Pediatric Blood & Cancer

RESEARCH ARTICLE

Preventing treatment abandonment for children with solid tumors: A single-center experience in Brazil

Sima Ferman[1] | Fernanda Ferreira da Silva Lima[1] |

Carollyne Rodrigues Souza Lage[1] | Senir Santos da Hora[1] |

Danielle Tavares Vianna[1] | Luiz Claudio Thuler[2]

[1]Department of Pediatric Oncology, Brazilian National Cancer Institute, INCA, Brazil

[2]Clinical Research Division, Brazilian National Cancer Institute, INCA, Brazil

Correspondence
Sima Ferman, Brazilian National Cancer Institute, INCA, Department of Pediatric Oncology, Praça Cruz Vermelha 23, 5° andar, Centro, Rio de Janeiro/RJ 20230-130, Brazil.
Email: sferman@inca.gov.br

Abstract

Background: High rates of treatment abandonment have been considered one of the major limitations to achieving high cure rates of childhood cancer in developing countries. The aims of this study were to report the prevalence and factors associated with treatment abandonment for children diagnosed with solid tumors in one reference center in Brazil and to describe effective strategies to prevent it.

Procedures: A retrospective review was conducted using data from 1139 children (0–18 years) treated for solid tumors at the Brazilian National Cancer Institute, during the period between January 2012 and December 2017. Treatment abandonment was defined as recommended by the International Society of Pediatric Oncology. The impact of implementing a patient-tracking system was evaluated. Descriptive statistics were used to analyze patient characteristics. Chi-square test was used for statistical analysis, with the significance level <0.05.

Results: Of 1139 patients, 1.66% refused or abandoned treatment. Although from 2012 to 2013 there was an increase in the abandonment rate, it then decreased by 63.8% from 2013 to 2017 (2.5% to 0.9%). In the multivariate model, only retinoblastoma diagnosis was associated with abandonment (odds ratio = 5.0; 95% confidence interval, 1.2–20.4; $P = 0.025$). In our cohort, abandonment rates were not associated with increased death.

Conclusion: Monitoring missed appointments, and early interventions to address issues associated with providing resources to help families during treatment were effective in achieving very low abandonment rates.

KEYWORDS
abandonment, childhood cancer, low- and middle-income country, refusal

1 | INTRODUCTION

In the past several decades, there has been major improvement in outcomes for children with cancer. Survival rates of childhood cancer in high-income countries are around 80%.[1,2] Despite improvement in cure rates for childhood cancer in high-income countries, the corresponding rates remain suboptimal in low- and middle-income countries.[3,4] Many factors have been attributed to these results, such as access to treatment, late diagnosis, and socioeconomic and educational factors.[5,6] Treatment abandonment has also been implicated among the causes of treatment failure.[7,8]

Treatment abandonment has been defined as failure to start or complete therapy for a disease that could be cured or definitively controlled, and missing treatment for a consecutive period, defined as a hiatus of four or more weeks in the scheduled treatment, without a medically indicated cause.[7–10] In low- and middle-income countries, abandonment rates reported are variable, ranging from 0 to 74.5%.[11] Reasons for abandonment are multifactorial and include caregivers' limited education, socioeconomic pitfalls, feeling of incurability, religious beliefs, and fear of components of treatment, among others.[12]

Treatment abandonment has been addressed in Latin America, especially in patients with childhood cancer[13–16] and leukemia[17,18] as an important cause of treatment failure, and strategies to overcome this problem have been implemented. However, fewer studies have focused specifically on solid tumors.[19,20] Therefore, the aim of this study was to describe strategies to prevent treatment abandonment in children diagnosed with solid tumors in one reference center in Brazil, and to report its prevalence and associated factors.

