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Therapy-Related Myeloid Neoplasms After Pediatric Solid Cancer in A Single Reference Cancer Centre in Brazil

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Abstract

Pediatric cancer overall survival has increased due to improvements in treatment. However, long-term adverse effects are a challenge for this population. Secondary myeloid neoplasm (MN) is one of the complications of solid tumor treatment. Therapy-related myeloid neoplasms (t-MN), therapy-related acute myeloid leukemia (t-AML), and therapy-related myelodysplastic syndrome (t-MDS) are the most common events. The aim of this study was to report a large pediatric sample and the relevance of t-MN after pediatric solid tumor therapy. We conducted a retrospective study between 2000-2016 in a cohort of pediatric patients treated for solid tumors who developed a secondary MN by medical records review and analysis. Seven from 2178 pediatric patients who were previously treated for solid tumors, were diagnosed with t-MN in a reference cancer center in Brazil. The median age at primary tumor diagnosis was 12.8 years old. Osteosarcoma, atypical primitive neuroectodermal tumor (PNET), Ewing sarcoma, and retinoblastoma were the most frequent solid tumors associated with t-MN. Three patients had a story of familiar cancer, and one patient with osteosarcoma had Li-Fraumeni syndrome confirmed. The median latency period to secondary MN was ten months and the prevalence rate was 0.32%. Two patients developed t-MDS and five, t-AML. All these patients received cytotoxic agents' high doses that may have been associated with t-MN development. t-MN initial control, as well as unfavorable cytogenetic abnormalities, may have contributed to the poor outcome. We described the rarity of t-MN related to previous solid tumor therapy in a large pediatric sample in a Brazilian Cancer Center and their poor prognosis.

Keywords: Solid Tumor, Therapy-Related Myeloid Neoplasm, Childhood

Abbreviations

AML: Acute myeloid leukemia
BFM: Berlin-Frankfurt-Münster
FISH: Fluorescence in situ hybridization

G-CSF: Granulocyte colony stimulating factor
GALOP: Grupo América Latina de Oncologia Pediátrica
GCBTO Grupo Cooperativo Brasileiro de Tumores Ósseos
INCA: Instituto Nacional de Câncer
LA-RETINO: Latino-Americano de Retinoblastoma
MN: Myeloid neoplasms
MDS: Myelodysplastic syndrome
NHC: National Health Council
POG: Pediatric Oncology Group
PNET: Primitive neuroectodermal tumor
RB: Retinoblastoma gene
SFOP: Société Française d'Oncologie Pédiatrique
t-AML: Therapy-related acute myeloid leukemia
t-MN: Therapy-related myeloid neoplasm
t-MDS: Therapy-related myelodysplastic syndrome
TP53: Tumor protein P53
WHO: World Health Organization

Introduction

Advances in treatment have greatly improved pediatric cancer overall survival in the last years [1]. However, treatment's late effects, such as secondary neoplasms, are still a challenge for this population [1,2]. Second neoplasm development after primary cancer treatment is one of the most devastating effects of childhood cancer and it's a crescent concern for this population exposed to cytotoxic agent's risks [1-4].

Therapy-related myeloid neoplasms (t-MN) like acute myeloid leukemia (t-AML) and myelodysplastic syndrome (t-MDS) are one of the severe complications in pediatric solid tumor therapy [2,4]. These conditions are described in World Health Organization (WHO) classification as therapy-related myeloid neoplasms [3]. Prognosis is equally adverse with high mortality rates. t-MDS stands for 20-30% and t-AML for 70-80% of the cases. t-AML has a shorter latency period [2,5,7], emerges 1-5 years after cytotoxic agent exposure and it is associated with topoisomerase II inhibitors, while t-MDS is mostly diagnosed 5-10 years after exposure and associated to alkylating agents and/or radiation therapy. Alterations in chromosomes 5 and 7 [del(5q)/-5; del(7q)/-7], complex karyotype and TP53 mutations are seen in t-MDS as well as rearrangements in KMT2A gene (11q23 chromosome region) rearrangements are seen in t-AML [4,8].

Pediatric cancer survivors have three to ten higher risk to present a secondary neoplasm [8-12] and approximately 10% of them de-velop acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) after cancer treatment [12]. Myeloid neoplasms related to pediatric solid tumors therapy are more severe than in adult patients [2,3].

