Interaction of pediatrician, oncologist and therapist in the complex therapy of children's patients

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Abstract. The interaction of pediatricians with pediatric oncologists is important for the optimization and treatment of children suffering from oncological diseases. Modern practice strives for a combined approach that includes the interaction of specialists from different fields of medicine in order to improve the quality of medical services provided. The purpose of the article is to provide pediatricians with updated information about the state of pediatric cancer care. In this paper, the following aspects are highlighted, which are aimed at optimizing and applying innovations in the treatment of oncological diseases in children, in particular: reducing the toxicity of drugs in treatment, studying cancer biology, considering new treatment methods, monitoring the disease, since these areas are key topics of general pediatric medicine. The review of immunotherapy and combined approaches in the treatment of oncological diseases of children was carried out. Attention is paid to precision oncology aimed at identifying drugs that will work with specific mutations in the field of tumor destruction. Issues related to the interaction of a pediatrician, oncologist and ENT in combination therapy are also considered.

1 Introduction

The diagnosis of cancer is a serious shock for the child and his family. Childhood cancer affects almost all aspects of the health of children and adolescents. Fifty years ago, the survival rate after cancer was less than 10%. However, the achievements over the past few decades have led to a significant improvement in results: more than 85% of children diagnosed with cancer survive for a long time Despite a 71% decrease in cancer mortality in this age group from 1970 to 2019, cancer remains the leading cause of death from diseases among children. According to the latest statistics, in 2022, it is estimated that 10,470 new cases of cancer will be diagnosed among children from birth to 14 years old [1].

The results of cancer treatment in children have improved significantly at the present stage, and yet this success is unevenly distributed between cancer types or patients. The data on pediatric oncology highlights the need to improve access to medical care, including

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clinical trials and expanded testing for all patients. In cancers such as brain tumors and sarcomas, continuous progress in understanding the biology of tumor heterogeneity is an important step towards finding new therapeutic combinations to improve outcomes. Children who have had cancer need access to the latest technologies aimed at reducing or better managing the toxic effects of therapy. With advances in treatment and survival, patients with pediatric oncology still need long-term multidisciplinary specialized care. This review discusses the main areas of pediatric oncology: toxicity reduction, cancer biology, new treatment methods, detection and monitoring to highlight recent achievements and areas for further improvement.

2 Materials and methods

Studies on optimizing the treatment of children with oncological diseases emphasize the importance of interaction between a pediatrician, oncologist and ENT within the framework of combination therapy. Effective treatment of children with oncological diseases requires an integrated approach and coordinated work of various specialists. In this work, an analysis of scientific articles and literature was carried out, which helped to identify modern methods and strategies for the treatment of this category of patients. A review of scientific articles, publications, clinical studies, as well as guidelines and recommendations related to the treatment of oncological diseases in children was conducted. This analysis allowed us to evaluate modern approaches and best practices in the field of combination therapy. Emphasis is placed on a multidisciplinary approach combining the efforts of pediatricians, oncologists and otolaryngologists to optimize treatment.

3 Results

Children with oncological diseases should be treated in a specialized cancer center. The doctors of these centers have extensive experience in treating children with cancer and access to the latest research. In many cases, a team of doctors works with the child and family to provide medical care. Treatment options and recommendations depend on several factors, including the type of cancer, possible side effects, patient preferences and general health. Individual methods and types of treatment of pediatric oncological diseases are shown in Figure 1.

An important direction of optimizing the means and methods of oncological care for children is the reduction of toxicity. Thus, thanks to the joint efforts of national clinical trials for decades, excellent results have been achieved in the treatment of some pediatric patients with cancer variants such as newly diagnosed B-cell lymphoblastic leukemia of standard risk (> 90% relapse-free and overall survival) [2]. However, despite these excellent results, modern treatment regimens lead to a significant risk of both short-term (during therapy) and long-term (after therapy) side effects, and many children who have had cancer are diagnosed with 1 or more chronic health problems [3].

