

Analysis of Early Treatment of Childhood Cancer in Brazil

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Análise do Tratamento Precoce do Câncer Infantojuvenil no Brasil

Análisis del Tratamiento Temprano del Cáncer Infantil en Brasil

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ABSTRACT

Introduction: The early treatment of childhood cancer should be implemented as soon as possible because it favors a good prognosis for the patient, increasing survival and reducing the risk of oncologic complications. **Objective:** Understand the factors associated with the early implementation of cancer treatment in the Brazilian pediatric population. **Method:** Ecological study, with data on cases of all types of cancer diagnosed in Brazil from 2013 to 2019 in the juvenile population (0 to 19 years old) available on PANEL-Oncology. **Results:** 39,711 cases were included, of which 29,381 (74%) underwent timely treatment, that is, 30 days before Federal Law 12.732/12-mandated maximum period. Among the main factors associated with more time until the arrival at the therapeutic institution, the following stand out: malignant neoplasms, with non-surgical therapeutic modality, residents of the North region, between 0 and 19 years, and neoplasms affecting the eyes and the central nervous system. **Conclusion:** The findings of this study reveal essential data in line with the literature, portraying the current situation of cancer treatment in children and adolescents in Brazil, and issues that if resolved can contribute significantly to reduce the morbimortality.

Key words: health services accessibility; neoplasms; time-to-treatment; comprehensive health care; adolescent.

RESUMO

Introdução: O tratamento precoce do câncer infantojuvenil possibilita um prognóstico significativo para o paciente, aumentando a sobrevida e diminuindo os riscos de complicações oncológicas, o que torna imperiosa a sua instituição o mais rápido possível. **Objetivo:** Analisar os fatores associados à instituição precoce do tratamento oncológico na população pediátrica brasileira. **Método:** Estudo ecológico, com dados de casos de todos os tipos de câncer diagnosticados no Brasil de 2013 a 2019, na população infantojuvenil (0 a 19 anos), disponibilizados no PAINEL-Oncologia. **Resultados:** Foram incluídos 39.711 casos, dos quais 29.381 (74%) realizaram o tratamento oportuno, isto é, 30 dias antes do prazo máximo estipulado pela Lei Federal nº. 12.732/12. Entre os principais fatores associados ao maior tempo até a chegada à instituição terapêutica, destacam-se: neoplasias malignas, com modalidade terapêutica não cirúrgica, residentes da Região Norte, entre 11 e 19 anos, e neoplasias que acometem os olhos e o Sistema Nervoso Central. **Conclusão:** Os achados deste estudo apontam dados essenciais, em consonância com a literatura, para visualização da situação atual do tratamento oncológico na população infantojuvenil no Brasil, ao mesmo tempo que demonstram problemáticas que, se solucionadas, podem contribuir significativamente para a queda da morbimortalidade.

Palavras-chave: acesso aos serviços de saúde; neoplasias; tempo para o tratamento; assistência integral à saúde; adolescente.

RESUMEN

Introducción: El tratamiento temprano del cáncer infantil y adolescente permite un pronóstico significativo para el paciente, lo que hace imperativa su institución lo antes posible. **Objetivo:** Analizar los factores asociados con la institución precoz del tratamiento del cáncer en la población pediátrica brasileña. **Método:** Estudio ecológico, con datos de casos de todos los tipos de cáncer diagnosticados en Brasil de 2013 a 2019 en la población juvenil (0 a 19 años) disponibles en el PANEL-Oncología. **Resultados:** Se incluyeron 39.711 casos, de los cuales 29.381 (74%) recibieron tratamiento en forma oportuna, es decir, 30 días antes del plazo máximo estipulado por la Ley Federal nº. 12.732/12. Entre los principales factores asociados a más tiempo hasta la institución terapéutica, se destacan: neoplasias malignas, con modalidad terapéutica no quirúrgica, residentes de la región norte, entre 11 y 19 años, y neoplasias que afectan los ojos y el sistema nervioso central. **Conclusión:** Los hallazgos de este estudio señalaron datos esenciales, en línea con la literatura, visualizar la situación actual del tratamiento del cáncer en niños y adolescentes en Brasil, señalando problemas que, de ser resueltos, pueden contribuir significativamente a la disminución de la morbimortalidad.

