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Childhood cancer in Italy: background, goals, and achievements of the Italian Paediatric Hematology Oncology Association (AIEOP)

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Abstract

This article reviews the primary goals and achievements of the Italian Association for Pediatric Hematology-Oncology (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP]), a national cooperative group that has been working for children and adolescents with cancer in Italy since 1975.

Keywords

Childhood cancer, Italy, Pediatric Hematology Oncology Association, AIEOP, network

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Introduction

The Italian Association for Pediatric Hematology-Oncology (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP]) is a national cooperative group that has been working for children and adolescents with cancer in Italy since 1975. This article describes the Association's main goals and achievements and serves as a tribute paid by the community of Italian pediatric oncologists to Professor Giuseppe Basso, who died of coronavirus disease 2019 (COVID-19) in February 2021. Giuseppe Basso was an eminent Italian pediatric oncologist whose focus on the importance of networking and involving all Italian pediatric oncology centers, large and small, in developing treatment protocols and furthering

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research has had a profound effect on the AIEOP. Dr. Basso was an eminent Italian paediatric oncologist, a brilliant researcher, and a passionate physician with an extraordinary dedication to his patients. He was a model for Italian paediatric oncologists, who will continue to strive to follow his example.

Discussion

The AIEOP is a scientific society accredited by the Italian Ministry of Public Health. It has approximately 550 members (not only physicians, but also biologists, nurses, psychologists, and physiotherapists) and a network of 49 treatment centres. These AIEOP centres are part of Italy's national health system. They are dedicated to the treatment of children and adolescents with oncologic or haematologic or immunologic diseases. The centres have been identified and accredited in accordance with requirements concerning the qualitative, structural, technological, and quantitative standards of hospital care established in the AIEOP regulations. The centres cooperate with one another, adopting shared treatment protocols. They are distributed all over the country, with 25 centres in northern Italy, 9 in central Italy, and 16 in southern Italy and the islands of Sicily and Sardinia (Figure 1). There are no paediatric oncology–haematology units in Italy that are not affiliated to the AIEOP.

The various AIEOP centres have different volumes of activity and different specificities. They nonetheless cooperate in networks that, in several geographic areas, are often based on "hub and spoke" models.[1] This approach serves the dual purpose of offering the best possible care for every patient close to home, avoiding pointless migrations, wherever possible[2]; and, at the same time, providing only in selected referral centres those treatments that are too complex to be administered at all centres (such as stem cell transplantation, surgical procedures demanding particular expertise, radiotherapy, and early-phase clinical trials).

The AIEOP has a clearly defined organization. It has a statute and regulations, a president and a board of directors elected by its members (who remain in office for 3 years), a general meeting, and an annual national conference. In recent years, the AIEOP has also developed an operations unit (the Daniele and Luciano Pederzani centre), complete with human resources (clinical trial assistants, data managers) and dedicated facilities for clinical research activities.

Within the AIEOP, the research pathways and treatment programs are decided and coordinated by a number of working groups. Sixteen groups are dedicated to a particular type of disease: 9 haematologic and onco-haematologic diseases, 6 solid tumours, and 1 immunologic diseases. Another 13 groups are concerned with issues common to all these diseases, including a psychosocial working group, one that focuses on supportive therapy and infections, one for nursing aspects, one concentrating on late sequelae,

Figure 1. A map of the 49 Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP] centers.

one dedicated to adolescents, and one (recently set up) for young investigators.

The AIEOP statute defines the Association's goals as follows:

- To ensure, coordinate, and promote treatment and research activities in the field of paediatric haematology and oncology;
- To develop and standardize shared treatment protocols;
- To promote scientific and clinical cooperation among those involved in the field of paediatric haematology and oncology;
- To disseminate knowledge, through conferences, interdisciplinary meetings, and scientific publications, regarding the problems of children and adolescents with haematologic, oncologic, and immunologic diseases, also nurturing relations with universities, ministries, and other national and international bodies with similar goals;
- To interact with all relevant public and private associations to disseminate knowledge regarding the problems of children and adolescents with acute or chronic haematologic and neoplastic diseases.