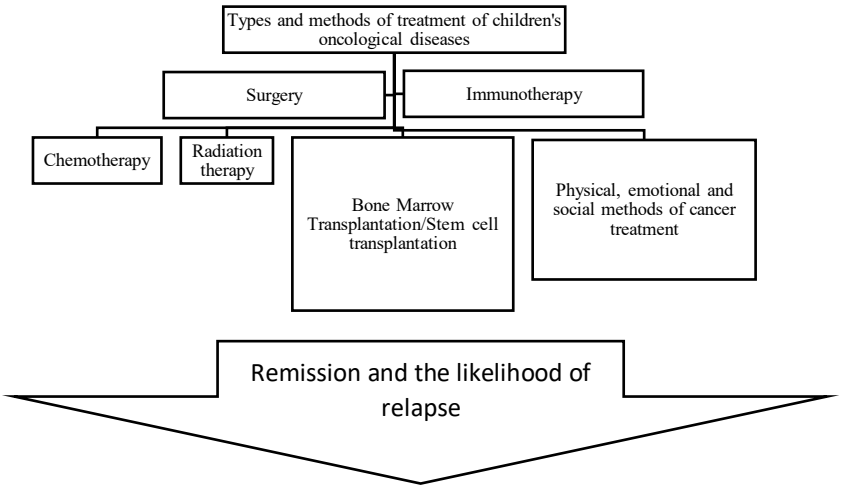

Fig. 1. Distribution of methods and types of treatment of pediatric oncological diseases [1]

When achieving generally excellent results, the logical next step is to determine how best to mitigate or reduce the level of toxicity while maintaining excellent overall survival.

Table 1 provides examples of just some of the toxic effects encountered during targeted cancer therapy to highlight the range of approaches to reduce or avoid these long-term effects. These approaches include protective drugs, the use of various chemotherapy regimens, and the overall reduction of exposure to agents through optimization and risk stratification.

Table 1. Examples of long-term side effects of cancer treatment in children and interventions

Type of cancer	Examples of long-term side effects from therapy [4]	Examples of interventions to reduce long-term side effects [5]
Hodgkin's lymphoma	Gonadal dysfunction: the possibility of decreased fertility or infertility in both men and women Thyroid complications: hypothyroidism; increased risk of thyroid cancer	Options for maintaining fertility at diagnosis and during long-term follow-up visits are discussed Thyroid complications: reduced risk by reducing the use of radiation therapy
Acute lymphoblastic leukemia	Growth disorders, including short stature, premature puberty or delayed puberty Metabolic syndrome, obesity	Growth disorders: improve when cranial radiation therapy is replaced with intrathecal chemotherapy Dietary interventions and exercise
Neuroblastoma	Hearing loss: related to the effects of platinum compounds Cataract	Reduce the duration and intensity of treatment, whenever possible, by stratifying the risk
Wilms ' tumor	Cardiac toxicity: associated with anthracyclines, irradiation of the heart Renal dysfunction: damage to the glomeruli and tubules; end-stage kidney disease in patients with bilateral Wilms tumor or receiving radiation therapy for unilateral disease	Cardiac toxicity: use of cardioprotective agents (dexrazoxane) and minimization of chemotherapy and radiation when possible Kidney dysfunction: operation with preservation of nephrons in bilateral disease, without the use of nephrotoxic agents (for example, nonsteroidal anti-inflammatory drugs)

One approach to reducing toxicity is to reduce cumulative doses of chemotherapy. If we consider leukemia as an example, then it is advisable to prescribe chemotherapy for risk groups.

Patients with a standard risk of leukemia are exposed to less accumulation of anthracyclines compared to patients with high-risk leukemia [6]. In addition, based on clinical studies conducted in the field of pediatric oncology, children received an additional year of supportive chemotherapy for the treatment of B-cell lymphoblastic leukemia according to some joint treatment protocols.

Current practice has excluded this additional year of therapy for children, since with modern intensive care regimens, the risks of such practice are quite high [7]. The reduction or cancellation of radiation therapy is another example of therapy modifications that can reduce late consequences, such as secondary malignancies. Recent data have demonstrated that radiation therapy can be canceled in patients with Hodgkin's lymphoma who demonstrate an adequate response to chemotherapy [8].

There are new chemotherapeutic drugs aimed at maintaining antitumor activity while reducing damage to normal tissues. Liposomal chemotherapy drugs, such as doxorubicin, are at various stages of preclinical trials. In addition to the less toxic drugs of traditional chemotherapy, immunotherapeutic treatments with a reduced or different toxicity profile compared to chemotherapy aimed at DNA damage have appeared. To date, immunotherapy has been most successful in the treatment of childhood leukemia and lymphoma, and the long-term toxicity profiles of these treatments continue to be studied [9, 10].