Palabras claves: accesibilidad a los servicios de salud; neoplasias; tiempo de tratamiento; atención integral de salud; adolescente.

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INTRODUCTION

Cancer is a clinical manifestation of uncontrolled growth of cells due to changes of their life cycle; the body loses control of cell division, and these structures are able to invade other tissues of the organism¹. For each year of the triennium 2020-2022, nearly 625 thousand cases are estimated, which shows the importance and necessity to discuss the theme².

It is known that neoplasms bring fear and anxiety for children and adolescents affecting the dynamics of the individual, family and social group they belong. Stigmas come together with the disease, stimulating measures of adaptation and coping³.

Epidemiological estimates of childhood cancer are greatly relevant for care planning. The National Cancer Institute José Alencar Gomes da Silva (INCA)² estimates 4,310 new cases for each year of the triennium 2020-2022 for children and adolescents, being more frequent in the Southeast (3,690), Northeast (2,190) and South (1,310) regions and less in the North (630) and Midwest (640) regions².

The National Policy of Oncologic Attention⁴ established that care is provided in every level of oncologic support from prevention to treatment within the scope of full attention. In complementation, Law 12,732 dated November 22, 2012⁵ determined that oncologic patients have access to treatment in until 60 days after the diagnosis. However, it is known that, in fact, the law is not complied with due to sub-funding of the health system, poor training, sociodemographic factors and failed network articulation⁵⁻⁷.

In order to intensify and check whether this law is being met, Law 13,685 dated June 25, 2018⁸ determined that oncologic services must report cancer cases in the country to detect potential gaps^{8,6}.

Monitoring of oncological care is critical to identify what can impede and delay the treatment. Currently, in partnership with INCA, the Ministry of Health integrates the “*PAINEL-Oncologia*”, whose goal is to provide clear and thorough information of the Brazilian reality about the time from the diagnosis and beginning of the oncologic treatment, allowing the user to review the information based in the available reports and discuss the scenario found. It is an agile, accessible, tool to monitor the time of the first oncologic treatment¹⁰.

The present study aims to analyze the factors associated with early treatment for childhood cancer in Brazil from 2013 to 2019, utilizing the database of “*PAINEL-Oncologia*” at DATASUS, the Informatics Department of National Health System (DATASUS).

METHOD

Ecologic study with data from all the cases of the types of cancer diagnosed in Brazil from 2013 to 2019 in the childhood population (0 to 19 years) in order to analyze the factors associated with early oncologic treatment.

The data from the cases were extracted from “*PAINEL-Oncologia*” with access to unidentified database in November 2020 which are also originated from the Outpatient Information System (SIA), through the Individualized Outpatient Production Form (BPA-I) and Authorization for High Complexity Procedure (Apac), the Hospital Information System (SIH) and of the Cancer Information System (Siscan) managed by the Ministry of Health, Secretary of Health together with Health State and Municipal Secretaries processed by DATASUS of the Executive Secretary of Health.

The case was defined from the combination of the National Health Card (CNS) with ICD-10 – International Classification of Diseases and Health Related Problems¹¹. A card with more than one ICD means different cases in the platform^{9,12}.

The following variables were selected:

