Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

Submitted on: 11/06/2021
Approved on: 03/27/2022

ORIGINAL ARTICLE

Neurodevelopmental sequelae in children treated for blood cancers

Rafael Schlossmacher[1], Aline Debs Diniz[1], Leticia Cristina de Oliveira[1], Amanda Schuchovski Ribeiro[1] ,Camile Cripa Vicentini[2], Maria Fernanda Rosa Bertolini[1], Adriana Jasper[3,4]

Keywords:
Neurodevelopmental Disorders, Hematology, Medical Oncology, Pediatrics.

Abstract

Introduction: Pediatric cancer is the second cause of hospitalization of children in Brazil and the primary reason for potential years of life lost. A wide range of therapies have been discussed in studies on the subject. Although they have improved patient outcomes, they are not free of side effects. **Objective:** This study analyzes the neurodevelopmental impacts of cancer treatment on patients seen at a tertiary pediatric hospital in Curitiba/PR. It also presents an epidemiological analysis of children undergoing treatment for blood cancers at a referral hospital in Curitiba/PR. **Method:** The records of 156 patients seen in the Hematologic Oncology Department of a referral hospital in the city of Curitiba/PR were selected. A descriptive analysis of the data was carried out, which were presented in absolute numbers and proportions, followed by correlations between the identified neurodevelopmental sequelae and the cancer types, together with the respective therapies prescribed. **Results:** Acute lymphoblastic leukemia was the most prevalent type of cancer, with 52.6% of cases, followed by central nervous system tumors and acute myeloid leukemia. The main side effects were anxiety; depression; aggressiveness; attention deficit hyperactivity disorder (ADHD); cerebral palsy; auditory, visual, motor and speech impairment. **Conclusion:** Despite the significant reduction in morbidity and mortality, cancer therapies may cause early and late sequelae in patients undergoing treatment.

[1] Positivo University, Doctoral Student - Curitiba - PR - Brazil.
[2] Pequeno Príncipe Hospital, Hematologic Oncology Department - Curitiba - PR - Brazil.
[3] Pequeno Príncipe Hospital, Preceptor at the Neonatal ICU Residency Program - Curitiba - PR - Brazil.
[4] Positivo University. Professor in the Medicine Program - Curitiba - Paraná - Brazil.

Correspondence to:
Rafael Schlossmacher.
Universidade Positivo. Cidade Industrial de Curitiba, Curitiba - PR, Brazil. CEP: 81290-000. E-mail: rafaelschloss@gmail.com

Residência Pediátrica; 2023: Ahead of Print. DOI: 10.25060/residpediatr-2023.v13n2-764

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION

Every year, 200,000 children are diagnosed with cancer worldwide. In 2018 alone, 12,500 new cases of pediatric cancer were diagnosed in Brazil, making it one of the leading causes of hospitalization of children in the country (12%), second only to malnutrition (22%). Cancer ranks second among the causes of death of children and is the primary reason for potential years of life lost. At a global level, leukemia is the most common type of cancer diagnosed in children, followed by central nervous system tumors and lymphoma.[1, 2, 3]

With the continuous advances in the management and treatment of pediatric cancers, children who once did not have much prospect of improvement, are now enjoying improved outcomes and an extension in years of survival. The concern now resides in the different side effects produced by the most commonly used therapies, which directly impact the quality of life of patients.[4, 5]

Childhood cancer is characterized by short latency periods, greater aggressiveness and accelerated growth, when compared to neoplastic disease in adults. On the other hand, they respond better to treatment and are considered to yield better outcomes.[2]

In most cases, treatment consists of surgical resection, chemotherapy and/or radiotherapy. Antineoplastic chemotherapy is based on the administration of potent drugs to promote the systemic obliteration of cancerous cells. However, these medications are not cell-specific, which causes them to reach and destroy healthy cells throughout the body, causing toxicity and several side effects.[2, 6]

Due to the aggressive nature of these medications, many survivors of childhood cancer are at high risk of late morbidity and mortality. Long exposure to these drugs may indeed cure cancer and improve patient outcomes, but may also cause different sequelae in the long term, which can manifest during therapy, soon after, or several years after the end of treatment. Side effects include impaired growth and development; and neurocognitive, cardiopulmonary, endocrine, metabolic, renal, and gastrointestinal dysfunction, among others. About 70% of the children who complete cancer treatment present late side effects, with 30% suffering severe and fatal adverse effects.[5, 7]