2 | METHODS

2.1 | Setting

Brazil is a Latin American upper-middle-income country with a population of over 208 million inhabitants, of whom approximately 23% are younger than 15 years.[21,22]

The Brazilian National Cancer Institute (INCA) is a branch of the Ministry of Health for the development and coordination of integrated actions for cancer prevention and control in Brazil. These actions are of a multidisciplinary nature and include medical and hospital care provided directly and completely free of charge to cancer patients, within the country's Unified Health System, known as SUS.[23,24]

The Pediatric Oncology Department is a referral center for children with cancer in Brazil. About 250 new patients with cancer, aged 0 to 19 years old, are admitted annually. Of the 250 patients, 180 have solid tumors. Many patients were socioeconomically underprivileged, did not have medical insurance, and were in a position of social vulnerability. These conditions were considered risk factors for abandonment of therapy.[15] Strategies have therefore been developed over the years to bring together the efforts of the institutional multidisciplinary team and volunteers as well as nonprofit organizations, to help with transportation, lodging, food, and ensuring patients are able to access their social rights.

2.2 | Study population

Records were reviewed of 1139 patients less than 19 years of age at diagnosis, treated with solid tumors at INCA, during the period between January 2012 and December 2017. Patients who were previously treated for cancer in other institutions were not eligible ($n = 5$).

The variables collected retrospectively from the medical reports of each patient, including those who abandoned treatment, were as follows: sociodemographic data (gender, age at diagnosis, ethnicity, and distance to institution) and clinical (final diagnosis, outcome, and treatment abandonment). Distance from home to treatment center was categorized as 0 to 50, 51 to 100, 101 to 150, 151 to 200, and >201 miles. Patients living 0 to 50 miles from the institution were considered close to the treatment center.[12] Treatment abandonment was defined as a failure to either start or complete therapy for a disease that could be cured or definitively controlled or missing treatment for a consecutive period of four or more weeks in the scheduled treatment.[9]

For those patients who abandoned treatment, additional information was evaluated, including oncologic treatment at the time of abandonment (before starting treatment, during local treatment, and on chemotherapy); time to abandonment (days from starting treatment; for those who did not start treatment, the time was considered zero); maternal information (age, level of education, marital status, number of children including the patient and the family's per capita income); time lapse before returning for treatment (days from abandonment to return; for those patients who refused surgery, this was considered zero). Oncologic status at the return was characterized as either disease progression or no disease progression. Outcome was characterized as alive with disease (AWD), no evidence of disease (NED), dead of disease (DOD), or lost to follow-up when appointments were missed for more than one year after completing therapy (LFU).

Data collection and entry were approved previously by the local ethics committee (CAAE number: 82799618.9.0000.5274; 19 February 2018).

2.3 | Interventions

2.3.1 | Interventions to all patients

Multidisciplinary evaluation

All patients were seen by the multidisciplinary team at diagnosis (pediatric oncologist, nurse, social worker, nutritionist, psychologist).

Action: Education about the disease and treatment planned for each patient. The difficulties to treatment adherence were identified and discussed with the team at a weekly meeting.

Monitoring for missing consultation

A trained health care professional registered daily all patients who missed a scheduled appointment at the oncology unit.

Action: The oncologic phase of treatment was identified in the database and/or the chart. Family members were contacted within 24 hours of the missed appointments by phone call and/or telegram to identify the reason for absence. The primary physician was informed about the reasons for the missing appointment as well as the multidisciplinary team.

Monitoring for appointment scheduling

Since 2014, in order to track those patients who ultimately did not schedule an appointment with the pediatric oncology assistant, the data manager also updated biweekly the last consultation of all patients followed at our institution. The time elapsed from the last appointment was registered automatically to warn health professionals that more than 15 days have passed since the patient last visited the hospital.

Action 1: The oncologic phase of treatment was identified in the database and/or the chart. Family members of patients on diagnostic investigation and during oncologic curative treatment were contacted within 24 hours of the missed appointments by phone call and/or telegram to identify the reason for absence. The primary physician was informed about the reasons for the missing appointment as well as the multidisciplinary team.

Action 2: The interventions performed were to provide more support by the multidisciplinary team by informing families about the importance of treatment and avoiding missing scheduled treatment;

to make appointments with multidisciplinary health members and the parents, scheduled when needed, strengthening the patient, family, and staff relationship; to make a phone call 24 hours before the scheduled appointment to reinforce the need to attend consultation; to provide social service support; to contact other family members for help; to connect current patients with past patients; to contact family health strategy and primary care physicians; to design an individualized approach based on family demands; and to make use of judicial intervention as the last resort.