This brief list of aims and goals outlines a particular feature of the AIEOP by comparison with other scientific societies, in that it not only promotes scientific research, but is also directly involved in managing treatment protocols and every aspect of patient care. Ever since it was first established, the

AIEOP has been developing clinical protocols for paediatric onco-haematologic diseases. All these clinical protocols have been undertaken as multicenter efforts owing to its collaborative network, which has emerged as a fundamental tool for improving the quality of these treatments and promoting the transfer of scientific evidence into clinical practice. Italian paediatric oncologists had realized in the 1970s that, working with such rare diseases, they could only advance their understanding and improve the available treatments, and their patients' consequent chances of cure, by means of a continuous and far-reaching cooperation, initially nationwide, and nowadays often on an international scale. Adopting cooperative treatment protocols and constantly participating in (often randomized) national and international clinical trials has been key to enabling the significant improvements in the cure rates for paediatric cancer, which have globally come to exceed 80%.

By way of example, Table 1 lists the results of some national studies coordinated by the AIEOP, or international studies in which the Association took part.[3-11]

Another characteristic that makes the AIEOP unique as a scientific society is that it directly manages its own databases for collecting patients' clinical information. The form called Mod.1.01 is for unequivocally recording the identification of all new patients of paediatric age with an oncologic or haematologic or immunologic disease and diagnosed or treated at one of the AIEOP centers. The form adopted in 1989 in a printed paper format was replaced in 2000 with an electronic version on a platform managed by the computing centre of the Italian Inter-University Consortium (CINECA). In 2013, it was approved as a "retrospective and prospective observational study protocol on subjects enrolled at AIEOP centers," and it was recently made compliant with the standards of the European General Data Protection Regulation. The total number of cases contained in the AIEOP 1.01 database has now exceeded 60,000, with a mean annual recruitment rate of more than 1700 patients.[12,13]

One type of analysis made possible by the Mod.1.01 database is a comparison between the number of cases actually treated at AIEOP centers (and registered with the model 1.01) and the number of cases expected in light of incidence rates derived from population-based registries. One such recent study, referring to 2013–2017, and to 9534 cases registered in the AIEOP database (8031 patients aged 0–14 and 1503 aged 15–19 years), reported an observed/expected (O/E) ratio of 0.81, but it was 1.06 for children and just 0.37 for adolescents (as well as differing significantly by type of tumor).[14] In other words, this study showed that practically all children with cancer in Italy were treated at AIEOP centers, but the same could not be said of the older adolescents. Such an evident gap in access to care, and to clinical trials for adolescents with cancer, is an internationally recognized challenge.[15,16] Some progress has been made, however: the percentage of adolescents treated at AIEOP centers has increased over the years, with the corresponding O/E ratio rising from 10% in 1989–2006[17] to 28% in 2007–2012,[18] and to 37% in 2013–2017.[14]

The Mod.1.01 registry contains each patient's main demographic information, and details of their diagnosis and follow-up. It is linked to various other disease-specific registries activated for each treatment protocol, as well as with other registries, including one for haematopoietic stem cell transplants and cell therapies, a registry of patients who have completed their treatments, and one relating to long-term survivors. This last registry is part of an international scheme, the "European Survivorship Passport [SurPass]," for patients cured of cancer, developed with a fundamental contribution from the AIEOP.[19] A significant proportion of childhood cancer survivors remain at high risk of late treatment-related effects. At least 60% of them develop adverse health-related outcomes, some of which can appear several years after they have completed their treatment. These sequelae can range from fertility issues to endocrine impairments, from heart conditions to altered lung function, and also to the development of secondary tumours.[20] These long-term consequences may be severe and need appropriate treatment, but it is especially important for them to be correctly and promptly identified. The survivorship passport is an essential tool for this purpose. It is a document that contains a structured summary of each patient's diagnosis and treatment. Based on these details, it generates personalized recommendations regarding their follow-up, and the tests that it is important to conduct in each case, in accordance with international guidelines. The passport is delivered directly to patients and accompanies them for the rest of their lives, with the purpose of ensuring a timely diagnosis of any late side effects of the treatment they have received.

The Mod 1.01 registry is also linked to a Central Diagnosis Review platform. Another important organizational feature developed over the years by the AIEOP and serving all its treatment centers and patients is a centralized review process for all diagnoses. For such rare and heterogeneous diseases as paediatric tumours, arriving at a correct histologic and molecular diagnosis is a challenge, and crucial to a patient's whole subsequent care pathway. Over the years, the AIEOP has identified specific reference laboratories with demonstrable experience, to which tumor samples are submitted for a final confirmatory diagnosis.[21] This centralized review is indispensable for patients to be included in treatment protocols. It should be seen as the gold standard, given the major discrepancies (sufficient to warrant a different treatment) between diagnoses established at local centers and the centralized diagnostic reviews, which reportedly occur in 5%–30% of cases of paediatric neoplastic disease.[22,23] In parallel, the AIEOP has identified certain reference figures with particular expertise on the various types of tumor who are involved

Table 1. A brief selection, by way of example, of Italian studies coordinated by the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) and international studies in which AIEOP participated.