Although t-AML and t-MDS treatment results are better in pediatric population than in adults, 5-year event-free and overall survival rates are not so good, 14 and 30%, respectively [11-14]. Primary cancer treatment is the main identified risk factor associated with secondary myeloid neoplasms' development. Topoisomerase II inhibitors, alkylating agents and radiation therapy are the most studied [2,8,11]. Primary tumor type, cytotoxic agent dosage and management may also interpose risks [8], although evidence is not clearly established yet. Presence of genetic mutations also increases susceptibility to cancer [17]. Therefore, the incidence seems to be more dependent on previous disease and treatment [18].

Of the majority of patients with t-MN previously treated for malignancy, 70% were solid tumors and 30% were hematological neoplasms. t-MN's clinical, morphological and genetic features are related to previous treatment, although combined therapy may causes difficulty to define one specific agent [3]. Thus, it is not possible yet to divide disease according to therapy received.

t-MN pathogenesis involves activation of oncogenes and inactivation of suppressor genes leading to chromosomal alterations or even selection of a pre-existing treatment-resistant hematopoietic stem cell clone that can be explained by high TP53 gene muta-tions frequency in t-MN. This can clarify why only one small portion of patients treated with identical protocols for primary solid tumor develops t-MN, suggesting that some of them should have an associated hereditary predisposition that favors diseases arise, as Li-Fraumeni syndrome [3,7,17]. However, for the majority of cases, pathogenesis still remains unknown.

In Brazil, 12500 new cancer cases per year are estimated in the 2020-2022 period, according to Instituto Nacional de Câncer (INCA) [19]. Pediatric cancer represents 3% of total cancer cases. Early diagnosis and adequate treatment in specialized centers are essential for long-term survival [19,20].

Based on these reports and rarity of t-AML and t-MDS after pediatric primary solid tumors, we consider it essential to carry out further studies to better understand t-MN's development and specific characteristics to implement changes in future therapeutic strategies. At that time, the aim of this study was to report a large pediatric sample and the relevance of t-MN after pediatric solid tumor therapy in a single Brazilian cancer center.

Materials and Methods

Patients

Initially, we performed a review and analysis of medical records of pediatric patients under 18 years of age with solid tumor admitted at the National Cancer Institute (INCA) from January 2000 to January 2016, accounting for 2776 patients. From this analysis, we selected patients who developed t-MN. We excluded patients who did not follow treatment in our center, patients who started their treatment in another center, but transferred to INCA; and patients with congenital diseases. This study was approved by the Ethics Committee of the Instituto Nacional de Câncer (CEP INCA 3·8·098·064) and was conducted according to the Helsinki Declaration.

Data Collection

Initially, we searched for patients with solid tumors under 18 years old registered and treated at INCA between January 2000 and January 2016. We selected those who had histopathological data and who developed a second neoplasm as AML and MDS related to therapy. Demographic characteristics, data concerning primary cancer, treatments, family history and t-MN were collected for selected patients reviewing their medical histories. Solid tumors and t-MN's histopathology were also reviewed.

Diagnostic Criteria, Therapy Regimen, And Latency Period Definition

t-AML/t-MDS diagnosis were made according to WHO classification criteria. Cytogenetic analysis was conducted by conventional method (G-banding) and fluorescence in situ hybridization (FISH). Therapy regimen for solid tumors included: Pediatric Oncology Group (POG), Société Française d'Oncologie Pédiatrique (POG-SFOP), Grupo América Latina de Oncologia Pediátrica (GALOP), Latino-Americano de Retinoblastoma (LA-RETINO) and Grupo Cooperativo Brasileiro de Tumores Ósseos (GCBTO), according to tumor type. t-AML patients were treated according to Berlin-Frankfurt-Münster (BFM) protocol for AML and patients with t-MDS received support therapy with granulocyte colony stimulating factor (G-CSF), erythropoietin and blood transfusions. Latency period was defined as interval between the end of solid tumor therapy and t-MN diagnosis.

Statistical Analysis

Descriptive analysis was performed by obtaining the frequency of the result in relation to the independent variables, thus demonstrating the main characteristics of patients, solid tumors, and t-MN. Statistical R program, version 5·2 (free software for statistical computing and graphics) was used to create a database and perform descriptive analysis.

Results

We detected 2776 patients under 18 years old admitted at INCA over a 16-year period. Of these patients, 2178 (78%) had a solid tumor diagnosed and were treated at INCA. The others 598 (22%) patients were excluded once they did not confirm a cancer diagnosis or had benign pathologies and were referred to other institutions. The most frequent solid tumors were central nervous system (CNS) with 361 (16.57%), followed by osteosarcoma 319 (14.64%), adrenal tumor 310 (14.23%) and Wilms tumor 242 (11.11%) (Table 1). Of the 2178 patients, 99.6% (2171) had no therapy-related myeloid neoplasms and were excluded. Only seven patients who had myeloid neoplasms after solid tumor therapy were identified.

