Rare tumors in pediatric patients: first report in Argentina

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Abbrevations

COG	Cancer Oncology Group
CT	Chemotherapy
DNA	Desoxirribonucleic acid

GANT	Gastrointestinal Autonomic Nerve Tumor
GIST	Gastrointestinal Stromal Tumor
ICCC	International Classification of Childhood Cancer
ICD-O-3	International Classification of Disease for Oncology
PCR	Polymerase Chain Reaction
PTS	Patients
RDT	Radiotherapy
ROHA	Registro Oncopediátrico Hospitalario Argentino
RT	Rare Tumors
SEER	Surveillance Epidemiology and End Results Program
TREP	Tumori Rari in Eta Pediatrica
VHL	Von Hippel Lindeau

Abstract

Background: cooperative clinical trials has increased the knowledge on pediatric tumors; however, this is not the case for rare tumors (RT).

Objective: To describe the incidence, clinical characteristics and outcome of RT in the pediatric age diagnosed at Garrahan Hospital.

Material and methods: Retrospective descriptive study of patients (pts) between 0 and 18 years admitted between January 2007 and December 2017, with diagnosis of RT.

Results: Of 1 657 pts with diagnosis of solid tumors, 164pts (9.9%) corresponded to RT, 71.95% (118pts) were under 14 years old and 81.7% (130pts) were male. In order of frequency RT were: thyroid carcinoma 60pts, adrenal carcinoma 14pts, lung tumors 14pts, melanoma 13pts, salivary glands carcinoma 11pts, gastrointestinal tumors 8pts, non-gonadal germinal tumors 7pts, pancreatic tumors 7pts, renal carcinoma 6pts, nasopharyngeal carcinoma 5pts, pheochromocytoma/paraganglioma 5pts, thymic carcinoma 1pte. The treatment received depended on the type of tumor and stage. With a median follow-up of 34.9 months (range: 1-128.5 months), 133pts (78.7%) are alive and only 10pts (6%) were lost to follow-up.

Conclusion: Knowing these initial data will allow us to propose new registration strategies and to develop multidisciplinary proposals for diagnosis, treatment and follow-up.

Introduction

Malignant tumours are relatively rare in children when compared to adults; however, they are the second most common cause of death in adolescents and children over one year of age, following accidents. The yearly incidence of cancer is estimated at around 1 in 7 000 children under the age of 15, with more than 12 000 new cases per year in patients under 20 years of age in the United States[1]. In Argentina, 21 912 tumours were diagnosed in children under the age of 15 between 2 000 and 2 016, with an average of 1 289 new cases per year, corresponding to an adjusted rate of 129 cases per million inhabitants under the age of 15.[2]

Since the 1 970s, because of the efforts of different cooperative groups and the creation of national and international clinical protocols, knowledge on these diseases has increased, thereby improving the prognosis and disease course. Unfortunately, this is not true for rare tumours.

According to the definition of the 2 002 Rare Diseases Act, all diseases affecting less than 200 000 people in a year in the United States[3] are defined as such; however, according to this definition, all childhood cancers would be listed as rare. Here, we will define rare tumours in children as any solid malignancy characterized by an annual incidence rate of less than 2 per million and not included in any research protocol[4]. In the International Classification of Childhood Cancer (ICCC)[5] these cancers are included in group XI, classified as carcinomas and other epithelial tumours, and group XII, miscellaneous and unspecifiedtumours. The specific features of rare tumours are low prevalence in children less than 5 years of age (with the exception of adrenocortical carcinomas), predominancein adults, having an epithelial rather than mesenchymal

origin, and infeasibility of multicentre studies because of the small number of patients[3].

In recent years, collaborative groups have been established with the intention to investigate this group of rare entities. In 2 000, in Italy the national collaborative group was created through TREP (TumorI Rari in età Pediatrica) project, from which here we used the definition of rare tumours. Subsequently, in 2 002 different North-American groups (Pediatric Oncology Group, Children's Oncology Group, the Intergroup Rhabdomyosarcoma Study Group, and the National Wilms Study Group) started to work together with the aim to create an organizational framework to facilitate the study of raretumours and develop registries, tumour banks, and clinical research studies for these diseases[6].

In our country, the Argentine Childhood Oncology Hospital Registry (ROHA) is a cooperative registry system of oncology-haematology patients under 15 years of age that have been diagnosed since 2 000, with an extension of the age of inclusion to 19 years since 2 010. The main aim of the registry is to record data on new cases of childhood cancer in Argentina. These data include personal characteristics of the patients as well as clinical and histopathological details of the tumours. The registry provides information on the incidence and features of cancer specifically in different segments of the population and variation of incidence over time. Coding systems for morphology and topography of the International Classification of Disease for Oncology (ICD-O-3)[7]and the ICCC[5] are used. As mentioned above, in the ICCC rare tumours are divided into group XI (adrenocortical, thyroid, and nasopharyngeal carcinomas, melanomas, and other and unspecified carcinomas), XII (other specified and

unspecified tumours) and we should add group VI (renal tumour) in which renal carcinomas are included.