2.3.2 | Interventions to high-risk patients

All patients at diagnosis were evaluated by the multidisciplinary team with attention to risk factors for nonadherence to treatment. We classified patients with higher risk of abandonment those with at least one of the criteria: low socioeconomic status, reduced social and family network, low caregiver education/literacy, low maternal age, lack of understanding the need of therapy, religious beliefs, infant and adolescent age, potentially mutilating surgery, and residence distant from the treatment center. Some of these criteria have previously been identified in the systematic review done by Gupta et al.[11]

Action 1: Patients with risk factors were seen more frequently by the multidisciplinary team (pediatric oncologist, nurse, psychologist, social worker, and data manager) to educate parents about the importance of adherence and provide support for difficulties identified.

Action 2: Interventions by governmental and nonprofit organizations to strengthen resources for travel and transportation, lodging, and food. Strategies were individualized according to the problem identified.

2.3.3 | Patient tracking

In cases where abandonment occurred, post abandonment interviews were done to evaluate causes of abandonment and needed interventions.

Action: In addition to the interventions to high-risk patients previously described, the patient was restaged, to define the best management according to patient status and rescue possibility and follow-up the course of the disease.

2.4 | Data analysis

Descriptive analysis was used to describe patient characteristics. Continuous data description includes central tendency (median) and dispersion (range). One graphic was used to describe the prevalence of treatment abandonment. Median follow-up time for patients who abandoned treatment was calculated from the date of starting treatment to last follow-up or death. Category variables were described in frequency distribution tables, and the Chi-square test was used for statistical analysis, with significance level < 0.05. A regression model was performed using the forward stepwise method. Variables with a P value < 0.20 in univariate analysis were selected for multiple regression modeling. Only variables with $P < 0.05$ were retained in the final model. All statistical tests were two-tailed. Outcomes of patient data were analyzed in March 2018. Data were analyzed using SPSS version 21.0 (São Paulo, Brazil).
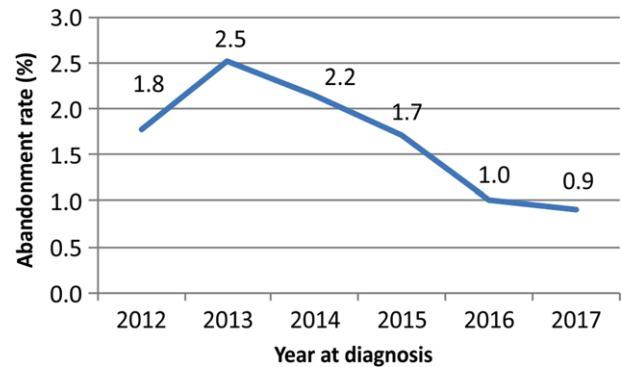
FIGURE 1 Abandonment rate over the years, 2012–2017

3 | RESULTS

3.1 | Demographics

A total of 1139 patients with solid tumors were diagnosed between January 2012 and December 2017. Table 1 shows clinical and sociodemographic characteristics of all patients including those who abandoned treatment. The male:female ratio was 1:1, and 53.6% were of nonwhite ethnicity. The median age at diagnosis was six years (range, 0–18 years). Treatment abandonment was significantly more frequent among patient with retinoblastoma, followed by Wilms tumor, neuroblastoma, and osteosarcoma ($P = 0.023$), and in children younger than five years of age at diagnosis ($P = 0.049$). In the multivariate model, only retinoblastoma diagnosis was associated with abandonment (odds ratio = 5.0; 95% confidence interval, 1.2–20.4; $P = 0.025$). Age was not retained by the model, although significant in the univariate analysis.

Treatment abandonment during the whole period was 1.66%. Although from 2012 to 2013 there was an increase in the abandonment rate, there was a 63.8% reduction in patients who abandoned treatment from 2013 to 2017 (2.5% to 0.9%; Figure 1).

