-type tumors occurring in children (melanoma, carcinomas)²⁻⁵. In addition, special attention has been paid to patients with pediatric-type tumors (e.g., rhabdomyosarcoma, medulloblastoma) who are no longer of pediatric age: in particular, 2 studies showed that young adult patients with rhabdomyosarcoma⁶ and medulloblastoma⁷ fared better when enrolled in pediatric trials, or at least treated ac-

Key words: adolescents, adolescents with cancer, young adults, pediatric oncology, psychosocial support, youth project, access to care.

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None of the authors have any conflicts of interest or competing financial interests to declare.

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according to the children's protocols, and much the same picture emerged for patients with synovial sarcoma, a tumor type spanning the pediatric and adult age groups⁸. On the other hand, adult patients with Wilms' tumors had a worse prognosis than is usually reported for children enrolled in clinical trials, apparently due to undertreatment or unsuitable treatment, or poor compliance with treatment guidelines⁹. For many years now there has been no upper age limit for admitting patients with pediatric cancers to our pediatric unit: a large number of adolescents, and also patients up to 25 or even 30 years old with pediatric tumors, have consequently been referred to our unit.

The pattern of patients' age: the first focus on adolescents

Between 1985 and 2010, the INT's pediatric oncology unit treated 4,110 patients: 880 were between 15 and 19 years old, while 206 were over 20; 26% of all treated pa-

tients were more than 15 years old. Figure 1 gives an idea of the "epidemiology" at our unit by patients' age, showing INT's relative proportions of teenagers or young adults and children (0-14-year-olds) with solid tumors treated at AIEOP centers, and the proportion of cases expected to occur in Italy based on the incidence rates drawn from population-based cancer registries (AIRTum)¹⁰. The picture that emerges confirms that the INT's pediatric oncology unit focuses much more on adolescents than the other AIEOP centers. It is also noteworthy that the proportion of adolescents seen at the INT has increased in the last decade. Figure 2 shows the different tumor types seen at the INT and the different pattern of cancer occurrence by age group. Figure 3 compares the numbers of solid tumors treated at the INT and at the other AIEOP centers in 1989-2006¹⁰: in the group of patients over 15, the number of cases treated at the INT accounts for 40% of all cases seen at Italian pediatric oncology units; and for certain tumor types (brain tumors, soft tissue and bone sarcomas), around 1 in 2 cases of adolescents registered in the AIEOP database were treated at the INT.

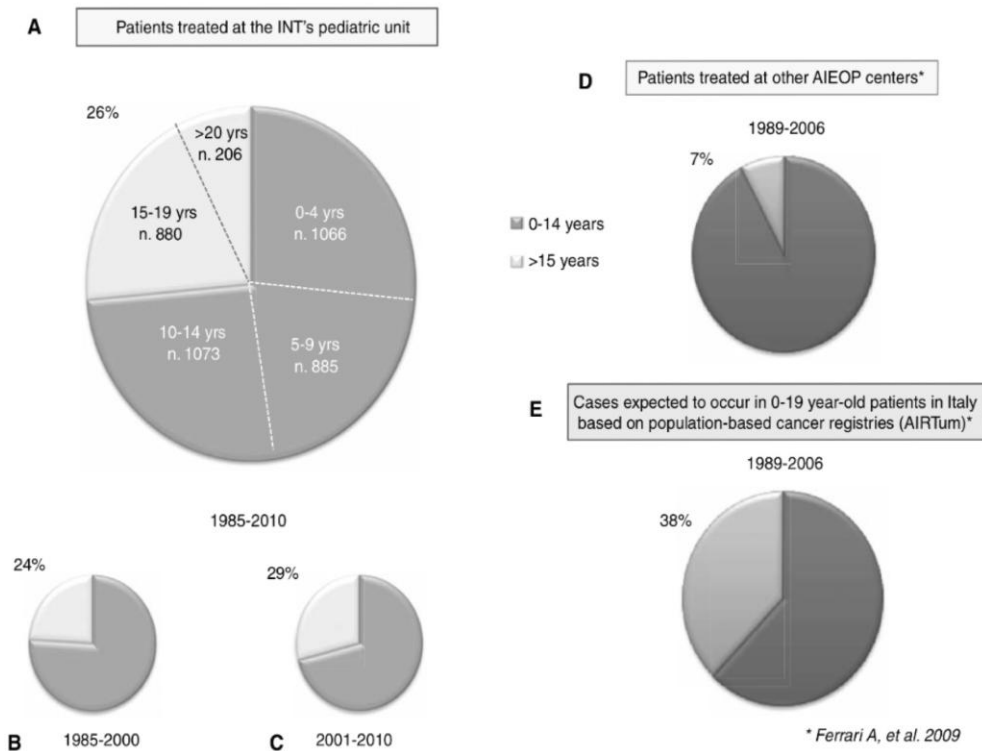


Figure 1 - Proportions of adolescents/young adults and children treated at the INT pediatric oncology unit (A: 1985-2010, B: 1985-2000, C: 2001-2010), and comparison with the proportions of patients with solid tumors treated at AIEOP centers (D), and the cases expected to occur in Italy judging from the incidence rates drawn from population-based cancer registries (E).

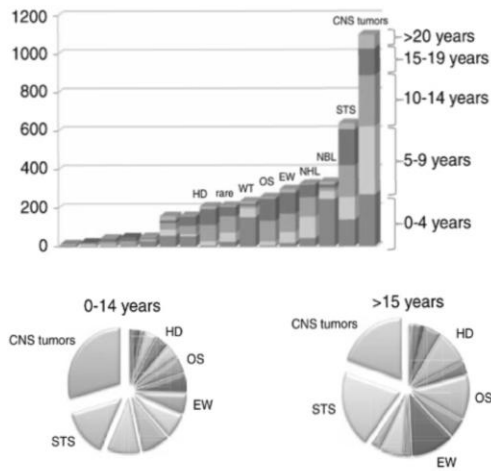


Figure 2 - Tumor types seen at the INT pediatric oncology unit (1985-2010) and age-related patterns of cancer. Central nervous system tumors were most frequent among 0-14-year-olds, whereas soft tissue and bone sarcomas became predominant among >15-year-olds. CNS, central nervous system; STS, soft tissue sarcoma; NBL, neuroblastoma; NHL, non-Hodgkin's lymphoma; EW, Ewing's sarcoma; OS, osteosarcoma; WT, Wilms' tumor; rare, rare tumors; HD, Hodgkin's disease.

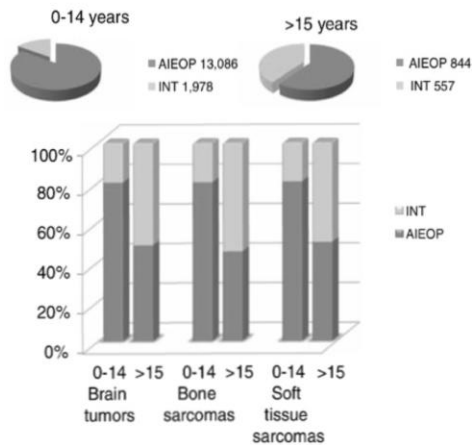


Figure 3 - Solid tumors treated in 1989-2006 by the INT pediatric oncology unit and other AIEOP centers: in the 0-14-year-old group, the cases treated at the INT account for 13% of all cases seen in Italian pediatric oncology units, but this proportion rises to 40% for patients >15 years old. For certain tumor types (brain tumors, soft-tissue and bone sarcomas), around 1 in 2 adolescent cases registered in the AIEOP database were treated at the INT.

As another example of how the INT's pediatric oncology unit focuses on adolescents, Figure 4 shows the cases registered by Italian AIEOP centers in the European pediatric Soft Tissue Sarcoma (EpSSG) database from 2005 to June 2011. One in 3 of all Italian cases were referred to our

center and the median age of the patients recruited was 14.5 years for the INT cases and 6 years for all the other Italian centers. The age-related pattern of patient referral depended on the type of unit: in Padua (where the unit is part of a general hospital), the median age of the cases registered was 10 years and patients were evenly distributed between sarcoma types; at 2 pediatric hospitals (the Gaslini Hospital in Genoa and the Ospedale Pediatrico Bambino Gesù in Rome) the median age of patients was 4 years, with a preponderance of rhabdomyosarcoma cases. At the other end of the spectrum is the Youth Area Project at the Centro di Riferimento Oncologico (CRO) in Aviano, which is not a pediatric unit but is nonetheless officially affiliated to the AIEOP because it has all the facilities needed to treat adolescents. The Aviano center is dedicated to 14- to 24-year-olds but was only able to register 9 patients in the EpSSG database. These figures demonstrate that a particular focus on adolescents has been a feature of our unit for many years, long before any formal youth project was developed.