Solid Tumors	Number of patients (%)
Nasopharyngeal carcinomas	
Lymphoepithelioma	20 (0.92%)
Epidermoid carcinoma, NOS	2 (0.09%)
Undifferentiated carcinoma, NOS	10(0.45%)
Thyroid Carcinomas	99 (4.4%)
Ameloblastic fibrosarcoma	1 (0.04%)
Germ cell and trophoblastic neoplasms	
Germ cell tumor	94 (4.31%)
Embryonal carcinoma, NOS	1 (0.04%)
Endodermal sinus tumor	24 (1.10%)
Immature teratoma	25 (1.14%)
Seminoma	9 (0.41%)
Teratocarcinoma	2(0.09%)
Choriocarcinoma	4(0.18%)
Malignant neuroepithelial tumors	
Retinoblastoma	150(6.88%)
Medulloepithelioma	3(0.13%)
CNS rhabdoid tumor	8(0.36%)
Papillary glioneuronal tumor maligno	6(0.27%)
Anaplastic ganglioglioma	2(0.09%)
PNET	129 (5.92%)
Rhabdomyosarcoma	80 (3.67%)
Ewing sarcoma	42 (1.92%)
Sarcomas (fibrosarcoma, fusiform cells sarcoma, epithelioid sarcoma, desmoplastic small round cell tumor, fibromixosarcoma)	119 (5.46%)
Others sarcomas	
Synovial sarcoma	38 (1.74%)
Hemangiosarcoma	3(0.13%)
Kaposi sarcoma	1(0.04%)
Malignant peripheral nerve sheath tumor	11 (0.50%)
Alveolar soft part sarcoma	5 (0.22%)
GIST - gastrointestinal stromal tumor	5 (0.22%)
Osteosarcoma	319 (14.64%)
Wilms tumor	242 (11.11%)
Adrenal tumors	
Neuroblastoma	310(14.23%)
Pheochromocytoma	1 (0.04%)
Adrenocortical carcinoma	11 (0.50%)

Solid Tumors	Number of patients (%)
Liver tumors	
Hepatoblastoma	37 (1.69%)
Fibrolamellar hepatocellular carcinoma	4 (0.18%)
CNS tumors (medulloblastoma, medulloepithelioma, ependymoma, astrocytoma, ganglioglioma, oligodendroglioma, glioblastoma, glioma, fibrosarcoma)	361 (16.57%)
Total	2.178

*NOS-Not Otherwise Specified, PNET-Primitive Neuroectodermal Tumor, GIST-Gastrointestinal Stromal Tumor, CNS-Central Nervous System

Table 1: Solid tumors diagnosis frequency distribution (n=2.178)

Among seven patients, three (43%) were male and four (57%) were female. The median age at primary tumor diagnosis was 12•8 years old, ranging from six months to 14.3 years old. Osteosarcoma (28.6%), atypical primitive neuroectodermal tumor (PNET) (14•2%), Ewing sarcoma (28.6%) and retinoblastoma (28.6%) were the most frequent solid tumors associated to t-MN. Two (29%) patients developed t-MDS and five (71%), t-AML (Table 2). The estimated t-MN prevalence rate among solid tumors was 0.32%. The median latency period to secondary MN was ten months, ranging from five to 31 months (Table 3).

Patients characteristics	
Median age at primary tumor diagnosis (years) (range)	12.8 (0.6-14.3)
Median latency period (months) (range)	10 (5-31)
	Number of Patients (%)
Male	3 (42.9%)
Female	4 (57.1%)
Primary tumor	
Osteosarcoma	2 (28.6%)
Ewing sarcoma	2 (28.6%)
Retinoblastoma	2 (28.6%)
PNET	1(14.2%)
t-MN	
t-AML	5 (71.4%)
t-MDS	2 (28.6%)
Karyotype	
del(7)(q31)	1
normal	1
complex	1
inv(*16*)(p13q22)	1
KMT2A rearrangement	2
NM	1

Abbreviations: PNET, primitive neuroectodermal tumor; t-MN, therapy-related myeloid neoplasm; t-AML, therapy-related acute myeloid leukemia; t-MDS, therapy-related myelodysplastic syndrome; del, deletion; inv, inversion; NM, no mitosis