3.2 | Treatment abandonment

The demographic and social characteristics of patients who abandoned treatment are shown in Table 2. Nineteen of 1139 patients were found to have abandoned treatment from 2012 to 2017. The median follow-up was 23.8 months (9.8–48.2). The median time from starting treatment to abandonment was 73 days (0–368). A total of 10 patients abandoned after starting chemotherapy and four before starting treatment. Five patients refused local surgical treatment: enucleation ($n = 2$) and amputation ($n = 3$). All patients returned, even after abandonment. The median time to return to treatment center after abandonment was 61 days (32–443).

The reasons for abandoning treatment are described in Table 3. Lack of understanding the need for therapy was observed in 9/19 (47.4%) cases, followed by transport and financial difficulties (7/19 cases = 36.8%), in 6/19 (31.6%) distance from treatment center was an impeding factor (>50 miles).

In our cohort, abandonment was not associated ($P = 0.084$) with increased death: 36.8% (7/19) versus 20.1% (225/1120).

TABLE 1 Clinical and sociodemographic profile of pediatric oncology patients admitted between 2012 and 2017

Variables	Treatment compliance (n = 1120)		Abandonment (n = 19)		Total	P
	n	%	n	%		
Gender						0.778
Male	567	98.4	9	1.6	576	
Female	553	98.2	10	1.8	563	
Age at diagnosis (years)						0.049
<5	457	97.2	13	2.8	470	
5–10	288	99.3	2	0.7	290	
>10	375	98.9	4	1.1	379	
Ethnicity						0.079
White	520	99.0	5	1.0	525	
Nonwhite	597	97.7	14	2.3	611	
Diagnosis						0.023
Retinoblastoma	77	95.1	4	4.9	81	
Wilms tumor	71	95.9	3	4.1	74	
Neuroblastoma	84	96.6	3	3.4	87	
Osteosarcoma	86	97.7	2	2.3	88	
Soft-tissue and other extra osseous sarcomas	184	97.9	4	2.1	188	
Malignant epithelial neoplasms	63	98.4	1	1.6	64	
Brain tumors	289	99.3	2	0.7	291	
Other solid tumors	266	100.0	0	0.0	266	
Distance to institution[a]						0.059
0-50 miles	859	98.5	13	1.5	872	
51–100 miles	103	97.2	3	2.8	106	
101–150 miles	64	100.0	0	0.0	64	
151–200 miles	45	93.7	3	6.3	48	
>201 miles	49	100.0	0	0.0	49	

[a]Driving directions with Google Maps from address provided by family to INCA.

4 | DISCUSSION

Abandonment rates greatly vary worldwide.[11,25,26] Reports on treatment abandonment in solid tumors have shown higher rates in low- and middle-income countries.[19]

In this study, the abandonment rate found during the whole period (1.66%) was in agreement with the estimated rate for Brazil (less than 5%), as reported by Friedrich et al.[25] Accordingly, the value found also fits what is predicted for upper-middle-income countries.[11] However, a higher abandonment rate (18.4%) was observed in a higher-middle-income country.[19] It is interesting to note that after an initial period of slight increase, the abandonment rate decreased progressively, reaching its lowest at 0.9% in the last year of the period evaluated. The initial peak was attributed to the greater identification of cases of abandonment soon after the implementation of coping strategies. After this initial period, the observed fall may reflect the effectiveness of the measures applied to avoid treatment abandonment. A study performed in Recife, in Brazil, with patients with acute lymphoblastic leukemia, has shown a reduction in abandonment of therapy in three consecutive periods: 16% vs 1.3% vs 0.5% due to

a creation of a pediatric oncology program and social preventive measures.[18]

To identify possible risk factors for abandonment, we considered that the type of malignancy could be a risk factor. In our cohort, a higher rate was found for retinoblastoma, compared with other solid tumors.[20,26–28] Similarly, Vasquez et al, in 2018 in Peru, found a significant association between a higher risk of abandonment in patients with retinoblastoma.[19] We did not find a higher frequency of treatment abandonment among patients younger than five years at diagnosis, as has been reported in other studies.[13,29] More recently, Vasquez et al found no association between age and risk of treatment abandonment in Peru.[19]