Meanwhile, it has become clear that adolescents and young adults (AYA) are less likely to gain access to optimal cancer services at comprehensive cancer centers and to be enrolled in clinical trials, which is purportedly one of the main reasons why there has been little improvement in the survival trends for adolescents by comparison with the advances seen in children in recent decades^{11,12}.

In 2006, our group became formally involved in the International Working Group on Adolescent/Teenage and Young Adult Oncology¹³, developed under the auspices of the International Society of Pediatric Oncology (SIOP) to study the issue of such patients' accrual in clinical trials¹¹. More recently, we have also warmly supported the creation of an Italian AIEOP Committee on Adolescents, and we have implemented tailored services at our unit with a view to launching a youth project.

The INT Youth Project

A recently-published paper described various attempts to create comprehensive AYA programs around the world and the key features of a potentially successful project¹⁴. In the light of said paper, when developing our Youth Project we looked at past and present experiences, the core elements of AYA-focused programs and the potential barriers, as well as our prior experience of treating adolescents and young adults at our own pediatric oncology unit.

Despite the appeal of an initial proposal to create a new unit specifically for AYA patients, it was soon clear that such a scheme was unfeasible for administrative, logistic and economic reasons. Hence the idea to develop a Youth Project within our pediatric oncology unit based on our experience with AYA patients, in the conviction that adolescent patients may benefit from a

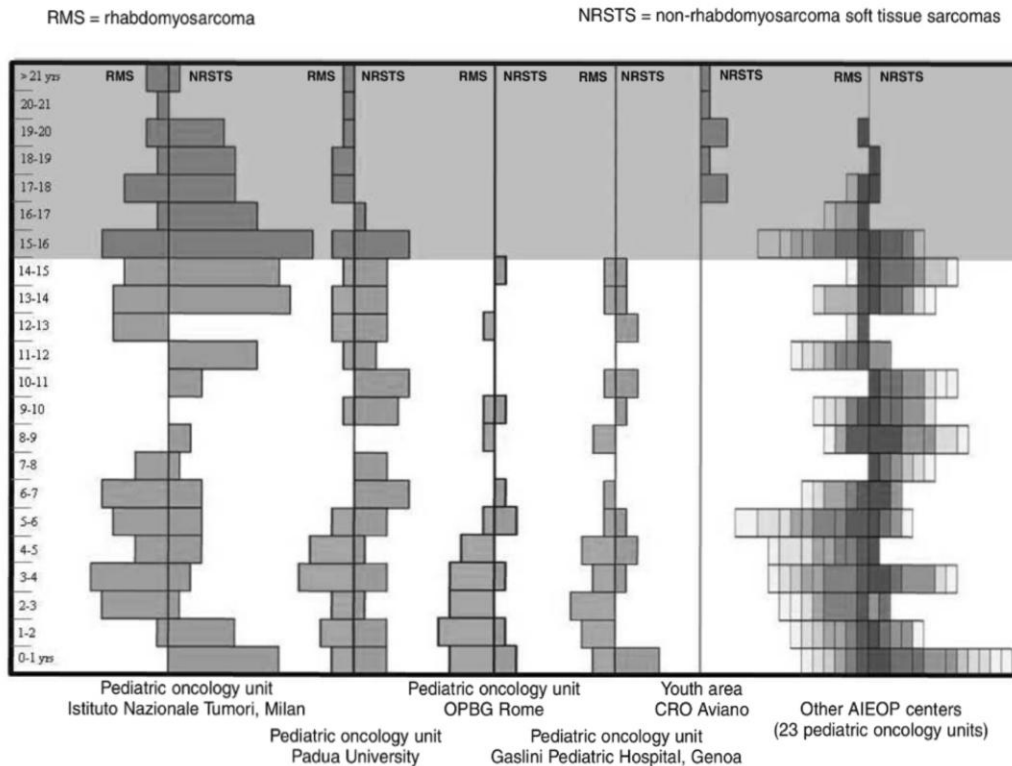


Figure 4 - Cases listed by Italian AIEOP centers in the European pediatric Soft Tissue Sarcoma (EpSSG) database from 2005 to June 2011, by patient age (rhabdomyosarcomas on the left, non-rhabdomyosarcoma soft-tissue sarcomas on the right). The INT treated 173 of the 520 cases (100 non-rhabdomyosarcoma soft-tissue sarcomas and 73 rhabdomyosarcomas). The pattern of case registration by patient age changes according to the type of center. OPBG, Ospedale Pediatrico Bambino Gesù, Rome; CRO, Centro di Riferimento Oncologico, Aviano; AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica.

multidisciplinary team typical of the pediatric oncology setting. In such a setting pediatric oncologists team up with surgeons, radiotherapists, nutritionists, infectious disease experts, neurologists and endocrinologists, as well as with psychologists and social workers. In fact, numerous published studies have reported significantly better outcomes for adolescent patients with various tumors treated at pediatric cancer centers than for similar cases admitted to adult facilities^{6,15-20}. In addition, developing such a project as an offshoot of our existing activities was far more straightforward (and feasible) than setting up a separate AYA unit with new professional figures, new accountabilities, new spaces.

The INT pediatric oncology unit thus officially launched its Youth Project in 2011, focusing on adolescents (over 15 years old) and young adults (up to 25 years old) with pediatric tumors. Patients in this age range are admitted to our inpatient and outpatient wards and managed by the same staff as our children, though they may also have access to particular services (regarding their psychosocial support, fertility preserving measures,

and access to care after completing their cancer therapy). Since our unit was originally designed for children (with cartoons on the walls and the involvement of clowns on the ward), one of the main aims of the Youth Project is to help the older patients feel more at home in the hospital by providing dedicated, adequately equipped multifunctional rooms and various activities and events.

Psychological support

For many years we have known that proper management of adolescents with cancer also calls for medical staff with particular skills to cope with the complex psychological world of teenagers and the dramatic psychological impact of a cancer diagnosis at this age²¹⁻²⁴. Providing psychological support was consequently considered a fundamental aspect of our Youth Project. We are convinced that an important initial psychological management effort must involve the whole medical team (doctors and nursing staff as well as social workers and teachers) in providing emotional support for adolescents faced with the anguish associated with a diagnosis

of cancer and the prospect of therapies, and also to identify cases needing specialist counseling. The unit's staff also receive specific training on these issues at meetings and courses. Clinical psychology specialists represent the second level of intervention and 3 such specialists are permanent staff members available on a daily basis and working in close cooperation with the other members of staff to establish a genuine, ongoing relationship with patients. One of our clinical psychologists is dedicated specifically to adolescent patients and meets all new patients when they are admitted to the unit.

A previously published study of ours described the interaction of our psychologists with the other staff members, the pattern of referral and reasons for psychological consultation, and the type of psychotherapy provided²⁴. The study showed that adolescents require different psychological support than children. To give an example, the number of psychological interviews per patient was 2.8 for children and 7.8 for older patients, and long-term psychotherapy was needed for 1% of patients under 15 and 10% of those ≥ 15 years old. The study also confirmed that adolescents are complicated and have particular emotional, social and psychological problems, very diverse levels of maturity and different needs, and how they cope with the trauma of cancer can consequently vary enormously. The main goal of our psychologists' activity was to help patients handle their emotional response to their diagnosis, but a number of patients had psychological support for problems of treatment compliance. There were also certain particular situations (sometimes developing after the cancer treatment was completed), including difficulties in returning to normal life, problems relating to drug addiction, attempted suicide, anorexia and obsessive-compulsive disorder²⁴⁻²⁷. Several studies on adolescents and young adults have been developed as part of the Youth Project (Table 1).

Fertility and sexuality

Preserving fertility is a major issue for AYA patients needing radiation to the gonads and chemotherapy regimens containing alkylating agents²⁸. Cooperation with gynecology departments at other hospitals in Milan enables a sperm cryopreservation service to be routinely offered to men at risk of temporary or permanent azoospermia before they undergo cytotoxic therapy. More recently, cryopreservation of oocytes has also become available. Oophoropexy is considered for all female patients needing pelvic irradiation²⁹. It is very important to tell patients about the risks to their fertility and the psychologist is usually involved in doing so, because potential damage to their reproductive capacity can have a devastating impact on young people. Another major issue concerns the possible impact of cancer on an individual's psychosexual identity, maturation, and sexual function³⁰, and this is a further area of intervention for our psychologists.