Large-scale sequencing efforts in pediatric oncology over the past decade have significantly expanded the understanding of changes in the germ line in children with cancer [11]. This is important not only for the predisposition to cancer and the biology of the tumor, but also for how the genetic composition of a child can change the way drugs are metabolized. Such pharmacogenomic analyses may reveal the need to reduce the dose of certain medications or use certain medications to treat patients with certain genetic factors that may make the drug more effective. Since about 20% of children with cancer can be hospitalized due to the fact that they have experienced serious side effects from treatment [12], this is becoming an increasingly important area, given the steady increase in access of patients with tumors and germ line sequencing. In addition, early prognosis of oncological diseases of patients whose tumors may not respond to the drug may help doctors consider the use of alternative options in the treatment. One example of this is the reaction to platinum preparations, which decreases due to mutations in the genes of the ERCC excision repair protein family [12].

Until new treatments are available, some side effects are currently unavoidable, such as the possibility that some treatments may affect fertility. Patients experiencing life-threatening emergency oncological care often do not have time to preserve fertility before the start of gonadotoxic treatment. Cumulative exposure to cyclophosphamide and equivalent drugs significantly reduces a child's future ability to have children [13]. Women and men in the post-puberty period have the possibility of cryopreservation of eggs or spermatozoa before treatment [14]. There have been recent advances in fertility preservation, which make it possible to increase the chances of future fertility while successfully treating cancer in a child. For example, prepubescent women in some specialized centers now have access to research protocols that attempt ovarian cryopreservation to preserve fertility [15]. Infertility can have a serious impact on the quality of life of an adult.

Real medical statistics show that some children, after undergoing cancer treatment, still do not survive. Children diagnosed with brain tumors, such as diffuse internal ponta glioma (DIPG), and bone tumors, such as osteosarcoma and Ewing's metastatic sarcoma, have not seen a significant improvement in results over decades. With regard to these types of cancer, specialists strive to continue clinical research and study the biological origin of these tumors

(heterogeneity, metastatic potential, evasion of immunity, resistance to treatment and stemness - the ability of cancer cells to undergo "self-renewal and differentiation" [16]) and appropriate interventions that will be used to increase the survival rate of such cancer patients.

One of the tasks is to achieve an understanding of which of the subsets of tumors can lead to the worst clinical results, after which aggressive subtypes of tumors should be studied to determine specific vulnerabilities, which, ultimately, will give the key to new treatments for testing on patients with aggressive subtypes of tumors. Neuroblastoma is an example of a solid tumor in which ALK mutations and N-Myc amplification have been found to lead to cancer progression and are associated with worse outcomes [17]. ALK inhibitors (e.g., crizotinib, lorlatinib, etc.) are being studied in the treatment of high-risk neuroblastoma with an ALK mutation, which is an example of a biological change in treatment. Currently, certain targeted efforts are being made to identify risk groups for the development of bone sarcomas.

For rare tumors, every sample is valuable. National and international efforts to improve the bank of biological samples of intractable cancers are a priority. The industry continues to rely on the willingness of pediatric patients and their families to participate in scientific research aimed at improving the study of these cancers [18]. Optimization of sample storage and annotation conditions through data harmonization is a constant priority. For cancers such as DIPG, biopsy samples were not saved, and the diagnosis was made only on the basis of clinical data or MRI results. Recent advances in the field of neurosurgical methods of stereotactic biopsy now make it possible to safely obtain material for biopsy in case of suspicion of DIPGS [19]. Such diagnostic biopsy material allows a deeper understanding of the biology of DIPG, and the researchers hope that such samples will begin to provide clues to new therapeutic approaches.

In addition to obtaining the material during the initial diagnostic biopsy, the material for biopsy during relapse is also invaluable. Tumors change over time and after exposure to cytotoxic chemotherapy. Some subpopulations of the tumor may develop resistance, which ultimately leads to a relapse of the disease [20]. Historically, with cancer in children, a biopsy was not always performed during a relapse in order to save children from additional procedures. Given the need for a better understanding of disease recurrence to improve results and the possibility of participating in clinical trials, there has been a shift in practice, and today pediatric patients are more likely to be offered a repeat biopsy if they suspect disease progression [21]. The MATCH study demonstrated the possibility of identifying personalized therapy options for pediatric patients with intractable cancer [22].