In our study, the variables gender and ethnicity were not significantly associated with risk of treatment abandonment. Some previous studies have also found this result.[19,29] However, it has been reported that Chinese females had a higher risk of refusing treatment and treatment abandonment compared with males.[30] In addition, Alvarez et al reported an association between indigenous race/ethnicity and treatment abandonment in Guatemala,[13] suggesting that race/ethnicity may be a surrogate for another factor such as cultural beliefs

TABLE 2 Demographic and social characteristics of patients who abandoned treatment and impact on the outcome

Abandonment patient characteristics (n = 19)	n	%
Gender		
Male	9	47.4
Female	10	52.6
Median age at diagnosis (range)	2.3 years	(0.2–15.5)
Median time to abandonment (Range)	73 days	(0–368)
Oncologic treatment at abandonment		
On chemotherapy	10	52.6
Local treatment (surgery or RXT)	5	26.3
Before starting treatment	4	21.1
Maternal age		
≤18	2	10.5
19–28	6	31.6
≥29	11	57.9
Maternal level of education		
Primary	10	52.6
Secondary or greater	7	36.9
Unknown	2	10.5
Per capita income in minimum wages[a]		
<0.25	6	31.6
0.25–< 0.5	9	47.4
0.5–1.0	1	5.2
Unknown	3	15.8
Number of children		
≤3	14	73.7
>4	5	26.3
Maternal civil status		
Single	12	63.1
Married/stable union	5	26.3
Widow	1	5.3
Unknown	1	5.3
Refusal to surgery		
No	14	73.7
Yes	5	26.3
Oncologic status at return		
Without disease progression	10	52.6
With disease progression	9	47.4
Outcome[b]		
NED	8	42.1
AWD	2	10.5
DOD	8	42.1
LFU	1	5.3

[a]At the time of the study, the monthly minimum wage was equivalent to 333.9 USD in 2012 to 287.50 USD in 2017.
[b]AWD, alive with disease; DOD, dead of disease; LFU, lost to follow-up when more than one year missing appointments after completing therapy; NED, no evidence of disease.

TABLE 3 Reasons for abandoning treatment (n = 19)

Reason	N[a]	%[a]
Lack of understanding the need of therapy	9	47.4
Transport/financial difficulties	7	36.8
Distance to treatment center	6	31.6
Refusal of mutilating surgery	5	26.3
Reduced family network	5	26.3
Religious beliefs	2	10.5
Young maternal age	2	10.5
Adolescent patient refusal	1	5.3

[a]The same patient might have had more than one reason.

surrounding the attitudes toward Western medicine and alternative treatments. Perhaps this did not occur in our cohort due to the intense miscegenation of the Brazilian people and the consequent difficulty in defining ethnicities. Different from what was described in Guatemala, the greater distance between the patient's residence and INCA did not present as a factor for greater risk of treatment abandonment.[13]

The negative impact of poverty has been strongly related to treatment abandonment.[25] Most patients who abandoned treatment in our institution (79%) had a per capita income of less than 0.5 minimum wage per month. We can speculate that the precarious living conditions in this cohort is the main determinant for the observed abandonment; in respect to bone and soft-tissues sarcomas and retinoblastomas, the need of mutilation surgery may have impacted the family's decision to adhere to treatment. Despite these difficulties, the measures implemented were successful in lowering abandonment rates. The financial aid for transportation offered by the government to low-income families that live farther from the treatment center might be a factor to mitigate the impact of this variable in the treatment of children with cancer.

Mortality rates associated with untreated pediatric cancer are known to be high. Previous studies have shown that treatment delays and abandonment are strongly associated with treatment failure and poor outcomes.[13,17,28,29,31,32] Sitorus et al demonstrated that survival rates were lower and tumor progression was higher for patients with retinoblastoma who temporarily refused and then returned to treatment, compared with those who adhered to treatment.[33] Interestingly, in our abandonment cohort, 9/19 (47.4%) patients are alive. Four of these nine patients who returned had disease progression but were able to be rescued with intensive treatment. The diagnosis of patients who are alive is Wilms tumor (n = 2), retinoblastoma (n = 2), neuroblastoma (n = 2), infantile fibrosarcoma (n = 1), and medulloblastoma (n = 2). A possible explanation for this result could be related to tumor biology. The follow-up of these patients for a longer period may also allow a better understanding of this result.