Study	Patients, n	Patient ages	Methods	Results
Acute lymphoblastic leukaemia: AIEOP prospective study (1982–2000)[3]	4865	0–18 y	Treatment characterized by gradual intensification of systemic therapy and reduction of cranial radiotherapy	Gradual improvement in results, with a reduction in the isolated central nervous system relapse rate; 10-year survival rates rose over the years (EFS from 53% to 72% and OS from 64% to 82% in study 82 and study 95, respectively)
Acute lymphoblastic leukaemia: AIEOP–BFM prospective randomized controlled trial (2000–2006)[4]	4741	1–18 y	Introduction of standardized quantitative assessment of MRD, based on immunoglobulin and T-cell receptor gene rearrangements as polymerase chain reaction targets, at two time points, to stratify patients in a large prospective study	In patients with precursor B-ALL: MRD-SR (42% of cases; MRD was negative at day 33), 5-year EFS 92.3%; MRD HR (6%; MRD 10^{-3} or more at day 78), 5-year EFS 50.1%; MRD IR (52%; others), 5-year EFS 77.6% ($p < 0.001$); MRD was highly predictive for relapse in childhood precursor B-ALL
Acute myeloid leukaemia: AIEOP prospective study (2002–2011)[5]	504	0–18 y	Patients treated with chemotherapy ± autologous or allogeneic HSCT; stratification as HR or SR	Complete remission, early death, and induction failure rates were 87%, 3%, and 10%, respectively; 8-year OS, EFS, and DFS were 68%, 55%, and 63%, respectively; OS, EFS, and DFS for SR and HR patients were 83%, 63%, and 66%, and 64%, 53%, and 62%, respectively; DFS was 63% and 73% for HR patients given autologous and allogeneic HSCT, respectively
Hematopoietic stem cell transplantation: AIEOP randomized trial (2008–2012)[6]	173	0–18 y	Efficacy of two different doses of rabbit ATLG to prevent graft-versus-host disease in children with haematologic malignancies given transplants from an unrelated donor	Children with haematologic malignancies receiving transplants from matched unrelated donors benefited more from a 15 mg/kg dose of ATLG than from a 30 mg/kg dose; ATLG at 15 mg/kg should be regarded as the standard dose for unrelated donor allogeneic HSCT in this patient population
Neuroblastoma: AIEOP prospective study (1985–1997)[7]	359	1–15 y	Patients with stage 4 neuroblastoma, treated with three consecutive high-dose protocols	Five-year OS for the three studies was 26%, 23%, and 28%; attempts to intensify chemotherapy were associated with more severe toxicity, but no significant improvement in survival
Nephroblastoma: AIEOP prospective study (1991-2008)[8]	99	3–125 mo	Patients with nonanaplastic stage III Wilms tumor, treated in two consecutive studies with surgery, chemotherapy, and abdominal radiotherapy	Overall series: 4-year DFS 85%, OS 92%; 4-year DFS was 73% in N1 and 98% in N0 patients; this study was the first to investigate prognostic factors in stage III Wilms tumor and propose a subclassification of stage III tumours (N1 patients needing intensified therapy)
Ewing sarcoma: cooperative study with ISG and SSG (1999–2008)[9]	102	2–40 y (median 16)	Patients with metastatic disease (limited to lung/pleura or a single bone), treated with intensive chemotherapy, surgery, or RT, high-dose busulfan/melphalan plus autologous stem cell rescue, and total-lung RT	Five-year EFS 43%, OS 52%; unfavourable prognostic factors: poor response on primary tumor and incomplete radiologic remission of lung metastases after primary chemotherapy; this intensive approach is feasible and long-term survival is achievable in ~50% of patients
Ependymoma: AIEOP prospective study (2002–2014)[10]	160	1–21 y	Patients received focal RT (59.4 Gy); grade III/NED received chemotherapy (4 VEC) after RT; patients with ED received chemotherapy, second-look surgery, and RT 59.4 Gy followed by an 8-Gy boost; children age 1–3 y with grade II tumours showing NED could receive 6 VEC courses alone	For the whole series, 5-year PFS and OS were 65.4% and 81.1%, with no toxicity-related deaths; when feasible, the RT boost seemed effective in improving prognosis; even after multiple procedures, complete resection confirmed its prognostic strength, along with tumor grade
Rhabdomyosarcoma: EpSSG prospective randomized study (2005–2016)[11]	371	6 mo–21 y	AIEOP centres were the major contributors to enrolment; the concept of maintenance therapy was piloted at AIEOP centers; patients with high-risk rhabdomyosarcoma, randomized to stop treatment or receive maintenance chemotherapy after induction therapy	Maintenance chemotherapy with vinorelbine and low-dose oral cyclophosphamide increased 5-year OS (to 86.5% vs 73.7%, $p = 0.009$); after this study, the maintenance therapy ideated at AIEOP centers became standard of care for high-risk rhabdomyosarcoma