Table 1 - Psychological research on adolescents and young adults in the Youth Project

Psychological research

- A study on the legal and ethical issues and methods for obtaining informed consent for minors, particularly regarding phase I-II clinical trials on cases of relapsing/refractory tumors, when taking the approach used for adults implies informing patients of their adverse prognosis and limited chances of benefitting significantly from the use of experimental drugs.
- A study on quality of life and psychological state in a population of female patients previously given chest irradiation for childhood cancer and subsequently screened for second primary breast cancer.
- A study on the possible role of mirror therapy for phantom pain in amputated patients.
- A study on the delay in cancer diagnosis (which is longer in adolescents than in children) and its psychological impact.
- A study on our adolescent patients' spiritual needs and religious orientation, and on the role of spirituality in their coping process.
- A study on the return to school after cancer has been diagnosed and treated; a large project in cooperation with the Milan State University and the San Gerardo Hospital in Monza, supported by the Near/Magica Cleme Foundation, has led to the production of a movie on teenagers with cancer (entitled "I like that tall guy with the crutches"); the movie will be shown in secondary schools and at oncology meetings and medical schools (as a teaching tool).
- A study on the psychological impact of demolitive surgery; the first subset of patients we plan to interview includes teenagers who undergo prophylactic surgery for familial adenomatous polyposis (FAP), to assess any differences relating to the laparoscopic approach versus laparotomy.
- A study on patients' personality and how it affects long-term survivors' quality of life (particularly in sarcoma patients).

Social support and school

Schooling activities are fundamental in reducing teenagers' maladaptive reactions to their disease and avoiding the negative impact on their future social life of losing a year at school³¹. Three levels of intervention are organized: a) efforts to enable patients to attend their own school regularly, whenever possible; b) a hospital-based school for when patients are admitted to hospital or obliged to stay far away from their homes for lengthy periods, e.g., patients coming from outside the area to receive radiotherapy; and c) a homeschooling program for patients unable to attend school. Four teachers including a high-school teacher and 5 educators are part of the unit's team and cooperate directly with patients' own school teachers. When dealing with young adults, the unit's team may also need to address problems relating to a patient's job and our social workers have a major part to play. The unit's staff includes 2 social workers, who welcome all inpatients and outpatients and their families when they first come to the unit. For adolescents, the initial talk with the social worker is often the first step they take to reorganize their lives around the new needs stemming from the diagnosis of cancer. Social workers play an essential role in assisting families in various ways: they provide informa-

tion on social and economic support opportunities, helping to deal with the related paperwork; they arrange for hospitality for families coming from other regions; and they provide support for foreign patients.

Spaces

Since the medical spaces used for adolescent inpatients and outpatients at our pediatric oncology unit have remained the same as for children, the Youth Project has focused on providing tailored recreational spaces by converting 3 rooms previously used for other purposes (2 laboratories and a nurses' locker room):

- one is now a 30 m² multifunctional room for socializing and recreation with couches, TVs, computers with connection to the Internet, musical instruments, a library with books, magazines and DVDs, a radio, and a corner for face makeup;
- one is a 20 m² classroom with computers, a quiet room where adolescents can go to study (alone or with a teacher) or read;
- finally, a 30 m² gym will be built on the same floor as the inpatients ward, with an exercise bike, a rowing machine, treadmill and various other equipment. A personal trainer with specific skills in physiotherapy and the management of disabled patients will be periodically available to assist patients at the gym.

These spaces have been devised as places where adolescent and young adult patients can take some time off and not be disturbed, where they can interact with their peers and organize their own activities; these areas will be accessible only to 15- to 25-year-old patients and possibly their friends but not to parents or younger patients.

Activities

Various activities, events and courses (e.g., arts, music, photography, makeup, new technologies) for adolescent and young adult patients ("Magic Time") have been planned. In particular, with the collaboration of various professionals who work with the patients, we have started with the project of a stylist collection made by teenagers, with its own brand (B.LIVE), a planned fashion show, and a photographic book.

Philanthropic financial support

The limited budget of hospital administrations has often been seen as the main obstacle to the development of any new scheme. Our project was created as an offshoot of the pediatric oncology unit partly to avoid additional costs for the INT. We are striving to show the community and the mass media the potential indirect benefits of our program (new services, patient satisfaction, better enrollment in clinical trials) because other sources of funding have been needed to prepare the

spaces dedicated to the project. A charity called the *Associazione Bianca Garavaglia* (ABG) has been supporting our unit for 25 years and recently adopted the Youth Project as its main objective. Like other charities elsewhere, e.g., the Teenage Cancer Trust³² in the UK and the Lance Armstrong Foundation³³ in the USA (although the ABG is far less powerful), the ABG has made an important contribution not only to covering expenses but also stimulating new ideas and actions. More recently, the ABG has been helped by another partner, the Near/Magica Cleme Foundation, which focuses particularly on organizing activities and events.

Access to care after cancer therapy

The issue of access to appropriate medical care for teenagers and young adults who have successfully completed their cancer therapy is a major challenge for a dedicated AYA program³⁴. Most of these patients require careful long-term monitoring because of the risks of relapse and sequelae. In addition, competent and appropriate psychosocial follow-up is needed, partly to identify unexpressed needs and any psychopathological consequences of the cancer diagnosis and treatment, which can significantly affect these patients' future life, and partly to help adolescents who are cured of cancer reach an independent adulthood. Various models have been suggested for an adolescent's access to care after cancer therapy and the transition from a child-oriented to an adult-oriented healthcare system has sometimes reportedly been traumatic for patients. For many years our unit has adopted flexible models that are adapted to patients' different ongoing needs in the light of their prior clinical history. Long-term survivors continue to be managed by the physicians who first treated them and, although 2 permanent members of staff are especially dedicated to this service, all clinicians are involved in the follow-up. Visits are scheduled according to the characteristics of each patient's cancer and its treatment, and are generally continued up to the tenth year after completing cancer treatment, irrespective of the patient's age. Financial support to cover traveling expenses may be available for needy families. Afterwards, follow-up is tailored to the different situations based on at least 3 possible options:

- yearly contact by phone for "low-risk" cases, i.e. patients who were not heavily treated (no radiation or alkylating agents) or who carry no risk of functional sequelae;
- in selected cases, when specific expertise is required (e.g., melanoma patients are probably more adequately monitored by dermatologists), a transfer to INT departments for adults is proposed (single-site switch model), although the link with the pediatric staff is maintained in order to update the pediatric oncology database and support the patient's transition;

- for “high-risk” patients there are dedicated programs, e.g., physical, neurological and psychological rehabilitation programs for survivors of brain tumors, accurate cardiologic monitoring for patients treated with anthracyclines, endocrine function monitoring, early breast screening after radiotherapy to the chest wall (and, more in general, for radiation-induced second neoplasms).

As for the cooperation with other groups, our unit works with the AIEOP Off-Therapy Registry, a hospital-based database established in 1980 where the various AIEOP centers collect demographic and clinical data on patients off therapy. We are also partners in the European PanCare network (www.pancare.eu), the aim of which is “to ensure that every European survivor of childhood and adolescent cancer receives optimal long-term care” by developing dedicated collaborative research and activating forms of cooperation with the European Community to increase awareness of the problems involved and to find dedicated funds.

Metrics

One of the challenges in developing an AYA program is to define and measure the potential success of the program. Of course, the gold standard of improved survival rates will be difficult to measure at a local level in a short period. While the simple number of adolescent cases treated in the unit may not be considered a measure of success, patient-reported experiences or satisfaction, particularly with respect to psychosocial and other support, may not be seen as an effective measure by the hospital administration. Various possible metrics can be considered concerning overall patient care (e.g., percentage of patients enrolled in clinical trials, percentage of patients receiving fertility preservation counseling, percentage of patients of school age receiving teaching support, social interaction), patient and provider knowledge and satisfaction (measured by surveys), and research (grants received, publications)¹⁴. Concerning our project, we are not under major pressure by the hospital administration because we have not required more human and financial resources. Within our group, we believe that the satisfaction of the patients is our major metric. However, we hope that our experience may influence other Italian pediatric as well as adult oncology centers to dedicate more attention – as well as time, spaces and resources – to adolescents and young adults. The development of other youth projects and national cooperative programs between pediatric and adult oncology groups may be considered a measure of the possible success of our project.

