Time until the Beginning of Cancer Treatment in Children and Adolescents in Brazil

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Tempo até o Início do Tratamento Oncológico em Crianças e Adolescentes no Brasil

Tiempo hasta el Inicio del Tratamiento del Cáncer en Niños y Adolescentes en el Brasil

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ABSTRACT

Introduction: Cancer in children and adolescents is the main cause of death by disease in this age range in Brazil, with high incidence rates, and the time until the beginning of the treatment is crucial for the prognosis. **Objective:** To investigate factors associated with the implementation of childhood cancer treatment in Brazil in the first 30 days after the diagnosis. **Method:** Cross-sectional, analytical and quantitative study carried out with the population aged 0 to 19 years in Brazil who initiated cancer treatment between 2017 and 2021. Data were collected based on *PAINEL-Oncologia* and analyzed utilizing absolute and relative frequencies and calculating the prevalence ratios between the time of diagnosis and treatment by Geographic Region, neoplasm groups and age group**. Results:** Approximately 80% initiated treatment within 30 days, and the factors associated with this higher prevalence ratio were: younger age, surgery as the initial therapeutic modality and diagnosis in the South and Midwest Regions. The neoplasms *in situ* and of uncertain behavior were the group with higher frequency when compared to other types analyzed. The difference in time found in the Regions stands out, showing heterogeneity of the distribution of oncology reference services. No significant difference was found in relation to sex. **Conclusion:** The heterogeneity of the timely time of treatment in the Regions was noticed, especially in terms of access to treatment centers and the complexity of the oncological condition. Therefore, it is important to carry out studies addressing the pathway to access the therapeutic institution in all Regions.

Key words: neoplasms; time for treatment; pediatrics; access to health services.

RESUMO

Introdução: O câncer infantojuvenil é a principal causa de morte por doença nessa faixa etária no Brasil com elevadas taxas de incidência, sendo o tempo até o início do tratamento crucial para o prognóstico. **Objetivo:** Investigar os fatores associados à instituição do tratamento do câncer infantojuvenil no Brasil nos primeiros 30 dias após o diagnóstico. **Método:** Estudo transversal, analítico e quantitativo, realizado com a população de 0 a 19 anos que iniciou o tratamento oncológico de 2017 a 2021 no Brasil. Os dados foram coletados com base no PAINEL-Oncologia e analisados utilizando frequências absolutas e relativas. Além disso, foram calculadas as razões de prevalência entre o tempo de diagnóstico e tratamento por Região Geográfica, grupos de neoplasias e faixa etária. **Resultados:** Aproximadamente 80% iniciaram o tratamento em até 30 dias e os fatores associados a essa maior prevalência são: menor idade, cirurgia como modalidade terapêutica inicial e diagnóstico nas Regiões Sul e Centro-Oeste. As neoplasias *in situ* e de comportamento incerto foram o grupo com maior frequência quando comparado aos outros tipos analisados. Destaca-se a diferença no tempo entre as Regiões, evidenciando heterogeneidade da distribuição dos serviços de referência em Oncologia. Não houve diferenças significativas em relação ao sexo. **Conclusão:** Notou-se a heterogeneidade do tempo oportuno de tratamento nas Regiões, sobretudo no acesso às unidades de tratamento, e na complexidade do quadro oncológico. Mais estudos sobre o percurso até a instituição terapêutica em todas as Regiões são necessários.

Palavras-chave: neoplasias; tempo para o tratamento; pediatria; acesso aos serviços de saúde.