Different factors may affect the moment at which these adverse effects appear, such as the type of therapy used and age at the time of exposure to cancer medication. Some of these effects are related to the use of radiotherapy, with signs manifesting throughout the life of the patient including changes in growth, hypothyroidism, among other endocrine disorders. Late effects from chemotherapy include kidney failure, cardiomyopathy, and hearing loss.[8]

The sequelae generated by cancer treatment are not the only factor related to the disease to negatively affect the lives of children with cancer. Inability to attend school due to physical, cognitive, or emotional impairment; the frequency of unpredictable, prolonged hospitalization; changes and adjustments to daily family life; and the socioeconomic burden associated with cancer treatment must also be considered. Healthcare staff training and a multidisciplinary approach to care must be introduced so that the specificities of each patient are considered in order to mitigate the impacts generated by the treatment on the child's global development and conduct the patient's future reinsertion in school and society.[3]

OBJECTIVES

This study looked into the potential correlations between impacts derived from blood cancer treatment on child neurodevelopment, prescribed therapies, and types of cancer. The authors performed an epidemiological analysis of the electronic medical records of children prescribed treatment for blood cancers at a referral hospital in the Brazilian city of Curitiba.

METHOD

This retrospective observational study was carried out from January 1, 2019 to December 31, 2020. It included the medical records of patients seen at the Hematologic Oncology Department of a pediatric tertiary hospital in Curitiba. The Hematologic Oncology Department of this high complexity hospital is a referral service for the diagnosis and treatment of blood cancers. The local healthcare team contains hematologists/oncologists, resident physicians, and a multidisciplinary team with pedagogues, psychologists, social workers and physicians from other medical specialties.

This study included the medical charts of patients aged between five and 15 years staying in the hematologic oncology ward during the study period. Subjects in this age group are enrolled in the hospital's pedagogical follow-up service carried out by specialized professionals participating in the Hospital Schooling Program.

Medical charts with incomplete data or missing the opinions of a psychologist/pedagogue about the child's school performance were excluded. The medical charts of children who did not undergo cancer treatment, were in palliative care, or died within less than six months were also excluded. The Ethics and Research Committee approved the study and granted it certificate no. 30779120.0.0000.0097.

The study included 156 from a total of 226 medical charts analyzed.

Patient data were collected from electronic medical record systems VM and MV PEP and saved on a spreadsheet previously designed by the authors for further analysis. The variables of interest were: sex, origin, diagnosis, treatment, neurodevelopment, school performance, and death. Data on the incidence of hearing, visual, motor, speech, and neuropsychiatric symptoms were also collected. The analysis of the medical records included patient hospitalization and outpatient follow-up.

Based on the data collected, relationships were established between cancer types and treatments potentially causing neurodevelopmental sequelae and decreased school performance.

The results were presented in absolute numbers and proportions, based on the descriptive analysis of the data obtained. The chi-squared test and Fisher's exact test were performed on SPSS 17.0 to compare between qualitative variables, adopting a significance level of 95% ($p<0.05$).

RESULTS

We found a higher proportion of males among patients, with 57.1% (n=89) of the included population, versus 42.9% (n=67) of females. In terms of origin, 37.8% (n=59) came from the countryside of the State of Paraná, 28.8% (n=45) were from Curitiba, 26.9% (n=42) resided in the Greater Metropolitan Area of Curitiba, and 6.4% (n=10) came from other Brazilian States.

As for cancer types, acute lymphoblastic leukemia (ALL) was the most prevalent with 82 patients, followed by different types of central nervous system (CNS) tumors with 45 patients, and acute myeloid leukemia (AML) with 12 patients. The remaining cancers accounted for a small portion of the diagnosed conditions. Graph 1 shows the proportions of types of cancer in our population.

Graph 2 shows the main neurodevelopmental sequelae and the absolute and relative number of cases in our patient population.

Fifty children (32.1%) in our series had neurodevelopmental sequelae, with motor, hearing, and speech impairments equally prevalent, each present in 9% (n=14) of the population.