- a. Sex: female; male.
- b. Federation Unit (UF) of the diagnosis: allows to select cases per State of the clinic which made the diagnosis grouped per geographical regions and compared with the national scenario.
- c. Age-range: infants and neonates (<2 years), preschoolers (2 to 4 years), students (5 to 10 years), adolescents (11 to 19 years) and young (0 to 19 years) as a group.
- d. Diagnosis: neoplasm (ICD-10) reported in the diagnosis grouped in three categories: “Malignant Neoplasms”, C00-C97 – malignant neoplasm except C-44 and C73 as determined by Law 12,732/12⁵; D00-D09, “Neoplasms *in situ*”, and D37-D48, “Neoplasms of uncertain or unknown behavior. D00-D09 and D37-D48 codes address “Other neoplasms”.
- e. Therapeutic modality: first treatment procedure: surgery, chemotherapy, radiotherapy and both (chemotherapy + radiotherapy at the same date of treatment). Thus, the modality was grouped as “surgery” and “non-surgery”.
- f. Staging: staging 0, I, II, III and IV reported in the treatments of chemotherapy, radiotherapy and in both. Surgery does not have the staging information because is retrieved from SIH is retrieved from SIH where this data is not shown.
- g. Time of treatment: time in days calculated between the date of the diagnosis and the date of the first treatment: 0 to 30 days, 31 to 60 days, more than 60 days and no

information. Later, reduced to ≤ 30 days, > 30 days. The analysis was conducted within 30 days prior to the maximum time of 60 days according to the referenced law. The cases without information about the time of treatment were excluded.

The data were tabulated in Microsoft Excel® 2016. Later, a descriptive analysis was completed through distribution of the variables of the study population. As these are categorical variables, proportions were calculated, Pearson's chi-square test was utilized to compare the groups. Additionally, odds ratio (OR) were estimated by the univariate logistic regression with its respective confidence interval of 95% (CI95%) and significance level of 5% for statistical tests. The Statistical Package for Social Sciences (SPSS), version 25.0 was adopted for all the analyzes. Even if OR overestimates the power of the association with studies like this, compared with the prevalence ratio (PR), the choice of this measure of association is justified because OR allows the identification of possible associations when PR can be misleading^{13,14}.

The submission to IRB was waived because only secondary data were utilized.

RESULTS

Of the 49,723 cases of childhood cancer from "PAINEL-Oncologia"⁹ in the period investigated no information about the time to begin the treatment of 10,012 cases (20.13%) was found, and this portion was excluded. For the remaining 39,711 cases included, 29,381 (74%) submitted to early treatment, 30 days prior to the deadline determined by Law 12,732/12⁵ formed the final casuistic investigated in this study.

There were low odds of malignant neoplasms to be treated earlier compared with other neoplasms. However, no significant difference was found per sex. Neoplasms referred for surgical treatment had more odds of beginning the treatment in until 30 days from diagnosis in view of other therapeutic modalities.

Adolescents were more prone to late treatment as opposed to infants, neonates and preschoolers.

In addition, there was significant difference in cases treated among geopolitical regions, with low possibilities of early treatment in the North (OR 0.399 [CI95% 0.367-0.434]) and Southeast (OR 0.920 [CI95% 0.883-0.959]) regions and more possibilities in the South (OR 1.430 [CI95% 1.345-1.521]), Midwest (OR 1.316 [CI95% 1.202-1.441]) and Northeast (OR 1.065 [CI95% 1.015-1.118]) regions.

Sociodemographic, diagnostic and therapeutic data according to the time from the diagnosis of neoplasm until the beginning of the treatment are presented in Table 1.

Neoplasms with low possibilities of treatment initiated in until 30 days since the diagnosis were in descending order: C69-C72 (eyes, brain and other parts of the Central Nervous System); C00-C14 (lip, oral cavity and pharynx); C51-C58 (female genital organs); C45-C49 (mesothelial and soft tissues); C43-C44 (melanoma and other skin malignant neoplasms); C76-C80 (ill-defined, secondary and unspecified sites); C60-C63 (male genital organs) and C40-C41 (bones and articular cartilage). The detailed description of childhood neoplasms according to the time from the diagnosis until the beginning of the treatment is shown in Table 2.

In counterpart, the following neoplasms had more possibilities of early treatment in descending order: C15-C26 (digestive organs); C50 (breast); D37-D48 (uncertain type or unknown); C64-C68 (urinary tract); C81-C96 (unspecified lymphoid, hematopoietic and related tissues) and C73-C75 (thyroid and other endocrine glands). ICD-10 C30-C39 neoplasms (respiratory and intrathoracic organs) did not have risks significantly different than the total investigated and all neoplasms *in situ* were treated early.