RESUMEN

Introducción: El cáncer en niños y adolescentes es la principal causa de muerte por enfermedad en este grupo de edad en el Brasil, con altas tasas de incidencia, y el tiempo hasta el inicio del tratamiento es crucial para el pronóstico. **Objetivo:** Estudiar los factores asociados a la institución del tratamiento del cáncer infantil en Brasil en los primeros 30 días después del diagnóstico de 2017 a 2021. **Método:** Estudio transversal, analítico y cuantitativo, realizado con la población de 0 a 19 años en el Brasil que iniciaron el tratamiento del cáncer entre 2017 y 2021. Los datos fueron recolectados con base en los datos de PAINEL-Oncología y analizados utilizando frecuencias absolutas y relativas, y calculando las razones de prevalencia entre el momento del diagnóstico y el tratamiento por Región Geográfica, grupos de neoplasia y grupo de edad. **Resultados:** Aproximadamente el 80% inició tratamiento dentro de los 30 días, y los factores asociados a esta mayor razón de prevalencia fueron: menor edad, cirugía como modalidad terapéutica inicial y diagnóstico en las Regiones Sur y Centro Oeste, siendo las neoplasias *in situ* y de comportamiento incierto el grupo con mayor frecuencia en comparación con los otros tipos analizados. Destaca la diferencia en el tiempo entre Regiones, evidenciando la heterogeneidad de la distribución de los servicios de referencia en Oncología. El sexo del paciente no presenta interferencia significativa. **Conclusión:** Se notó la heterogeneidad del momento oportuno del tratamiento en las Regiones, especialmente en cuanto al acceso a las unidades de tratamiento y la complejidad de la condición oncológica. Por lo tanto, es importante realizar más estudios sobre el camino a la institución terapéutica en todas las Regiones.

Palabras clave: neoplasias; tiempo para el tratamiento; pediatría; acceso a los servicios de salud.

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INTRODUCTION

Cancer is a disease with great potential for morbidity and mortality in all regions of the world[1]. When diagnosed in childhood or adolescence, it causes physical, social, economic, and emotional impacts on the life of the individual, their support network and society, since, when not cured, it can represent a loss of approximately 70 years of life[2,3].

Child and adolescent cancer is considered a disabling chronic disease, mainly due to the complexity of the treatment, which can cause side effects and the need to interrupt the school and social routine[4]. In Brazil, on March 8, 2022, Law nº. 14,308[5] was approved, establishing the National Policy for Pediatric Oncology Care, which aims to increase survival, reduce mortality and treatment abandonment, and provide quality of life to children and adolescents affected by the disease.

A factor of great impact on the prognosis is the time until the start of treatment, since the cancer is usually more aggressive in this age group and can be fatal when not treated properly or in a timely manner[6,7]. Law nº. 12.732/12[8], known as the 60 Days Law, which came into force in May 2013, ensures that patients with malignant neoplasms have free access to treatment within 60 days. However, with regard to pediatric neoplasms, it would be of great value to reduce the time until the beginning of treatment due to the aggressive nature of the disease[9].

The organization of the Health Care Network (HCN) needs to ensure the start of cancer treatment as soon as the diagnosis is made and, for this, it needs to identify possible obstacles along the way, which makes PAINEL-Oncology an extremely important tool regarding the analysis of the time of the first cancer treatment, as it gathers important data about this monitoring[10].

A previous study, which analyzed the time to the oncological therapeutic institution in children and adolescents between 2013 and 2019, pointed out that there is no great need for a reduction in time, but that this would be crucial for better outcomes in childhood cancer [11]. This study aimed to analyze the factors associated with the institution of treatment of childhood cancer in Brazil in the first 30 days after diagnosis, between 2017 and 2021, in order to present the panorama of factors related to the therapeutic institution within 30 days.

METHOD

Cross-sectional, quantitative, analytical study, based on data from PAINEL-Oncology[12]. The population studied was children and adolescents (from 0 to 19 years old) in Brazil who started cancer treatment between 2017 and 2021. The final sample consisted of all cases with information about the time until the start of treatment.

All cases with information on the time to start treatment were included in the research, excluding those diagnosed with the two exceptions contained in Law nº. 12.732/12[8] – other malignant neoplasms of the skin (C44) and malignant neoplasm of the thyroid gland (C73).

Data collection took place from May to June 2022 through the PAINEL-Oncology platform. Case information was extracted through access to the unidentified database, which is managed by the Ministry of Health and processed by the Department of Informatics of the Unified Health System (DATASUS)[12].