In terms of neurodevelopment, 21.4% (n=3) of the children with hepatoblastoma had some type of hearing and/or speech impairment (p=0.01). Three patients (21.4%) with ALL, the main type of cancer found in our population, had motor deficits (p=0.022); and 7.1% (n=1) had hearing and/or speech impairments (p< 0.0001). We also found that 71.4% (n=5) of the children diagnosed with CNS tumors showed signs of aggression or attention deficit hyperactivity disorder (ADHD) (p=0.022), and more than half of them (n=8 / 57.1%) had some type of hearing and speech impairment (p=0.026). A large number of these same patients with CNS tumors, which accounted for 71.4% (n=10) of the population, presented motor deficits, (p=0.001). Of the neurodevelopmental disorders documented in the study, only auditory and/or speech impairments, motor deficit, ADHD, and aggressiveness were correlated with the analyzed cancer types. No statistical significance was found in the potential correlation between sequelae and anxiety/depression, visual impairment, or cerebral palsy. The described correlations are seen in Tables 1 and 2.

Twelve main types of treatment were prescribed to these patients, as seen in Graph 3.

Tables 3 and 4 show the statistically significant correlations between cancer treatment type and neurodevelopmental sequelae. The strongest correlation was seen between hearing and speech impairments and cancer treatment. These impairments were seen in 71.4% (n=10) of the patients treated with chemotherapy ($p<0.0001$), 64.3% (n=9) of the patients prescribed radiotherapy (p=0.002), 57, 1% (n=8) of the individuals submitted to surgery (p=0.001), and in 21.4% (n=3) of the children treated with cisplatin (p=0.025). Our analysis showed that 70% (n=7) of the patients treated with the protocol of the Brazilian Group for the Treatment of Acute Lymphoid Leukemia (GBTLI) developed anxiety or depression (p=0.038); 14.3% (n=2) of the children treated with the Baby Brain regimen were diagnosed with motor deficit (p=0.041); and 57.1%(n=4) of the patients submitted to surgery had symptoms of aggression or ADHD.

No significant correlation was found between cancer types and age. Likewise, no correlations were found between the type of tumor, patient sex, or proportion of deaths, as seen in Table 5.

Twenty patients (12.8%) died. With regard to school performance, 83.3% (n=130) did not report underperformance caused by the disease or treatment, while 16.7% (n=26) experienced some level of learning disability. No significant correlation was found between type of tumor and occurrence of learning disability.

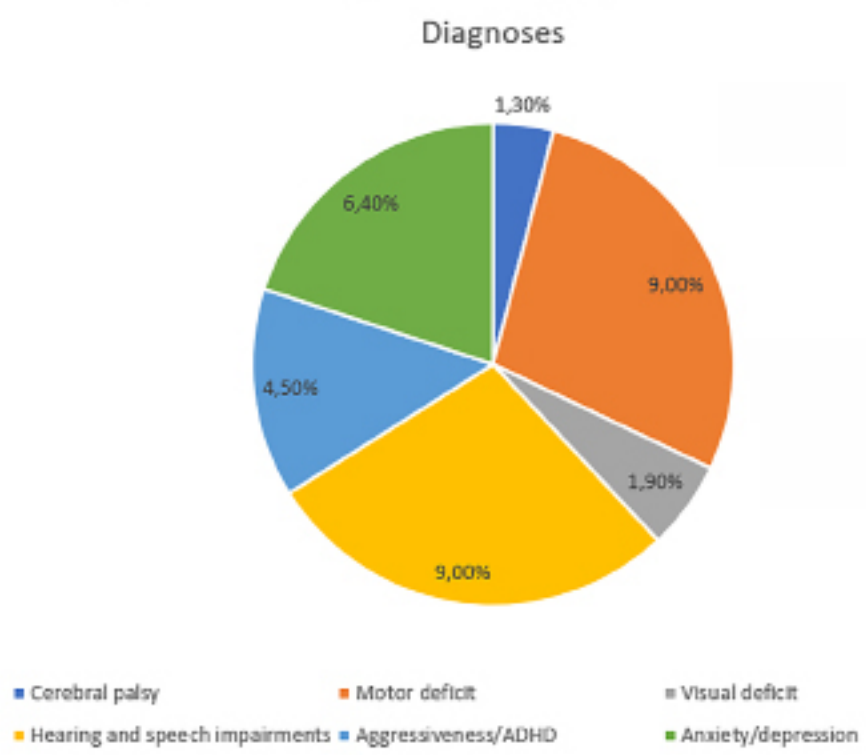
The analysis of age versus neurodevelopmental and learning-related sequelae found that 50% (n=13) of the children aged between six and 10 years had learning disability (p=0.031) and 80% (n=8) of the children aged between 11 and 16 years were diagnosed with anxiety or depression (p=0.001).