Table 2: t-MN patients characteristics frequency distribution (n=7)

Cancer familiar history was observed in three of these patients. Only one with osteosarcoma was associated with Li-Fraumeni syndrome and had the involvement of TP53 gene mutations confirmed by MLPA (multiple linkage dependent probe amplification). Regarding treatment, all patients received at least two alkylating agents in combination with a topoisomerase II inhibitor. Furthermore, three patients underwent radiotherapy. Osteosarcoma patients were treated according to the GCBTO protocol and developed t-MDS. Both relapsed from the primary tumor, nevertheless, they had different latency periods, eight and 25 months, while Ewing's sarcoma patients developed t-AML and presented a difference of ten to 25 months in latency period. These patients received different treatment protocols for primary tumors: POG 8850 and GALOP (Tables 3, 4). Retinoblastoma patients emerged with t-AML eight to 31 months after the conclusion of the primary tumor´s treatment (LA-RETINO protocol) (Table 3, 4). Only the PNET patient, who developed t-AML after a five-month latency period, survived twice cancer. The treatment used was POG-SFOP protocol with doses adjusted for children under three years of age. The majority of patients had high-risk cytogenetic alterations such as deletion 7q, KMT2A rearrangement and complex karyotype. One patient had a normal karyotype and the other had no mitosis for analysis. Only the patient who remains alive until now presented a chromosome alteration inv (16) (p13q22) associated with a good prognosis (Table 3).

Patients	1	2	3	4	5	6	7
Primary tumors' characteristics							
Age at diagnosis (years)	0.6*	13.11	12.11	2.0	14.3	12.8	2.3
Sex	F	M	F	M	F	M	F
Primary tumor	PNET	Ewing sarcoma	Ewing sarcoma	Retinoblastoma	Osteosarcoma (Li Fraumeni)	Osteosarcoma	Retinoblastoma
Family history of cancer	-	yes	-	-	yes	yes	-
Treatment protocol	POG SFOP	POG 8850	GALOP	LA-RETINO	GCBTO	GCBTO	LA-RETINO
Treatment							
Alkylating agent	3 + 1 AO	2	2 + 1 AO	3	1 + 1 AO	2 + 1 AO	3
Topoisomerase inhibitor	1	3	2	3	1	2	3
Radiotherapy (cGy)	-	1440	1260	-	-	-	3500
Relapse	no	no	no	no	yes	yes	no
t-MN characteristics							
Age at diagnosis	2.7	17.1	14.2	6.1	19.1	14.6	4.2
Type of t-MN	t-AML	t-AML	t-AML	t-AML	t-MDS	t-MDS	t-AML
Cytogenetic abnormality	inv. (16) (p13q22)	del (7) (q31)	no mitosis	*KMT2A* rearrangement	complex karyotype	normal karyotype	*KMT2A* rearrangement
Treatment protocol	BFM	BFM	-	BFM	-	-	BFM
Complete remission	yes	yes	-	yes	-	-	no
BMT	-	-	-	yes	-	-	-
Relapse	no	yes	-	yes	-	-	-
Latency period (months)	5	25	10	31	25	8	8
Outcome	alive	death	death	death	death	death	death

Abbreviations:*months; PNET, Primitive neuroectodermal tumor; POG, Pediatric Oncology Group; SFOP, Société Française d'Oncologie Pédiatrique; GALOP, Grupo América Latina de Oncologia Pediátrica; LA-RETINO, Grupo Latino-Americano de Retinoblastoma; GCBTO, Grupo Cooperativo Brasileiro de Tumores Ósseos; cGy, centigray; OA, oral administration; t-MN, therapy-related myeloid neoplasm; t-AML, therapy-related acute myeloid leucemia; t-MDS, therapy-related myelodysplastic syndrome; BFM, Berlin-Frankfurt-Münster; BMT, bone marrow transplantation.

Table 3: Clinical characteristics of primary solid tumor and t-MN

Among patients with t-AML, four were treated with BFM protocol and one did not have clinical conditions for adequate treatment. Between them, three achieved complete remission. t-MDS patients received supportive care. Only one t-AML patient who presented early medullar and CNS relapse after first treatment was submitted to reinduction treatment (second line treatment) followed by BMT (9 months after t-AML diagnosis). The other patients did not have adequate time for the procedure or did not have an available donor.