DISCUSSION

Timeliness of treatment is essential for favorable prognosis of childhood cancer, directly impacting the morbimortality for this age range. Treatment delay may be the result of wrong diagnosis, waiting list and decentralization of health services possibly causing referrals and intermunicipal or interstate transfers¹⁵.

Ordinance MS/SAES 1,399, dated December 17, 2019¹⁶ divided treatment clinics according to oncology specialization. Diagnosis, staging and oncologic treatment are able to be offered at: High Complexity Oncology Clinics (Unacon) if they have technical conditions and human resources for diagnostic and treatment of more prevalent cancers; High Complexity Oncology Care Centers (Cacon), providing care for all neoplasms; Referral High Complexity Oncology Care Centers, which are Cacons, with some attributes as a teaching hospital and available in an area depending on the number of new cancer cases in the population; and Oncology General Hospitals⁴. "PAINEL-Oncologia"⁹ where the data of this study were extracted from has information of cases diagnosed and treated in non-approved health clinics too.

Treatment of adolescents begins late when compared with infants, neonates and preschoolers. This finding may be associated with level of caretakers monitoring and high frequency of medical visits, typical of younger children¹⁷. In addition, adolescents are already more cognizant and discerning about the physical and psycho-emotional

Table 1. Sociodemographic, diagnostic and therapeutic variables according to the time from the diagnosis until the beginning of the treatment in the Brazilian childhood population, 2013-2019

Sex	Time until treatment		OR	CI (95%)	p-value ^a
	Until 30 days	More than 30 days			
Male	16,246 (40.9%)	5,795 (14.6%)	0.968	0.925-1.013	0.152
Female	13,135 (33.1%)	4,535 (11.4%)	1.0		
Diagnosis					
Malignant neoplasms	27,737 (79.3%)	10,053 (25.5%)	0.416	0.360-0.480	< 0.001
Other neoplasms (in situ OR uncertain profile)	1,434 (3.7%)	216 (0.5%)	1.0		
Therapeutic Modality					
Surgical	8,390 (21.1%)	732 (1.8%)	5,241	4.841-5.673	< 0.001
Non-surgical	20,991 (52.9%)	9,598 (24.2%)	1,0		
Age-range					
Neonates and infants (< 2 years)	3,139 (7.9%)	745 (1.9%)	1,481	0.764-0.774	< 0.001
Preschoolers (2 to 4 years)	5,819 (14.7%)	1,424 (3.6%)	1,437	1.350-1.529	
Students (5 to 10 years)	7,152 (18.0%)	2,319 (5.8%)	1,084	1.029-1.142	
Adolescents (11 to 19 years)	13,271 (33.4%)	5,842 (14.7%)	0,799	0.769-0.830	
Total (0-19 years)	29,381 (74,0%)	10,330 (26,0%)	1,0		
Region					
North	1,240 (3,1%)	1,092 (2,2%)	0.399	0.367-0.434	< 0.001
Northeast	8,366 (21.1%)	2,771 (6.8%)	1.065	1.015-1.118	
Southeast	11,495 (28.9%)	4,391 (11.0%)	0.920	0.883-0.959	
South	5,907 (14,8%)	1,452 (3,5%)	1.430	1.345-1.321	
Midwest	2,373 (6.0%)	634 (1.6%)	1.316	1.202-1.441	
Brazil	2,9381 (74.0%)	10,330 (26.0%)	1.0		

^(a) Pearson's chi-square test (χ^2).

aspects of the disease and its treatment and can resist to its beginning and continuation¹⁸. Handayani et al.¹⁹ saw this perspective too in their study where more delays were detected in 10 years-old patients or older.

Another greatly relevant aspect is the type of tumor impacting the resolution, morbimortality and quality of life of the patients. A correlation between the type of

cancer and time to begin the treatment was also found by Njuguna et al.²⁰ in their study with pediatric patients in Kenia where the treatment delay was longer for Kaposi's sarcoma and shorter for non-Hodgkin lymphoma and acute myeloid leukemia.