The combination of the National Health Card (CNS) with the tenth International Classification of Diseases and Related Health Problems (ICD-10) resulted in case definition [13]. That is, the same card with more than one ICD represents different cases on the platform[12,14].

The following variables were selected: a) Gender: female, male; b) Treatment time: interval between diagnosis and the beginning of the first cancer treatment. This was the outcome variable of the study and the time interval considered opportune was up to 30 days. This choice was based on national and international studies that found similar intervals between diagnosis and treatment[15-17]. In addition, a meta-analysis published in 2020[18] pointed out that the four-week delay in cancer treatment is associated with an increase in the risk of death ranging from 6% to 13%, which makes the interval opportune, such as the one carried out 30 days before the maximum deadline stipulated by Law nº. 12.732/12[8]; c) Federative Unit (UF) of the diagnosis: it allows the selection of cases according to the establishment in which the individual made the diagnosis, which were grouped by Geographic Regions and compared with the national reality. The North Region was selected as a comparison variable for the study of the prevalence ratio, since it was the Region with the lowest prevalence of instituting treatment within 30 days, according to PAINEL-Oncology[12]; d) State of residence: allows the selection of cases according to the State where the individual resides, grouped by Geographic Regions and compared with the national reality; e) Age group: categorizes the study population into infants and neonates (<2 years), preschoolers (2 to 4 years), schoolchildren (5 to 10 years), adolescents (11 to 19 years) and young people (0 to 19 years); f) Diagnosis: refers to neoplasm (ICD-10) informed in the diagnostic examination, grouped into three categories: "Malignant neoplasms", which meet the codes of malignant neoplasm (C00-C97) excluding the two exceptions contained in Law nº. 12.732/12[8] (codes C44 and C73); "*In situ* neoplasms", which meet the codes D00-D09, and "Neoplasms of uncertain or

unknown behavior", which meet the codes D37-D48, composed the category "Other neoplasms". In addition, the topographic categorization of malignant neoplasms was performed, which had as reference for the analysis of the prevalence ratio of non-malignant neoplasms *in situ* and of uncertain behavior; g) Therapeutic modality: refers to the procedure of the first treatment, which may be surgery, chemotherapy, radiotherapy and both (chemotherapy + radiotherapy with the same treatment date). Thus, the therapeutic modality was grouped as "surgical" and "non-surgical".

These variables will be analyzed by group of neoplasms in the present study, in order to know the prevalence of timely initiation of treatment among them, and whether there are significant divergences between the diagnosis interval and treatment.

The work respected the precepts of the Resolution of the National Health Council nº. 466/12[19] regarding research with human beings, since all information was obtained from reliable and freely accessible databases, which justifies the absence of the opinion of a Research Ethics Committee.

The results will be presented to the appropriate public agencies and the Federal University of Sergipe, which will allow a notion of the time until the beginning of pediatric cancer treatment in the country in recent years.

Data were tabulated in *Microsoft Excel®* 2016. Subsequently, a descriptive analysis of these data was performed by distributing the variables of the study population. As these are categorical variables, proportions were calculated, and the comparison between the groups was performed using Pearson's chi-square test and considering the significance level of 5% for said test. Additionally, univariate prevalence ratios (PR) were estimated, with their respective 95% confidence intervals (95% CI). All analyzes were performed using the *Statistical Package for Social Sciences* (SPSS) software, version 26.0.

RESULTS

In the period studied, 29,650 cases of childhood cancer were made available in PAINEL-Oncology with information on the time until the beginning of treatment.

The analysis of the prevalence ratio indicated that there is no significant difference regarding sex (95% CI: 0.985-1.009) at the timely start of treatment. However, it showed a gradual increase in the prevalence ratio of 3% (95% CI: 1.021-1.051) among schoolchildren, 6% among preschoolers (95% CI: 1.052-1.085) and 9% (95% CI: 1.070-1.110) among infants, when compared to adolescents, who were chosen as a comparison parameter, since they presented a lower prevalence in the timely institution of treatment.