There were no significant differences between school performance and place of origin of the children included the study.

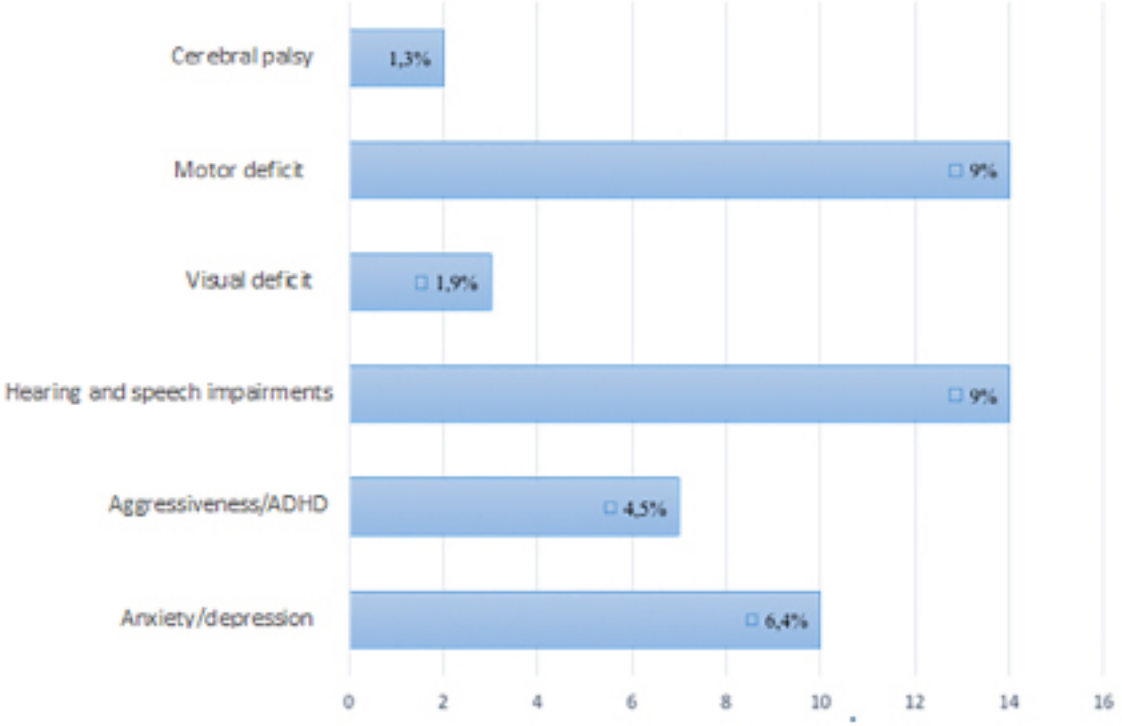
DISCUSSION

As described in the literature, ALL was the most common type of cancer we found, affecting 52.6% of the patients included in the study. Substantial progress has been achieved in the treatment of ALL in recent years, with prophylactic intrathecal chemotherapy as one of the main factors responsible for increased patient survival. Although mortality has decreased, side effects have seen an increase.[4]

As described in the literature, our study found that therapy for ALL affected the onset of neurodevelopmental sequelae such as neuropathies, paralysis, and/or motor deficit. Several studies have assessed the impact of intrathecal chemotherapy on the long-term quality of life of patients diagnosed with ALL. In a meta-analysis comprising 30 studies, the authors demonstrated changes in intellectual function, with a decline in intelligence and school performance, associated with cases of intellectual disability requiring special education. Recent



Graph 1. Blood cancer types in the study population.