The Italian AIEOP Committee on Adolescents

In the light of other research, the AIEOP investigated how many 15- to 19-year-olds were treated at pediatric

oncology units as compared with the numbers expected to be seen in Italy judging from incidence rates drawn from population-based cancer registries. It became clear that the AIEOP was failing to enroll adolescents in its trials: the ratio of observed to expected cases was only 0.10 for adolescents, as opposed to 0.77 for children up to 14 years old¹⁰. An AIEOP Committee on Adolescents was consequently founded to explore the reasons why adolescents were underrepresented in AIEOP clinical trials and to seek to improve this situation. This Committee was coordinated by our unit. First, we conducted a survey to assess the Italian pediatric oncology units’ adoption of inflexible upper age limits and we found that many centers set upper limits of 16, 15, or even 14 years of age, thus barring adolescents from admission to AIEOP centers³⁵. The Committee’s actions are now focusing on various issues:

- improving awareness: a press release has been launched on adolescent access to care, a brief documentary video has been uploaded on YouTube (<http://youtube/5WO26cV1qPc>), and various conferences have been organized; a document to be sent to the Ministry of Health as well as universities and hospitals has been prepared;
- increasing the number of adolescents referred to pediatric oncology units: an official document has been written to be sent to AIEOP centers with a view to removing administrative barriers and raising upper age limits for patient admission;
- addressing specific issues: links have been established with other AIEOP working groups to define adolescent-specific aims in their protocols, and adolescent-focused biological studies have been planned;
- cooperation with adult medical oncologists: cooperative schemes with adult cancer units have been developed because it has become clear that raising the upper age limits for pediatric centers and protocols can only really help if groups of adult patients are involved as well. To give an example, a protocol for treating adult rhabdomyosarcoma according to a pediatric-like strategy has recently been arranged in cooperation with the Italian Sarcoma Group.

Conclusions

It is now acknowledged that adolescents and young adults with cancer should be considered as a distinct group whose needs have been poorly addressed by healthcare systems in the past. Several dedicated programs are being developed in pediatric and medical oncology settings, or somewhere in between¹². While the ultimate goal would be to develop a new discipline – adolescent/teenage and young adult oncology – with tailored units and research schemes, this could be hin-

dered by practical, administrative and economic barriers. The approach taken by the INT's pediatric oncology unit can be taken as a pragmatic solution, implementing a project that makes no major changes to the hospital's organization and poses no major demands on the institution's administration and board. Although the location of our pediatric unit within a cancer referral center has played an important role in our project's creation – and this is not a common situation, at least not in Italy – we hope our experience might prompt other centers and the Italian health system to action. Suppressing upper age limits for patient admission and cooperating with adult oncology groups are key elements in our Youth Project, but further steps are clearly needed to improve the quality of care and research for AYA patients. New actions on our agenda include finding a testimonial (a famous sportsperson or actor) and developing a support group of peers, for instance to accompany patients to football matches, concerts and other events. In the future, greater involvement of adult-oncologist colleagues will hopefully extend our horizons to an older subset of patients (up to 30 years old) and might eventually pave the way to a dedicated AYA cancer unit.

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Gli adolescenti ammalati di tumore: il "Progetto Giovani" dell'Istituto Nazionale dei Tumori di Milano

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Riassunto. Gli adolescenti ammalati di tumore costituiscono un gruppo particolare di pazienti per cui esiste un problema di accesso alle migliori cure possibili: molti studi suggeriscono che i pazienti adolescenti hanno minori probabilità di guarire dei bambini, a parità di condizione clinica. Questo articolo descrive i punti chiave del Progetto Giovani della Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano, progetto dedicato agli adolescenti e ai giovani adulti, possibile modello clinico e organizzativo per affrontare i peculiari bisogni dei pazienti in questa fascia di età e di colmare i divari evidenti nell'accesso alle cure e nell'arruolamento nei trial clinici, nella gestione clinica e psico-sociale, nelle curve di guarigione. Viene descritta inoltre l'attività della Commissione Adolescenti istituita dall'Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP).

Parole chiave. Adolescenti e giovani adulti, cancro, pediatria oncologica, pediatria psicosociale.

Gli adolescenti con tumore e l'accesso alle cure

Gli ultimi cinque anni sono stati un momento cruciale per lo sviluppo in Italia di progetti dedicati agli adolescenti ammalati di tumori. Grazie alla pubblicazione di vari studi internazionali, si è sviluppata nell'ambito oncologico la consapevolezza del fatto che gli adolescenti ammalati stanno in una "terra di nessuno" tra il mondo dell'oncologia pediatrica e quello dell'oncologia dell'adulto¹⁻³: gli adolescenti e i giovani adulti con tumore rappresentano un sottogruppo di pazienti per cui esiste un problema di accesso alle cure di eccellenza e di arruolamento nei protocolli clinici, in particolare se paragonato all'ottimizzazione dei percorsi di cura in atto con successo nel mondo dell'oncologia pediatrica per il paziente di età inferiore ai 15 anni, grazie all'esistenza di efficienti reti cooperative: per l'Italia l'Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP <http://www.aieop.org>). Diversi studi – e tra questi lo studio di sopravvivenza EURO CARE 1995-2002⁴ (tabella 1) – hanno

Adolescents with cancer: the "Youth Project" at the Istituto Nazionale Tumori in Milan.

Summary. Adolescents with cancer are a particular group of patients who are less likely to gain access to optimal cancer services at comprehensive cancer Centers: many studies suggest adolescents fare less well than children with the same disease. The paper describes the key issues of the "Youth Project" of the Pediatric Oncology Unit IRCCS Fondazione Istituto Nazionale Tumori in Milan, dedicated to adolescents (over 15 years old) and young adults (up to 25 years old) with solid tumors. This project is a possible clinical and organizational model to address the unique needs of patients in this age group and for bridge the gap in access to care and in recruitment in clinical trials, in clinical and psycho-social management and in curves of healing. The paper also describes the activity of the Adolescent Commission established by the Italian Pediatric Hematology Oncology (AIEOP).

Key words. Adolescent and young adults, cancer, pediatric oncology, psychosocial oncology.

fatto emergere in modo chiaro come i pazienti adolescenti e giovani adulti abbiano minori probabilità di guarire dei bambini, a parità di condizione clinica. Il trend di costante miglioramento in termini di sopravvivenza osservato negli ultimi anni per i bambini, ma anche per i pazienti adulti, non si è osservato negli adolescenti e nei giovani adulti.

Tabella 1. Dati dello studio di sopravvivenza EURO CARE 1995-2002.

EURO CARE 1995-2002 Gatta et al. Eur J Cancer 2009	Sopravvivenza a 5 anni	
	pazienti < 15 anni	pazienti 15-24 anni
Leucemia linfoblastica acuta	85%	50%
Linfomi non-Hodgkin	82%	74%
Osteosarcoma	77%	60%
Sarcoma di Ewing	66%	48%

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Da molti anni, l'oncologia pediatrica italiana ha riconosciuto la complessità della gestione degli adolescenti malati, la peculiarità dei bisogni dei ragazzi che devono affrontare la diagnosi e la cura del tumore in un momento particolarmente delicato del processo di crescita: la necessità di realizzare una presa in carico globale del paziente adolescente – e della sua famiglia – con un'equipe multi-specialistica in cui, accanto all'oncologo, lavorano quotidianamente chirurgo, radioterapista, radiologo, patologo, endocrinologo, neurologo, ma anche psicologo, assistente sociale, educatore, intrattenitore. Di fatto, la maggior parte dei Centri di oncologia pediatrica, organizzati nel network dell'AIEOP, si è dotata di un team psico-sociale in grado di fornire un adeguato supporto ai ragazzi malati. Solo recentemente, però, è diventato evidente che tale supporto veniva dato solo ad una minoranza degli adolescenti con tumore, proprio perché solo una minoranza di essi aveva effettivo accesso ai Centri di oncologia pediatrica; questo, nonostante il fatto che due terzi dei tumori nella fascia di età tra 15 e 19 anni siano in realtà neoplasie tipiche dell'età pediatrica (tumori del sistema nervoso centrale, sarcomi, leucemie e linfomi). Sono stati pubblicati i risultati di uno studio che ha confrontato il numero di casi trattati nei centri AIEOP (oltre 22.000 pazienti - di cui 1745 adolescenti - dal 1989 al 2006) con il numero di casi attesi in Italia, calcolato in funzione dei tassi di incidenza ricavati dalla rete dei registri di popolazione (AIRTum - Associazione Italiana Registri Tumori, <http://www.registri-tumori.it>): se per i pazienti sotto i 15 anni, circa l'80% viene curato nei centri AIEOP, per i pazienti tra 15 e 19 anni il rapporto osservati/attesi è solo del 10%⁵. Lo studio ha inoltre riportato che sono quasi mille i ragazzi italiani che in questa fascia di età ogni anno scoprono di avere un tumore. Si può ipotizzare che, di questi, solo una minoranza riceva cure adeguate, perché di fatto solo in rari casi gli adolescenti non trattati nei Centri di oncologia pediatrica afferiscono a Centri di eccellenza dell'adulto e a protocolli dell'adulto; di conseguenza questi malati non sono curati né dall'oncologo pediatra né da un oncologo dell'adulto.