Malignant neoplasms had a lower prevalence ratio of starting treatment in the first 30 days after diagnosis (95% CI:0.824-0.845) compared to neoplasms *in situ* and/or of uncertain behavior. As for the therapeutic modality, neoplasms that had surgery as initial treatment – when compared to non-surgical modalities – showed an increase in prevalence of 35% (95% CI: 1.340-1.368) of having their treatment started in a timely manner.

An increase in the prevalence ratio of initiating therapy in a timely manner was seen gradually for the states of the Southeast Region (95% CI: 1.169-1.254), Northeast (95% CI: 1.171-1.258), Midwest (95% CI:1.207-1.305) and South (95% CI:1.255-1.348). Similar findings were found considering the variable Region of residence of the individuals, highlighting the variations in the number of those who reside and are diagnosed in the different Regions, as shown in Table 1.

Table 1 presents the data of the sociodemographic, diagnostic, and therapeutic variables of cancer in the child and adolescent population and their association with the institution of treatment in a timely manner.

Regarding the topographic diagnoses of malignant childhood and adolescent neoplasms, the lowest percentage of timely treatment for malignant neoplasms of the eyes, brain and other parts of the central nervous system (CNS) stands out, when less than 60% are able to perform the treatment within 30 days after diagnosis. In addition, the percentage of timely therapeutic institution was high for malignant neoplasms of the breast and digestive organs. Table 2 presents the specific diagnoses of childhood and adolescent neoplasms and the prevalence of timely treatment.

DISCUSSION

More than three-quarters of the participants in this research underwent treatment within 30 days after diagnosis, a finding similar to national and international studies [15-17] that found intervals lower than that recommended by the Law of 60 days[10]. However, it should be noted that since childhood cancer can be highly curable depending on diagnostic and therapeutic agility, it is of paramount importance to make this interval as short as possible[20].

Due to advances in the oncological therapeutic arsenal in recent years, most malignant neoplasms are treated with more than one therapeutic modality, the main ones being: surgery, radiotherapy and chemotherapy[21]. In addition, it is imperative that the treatment be carried out in specialized centers[20]. In the study by Gatta et al.[22], with children and adolescents from some European countries diagnosed between 2000 and 2007 and followed

Table 1. Prevalence and prevalence ratios between the demographic, diagnostic and therapeutic variables of cancer in the child and adolescent population and the institution of timely treatment. Brazil, 2017-2021

Variables	Timely treatment (prevalence)	RP	IC 95%	*p*
Gender				
Male	12,768 (79.2)	0.997	0.985-1.009	0.603
Female	10,744 (79.4)	1.0		
Diagnosis				
Malignant neoplasias.	21,214 (78.0)	0.834	0.824-0.845	<0.001
Other neoplasms (D00-D09 or D37-D48)	2,298 (93.5)	1.0		
Therapeutic modality				
Surgical	10,550 (94.8)	1.354	1.340-1.368	<0.001
non-surgical	12,962 (70.0)	1.0		
Age range				
Infants	2,390 (84.0)	1.090	1.070-1.110	<0.001
Preschoolers	4,054 (82.4)	1.069	1.052-1.085	<0.001
Students.	5,472 (79.9)	1.036	1.021-1.051	<0.001
Adolescents	11,596 (77.1)	1.0		
Region – diagnosis				
North Region	1,200 (65%)	1.0		
Southeast Region	9,033 (78.7)	1.211	1.169-1.254	<0.001
South Region	5,086 (84.5)	1.301	1,255-1,348	<0.001
Midwest Region	1,754 (81.6)	1.255	1.207-1.305	<0.001
Northeast Region	6,456 (78.9)	1.214	1.171-1.258	<0.001
Region – residence				
North Region	1,540 (67.4)	1		
Southeast Region	8,357 (79.0)	1.172	1.138-1.208	<0.001
South Region	5,068 (84.4)	1.252	1,214-1,291	<0.001
Midwest Region	1,951 (80.6)	1.196	1,156-1,238	<0.001
Northeast Region	6,596 (78.9)	1,170	1.135-1.207	<0.001

Source: PAINEL-Oncologia[12].
Captions: PR = Prevalence ratio; 95% CI = 95% confidence interval.

up until the end of 2017, the prognosis was better when the treatment was given in high-volume hospitals for the main tumors.