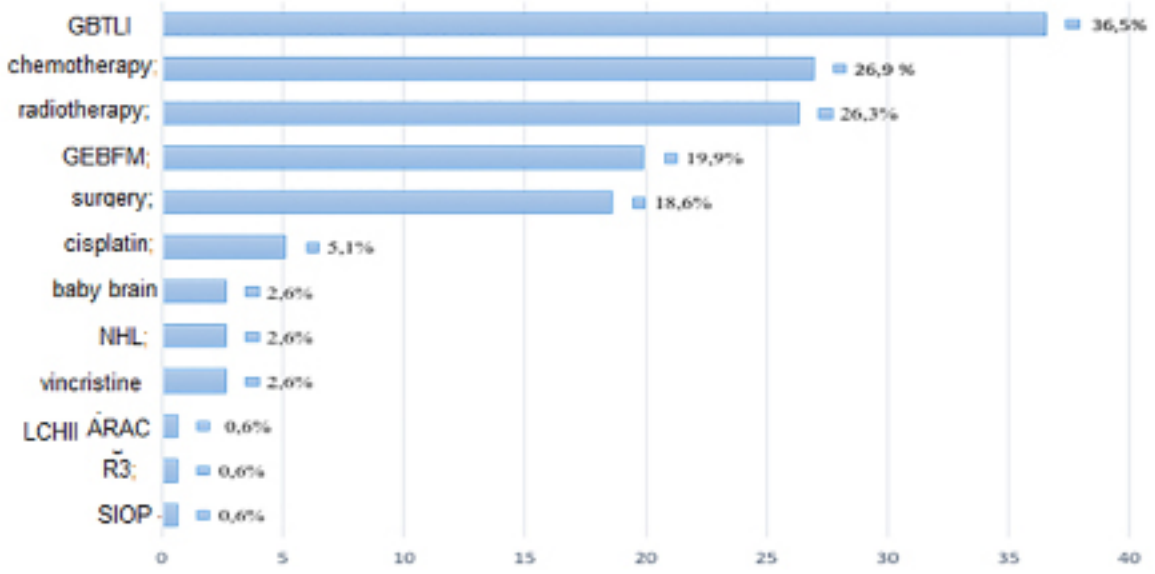
Graph 2. Neurodevelopment sequelae in relative and absolute numbers.

Table 1. Correlation between type of cancer and anxiety/depression, aggressiveness/ADHD and visual impairment.

Diagnosis	Anxiety/Depression			Aggressiveness/ADHD			Aggressiveness/ADHD		
	n	%	p-value	n	%	p-value	n	%	p-value
ALL	7	70	0.334	2	28.6	0.257	0	0	0.104
AML	1	10	1.000	0	0	0.656	0	0	1.000
CNS tumors	1	10	0.194	5	71.4	0.022	2	66.7	0.557
Hepatoblastoma	0	0	0.716	0	0	1.000	0	0	1.000
Burkitt lymphoma	1	10	0.285	0	0	1.000	0	0	1.000

Table 2. Correlation between type of cancer and motor deficit, cerebral palsy, hearing/speech impairment.

Diagnosis	Motor deficit			Cerebral palsy			Hearing/speech impairment		
	n	%	p-value	n	%	p-value	n	%	p-value
ALL	3	21.4	0.022	1	50	1.000	1	7.1	<0.000
AML	1	7.1	1.000	0	0	1.000	0	0	0.383
CNS tumors	10	71.4	0.001	1	50	1.000	8	57.1	0.026
Hepatoblastoma	0	0	1.000	0	0	1.000	3	21.4	0.010
Burkitt lymphoma	0	0	0.685	0	0	1.000	0	0	0.685



Graph 3. Cancer treatments prescribed to the patient population

Graph Key: GBTLI – Brazilian Group for the Treatment of Acute Lymphoblastic Leukemia; GEBFM - Berlin-Frankfurt-Münster European Group; LNH - Non Hodgkin lymphoma; LCHII ARAC - Langerhans' cell histiocytosis II / ARAC – cytarabine; RT – radiotherapy; SIOP – International Society of Pediatric Oncology.

studies featuring more thorough and comprehensive patient analysis described decreased focal attention as the main adverse effect, with specific effects on execution function (acting based on the information acquired) and decoding/interpretation (understanding and interpreting the information acquired).[4, 9]

We also found an association between CNS tumors and subsequent development of ADHD, as also demonstrated by Krull and Butler.[4, 10] According to Butler, the most common sequelae found in patients with CNS tumors were attention and memory deficits and altered speed of information processing.[4]

A report from the "Childhood Cancer Survivor Study" (CCSS) also mentions younger age at diagnosis as a risk factor for the aforementioned neurocognitive outcomes.[9] However, this correlation was not statistically significant in our population. Other risk factors include receiving a higher dose of cranial irradiation, exposing a large portion of the brain to radiation, and longer treatment.[10] The observed neurocognitive effects are apparently related to demyelination and

Table 3. Correlations between treatments occurrence of anxiety/depression, aggressiveness/ADHD, and visual impairment.