The current study indicated that neoplasms of lymphatic, hematopoietic and correlated tissues can start

Table 2. Childhood neoplasms according to the time from diagnosis until the beginning of the treatment, Brazil, 2013-2019

Malignant Neoplasms	Time until treatment		OR	CI (95%)	p-value ^a
	Until 30 days	More than 30 days			
(C00-C14) Malignant neoplasms of lip, oral cavity and pharynx	460 (1.16%)	301 (0.76%)	0,537	0.464-0.622	< 0.05
(C15-C26) Malignant neoplasms of digestive organs	1,130 (2.85%)	165 (0.42%)	2,408	2.042-2.839	
(C40-C41) Malignant neoplasms of bones, articular cartilage	2,164 (5.45%)	867 (2.18%)	0,878	0.809-0.952	
(C43-C44) Melanoma and other malignant neoplasms of the skin	177 (0.45%)	101 (0.25%)	0,616	0.482-0.788	
(C45-C49) Malignant neoplasm of mesothelial and soft tissues	1,862 (4.69%)	1,099 (2.77%)	0,596	0.551-0.644	
(C50) Malignant neoplasms of the breast	257 (0,65%)	40 (0,10%)	2,259	1.618-3.154	
(C51-C58) Malignant neoplasms of female genital organs	649 (1.63%)	402 (1.01%)	0,568	0.500-0.644	
(C60-C63) Malignant neoplasms of male genital organs	539 (1.36%)	225 (0.57%)	0,842	0.720-0.989	
(C64-C68) Malignant neoplasms of urinary tract	1,539 (3.88%)	293 (0.74%)	1,847	1.627-2.097	
(C69-C72) Malignant neoplasms of the eyes, brain and other parts of the Central Nervous System	2,755 (6.94%)	2,247 (5.66%)	0,431	0.406-0.458	
(C73-C75) Malignant neoplasms of the thyroid and other endocrine glands	844 (2.13%)	255 (0.64%)	1,164	1.010-1.341	
(C76-C80) Malignant neoplasms of ill-defined, other secondary and unspecified sites	1,257 (3.17%)	565 (1.42%)	0,782	0.707-0.866	
(C81-C96) Malignant neoplasms of unspecified lymphoid, hematopoietic and related tissues	13,914 (35.04%)	3,401 (8.56%)	1,438	1.377-1.503	
(D00-D09) In situ neoplasms	108 (0.27%)	0 (0%)	-		
(D37-D48) Neoplasms of uncertain or unknown behavior	1,326 (3.34%)	216 (0.54%)	2.158	1.866-2.497	
(C30-C39) Malignant neoplasms of the respiratory tract and intrathoracic organs	400 (1.01%)	153 (0.39%)	0.919	0.762-1.109 ^b	1.109 ^b
Brazil	29,381 (74.0%)	10,330 (26.0%)	1,0		

^(a) Pearson's chi-square test (χ^2).

^(b) Non-significant result ($p=0.198$) by Pearson's test.

treatment early, nevertheless, neoplasms of the Central Nervous System and eyes tend to start treatment later than 30 days from the diagnosis. From the epidemiologic perspective, acute leukemia is the most important neoplasm for the pediatric population followed by Central Nervous System tumors²¹. Retinoblastoma is the eye malignant tumor most frequent in infancy²¹.

The analysis of the data revealed that tumors of the Central Nervous System took more than 30 days to initiate treatment, possibly associated with difficulty to access specialized clinics because of the complexity of the treatment for the age-range investigated²¹. This same pattern was described in the "Panorama da Oncologia Pediátrica do Rio de Janeiro"²² in 2019: the treatment

of Central Nervous System tumors began 46 days after the diagnosis. Mou et al.¹⁵ demonstrated in their study that the transfer to the specialized clinic may explain this scenario because depending on the type of cancer, not all Unacons are able to offer the treatment and delays of one week or more may occur.