La Commissione AIEOP

Gli oncologi pediatri italiani si sono resi conto che il network AIEOP, operativo da oltre 30 anni, è efficiente nel servire i bambini, ma non gli adolescenti. È stata quindi creata una Commissione Adolescenti, con lo scopo di indagare le possibili cause dell'inadeguato accesso alle cure e dell'insoddisfatto tasso di guarigione degli adolescenti rispetto ai bambini. L'oggetto primario dell'azione è il paziente di 15-18 anni con tumore pediatrico, ma in secondo luogo anche i pazienti fino a 21-24 anni, se affetti da neoplasia tipica del bambino. L'obiettivo principale è quello di mettere a disposizione la migliore cura possibile.

Uno studio della Commissione ha individuato un primo problema da affrontare: molti Centri di oncologia pediatrica in Italia fissano arbitrariamente limiti massimi di età, per l'accesso in reparto, a 16, 15 o anche 14 anni (quasi il 50% dei Centri AIEOP)⁶. Questi limiti, fissati dalle amministrazioni ospedaliere o dalle Regioni, rappresentano vere e proprie barriere al trattamento degli adolescenti con i protocolli pediatrici, anche se affetti da tumori tipici dell'età pediatrica come rhabdomyosarcoma, medulloblastoma o leucemia linfoblastica acuta. Un primo obiettivo concreto della Commissione AIEOP è quindi quello di modificare i limiti di età di accesso ai Centri di oncologia pediatrica, con un'azione locale, a livello delle aziende ospedaliere, ma anche con un'azione istituzionale. Finalità principale è quella di poter definire un piano di azione a livello del Piano Oncologico Nazionale; tuttavia azioni vanno attivate a più livelli, a livello di Università e Scuole di Specialità, a livello mediatico (divulgazione e informazione sul problema), a livello internazionale, con la creazione di sinergie con i vari gruppi di lavoro internazionali come l'International Working Group on Adolescents and Young Adults della International Society of Pediatric Oncology (SIOP, <http://www.siop.nl>), la Livestrong Foundation degli Stati Uniti (<http://www.livestrong.org>), la Teenager Cancer Trust, TCT della Gran Bretagna (<http://www.teenagecancertrust.org>).

Un punto chiave è rappresentato dalla collaborazione che il mondo dell'oncologia pediatrica deve instaurare con i gruppi cooperativi di oncologia medica dell'adulto, che devono essere coinvolti in progetti su adolescenti e giovani adulti. La comunicazione e la collaborazione tra il mondo dell'oncologia pediatrica e quello dell'oncologia degli adulti devono essere migliorate. Esistono infatti differenze culturali e logistiche (diversi sistemi di classificazione, differenti modalità di raccogliere i dati), diversi modelli di lavoro e diverse strategie (per esempio, l'oncologia pediatrica lavora molto attraverso network cooperativi nazionali e internazionali e con studi di fase 3, là dove l'oncologia degli adulti ha in genere come obiettivo principale gli studi di fase 1-2 e i protocolli sui nuovi farmaci). La collaborazione reciproca appare come una condizione indispensabile anche per rispondere alle domande sulle differenze biologiche e cliniche dei tumori in relazione all'età: sono moltissime le evidenze di come i diversi tumori abbiano comportamento biologico e clinico diverso nelle diverse età (ad esempio, il rhabdomyosarcoma ha un comportamento più aggressivo quando insorge nell'adulto rispetto al bambino;⁷ al contrario, il carcinoma della tiroide del bambino ha caratteristiche biologiche diverse e prognosi migliore di quello dell'adulto⁸). Con l'età, cambia però anche la biologia dell'ospite: la diversa maturità e funzionalità degli organi (ad esempio rene e fegato), la composizione e distribuzione corporea, lo stato ormonale, le diverse comorbilità.

Anche i diversi fattori psicosociali e comportamentali possono influenzare, ad esempio, la farmacocinetica dei chemioterapici e quindi la risposta alle terapie e, in ultima analisi, le possibilità di guarigione.

La Commissione AIEOP ha come elemento chiave la collaborazione e il coinvolgimento di diverse figure (i cosiddetti "stakeholders" = "diretti interessati"): i Centri AIEOP e quindi i medici, ma anche gli infermieri, gli psicologi e gli assistenti sociali, i gruppi di genitori e parenti, come la FIAGOP (Federazione Italiana Associazioni Genitori Oncoematologia Pediatrica, <http://www.fiagop.it>), i gruppi di guariti, i gruppi di pari, gli oncologi dell'adulto.

Ulteriore finalità della Commissione AIEOP è quello di stimolare la creazione di progetti locali dedicati agli adolescenti e, eventualmente, di coordinarne l'azione. Fino a poco tempo fa, pochi Centri in Europa avevano attivato programmi specifici. In Italia, il primo è stato il Centro di Riferimento Oncologico (CRO) di Aviano, ospedale dedicato all'oncologia dell'adulto, con l'Area Giovani attivata nel 2007 come progetto trans-dipartimentale a isorisorse, dedicato ai pazienti di 14-24 anni (<http://www.areagiovanicro.it>). Recentemente, l'Istituto Gaslini di Genova, ospedale a indirizzo pediatrico con un ridotto accesso di pazienti sopra i 14 anni, ha guidato un progetto nell'ambito della Rete emato-oncologica ligure per strutturare l'attività di consulenza e gestione condivisa di pazienti adolescenti ricoverati presso strutture di cura dell'adulto. L'iniziativa più ampia in Italia è però quella della Unità di Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano.

Il "Progetto Giovani" della Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano

La Struttura Complessa di Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano (<http://www.istitutotumori.mi.it>) è l'unico Centro di oncologia pediatrica in Italia ad essere parte di un Istituto oncologico (in genere, l'oncologia pediatrica nasce all'interno di un ospedale pediatrico o come parte di un dipartimento pediatrico all'interno di un ospedale generale). Questa particolare collocazione ha facilitato lo strutturarsi di una stretta collaborazione con oncologi medici dell'adulto e ha permesso nel corso degli anni lo sviluppo di una peculiare esperienza nella cura di alcuni tipi di tumore a cavallo dell'età adolescenziale-adulta (ad esempio, i sarcomi dell'osso e delle parti molli o le neoplasie germinali), così come di situazioni cliniche specifiche come un tumore tipico dell'adulto (melanoma, carcinoma) che insorge in un bambino o in un adolescente^{9,10}, oppure, al contrario, tumori di tipo pediatrico che colpiscono giovani adulti^{7,11,12}. Di fatto, non è mai esistito un limite massimo di età per il ricovero di pazienti affetti da tumori pediatrici: di 4.110 pazienti con tumore solido curati dal 1985 al 2010, il 26% era di età maggiore di 15 anni (880 di età compresa tra 15 e 19 anni, 206 maggiori di 20 anni).

Anche se da sempre vi è stata un'attenzione speciale ai pazienti adolescenti rispetto al quadro generale dell'oncologia pediatrica, recentemente è emersa la necessità di creare un Progetto dedicato ai pazienti in questa fascia di età. Nel 2011 è stato ufficializzato il "Progetto Giovani", dedicato agli adolescenti (pazienti tra 15 anni e 18 anni) e ai giovani adulti (tra 19 e 25 anni), questi ultimi se affetti da tumori di tipo pediatrico, con lo scopo di: a) standardizzare l'accesso dei pazienti a servizi speciali come il supporto psicosociale, le misure di conservazione della fertilità e l'accesso alle cure dopo la conclusione della terapia, b) creare – in un Reparto inizialmente nato per curare i bambini – spazi e iniziative dedicati esclusivamente ai pazienti in questa fascia di età; c) creare un modello che nell'ambito di un movimento nazionale possa sensibilizzare altri Centri verso lo stesso obiettivo: miglioramento della qualità di cura degli adolescenti.