The present study showed that neoplasms with initial surgical intervention had a higher prevalence ratio of starting treatment in less time. This finding may be associated with the ease and heterogeneous distribution of surgical procedures around the country when compared to other therapeutic modalities. A similar association was seen in the study by Grabois et al.[23], who highlighted that chemotherapy and radiotherapy presented a more geographically concentrated pattern than clinical and surgical oncological procedures, since these are not necessarily performed in highly complex hospitals.

In order to avoid delays in the process between the diagnostic suspicion and the therapeutic institution, it is recommended that the patient be referred to the reference service when the suspicion is imminent in order to make the diagnosis and then start treatment at the same institution, as studies have shown that the need for transfer after diagnosis correlates with the length of time until treatment[15,16,20,24]. This finding may be due to the delay in referral and the need to travel greater distances to the institution that will provide the treatment, which may imply costs during the displacement and stay of the patient and their guardian, in addition to the possible need for them to be temporarily absent from their work activities, generating impacts throughout the family. In the meantime, the need for structural support for patients and their guardians stands out, such as facilitating transportation to the treatment center and support residences during cancer treatment. A study analyzed the flows of trips made by children and adolescents with cancer attended by sus between 2003 and 2007 and showed that most of the visits (48.3%) occur in the largest metropolises and include the structure of the country's urban network [23]. However, approximately 10% of trips occur outside this flow[23], which points to the need to distribute services depending on population demand.

Table 2. Prevalence and reasons for prevalence of specific diagnoses of childhood and adolescent neoplasms and timely therapeutic institution. Brazil, 2017-2021

|Neoplasias	Timely treatment (prevalence)	RP	IC 95%	*p*
C00-C14 - Malignant neoplasms of the lip, oral cavity, and pharynx	395 (72.7)	0,778	0.738-0.820	<0.001
C15-C26 - Malignant neoplasms of digestive organs	1,547 (93.7)	1.002	0.986-1.019	0.788
C30-C39 - Malignant neoplasms of the respiratory tract and intrathoracic organs	458 (84.7)	0.906	0.872-0.940	<0.001
C40-C41 - Malignant neoplasms of bones and articular cartilage	1,823 (76.4)	0,817	0.797-0.838	<0.001
(C43) Melanoma	96 (85.7)	0.917	0.849-0.990	0.002
C45-C49 - Malignant neoplasms of mesothelial tissue and soft tissues	1,483 (69.8)	0.746	0.725-0.768	<0.001
(C50) Breast malignant neoplams	326 (94.5)	1.011	0.983-1.039	0,476
C51-C58 - Malignant neoplasms of female genital organs	609 (71.7)	0.767	0.735-0.801	<0.001
C60-C63 - Malignant neoplasms of male genital organs	458 (77.1)	0.825	0.788-0.863	<0.001
C64-C68 - Malignant neoplasms of the urinary tract	1,026 (87.7)	0.938	0.916-0.961	<0.001
C69-C72 - Malignant neoplasms of the eyes, brain, and other parts of the central nervous system	2,048 (59.0)	0,631	0.613-0.650	<0.001
(C74-C75) Malignant neoplasms of other endocrine glands	558 (77.6)	0.830	0.797-0.865	<0.001
C76-C80 - Malignant neoplasms of ill-defined, secondary, and unspecified sites	1,743 (79.5)	0,850	0.830-0.871	<0.001
(C81-C96) Malignant neoplasms, declared or presumed to be primary, of lymphatic, hematopoietic and related tissues	8,644 (82.4)	0.881	0.869-0.893	<0.001
(D00-D09) and (D37-D48) Neoplasms in situ and neoplasms of uncertain or unknown behavior	2,298 (93.5)	1.0		

Source: PAINEL-Oncologia[12].
Captions: PR = Prevalence ratio; 95% CI = 95% confidence interval.