Some types of tumors were treated earlier as primary tumors (lymphatic, hematopoietic and correlated tissues). Handayani et al.¹⁹ found the same pattern in their study conducted in Indonesia where more delay was detected for neurologic tumors and less for hematopoietic until the beginning of the treatment.

Malignant neoplasms tend to be treated late; the delay of childhood cancer treatment means worst prognosis because it is more aggressive and faster than in adults²³. Thus, early treatment leads to better outcomes as concluded by Haana et al.²⁴ in their analysis that a four-weeks delay increases the risk of death from 6% to 13% according to the type of tumor and treatment²⁴.

It is important to understand the impact of the transference of the patient to be treated after the diagnosis because it is significantly correlated with extended diagnosis/treatment interval¹⁵; the difference of the timeliness of the treatment needs to be evaluated since it depends on the modality of the treatment and the Brazilian regions.

The goal of cancer treatment is to cure, prolong life and improve the quality-of-life through three modalities: surgery, radiotherapy and chemotherapy¹. This study revealed that surgeries were more likely to occur in until 30 days from the diagnosis compared with other modalities, because it is already consolidated through SUS hospitals and clinics, contrary to the other two that need to be applied in high complexity approved clinics²⁵.

Possibly associated with public policies and distribution of the services, the North region, among the Brazilian regions was not prepared to initiate the therapy rapidly. The study of Grabois et al.²⁵ concluded that children and adolescents with cancer had to travel long distances from their houses to be treated by SUS since health units are located mostly in the vicinities of the State's capitals. Another study indicated that some cases originated in cities of the States of Pará and Maranhão had to travel more than one thousand kilometers to be consulted at an oncologic public hospital²⁶.

In addition, Grabois et al.²⁷ have also highlighted in another study that the population of the Northern region had less access to chemotherapy, radiotherapy, admission and pediatric oncologic surgery. The same occurred in the Northeast region most of all in suburban areas, however, as the current study concluded, it is more likely that the treatment begins in until 30 days in this region than, for

instance, in the Southeast region. South, Midwest and Northeast regions are able to start treatment in until 30 days.

As regional variations in time to begin the treatment exist, there are also variations in relation to mortality as it depends on the conditions of access, use and performance of the health services, neoplastic risk factors, quality of the data of the Mortality Information System(SIM)²⁸, because there are high proportions of ill-defined causes of death in the North and Northeast²⁹. This can also be associated with the results of the institution which provides therapeutic care. It is clear the importance of the distribution of the services to meet the demands of the population of a certain region in order to promote more equity among the States²⁵.

The lack of detailed information about the treatment of 10,012 cases (20,13%) stands out. Jorge et al.³⁰, in a comprehensive study about the quality of the information registered in various Health Information Systems of SUS found important completeness gaps of the cases reported in relation to the universe – defined with the support from other databases – and the own quality of the data according to the frequency of the fields filled with “ignored”. Although not a specific limitation of the present study but of all utilizing secondary information equivalent to “*PAINEL-Oncologia*”, poor detail of cancer cases damages the analysis of the quality of the care³⁰.

Only cases diagnosed with information about the treatment found in the platform “*PAINEL-Oncologia*” were analyzed, which is one of the study limitations, directly affecting the analysis and interpretation of the data. In addition, there are scarce literature on the theme, which impedes comparison of the results encountered. The choice of OR as measure of association may have overestimated the power of the associations. Seemingly, new studies are necessary to foster more knowledge about the time to begin the oncologic treatment for the population investigated.

CONCLUSION

It was not found the necessity of reducing the time for timely treatment for childhood cancer in Brazil between 2013 and 2019 based in the analysis of the associated factors but it is essential for better outcomes for this population.

Concurring with the literature, the findings point out essential data to have a perspective of the current status of childhood oncologic treatment in Brazil and at the same time, disclosed problematics that, if resolved, can contribute significantly for morbimortality drop.

CONTRIBUTIONS

All the authors contributed substantially for the study design/conception, acquisition, analysis and/or interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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