Nell'impossibilità amministrativa, logistica ed economica di creare un Reparto specifico per gli adolescenti e i giovani adulti, si è deciso di sviluppare un progetto all'interno della Struttura Complessa di Pediatria Oncologica: i pazienti adolescenti sono ammessi a Reparto, day-hospital e ambulatorio pediatrico e sono curati dallo stesso personale che si occupa dei bambini, così beneficiando della presa in carico globale tipica dell'oncologia pediatrica: in cui il paziente e la sua famiglia (e nel caso di ragazzi grandi anche gli amici, o la fidanzata) sono gestiti da un team multidisciplinare in cui gli oncologi lavorano in stretta collaborazione con psicologi, assistenti sociali, esperti di fertilità, esperti di make-up. I ragazzi hanno però accesso a servizi medici e a spazi/iniziativa dedicati. Il progetto non ha di fatto costi aggiuntivi per l'amministrazione dell'Istituto e non prevede modifiche logistiche/organizzative né necessità di nuove figure professionali; gli stessi spazi dedicati sono ricavati da aree pre-esistenti.

IL PROGETTO GIOVANI: I SERVIZI

Obiettivi principali del "Progetto Giovani" sono quelli di standardizzare l'accesso dei pazienti a servizi speciali come il supporto psicosociale, e le misure di conservazione della fertilità, nell'ambito della presa in carico globale da parte dell'équipe terapeutica, incluse le cure dopo la conclusione del trattamento.

Fornire un supporto psicologico adeguato deve essere un obiettivo prioritario di chiunque voglia occuparsi di adolescenti malati. L'adolescenza è un'età particolare e delicata, caratterizzata da bisogni specifici e vissuti emotivi, spirituali e relazionali peculiari, con un livello di maturità che varia molto da individuo a individuo. In questo periodo, i ragazzi percepiscono i cambiamenti del loro corpo e dei loro orizzonti di libertà e indipendenza. Intorno al corpo sono investite grandi energie, e fare i conti con un corpo che non funziona,

che fa male, che può morire, rappresenta un'esperienza fortemente traumatica, che mette in pericolo l'identità stessa della persona. La migliore gestione degli adolescenti malati di tumore richiede uno staff medico con competenze specifiche, per far fronte alle richieste e ai bisogni del complesso mondo psicologico dei giovani pazienti e al drammatico impatto psicologico che la diagnosi di tumore a questa età comporta. La gestione psicologica deve coinvolgere innanzitutto il team al completo (medici e infermieri, assistenti sociali e insegnanti), fornendo il primo supporto emotivo e identificando i casi che richiedono la consultazione dello specialista. Presso la Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano, tre specialisti di psicologia clinica fanno parte stabilmente dello staff medico con cui collaborano quotidianamente (due specialisti si occupano in modo specifico degli adolescenti e incontrano ogni nuovo paziente ricoverato)¹³.

Il supporto psicologico va di pari passo con quello sociale. Quattro insegnanti (inclusa un docente di scuola superiore) e cinque educatori fanno parte dello staff. Le attività scolastiche sono fondamentali nel ridurre le reazioni disadattive alla malattia. La perdita di un anno di scuola può avere un importante impatto negativo sulla futura vita sociale e sono stati organizzati pertanto diversi livelli di intervento, da supporti per rendere i pazienti in grado di frequentare regolarmente la propria scuola, alla "scuola in ospedale" per i pazienti ricoverati oppure costretti a stare lontani da casa per lunghi periodi, alla "scuola a casa". Quando si ha a che fare con giovani adulti, può accadere che il personale debba confrontarsi anche con problemi che riguardano il lavoro dei pazienti; un ruolo fondamentale, a questo proposito, è svolto dagli assistenti sociali, i quali aiutano le famiglie in vari modi: dai possibili aiuti economici all'ospitalità presso strutture convenzionate, al supporto ai pazienti stranieri. In molti casi, per gli adolescenti, l'incontro iniziale con gli assistenti sociali è spesso il primo passo per l'adattamento e la riorganizzazione esistenziale conseguente alla malattia.

Un altro aspetto fondamentale per i pazienti adolescenti e giovani adulti, soprattutto quelli la cui terapia antitumorale prevede la radioterapia sulla regione pelvica o l'uso di regimi chemioterapici contenenti alchilanti, è quello della conservazione della fertilità¹⁴. Chi vuole occuparsi di pazienti in questa fascia di età deve essere in grado di fornire servizi come la crioconservazione degli spermatozoi, la trasposizione delle ovaie o, anche se più complessa, la crioconservazione degli ovociti. All'Istituto Nazionale dei Tumori di Milano, la cooperazione con Dipartimenti di Ginecologia presso altri ospedali di Milano ha recentemente permesso l'implementazione di questi servizi. L'intervento degli psicologi è assai utile anche in questo contesto.

Un ulteriore problema è quello dell'accesso alle cure mediche appropriate per gli adolescenti e

giovani adulti che hanno completato con successo la terapia specifica. La maggior parte di questi pazienti richiede un attento monitoraggio a lungo termine a causa dei rischi di ricaduta, ma anche per rischi di sequele iatrogene; inoltre è necessario un competente follow-up psicosociale, sia per individuare le esigenze inesprese e le eventuali conseguenze psicopatologiche della diagnosi e del trattamento, sia per aiutare gli adolescenti in remissione a costruire una vita adulta indipendente. Vari modelli sono stati proposti per promuovere l'accesso alle cure/controlli dopo la terapia e per regolare il passaggio, a volte traumatico, dal sistema sanitario centrato sul bambino a quello degli adulti. Il modello proposto dalla Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano prevede uno schema flessibile, in cui le visite di controllo vengono effettuate nell'ambulatorio pediatrico, in giorni dedicati, programmate secondo le caratteristiche (della neoplasia e del trattamento ricevuto) di ciascun paziente, indipendentemente dall'età del malato. Dopo il decimo anno dalla fine delle cure, il follow-up prosegue solamente attraverso contatti telefonici annuali per i casi a "basso rischio" (pazienti curati senza radioterapia o agenti alchilanti, quindi senza elevati rischi di sequele funzionali), oppure secondo programmi dedicati per i pazienti ad "alto rischio" (per es., riabilitazione neurologica e monitoraggio endocrinologico per i pazienti guariti da tumore cerebrale, monitoraggio cardiologico per i pazienti trattati con antracicline, screening della mammella in fase precoce dopo la radioterapia alla parete toracica). In casi selezionati, quando è richiesta una competenza specifica (per es., i pazienti affetti da melanoma sono probabilmente più adeguatamente controllati dai dermatologi), è proposto un trasferimento ai Reparti dell'Istituto dedicati agli adulti (modello di switch sito singolo), anche se viene mantenuto comunque un contatto con il personale pediatrico. La struttura coopera con il Registro AIEOP Off-Therapy (database ospedaliero in cui i vari centri AIEOP raccolgono dati demografici e clinici sui pazienti fuori terapia) e con la rete europea PanCare (<http://www.pancare.eu/en>).

IL PROGETTO GIOVANI: IL "TEMPO MAGICO"

Il "Progetto Giovani" ha previsto la creazione di spazi multifunzionali dedicati, attraverso la riconversione di stanze in precedenza dedicate ad altre funzioni: una stanza multifunzionale per lo svolgimento di corsi, ma anche per semplice svago, arredata con poltrone, TV, computer e connessione Internet, strumenti musicali, libri, riviste, DVD, radio; una seconda stanza con diverse postazioni computer per leggere, chattare e anche studiare; una palestra, sullo stesso piano del Reparto, fornita di attrezzi vari, con un personal trainer con competenze specifiche nella fisioterapia e nella gestione di pazienti disabili.

Nel contesto del Progetto Giovani, il “Tempo Magico” è il contenitore di vari progetti, idee, attività, eventi, gestiti da professionisti ed esperti di varie discipline e pensati per provare a trasformare l’ospedale in un luogo ove garantire il maggior spazio possibile all’identità, alla creatività degli adolescenti. Il primo progetto è stato quello della collezione di moda: con la direzione artistica e il coordinamento di una nota stilista e di diversi professionisti, attraverso workshop settimanali, i ragazzi hanno ideato e realizzato un vero e proprio progetto di moda nelle sue diverse fasi, apprendendo strumenti e tecniche professionali, creando un marchio (B.LIVE), un logo che può essere letto in molti modi diversi), sviluppando i disegni di magliette e accessori, scegliendo tessuti ed accessori, fotografando il lavoro per poi produrre un libro che racconti il percorso della collezione ma anche le loro storie, per prepararsi all’evento della sfilata e poi della vendita della collezione, onde finanziare ulteriori progetti. La comunicazione via web, su un canale dedicato, ha permesso ai ragazzi di partecipare al progetto anche da casa.