The present study showed that the North Region had a lower prevalence of starting treatment within 30 days, which corroborates the findings of a study that pointed to the need to travel great distances in this Region, especially for chemotherapy and radiotherapy, since approximately 25% of children and adolescents had to leave their Region to access treatment[23]. Another study carried out in a public hospital located in the Northern Region of Brazil with children and adolescents who received a diagnosis of cancer in the period from 2008 to 2014 showed that only 24.4% of them lived in the same city as the treatment facility [25].

The same study points out, in relation to the Southeast Region, that approximately 60% of the Region's health networks are located in the State of São Paulo[23]. This fact may imply the need for residents of other states to travel greater distances to access treatment. In addition, this Region also demonstrated a satisfactory data record, which can enhance this finding[26].

In addition, a study carried out in Brazil between 2007 and 2011, based on hospital-based cancer records, showed, like this study, that there is no significant difference in the time of initiation of treatment according to sex[24]. International studies covering the same age group corroborate the findings of the aforementioned study [27,28].

It was also noted that adolescents took longer to start therapy, which corroborates the findings of the national

and international literature[17,24,27] that demonstrated an association between older age and the need for more days between diagnosis and treatment. Thus, in addition to the need for a high index of suspicion[29], it is necessary to pay attention to the needs of this group during cancer management.

As for the neoplastic classification, most people with malignant neoplasms were more likely to start treatment at an inopportune time when compared to those with *in situ* neoplasms or those with uncertain behavior. This difference was also found in the literary arsenal on the subject, which showed that the treatment must be individualized according to the classification and extent of the tumor, factors that have a significant effect on therapeutic delay[19,28]. It should be noted, however, that most tumors are classified as unspecified neoplasms, which can negatively affect the specificity of the treatment[16]. Thus, it is imperative to adopt measures to increase the specific diagnosis, given its direct impact on therapeutic efficacy.

The panorama of pediatric oncology in Rio de Janeiro and a study conducted in Indonesia showed that the interval between diagnosis and treatment tends to be longer for CNS tumors and shorter for leukemias and lymphomas, as found in the present study[16,27]. This may be combined with the smaller dispersion of the therapeutic arsenal of CNS tumors and also the greater dissemination of knowledge to lay people about neoplasms of the lymphohematopoietic lineage. On the other hand, the panorama carried out in the State of São Paulo pointed out the need for more days for leukemias and lymphomas than for CNS tumors[30].

The present study presented some limitations, such as the lack of national and international literature on this subject, the lack of information on the treatment in a considerable part of the cases made available on the PAINEL-Oncology platform – which can interfere with the results – and the analysis of the univariate prevalence ratio, which can leave important aspects unnoticed, since it observes the variables in isolation. The year 2017 was included in the study period, however, only from 2018 onwards, criticisms of the obligation of the ICD and the sus card were implemented in the non-specific anatomopathological procedure for cervical and breast cancers, through SAS Ordinance nº. 643[31]. It should be noted that the cases of the children included in the panel are only those who have CNS *Master*, demonstrating an analysis of this portion of cases. The option to include *in situ neoplasms in* the reference category added to the characteristic of the system of including only cases of anatomopathological confirmation may have generated some type of bias in the data[32]. From another perspective, the high degree of heterogeneity of the sample may contribute to elucidate the main factors associated with the shorter interval between diagnosis and treatment.

CONCLUSION

When analyzing the interval of days between diagnosis and the beginning of cancer treatment of children and adolescents treated by the SUS, it was evidenced that more than three-quarters of the final sample (79.29%) started treatment within 30 days. Among the factors that had the highest prevalence ratio in starting treatment in the first 30 days after diagnosis, the following stand out: younger age, those who had surgery as an initial therapeutic modality, and those diagnosed in the South and Midwest Regions.

It is hoped that this study will serve as a theoretical basis for the promotion of strategies by health management that aim to increasingly reduce the waiting time until the therapeutic institution, while encouraging new scientific studies that can analyze the multivariate prevalence ratio and bring to light other determining factors.

CONTRIBUTIONS

All authors contributed substantially in the design and/or planning of the study; in the collection, analysis and interpretation of data; in the writing and critical review; and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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