Treatment	Anxiety/Depression			Aggressivity/ADHD			Visual impairment		
	n	%	p-value	n	%	p-value	n	%	p-value
CT	2	20	1.000	4	57.1	0.085	2	66.7	0.177
RT	3	30	0.723	2	28.6	1.000	2	66.7	0.169
CX	0	0	0.210	4	57.1	0.023	2	66.7	0,089
GBTLI	7	70	0.038	2	28.6	1.000	1	33.3	1.000
BFM	9	90	0.688	0	0	0.346	0	0	1.000
Baby Brain	0	0	1.000	0	0	1.000	0	0	1.000
NHL	1	10	0.235	0	0	1.000	0	0	1.000
BMT	2	20	0.149	0	0	1.000	0	0	1.000
LCH 2 ARAC	0	0	1.000	0	0	1.000	0	0	1.000
CISPLATINA	0	0	1.000	0	0	1.000	0	0	1.000
VINCRISTINA	0	0	1.000	1	14.3	0.169	1	33.3	0.075
R 3	0	0	1.000	0	0	1.000	0	0	1.000
SIOP	0	0	1.000	0	0	1.000	0	0	1.000

Table 4. Correlation between treatments and motor deficit, cerebral palsy, hearing/speech impairment.

Treatment	Motor deficit			Cerebral palsy			Hearing/speech impairment		
	n	%	valor de p	n	%	valor de p	n	%	valor de p
CT	7	59	0.057	1	50	0.467	10	71.4	<0.0001
RT	9	64.3	0.002	1	50	0.458	9	64.3	0.002
CX	5	35.7	0.140	0	0	1.000	8	57.1	0,001
GBTLI	4	28.6	0.577	1	50	1.000	2	14.2	0.085
BFM	1	7.1	0.305	0	0	1.000	0	0	0.074
Baby Brain	2	14.3	0.041	0	0	1.000			
NHL	0	0	1.000	0	0	1.000	1	7.1	0.316
BMT	3	21.4	0.062	0	0	1.000	0	0	1.000
LCH 2 ARAC	0	0	1.000	0	0	1.000	0	0	0.600
CISPLATINA	0	0	1.000	0	0	1.000	0	0	1.000
VINCRISTINA	14	0	1.000	2	0	1.000	3	21.4	0.025
R 3	0	0	1.000	0	0	1.000	0	0	1.000
SIOP	0	0	1.000	0	0	1.000	0	0	1.000

Table 5. Type of cancer, sex, and death.

	Sex					Death				
Type of cancer	Female		Male			Yes		No		
	n	%	n	%	p-value	n	%	n	%	p-value
ALL	30	44.8	52	58.4	0.106	10	50	64	47.1	0.816
AML	7	10.4	5	5.6	0.364	3	15	9	6.6	0.366
CNS tumors	23	34.3	22	24.7	0,214	7	35	38	27.9	0.598
Hepatoblastoma	2	3	4	4.5	0.7	0	0	6	4.4	0.604
Burkitt lymphoma	2	3	3	3.4	1	0	0	5	3.7	0.622

white matter necrosis. The relationship between white matter volume in the prefrontal/frontal lobe and cingulate gyrus and attention span has been well documented.[4]

Early studies about the effects arising from the treatment of CNS tumors show that therapy is often associated with declines in intellectual function and school performance. However, the evaluation parameters used in these studies are less sensitive than the ones used in recent studies.[4] We found no statistical correlation between treatment and school performance. This may be explained by the lack of standardized tests to assess school performance in children, which makes such appraisal highly subjective.