Several institutions in low- and middle-income countries have implemented successful strategies to lower abandonment rates with the help of the government and/or nonprofit organizations. Most of these strategies have educational programs for parents, psychosocial and economic support, and preventive measures such as implementing a tracking system to detect missed appointments.[13,14,16,18,34]

In our study, we developed a simple tracking system for missing appointments and had the active participation of a multidisciplinary team for patients missing consultations. Common themes were refusal of local treatment (amputation and enucleation when indicated), difficulties coping with the impact of disease on the daily family routine, extreme poverty, difficulty in understanding medical instructions, and parents with social vulnerabilities. All the interventions were individualized to the needs of the patients and caregivers.

The limitations of the study include its retrospective nature; in addition, the specific information related to abandonment and maternal information was available only for patients who abandoned treatment. Paternal factors were not evaluated; nonetheless, they could have interfered in the abandonment rate. Also, the relatively small number of abandonment ($n = 19$) actually limits the generalization of our results. The strengths of this study include a large number of patients from a single institution. We think these interventions can be broadly applied in the design of strategies for improving treatment abandonment rates in children with cancer.

Although this strategy was successful in lowering the abandonment rate to less than 1%, there is still much to improve because our goal is that no child should abandon treatment. Therefore, intervention strategies to prevent and combat this issue need to be constantly improved.

In conclusion, monitoring missed appointments, and early interventions to address the issues associated with providing resources to help families during treatment, were effective in achieving very low abandonment rates.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

ORCID

Sima Ferman https://orcid.org/0000-0002-7076-6779
Fernanda Ferreira da Silva Lima
https://orcid.org/0000-0002-6658-3101
Carollyne Rodrigues Souza Lage
https://orcid.org/0000-0002-7761-097X
Senir Santos da Hora https://orcid.org/0000-0002-0161-3701
Danielle Tavares Vianna https://orcid.org/0000-0002-0536-0991
Luiz Claudio Thuler https://orcid.org/0000-0003-2550-6537