Attraverso la diretta partecipazione dei giovani pazienti alle scelte dei programmi, sono stati poi definiti altri workshop, intesi non solo come occasione di intrattenimento ma anche e soprattutto come percorsi che possano permettere esperienze speciali, finalizzati a una maturazione personale ed eventualmente a future attività professionali: corsi di fotografia e di arte, corsi di informatica e uso delle nuove tecnologie, un corso di giornalismo, un progetto sulla musica, con l’obiettivo di produrre un video clip e creare eventualmente una propria stazione radio.

Un aspetto fondamentale è quello dello sport. È esperienza comune che in seguito alla diagnosi di tumore e durante il periodo delle terapie, i ragazzi che in precedenza erano praticanti o amanti dello sport possano interrompere ogni esercizio fisico e possano non trovare le giuste motivazioni per riprenderlo nemmeno dopo la fine delle cure. Di fatto, però, non esistono evidenze scientifiche che controindichino in maniera assoluta lo sport durante le terapie oncologiche e, tanto più, alla conclusione di esse. Inoltre, in molti casi lo sport fa parte della vita di un giovane, come il gioco per il bambino. Attraverso lo sport si impara a conoscere il proprio corpo, si fa esperienza del superamento dei propri limiti, si rinforza il senso di competenza e di autostima. Per un adolescente malato, che deve fare i conti con un corpo improvvisamente sofferente, praticare uno sport può essere l’occasione preziosa per fare esperienza di sé, come di una persona che può essere forte nonostante la malattia, accettando nuove sfide. Per queste ragioni, lo sport ha un ruolo centrale all’interno del “Progetto Giovani”: sport da “guardare” (assistere insieme a partite o allenamenti di squadre professionistiche), sport da “imparare” (partecipare a eventi come conferenze/testimonianze di vari atleti), ma soprattutto sport da “vivere”: attività muscolare, dell’apparato cardiovascolare e respiratorio, controllo del peso corporeo,

esercizi di riabilitazione in palestra, attività di gruppo (in particolare i ragazzi escono in barca a vela insieme, ma fanno anche corsa, bici, trekking), e attività agonistica (con l’obiettivo di creare una squadra polisportiva). La collaborazione con Centri specialistici sportivi e di medicina sportiva permetterà di sviluppare anche progetti di ricerca scientifica e faciliterà l’accesso ad una attività sempre più strutturata.

IL PROGETTO GIOVANI: RICERCA, COMUNICAZIONE, COLLABORAZIONE

La ricerca scientifica rappresenta un elemento cardine del Progetto Giovani e più in generale della Pediatria Oncologica dell’Istituto Nazionale dei Tumori di Milano. Studiare le possibili differenze cliniche e biologiche delle diverse neoplasie in relazione all’età è il passo fondamentale per poter definire terapie mirate per il paziente adolescente. Studi specifici sui pazienti adolescenti e giovani adulti, in particolare sul problema dell’accesso alle cure e dell’arruolamento nei trial clinici, sono stati effettuati anche in cooperazione con altri gruppi internazionali dedicati. Un filone di ricerca particolare è quello legato agli aspetti psicologici, dalle possibili problematiche legate al trauma, alla compliance al trattamento, alle difficoltà nel ritorno alla vita normale. In questo ambito, sono stati effettuati e sono in corso studi specifici, sulla qualità della vita, sul consenso informato (in particolare per gli studi di fase 1-2 in casi di tumore refrattario o recidivato), sui bisogni spirituali e sulla personalità.

Un recente studio ha messo in luce come in molti casi i pazienti adolescenti arrivino alla diagnosi con ritardi eccessivi¹⁵; un’ulteriore indagine prospettica, su una serie di 425 pazienti (di cui il 28% adolescenti) ricoverati dal settembre 2007 al marzo 2011, ha evidenziato come il periodo di tempo medio dalla comparsa del primo sintomo alla diagnosi sia stato di 47 giorni per i pazienti di età compresa tra 0 e 14 anni e di 137 giorni per quelli di età maggiore di 15. Questo ritardo è dipeso sia da quanto rapidamente il paziente e la sua famiglia si sono rivolti ad un medico in seguito alla comparsa dei sintomi, sia dalla interpretazione dei sintomi da parte del primo medico che ha visitato il paziente e dalla conseguente adeguatezza e rapidità dell’invio ad un Centro oncologico. Di fatto, lo studio evidenzia come la consapevolezza che anche gli adolescenti possano ammalarsi di tumore sia ancora insufficiente non solo tra i giovani e le loro famiglie, ma anche in ambito medico. Tra le possibili misure correttive per ridurre il ritardo diagnostico negli adolescenti, lo staff coinvolto nel “Progetto Giovani” ha pensato di puntare l’attenzione sul problema della comunicazione, che in molti casi è insufficiente se non addirittura errata, studiando i percorsi di comunicazione dei teenagers e cercando di utilizzare gli strumenti e i canali utilizzati preferibilmente dai giovani.

Quindi: Internet, e Youtube, con la produzione di video informativi^{16,17}:

- <http://www.youtube.com/watch?v=5WO26cV1qPc>
- <http://www.youtube.com/watch?v=5hJBFT3u7G8>
- <http://www.youtube.com/watch?v=8I8IsLJwKm4>
- <http://www.youtube.com/watch?v=qWHLDOwGeVI>

Sono, altresì, stati organizzati convegni, locali e di portata nazionale e internazionale, ed è stata effettuata una vera e propria campagna di stampa, con articoli e interviste su giornali, radio e televisione.

Infine, resta cruciale l'aspetto della collaborazione. Il problema degli adolescenti malati deve diventare un "problema di tutti" perché solo lavorando insieme è possibile affrontare i molteplici aspetti della complessa gestione degli adolescenti con tumore (dai problemi psico-sociali a quelli dell'arruolamento nei protocolli clinici, dall'adeguato training per gli operatori alla comunicazione e diffusione del problema). Lavorare come gruppo ampio e cooperativo, coinvolgendo più Centri e più figure, quali, per esempio, i gruppi dei genitori e dei "guariti", può permettere la creazione di un movimento che si configuri come interlocutore forte, anche per azioni istituzionali. Una collaborazione fondamentale è quella che gli oncologi pediatri, che anche in altre parti del mondo sono stati in genere i promotori dei programmi dedicati agli adolescenti, devono sapere instaurare con gli oncologi dell'adulto, con coloro, cioè, che di fatto oggi continuano a gestire la maggior parte degli adolescenti malati. Un esempio riguarda il rhabdomyosarcoma, tipico tumore del bambino che però può insorgere a qualsiasi età. Sulla base di diversi studi^{7,18-20} che riportavano una peggior prognosi per gli adolescenti e per gli adulti rispetto ai bambini, ma anche sulla base di dati che suggerivano da un lato che gli adulti sono spesso trattati in modo non adeguato e dall'altro che quando il trattamento somministrato è simile a quello utilizzato negli schemi pediatrici le probabilità di guarigione sono migliori, la collaborazione tra oncologi pediatri e oncologi medici ha recentemente portato allo sviluppo di un protocollo dedicato ai pazienti adulti con rhabdomyosarcoma: organizzato dalla Rete Tumori Rari e dall'Italian Sarcoma Group, due network che si occupano soprattutto di tumori dell'adulto, in collaborazione con la Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano, il protocollo, primo nel suo genere anche a livello internazionale, prevede di curare gli adulti con un piano di trattamento molto simile a quello che viene utilizzato per i bambini.