In our study, patients with CNS tumors also had neuropathies, paralysis or motor deficit. According to Butler and as mentioned above, these complications are mostly associated with prophylactic intrathecal chemotherapy with methotrexate, which is performed in the vast majority of patients with ALL due to increased patient survival.[4]

Similarly, a CCSS report showed an association between intracranial radiotherapy and use of corticosteroids with neurocognitive impairment. The report evaluated primarily efficiency in performing tasks and emotional regulation and memorization skills. The authors found that 22.8% of post--cancer treatment patients had issues completing tasks, 12.4% had trouble memorizing things, and 12.3% could not regulate emotions properly.[9]

With regard to neuropsychiatric effects, we found a correlation between age at diagnosis and occurrence of depression and anxiety disorders, with a higher frequency observed in the group aged 11 to 16 years (incidence of 80%). This is consistent with what Bathia found in reports from parents of treated children, in which a significant correlation with depression, behavioral disorders and poor school performance is described. A review from the Children's Oncology Group (COG) described a strong relationship between the development of anxiety disorders and age at diagnosis, with incidence peaking in adolescence. The relationship between mood disorders and having a diagnosis of ALL may explain our findings, which show an association between treatment with the GBTLI protocol – the therapy of choice for children with ALL in Brazil – and late development of anxiety and depression disorders, as seen in other countries.[7, 11]

A review by the COG looked into the late psychological effects of different pediatric cancers and showed that most children had few psychosocial issues over time. However, the small group that developed side effects experienced higher rates of suicide, anxiety, post-traumatic stress disorder, and generalized stress, all associated with the way they perceived their physical limitations and cancer-related pain.[11] Our study did not discuss matters related to suicide or post-traumatic stress disorder, since we had insufficient data to analyze such potential correlations.

We also found an important correlation between hearing loss and chemotherapy (CT), radiotherapy (RT), and/or surgical resection of tumors. These are the main types of treatment for brain tumors, and they have sensorineural hearing loss as a common adverse effect.[6] This may explain the significant presence of hearing and speech impairment in patients diagnosed with CNS tumors and in patients prescribed treatment with cisplatin.

Although highly ototoxic, cisplatin is an efficient chemotherapeutic agent used extensively in the treatment of brain tumors. The literature indicates that more than half of the patients undergoing treatment with cisplatin suffer from hearing loss. The rate in our population was lower, with 21.4% of the patients. Cisplatin-induced hearing loss is characterized by gradual and permanent sensorineural damage, starting with high-frequency hearing loss and progressing to low-frequency hearing loss. Since low frequencies are closely related to speech, low-frequency hearing loss can cause speech disorders, delayed speech development, and learning disability, associated with worse school performance and quality of life.[12, 13, 14]

Hearing and speech impairments were found in 64.3% of the patients undergoing radiotherapy, as described in the literature, in which rates of impairment range from 0 to 54%. The risk and severity of ototoxicity by radiotherapy increase with intensity of radiation and proximity to the temporal bone.[6]

We observed an important relationship between hepatoblastoma and hearing loss. This association is explained by the fact that hepatoblastoma is treated with cisplatin.[15]

Cancer causes substantial morbidity and mortality in children and worsens the quality of life of patients and their families. The substantial progress seen in therapies developed for these patients has extended the survival of children diagnosed with cancer. However, these treatments have both short- and long-term side effects.

We had some trouble collecting data about school performance, since there was no standardized procedure to assess or record this variable in the medical charts. This may justify the fact that 83.3% of the children in our population did not present school performance issues. Proper tools are needed to objectively analyze school performance, improve the reporting of this variable in future studies, and ultimately enhance the management of pediatric cancer patients.

CONCLUSION

ALL was the most prevalent type of cancer in our population, affecting more than half of the patients, followed by CNS tumors, which accounted for almost a third of the cases of cancer included in our study. With regard to side effects on neurodevelopment, we found that 32.1% of the patients had sequelae including anxiety; depression; aggressiveness; attention deficit hyperactivity disorder (ADHD); cerebral palsy; and hearing, visual, motor and speech impairments.

Some sequelae were directly related to specific types of cancer – hearing, speech, and motor impairments were associated with ALL, while aggressiveness, ADHD, and hearing, speech, and motor impairments correlated with CNS tumors.

The analysis of prescribed therapies revealed statistically significant correlations between presence of hearing and/or speech impairment and chemotherapy, radiotherapy, and surgery, which were seen in 71.4%, 64.3% and 57.1% of the patients prescribed these procedures, respectively. We also found that 14.3% of the children treated with the Baby Brain protocol had motor deficits; 70% of the children treated with the GBTLI protocol had signs of anxiety and/or depression; and 57.1% of the children prescribed surgery developed signs of aggressiveness or ADHD.