Today, new treatment approaches are needed to continue improving treatment rates and reducing mortality in pediatric patients with cancer. Examples of targeted agents (antibodies, cell therapy, kinase inhibitors, antibody-drug conjugates, etc.) used in the treatment of cancer in children are listed in Table 2.

Attention should also be focused on the importance of such a direction as precision oncology. Its purpose is to identify drugs that are predicted to work against tumors with specific mutations, etc. As noted above, the MATCH study demonstrated the possibility of identifying personalized therapeutic options for pediatric patients with intractable cancer [22].

Table 2. Examples of targeted drugs for the treatment of cancer in children and adolescents

Type of cancer	Example of an achievable goal [23]	Examples of targeted agents [24]
Acute lymphoblastic leukemia	CD19 expression	Blinatumomab (biospecific activator of CD19-CD3 T cells, BiTE) T cells with chimeric antigen receptor CD19 (CAR)
Children's fibrosarcoma	NTRK fusion	NTRK inhibitors (larotrectinib, etc.)

Neuroblastoma	High expression of GD2 ALK mutation	Rituximab (monoclonal antibody against GD2) ALK inhibitors (lorlatinib, etc.)
Low grade gliomas	BRAF mutations	RAF inhibitors, pan-RAF inhibitors (tovorafenib) and MEK inhibitors
Hodgkin's lymphoma	CD30	Brentuximab vedotin (a drug conjugate with an antibody targeting CD30. The chemotherapeutic agent associated with CD30 is monomethylauristatin E [MMAE])
Mature B-cell lymphomas	CD20	Rituximab (chimeric antibody CD20)
Epithelioid sarcoma	SMARCB1 /INI1 mutations	Tazemetostat (EZH2 inhibitor)

Examples of recent successful cases of precision oncology in pediatric oncology include the use of NTRK inhibitors in rare solid NTRK tumors in children, such as pediatric fibrosarcoma and RAF/MEK inhibitors for the treatment of low-grade gliomas in children [23].

Currently, there are hundreds of immunotherapy methods for the treatment of cancer. In a broad sense, these treatments include engineered cells such as CD19 CAR-T cells for the treatment of childhood B-cell lymphoblastic leukemia, checkpoint inhibitors aimed at "awakening" the body's own immune system, manipulation of cytokines and agents aimed at remodeling the tumor microenvironment. Although there are problems with using CAR-T cells to treat solid tumors, impressive progress has been made in demonstrating the possibility of using CAR-T cells to treat currently incurable cancers in children, such as DIPG (diffuse internal pontinus glioma)[25]. Given the rapid growth of immunotherapy being developed for adults, there is significant potential for immunomanipulation for the treatment of cancer in children in the future. Currently, few children with cancer are treated with immunotherapy. In addition, oncologists are just beginning to study and understand the long-term side effects of immunomanipulation on the health of children and adolescents. As these data become available, it is important to keep in constant contact with general pediatricians to make sure that these consequences are recognized and effectively eliminated.

Tumors are known to be heterogeneous and develop resistance to treatment, including resistance to targeted agents. Tumors rarely show a long-term response to individual agents. Combined approaches to the "attack" of tumors using various methods are one of the ways to bypass the resistance. The combination of DNA-damaging agents with immunotherapy and the use of antibody-drug conjugates are two examples of new multimodal therapy methods that could potentially continue to change the treatment of cancer in children. The timing of immunotherapy (the order of drug delivery and/or the severity of immunosuppression during drug administration) is especially important when adding immunotherapy to existing treatment regimens. Preclinical data specifically concerning the timing of immunotherapy is a new topic of great interest [26].

Disease monitoring is carried out both during therapy and after completion of initial therapy for the treatment of cancer in children. Irradiation of children, for example, during chest X-rays and computed tomography, should always be avoided or minimized if possible. New technologies are emerging that are likely to revolutionize the ways in which tumor reactions and relapses are monitored.

When the tumor cells die, DNA fragments from the tumor cells enter the patient's bloodstream. This circulating tumor DNA (ctDNA- fragmented DNA of tumor origin in the bloodstream, which is not associated with cells) can be detected in the blood of cancer patients [27] and provides a wide range of future possibilities: more frequent monitoring of relapses of the disease at a level that may not be able to detect scanning, reduced exposure to radiation and identification of emerging stable subpopulations of tumor cells during therapy.