REFERENCES

1. Ward E, Desantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:83-103.
2. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28:2625-2634.
3. Gupta S, Rivera-Luna R, Ribeiro RC, et al. Pediatric oncology as the next global child health priority: the need for national childhood cancer strategies in low- and middle-income countries. *PLoS Med*. 2014;11:1-5.
4. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. *Cancer*. 2008;112 (3):461-472.
5. Howard SC, Marinoni M, Castillo L, et al. Improving outcomes for children with cancer in low-income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)-Part I. *Pediatr Blood Cancer*. 2007;48:364-369.
6. Howard SC, Wilimas JA. Delays in diagnosis and treatment of childhood cancer: where in the world are they important? *Pediatr Blood Cancer*. 2005;44:303-304.
7. Weaver MS, Arora RS, Howard SC, et al. A practical approach to reporting treatment abandonment in pediatric chronic conditions. *Pediatr Blood Cancer*. 2015;1-6.
8. Arora RS, Pizer B, Eden T. Understanding refusal and abandonment in the treatment of childhood cancer. *Indian Pediatr*. 2010;47:1005-1010.
9. Mostert S, Arora RS, Arreola M, et al. Abandonment of treatment for childhood cancer: position statement of a SIOP PODC Working Group. *Lancet Oncol*. 2011;12:719-720.
10. Weaver MS, Howard SC, Lam CG. Defining and distinguishing treatment abandonment in patients with cancer. *J Pediatr Hematol Oncol*. 2015;37:252-256.
11. Gupta S, Yeh S, Martiniuk A, et al. The magnitude and predictors of abandonment of therapy in paediatric acute leukaemia in middle-income countries: a systematic review and meta-analysis. *Eur J Cancer*. 2013;49:2555-2564.
12. Friedrich P, Lam CG, Kaur G, et al. Determinants of treatment abandonment in childhood cancer: results from a global survey. *PLoS One*. 2016;11:1-21.
13. Alvarez E, Seppa M, Rivas S, et al. Improvement in treatment abandonment in pediatric patients with cancer in Guatemala. *Pediatr Blood Cancer*. 2017;64:1-7.
14. Salaverria C, Rossell N, Hernandez A, et al. Interventions targeting absences increase adherence and reduce abandonment of childhood cancer treatment in El Salvador. *Pediatr Blood Cancer*. 2015;9:1609-1615.
15. Bonilla M, Rossell N, Salaverria C, et al. Prevalence and predictors of abandonment of therapy among children with cancer in El Salvador. *Int J Cancer*. 2009;125:2144-2146.
16. Rivera-Luna R, Correa-González C, Altamirano-Alvarez E, et al. Incidence of childhood cancer among Mexican children registered under a public medical insurance program. *Int J Cancer*. 2013;132:1646-1650.
17. Suarez A, Piña M, Nichols-Vinueza DX, et al. A strategy to improve treatment-related mortality and abandonment of therapy for childhood ALL in a developing country reveals the impact of treatment delays. *Pediatr Blood Cancer*. 2015;62:1395-1402.
18. Howard SC, Pedrosa M, Lins M. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA*. 2004;291:2471-2475.
19. Vasquez L, Diaz R, Chavez S, et al. Factors associated with abandonment of therapy by children diagnosed with solid tumors in Peru. *Pediatr Blood Cancer*. 2018;65 (6):e27007.
20. Friedrich P, Ortiz R, Fuentes S, et al. Barriers to effective treatment of pediatric solid tumors in middle-income countries: can we make sense of the spectrum of nonbiologic factors that influence outcomes? *Cancer*. 2014;120:112-125.
21. IBGE [Internet]. 2017; https://www.ibge.gov.br/estatisticas-novoportal/sociais/populacao/9103-estimativas-de-populacao.html?=&t=destaques. Accessed December 4, 2018.
22. The World Bank Group [Internet]. 2018; https://data.worldbank.org/country/brazil. Accessed December 4, 2018.

23. Brown S, Belgaumi A, Kofide A, et al. Failure to attend appointments and loss to follow-up: a prospective study of patients with malignant lymphoma in Riyadh, Saudi Arabia. *Eur J Cancer Care*. 2009;18(3):313-7.

24. Paim J, Travassos C, Almeida C, et al. The Brazilian health system: history, advances, and challenges. *Lancet*. 2011;377:1778-1797.

25. Friedrich P, Lam CG, Itriago E, et al. Magnitude of treatment abandonment in childhood cancer. *PLoS One*. 2015;10:1-15.

26. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. *Pediatr Blood Cancer*. 2007;49:941-946.

27. Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. *Br J Ophthalmol*. 2010;94:1432-1436.

28. Luna-Fineman S, Barnoya M, Bonilla M, et al. Retinoblastoma in Central America: report from the Central American Association of Pediatric Hematology Oncology (AHOPCA). *Pediatr Blood Cancer*. 2012;58:545-550.

29. Metzger ML, Howard SC, Fu LC, et al. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. *Lancet*. 2003;362:706-708.

30. Li EQ, Jin RM. Causes for refusal or abandonment during treatment of pediatric acute promyelocytic leukemia. *Leuk Res*. 2012;36:e193-194.

31. Kumar A, Moulik NR, Mishra RK, et al. Causes, outcome and prevention of abandonment in retinoblastoma in India. *Pediatr Blood Cancer*. 2013;60:771-775.

32. Mostert S, Sitaresmi MN, Gundy CM, et al. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics*. 2006;118:e1600-1606.

33. Sitorus RS, Moll AC, Suhardjono S, et al. The effect of therapy refusal against medical advice in retinoblastoma patients in a setting where treatment delays are common. *Ophthalmic Genet*. 2009;30:31-6.

34. Samudio A, Figueredo D, Lassaletta A, et al. Building a National Pediatric Cancer Center and network in Paraguay. *J Pediatr Hematol Oncol*. 2015;37:383-390.