ATLG: anti-T-lymphocyte globulin; B-ALL: B-cell acute lymphoblastic leukaemia; BFM: Berlin-Frankfurt-Munster; DFS: disease-free survival; ED: evidence of disease (incomplete resection); EFS: event-free survival; EpSSG: European Pediatric Soft Tissue Sarcoma Study Group; HR: high risk; HSCT: haematopoietic stem cell transplantation; IR: intermediate risk; ISG: Italian Sarcoma Group; MRD: minimal residual disease; NED: no evidence of disease (complete resection); OS: overall survival; PFS: progression-free survival; RT: radiotherapy; SR: standard risk; SSG: Scandinavian Sarcoma Group; VEC: vincristine, etoposide, cyclophosphamide.

in the centralized submission of biological material[24] and in the creation of tissue banks for biological studies.

The AIEOP's multiple activities demand a cooperative effort in terms of its economic support. To coordinate this aspect, the AIEOP supported the creation of a parallel foundation in 2007: the Fondazione Italiana Ematologia Oncologia Pediatrica (FIEOP) was established as a not-for-profit organization with goals of social solidarity. It is closely connected to the AIEOP and its purpose is to promote fundraising programs. Important support also comes from private individuals and charities, one of which particularly deserves mention for its ongoing consolidated partnership in recent years: Fondazione Umberto Veronesi.[25]

Another fundamental partnership for the AIEOP is with the Federation of Parents' Associations at the various AIEOP centers—the Federazione Italiana Associazioni Genitori Oncoematologia Pediatrica (FIAGOP)—founded in 1995 to create synergies among the various confederated parents' associations. The FIAGOP has always been active alongside the AIEOP, its goals focusing on information and communication (such as the promotion of social awareness campaigns in the mass media), as well as support for families and for research.

Whereas much has been done to create and develop an effective network dedicated to children and adolescents with haemato-oncologic diseases in Italy, there is still much to do, especially in light of the rapid changes that the field of paediatric onco-haematology has been experiencing in recent years, and is likely to see in the future.

That said, the AIEOP needs to strengthen its cooperative network of treatment centers. Paediatric oncologists take part in treatment protocols that are increasingly complex, and often designed in the context of international cooperative groups; they need to further lines of research that are sophisticated and costly. Given this situation, it is indispensable for the AIEOP's diverse centres to stay focused on their shared goals, which have made the AIEOP a successful model of scientific collaboration.

There is an evident need to further broaden the horizons of their cooperation with a multistakeholder committee to oversee implementation across programs and plans. It is indispensable to organize increasingly effective exchanges with other scientific societies. One example, already underway, concerns the adult oncology community: the Italian Association of Medical Oncology (Associazione Italiana Oncologia Medica [AIOM]) has joined forces with the AIEOP to work together on the challenges of adolescent and young adult patients with cancer. It is also important to strengthen AIEOP's cooperation with its international counterparts, particularly the European Society for Paediatric Oncology (the AIEOP is one of the European National Pediatric Hemato-Oncology Societies [NaPHOS]). Together with SIOPE, AIEOP can embark on concrete action to sustain innovation, which means new drugs and precision medicine for childhood cancers, but also novel strategies and new methodologic approaches (e.g. big data and artificial intelligence). Together with patients and parents' associations, the AIEOP can actively contribute to schemes undertaken by the European Parliament Commission to give priority to paediatric tumours in its various health care programs, and to take steps at regulatory level, for instance, to facilitate access to medicines and indispensable economic funds, and it can engage minds and pool resources to promote biological studies to better investigate the causes of paediatric cancer.

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