All patients received high cumulative doses from both alkylating agents and topoisomerase II inhibitors, except the one who survived and received lower doses. The first group comprises patients with Ewing sarcoma who received the highest doses of alkylating agents (one patient received 99.6g/m2 intravenous and the other received 71.4g/m2 intravenous added to 9g/m2 orally) and topoisomerase II inhibitors (one received 5.37g/m2 intravenous and the other 3.84g/m2 intravenous). Concerning cytotoxic agents' cumulative doses, followed by the Ewing sarcoma group, both patients in retinoblastoma group received equally 63.54g/m2 intravenous added to 150mg/Kg orally of alkylating agents and 3.75g/m2 intravenous added to 10mg/Kg orally of topoisomerase II inhibitors. Osteosarcoma patients are in the third group and received lower doses from both cytotoxic agents. Concerning alkylating agents, one received 2.53g/m2 intravenous added to 3150mg/m2 orally and the other received 480mg/m2 intravenous added to 18.2g/m2 orally. Topoisomerase II inhibitors doses were 725mg/m2 and 450mg/m2 intravenous (Table 4). Causes of death were: t-MN relapse (n=2), primary tumor relapse (n=1), prolonged aplasia added to infectious complications/coagulopathy (n=1), infectious / thrombotic complications (n=1) and t-MN progression due to lack of clinical conditions for appropriate treatment (n=1).

Patients	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Cytotoxic agents	**total doses per patient**						
Cyclophosphamide	50mg/Kg x 7 = 350mg/Kg	1,2g/m^2 x 8 = 9,6g/m^2	1,2g/m^2 x 7 = 8,4g/m^2	30mg/Kg x 5 = 150mg/Kg	-	500mg/m^2 x 5 = 2500mg/m^2	30mg/Kg x 5 = 150mg/Kg
Ifosfamide	-	9g/m^2 x 10 = 90g/m^2	9g/m^2 x 7 = 63g/m^2	9g/m^2 x 7 = 63g/m^2	-	-	9g/m^2 x 7 = 63g/m^2
Carboplatin	15mg/Kg x 7 = 105mg/Kg	-	-	-	-	-	-
Cisplatin	2mg/Kg x 7 = 14mg/Kg	-	-	90mg/m^2 x 6 = 540mg/ m^2	60mg/m^2 x 8 = 480mg/ m^2	60mg/m^2 x 6 = 36mg/m^2	90mg/m^2 x 6 = 540mg/ m^2
Etoposide	10mg/Kg x 7 = 70mg/Kg	500mg/m^2 x 10 = 5000mg/ m^2	495mg/m^2 x 7 = 3465mg/ m^2	450mg/m^2 x 7 = 3150mg/m^2	-	100mg/ x 5 = 500mg/m^2	450mg/m^2 x 7 = 3150mg/m^2
Teniposide	-	-	-	100mg/m^2 x 6 = 600mg/m^2	-	-	100mg/m^2 x 6 = 600mg/m^2
Doxorubicin	-	75mg/m^2 x 5 = 375mg/m^2	75mg/m^2 x 5 = 375mg/m^2	2mg/Kg x 5 = 10mg/Kg	37,5mg/m^2 x 12 = 450mg/m^2	37,5mg/m^2 x 6 = 225mg/m^2	2mg/Kg x 5 = 10mg/Kg
Actinomycin D	-	1,25mg/m^2 x 3 = 3,75mg/ m^2	-	-	-	-	-
Methotrexate	-	-	-	-	12g/m^2 x 12 = 144g/ m^2	12g/m^2 x 6 = 72g/m^2	-
Vincristine	0,05mg/Kg x 7 = 0,35mg/ Kg	2mg/m^2 x 8 = 16mg/m^2	1,5mg/m^2 x 7 = 10,5mg/m^2	0,05mg/Kg x 5 = 0,25mg/ Kg	-	-	0,05mg/Kg x 5 = 0,25mg/Kg

Vimblastine	-	-	6mg/m² x 48 = 288mg/m²	-	-	-	-
Procarbazine (oral)	28mg/Kg x 7 = 196mg/Kg	-	-	-	-		-
Cyclophosphamide (oral)	-	-	25mg/m² x 360 = 9000mg/m²	-	25mg/m² x 728 = 18200mg/m²	25mg/m² x 126 = 3150mg/m²	-
Methotrexate (oral)	-	-	-	-	1,5mg/m² x 208 = 312mg/m²	1,5mg/m² x 36 = 54mg/m²	-
Alkylating agents' total doses	469mg/Kg 196mg/Kg (Oral drug)	99,6g/m²	71,4g/m² 9000mg/m² (oral drug)	63,54g/ m² 150mg/Kg	480mg/m² 18200mg/m² (oral drug)	2536mg/m² 3150mg/m² (oral drug)	63,54g/ m² 150mg/Kg
Topoisomerase II inhibitors total doses	70mg/Kg	5378,7mg/m²	3840mg/m²	3750mg/m² 10mg/Kg	450mg/m²	725mg/m²	3750mg/m² 10mg/Kg