One important question that ctDNA can help solve is whether the results will improve the early detection and treatment of relapses. As ctDNA monitoring ("liquid biopsies") is increasingly included in prospective clinical trials, specialists will come to a more complete understanding of the potential of this technology. A recent example of the effectiveness of ctDNA was demonstrated in rhabdomyosarcoma of medium risk, negative at fusion, where researchers found that the presence of ctDNA in the patient's blood serum at diagnosis was associated with a worse outcome (statistically significant reduction in event-free survival and overall survival) [28].

4 Discussion

Oncological diseases in children require a comprehensive and attentive approach from specialists in various fields of medicine. The interaction of a pediatrician, oncologist and otolaryngologist in combination therapy is an important aspect of optimizing the treatment of children with oncological diseases. We will review the key aspects of this interaction.

1. Diagnostics and screening. Early diagnosis plays a crucial role in the successful treatment of cancer. Interaction between a pediatrician and an oncologist includes diagnosis and initial screening, while an otolaryngologist can help identify specific symptoms associated with throat, nose or ear cancer.

2. Integration of therapeutic methods. Combination therapy in oncology often includes surgery, chemotherapy, radiation therapy and innovative treatments such as immunotherapy. The team of specialists should discuss the optimal strategies for each patient in order to minimize side effects and maximize the effectiveness of treatment.

3. Managing side effects. In the process of treating children with cancer, side effects can become a significant problem. The interaction of specialists will help in the effective management of side effects of treatment, such as hair loss, skin problems, hearing problems and others.

4. Psychological support. The fight against cancer in childhood is often associated with psychological stress for the child and his family. Doctors should cooperate with psychologists and palliative care specialists to provide psychological support and improve the quality of life of patients [29].

After successful treatment, a period of rehabilitation and observation follows. It is important that specialists plan further stages of treatment and rehabilitation taking into account the characteristics of each patient.

Cooperation between a pediatrician, oncologist and otolaryngologist ensures optimal treatment, allowing patients to receive the necessary medical care and support at every stage of the fight against cancer.

In addition, it is important to ensure regular updating and exchange of medical information between specialists in order to maintain a complete picture of the patient's health and effectively monitor the progress of treatment. This may include:

– coordination of care. It is important to create an interdisciplinary team to coordinate the care of patients with cancer, where each specialist plays a role and is responsible for certain aspects of treatment.;

– development of an individual treatment plan. In this regard, it is important to take into account the characteristics of each patient, his state of health, age and features of cancer when developing an individual treatment plan and monitoring its implementation;

– training and informing patients and their families. It should be noted here that it is necessary to provide information about what to expect during treatment, side effects and ways to manage them, as well as support in making decisions regarding treatment and subsequent care [30];

– continuous training and exchange of experience. This should include participation in conferences, seminars and training courses aimed at the exchange of experience and the transfer of the latest methods of treatment and diagnosis;

– research and innovation. They may include participation in clinical trials and the development of new methods of treatment and diagnosis to improve treatment outcomes and increase the chances of recovery in children with cancer.

In general, close cooperation between a pediatrician, oncologist and otolaryngologist, as well as other specialists involved in the treatment of children with cancer, plays a key role in providing effective and comprehensive care, as well as increasing the chances of full recovery and improving the quality of life of patients.

5 Conclusions

At the present stage, the improvement of the results of cancer treatment in children is associated with new methods of treatment and genetic testing. Innovations in the field of cancer therapy in children include immunotherapy, targeted drugs and antibody-drug conjugates. Monitoring and early detection of relapses of the disease are important for improving treatment outcomes. Germ line sequencing can supplement knowledge about genetic factors associated with cancer. Strengthening partnership and communication between pediatricians and the pediatric oncology team is key to the success of treatment.

The simplified formulation of goals in pediatric oncology is to finally "overcome" the plateau of survival in some solid tumors and minimize toxicity for all children and adolescents diagnosed with cancer. In this article, we have identified several ways in which innovations are applied in the treatment of oncological diseases in children. Children with oncological diseases need long-term care both on time and after completion of treatment. Continuing to strengthen the partnership and communication between the patient's pediatric oncology team and the primary care pediatrician is essential to fulfill this mission.

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