IL PROGETTO GIOVANI: IL SUPPORTO

In un contesto globale di crisi economica, con impatto severo per le risorse sanitarie, la proposta di un progetto nuovo deve avere costi ridotti o nulli per l'amministrazione ospedaliera: il progetto deve autofinanziarsi e deve essere in grado di

dimostrare la propria utilità. Nell'impossibilità di definire come obiettivo il miglioramento dei tassi di sopravvivenza dei pazienti (non misurabile a livello locale e nel breve periodo), diversi indicatori di efficacia possono essere presi in considerazione, dal semplice numero dei casi di adolescenti "attratti" presso la struttura, a parametri che riguardano la cura complessiva del paziente (es. percentuale di malati arruolati negli studi clinici, percentuale dei pazienti che beneficiano di procedure di conservazione della fertilità, percentuale di pazienti in età scolare che beneficiano del sostegno didattico); dalle esperienze e grado di soddisfazione riferite dai pazienti a parametri più legati alla ricerca (pubblicazioni, finanziamenti ricevuti). Resta però indispensabile avere a disposizione risorse dedicate. Nel mondo anglosassone i gruppi che si occupano del problema degli adolescenti e dei giovani adulti hanno il sostegno governativo e il supporto di forti charities come la Teenager Cancer Trust in Gran Bretagna e la Lance Armstrong Foundation negli Stati Uniti. Il Progetto Giovani della Pediatria Oncologica dell'Istituto Nazionale dei Tumori di Milano non potrebbe esistere senza il fondamentale supporto dell'Associazione Bianca Garavaglia (<http://www.abianca.org>), che da 25 anni sostiene le attività del Reparto e che oggi ha fatto del "Progetto Giovani" il suo principale beneficiario. Più di recente, ad essa si è affiancata la Fondazione Magica Cleme (<http://www.magicacleme.org/it/home.asp>), che in particolare si occupa delle attività e degli eventi del "Tempo Magico". Oltre all'indispensabile sostegno finanziario, queste associazioni danno un contributo importante per stimolare idee e azioni, per fornire i supporti logistici, per individuare i canali di diffusione del Progetto e per identificare testimonial (sportivi o cantanti famosi) e collaboratori ulteriori.

La prossima sfida: la nascita di una nuova disciplina

È oggi evidente che gli adolescenti e i giovani adulti affetti da cancro devono essere considerati un gruppo distinto di pazienti, le cui esigenze sono state finora scarsamente considerate dai sistemi sanitari. Un reale cambiamento culturale è in atto: l'attenzione e le risorse dedicate a questi pazienti sono mutate ed è aperta la strada verso una nuova comprensione degli aspetti biologici, clinici e psicosociali dell'oncologia degli adolescenti.

Molti sono gli aspetti da affrontare: dall'accesso alle cure alla compliance al trattamento, dalla promozione della salute alla transizione attraverso i servizi di assistenza sanitaria dedicati alle diverse età. Diversi programmi dedicati sono in fase di sviluppo nel mondo, la maggior parte nati nel contesto dell'oncologia pediatrica (come il modello proposto dal Progetto Giovani), altri sviluppati nell'ambito dell'oncologia degli adulti, altri ancora in un qualche luogo tra le due specialità.

La sfida finale, però, sarebbe quella di fondare una nuova disciplina, una vera e propria nuova sub-specialità dell'oncologia, quella che gli anglosassoni chiamano "adolescent and young adult" (AYA) oncology, l'oncologia dell'adolescente e del giovane adulto, con Unità ospedaliere fatte su misura per questi pazienti, le loro peculiarità e sui loro bisogni, con personale dedicato adeguatamente formato e con schemi specifici di ricerca.

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Figure 4.1 Fashion Project



Figure 4.2 Music Project

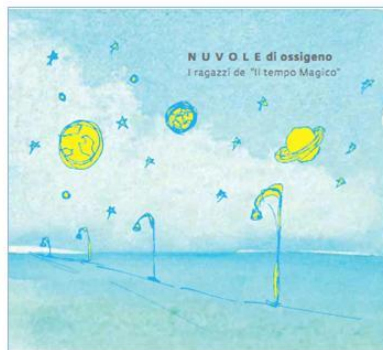


Figure 4.3 Sport Project



CONCLUDING REMARKS AND FUTURE DIRECTIONS

Even today the care of adolescent and young adult with cancer represents a challenge for oncology. The peculiarities of this complex caring context have brought in various international contexts to the proposal to establish a new discipline, the Adolescents and Young Adults Oncology (AYA Oncology), although economic limitations have hindered the realization of ad hoc departments so far. This is true also in Italy, where until now it has not been possible to realize ad hoc departments for teenagers; this implies meanwhile selecting care pathways that optimize the use of resources and that contain costs. As a specific action directed at improving access to care and inclusion in clinical trials of adolescent patients and young adults, it seems necessary to identify a limited number of cancer centers specifically dedicated, homogeneously distributed throughout the country, defining the essential services for the accreditation of these centers. The projects for teenagers and young adults may be part of an oncology center, of pediatric oncology, or could be independent projects. In any case, the essential functional and structural characteristics of a center specialized in the care of this special subset of patients should be:

- Abolition of age limits that may prevent or limit the access of patients to the pediatric center;
- The availability of a multidisciplinary management that includes a medical oncologist / pediatrician, a surgeon, a radiation oncologist and a clinical psychologist;
- Direct involvement of the medical oncologist and the pediatric oncologist in the managing of the patient's (or at least the availability of direct cooperation between these two figures);
- The availability of clinical protocols for the treatment of tumors that can occur in this age group;
- The presence of spaces and a staff dedicated to the management issues (psychologist, social worker, nurse dedicated, educators);
- A program for fertility preservation;
- A management program for the follow-up and for long-term issues.

Is also important to increase awareness of pediatricians and general practitioners on the oncological disease in adolescence. The first occasion to be informed took place in universities and specialty schools. It is therefore important that these issues are covered during the course of studies.

For example, it would be useful to disseminate the results of the studies of this thesis and of studies that are described in the scientific literature about the specific medical and psychological treatment of this subset of patients.

The fundamental role of psychology in the humanization of medicine finds in this context a new challenge. The role of psychology is essential as a liaison between the medical needs, on the one

hand, and the necessity of implementing them in practice through communication programs, awareness-raising training, development of new forms of support, and attention to the doctor-patient relationship.

Future research should be aimed at defining shared national and European standards in the treatment of adolescents with cancer, establishing and implementing guidelines on relevant topics including:

- Defining in what cases and situation using psychopharmacological therapies is recommended and when not (and related guidelines);
- Adjusting the informed consent to take part in phase I/II clinical trial, taking into account age specific vulnerability and our cultural context. Today indeed to get access to an experimental protocol, also patients aged 14 have to sign an informed consent in which it is written: "This procedure will not have a therapeutic effect for you and you will die". Qualitative studies are needed to define what is the best procedure to honestly inform a young patient, without reducing trust and destroying hope (this research is nearly to be started).
- Developing and validating diagnostic tools for the evaluation of protective/risk factors, for detecting promptly situations of poor compliance and improving the adolescent 's adaptation to the therapy and treatment. To date, there is a lack of validated tools for the assessment of personality factors that are at the same time reliable and sufficiently easy and short to be administered in a healthcare setting, where not always patients and/or operators have time and motivation to conduct a psychological evaluation.

The study of psychological responses to a serious organic disease is a potentially fruitful opportunity for understanding more in general the psychological aspects of the defenses and resources that the human mind has put in place to cope difficult situations, pain, change, and trauma. Pediatric Oncology is one of the contexts in which the presence of psychology is more accepted, so it represents an interesting starting point for a more general consideration about the role of psychological research in a working hospital; in fact an hospital context is quite different from a laboratory setting, with a number of distinctive characteristics and limits which require a high level of flexibility and adaptability in order to deal with continuously changing situations successfully. In particular, the course of a research work can be unpredictably influenced by a number of different variables concerning:

- the current institutional framework and organizational aspects;
- the relationship with patients, who have medical priorities and can be not or poorly cooperative; and with doctors, who need to approve the objectives of the research and support it;

- the needs related to treatments and diagnostic exams: the medical priorities dictate the times and places for the psychological intervention. The objectives of the studies must be respectful of the needs of the patients and not be an obstacle to the efficient execution of medical activity.

This thesis, which join together different but related studies on the treatment of cancer in adolescents and young adults, gives an account of the complexity, and in some cases the difficulty of carrying out psychological research in a hospital setting, where the constraints imposed by the clinic practice cannot be ignored, and it is necessary to flexibly take into account the issues that affect the real needs of the department in which research is conducted.

As for research, also the psychological intervention in this context is affected by the same complexity. The psychological support in case of serious organic disease cannot be centred only on traditional models of support and psychotherapy, based on a rigorous setting and on treatment of symptoms. We need new models that sustain the resources of the patients during treatments and even later, with preventive interventions and with different type of helps (psychological support, socialization, entertainment, school in hospital). We also need a new or at least renewed language which takes into account the changed ways of communicating and relating of the new generations (Internet, YouTube, Facebook, social network).

All the studies that compose this thesis arise from my daily attendance to the Pediatric oncology department and strict collaboration with physicians. These studies point out that the method and the demands of medical care can be harmonized with psychological methods and intervention through a close working relationship between psychologists and medical doctors.