Table 4: Cytotoxic agents: total doses per patient

Discussion

The t-MN, t-AML and t-MDS, are late complications that can emerge after pediatric solid tumors therapy. Besides treatment, primary tumor type and genetic features can be also associated with t-MN development, but this relationship still needs to be better clarified. The prognosis is often unfavorable and disease comorbidities are also strongly influenced by cytogenetic abnormality type [3,4,7].

In our study, the t-MN estimated prevalence rate in pediatric patients treated for a solid tumor was 0.32%, less than rates related in previous studies which are above 1% [4,12,21-25], probably because it is a single-center experience study and it has a small number of cases. We did not report overall survival due to the small number of patients, however, five-year survival often related in studies is less than 10% [21-24].

The most frequent pediatric solid tumors related to secondary myeloid neoplasms found in our study were Osteosarcomas and Ewing sarcomas. Our results agree with literature findings. On the other hand, in disagreement with literature, retinoblastomas were also frequent in our study [22-25]. It is important to emphasize that retinoblastomas are less common among childhood neoplasms in Brazil [19] and occupies third place in the sample study. Solid tumors such as neuroblastoma, medulloblastoma and Wilms tumor previously treated and associated with myeloid neoplasms development are related in previous studies [12,21-25], but these solid tumors were not found in ours. This result may be a reflection of small number of cases observed in this study as it is a single-center experience. In addition, neuroblastoma has a shorter survival and Wilms tumor's treatment has changed over the years to minimize toxicities and consequently t-MN risks.

AAs well as literature findings, t-AML presentation was more frequent than t-MDS. The median latency period was ten months, shorter than previous studies that were 12 months at least [12, 26-32]. All patients have received cytotoxic agents' high doses, except the patient with PNET that received lower doses, age-adjusted, who was the only survivor. Therefore, cytotoxic agents' high doses, as well as their frequency, may be relevant to t-MN development and prognosis. Hematopoietic stem cell transplantation (HSCT) is indicated as consolidation therapy for adverse prognosis t-AML since chemotherapy alone must not be sufficient, as shown in some studies [22-30]. In our analysis, the only patient submitted to HSCT did not maintain complete remission after the procedure. Nevertheless, this patient survived longer than the other t-AML patients who were not submitted to this treatment.

Besides cytogenetic abnormalities, TP53 and other mutations, such as the one involving the RB gene, are also relevant in t-MN pathogenesis and can be present since the first tumor diagnosis [7]. In this context, hereditary predisposition should be considered, once only a small portion of patients treated with identical protocols develops t-MN, suggesting that some of them may have a hereditary predisposition, associated with treatment resistance as we observed in our study. Of 2178 patients with solid tumors confirmed, only seven developed t-MN. In the future, patient genomic information will help to select "susceptible" patients who can receive individualized therapy, aiming to minimize toxicity and reduce t-MN development risk [32].

It is important to note, according to the literature review, that there are no records in Brazil on this specific subject so far. Beyond that, there are also few international studies reporting t-MDS or t-AML after pediatric solid cancer therapy available. In our study, we presented t-MN´s prevalence rate, the most frequent solid tumors, t-MN and latency period to t-MN development. Cytotoxic agents' high doses and frequency may have contributed to t-MN development, t-AML initial therapy and disease control (complete remission), as well as high-risk cytogenetic abnormalities may have contributed to an unfavorable outcome.

Conclusions

We highlight the rarity of t-MN after a solid tumor in a large pediatric sample from a single Brazilian cancer center. The median age at primary tumor diagnosis was 12.8 years old. The most frequent solid tumors associated with t-MN were Osteosarcoma, atypical primitive neuroectodermal tumor (PNET), Ewing sarcoma and retinoblastoma. Median latency period to secondary MN was ten months and prevalence rate was 0.32%. Furthermore, we emphasize the need for an adequate follow-up for early diagnosis of a second neoplasm, providing precise therapeutic strategies. More robust epidemiological studies are necessary to establish the role of different factors in the development of t-MN since poor results reinforce the severity of the disease.

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