Many of the cancer treatments currently prescribed present side effects that affect the neurodevelopment of children over time and add to the sequelae intrinsic to the disease process. Therefore, further studies about the prescribed therapies and the disease process are needed to improve the training provided to healthcare workers and the delivery of care to children and families facing cancer.

REFERENCES

1. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. Longo DL, editor. New England Journal of Medicine. 2015 Oct 15;373(16):1541–52
2. Iuchno CW, Carvalho GPD. Toxicidade e efeitos adversos decorrente do tratamento quimioterápico antineoplásico em pacientes pediátricos: revisão integrativa. Ciência & Saúde [Internet]. 2019 Mar 1 [citado, 30° de janeiro de 2021];12(1):e30329–9. Disponível em: https://revistaseletronicas.pucrs.br/ojs/index.php/faenfi/article/view/30329
3. Silva V de MG, Hora SS da. Impactos do Câncer na Vida Escolar de Crianças e Adolescentes: a Importância da Classe Hospitalar. Rev. Bras. Cancerol. [Internet]. 28º de setembro de 2018 [citado, 20° de fevereiro de 2021];64(3):401-4. Disponível em: https://rbc.inca.gov.br/revista/index.php/revista/article/view/47
4. Butler RW, Haser JK. Neurocognitive effects of treatment for childhood cancer. Mental Retardation and Developmental Disabilities Research Reviews. 2006;12(3):184–91.
5. Landier W, Skinner R, Wallace WH, Hjorth L, Mulder RL, Wong FL, et al. Surveillance for Late Effects in Childhood Cancer Survivors. Journal of Clinical Oncology. 2018 Jul 20;36(21):2216–22.
6. Bass JK, Hua C-H, Huang J, Onar-Thomas A, Ness KK, Jones S, et al. Hearing Loss in Patients Who Received Cranial Radiation Therapy for Childhood Cancer. Journal of Clinical Oncology [Internet]. 2016 Apr 10 [citado, 25° de abril de 2021];34(11):1248–55. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4933129/
7. Bhatia S, Constine LS. Late Morbidity After Successful Treatment of Children with Cancer. The Cancer Journal. 2009 May;15(3):174–80.
8. Lopes LF, Camargo BD, Bianchi A. Os efeitos tardios do tratamento do câncer infantil. Revista da Associação Médica Brasileira. 2000 Sep;46(3):277-84.
9. Cheung YT, Brinkman TM, Li C, Mzayek Y, Srivastava D, Ness KK, Patel SK, Howell RM, Oeffinger KC, Robison LL, Armstrong GT. Chronic health conditions and neurocognitive function in aging survivors of childhood cancer: a report from the childhood cancer survivor study. JNCI: Journal of the National Cancer Institute. 2018 Apr 1;110(4):411-9.
10. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. Journal of Clinical Oncology. 2018 Jul 20;36(21):2181.
11. Bitsko MJ, Cohen D, Dillon R, Harvey J, Krull K, Klosky JL. Psychosocial late effects in pediatric cancer survivors: a report from the Children's Oncology Group. Pediatric blood & cancer. 2016 Feb;63(2):337-43.
12. Clemens E, de Vries AC, am Zehnhoff-Dinnesen A, Tissing WJ, Loonen JJ, Pluijm SF, van Dulmen-den Broeder E, Bresters D, Versluys B, Kremer LC, van der Pal HJ. Hearing loss after platinum treatment is irreversible in noncranial irradiated childhood cancer survivors. Pediatric hematology and oncology. 2017 Feb 17;34(2):120-9.
13. Orgel E, O'Neil SH, Kayser K, Smith B, Softley TL, Sherman-Bien S, Counts PA, Murphy D, Dhall G, Freyer DR. Effect of sensorineural hearing loss on neurocognitive functioning in pediatric brain tumor survivors. Pediatric blood & cancer. 2016 Mar;63(3):527-34.
14. van As JW, van den Berg H, van Dalen EC. Platinum-induced hearing loss after treatment for childhood cancer. Cochrane Database of Systematic Reviews. 2016(8).
15. Sullivan MJ. Hepatoblastoma, cisplatin, and ototoxicity: good news on deaf ears. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2009 Dec 15;115(24):5623-6.