According to the data from this registry, in our country 1 291 patients under 15 years of age are diagnosed each year, of whom 367 have solid tumours[2], and 187 (51%) are seen at Garrahan Hospital.

Argentina is a large country with sociocultural and economic differences. Garrahan Hospital is a paediatric tertiary centre with 550 beds, with specialised care for oncology, haematology and solid organ transplantation patients and for children undergoing heart or brain surgery. It is the most important childhood cancer centre in Argentina, treating 420 new patients per year accounting for one-third of all paediatric patients with cancer in the country. The hospital has an area exclusively for comprehensive outpatient care of patient with cancer and 90 beds for inpatients.

The aim of this study was to describe the incidence and typical features of rare childhood tumours diagnosed at Garrahan Hospital, considering the above-mentioned overall population.

Material and methods

A retrospective descriptive study was conducted evaluating patients between 0 and 18 years of age seen at Garrahan Hospital from January 2 007 to December 2 017, with a histopathological diagnosis of one of the following:

- Thyroid carcinoma
- Melanoma
- Adrenal carcinoma
- Carcinoid tumours
- Pleuropulmonaryblastoma and other lung tumours
- Salivary gland carcinoma
- Pancreatic tumours
- Renal carcinomas
- Sex cord stromal tumors
- Nasopharyngeal carcinoma
- Pheochromocytoma-paraganglioma
- Gastrointestinal carcinomas
- Thymic carcinoma
- Breast carcinoma

A data base was designed containing the personal data of the patients, date of diagnosis established as the date of the histological report, histological report,

presence of a syndrome or predisposing condition, molecular studies, treatment and follow up.

Results

During the study period, 1 657 patients with solid tumours were seen at Garrahan Hospital. Of these patients, 164 (9.9%) had RT, accounting for a mean of 16 new patients per year. As shown in Table 1, 71.95% (118) of the patients were younger than 14 years, and the most common diagnoses were thyroid carcinoma, adrenal carcinoma, and melanoma. Among adolescents, thyroid carcinoma was the most frequent, while the remaining tumours had a similar frequency across ages. Overall, a male predominance was observed.

Of 60 patients diagnosed with thyroid carcinoma, eight (13.3%) had had previous disease. Six of these eight patients developed thyroid carcinoma as a second cancer: Two patients had a history of Hodgkin's lymphoma and had received radiation therapy (RDT) to the neck; one patient had a history of Sertoli-Leydig cell tumour with a DICER-1 mutation; one patient had had paramenigeal rhabdomyosarcoma and received RDT; one patient had had acute lymphoblastic leukaemia and hypopituitarism with relapse in the testis and also received RDT; one patient had a history of hepatocellular carcinoma (associated with glycogen storage disease type 1) and underwent liver transplantation. Additionally, one patient had a history of pituitary adenoma and another patient a history of autoimmune nodular goiter.

In six of 14 patients (43%) with adrenal carcinoma, study of a mutation of the p53 gene was performed, and it was positive in three. One of these three patient had Li Fraumeni syndrome, another had the mutation most commonly found in the south of Brazil (p.R337H), and the remaining one had a sporadic mutation of the gene. In the patient with pheochromocytoma, a mutation in the VHL gene was found.

In three of the five patients with nasopharyngeal carcinoma presence of Epstein-Barr-virus DNA was investigated using polymerase chain reaction (PCR). The results were positive in all three.

In two of seven patients with gonadal non-germ cell tumoursa mutation in the DICER-1 gene was found. Both patients had Sertoli-Leydig cell tumours. This mutation was also searched for two of four patients with pleuropulmonary blastoma, that were type I in both. The study was negative in one and results of the other patient were pending at the time of study closure.

The histological subtypes of some of the tumours are described in Table 2.

Regarding treatment of the patients with thyroid carcinoma, thyroidectomy was performed in all followed by radioactive iodine. In our centre, these patients are treated and followed-up at the Department of Endocrinology. Median follow-up was 38.4 months (range, 1-128 months). No event was observed in any of the patients. Four patients were lost to follow-up.

Patients with adrenal carcinoma were stratified according to the COG classification[8] into stage I (2patients), stage II (2patients), stage III (5patients), and stage IV (5patients). Patients with stage I and II disease were only treated surgically, while four stage III and three stage IV patients received chemotherapy (CT) according to the COG ARAR0332 protocol with cisplatin, doxorubicin, and etoposide. With a median follow-up of 24.6 months (range, 1-66 months), stage I and II patients were alive and disease free. Three patients died, all of whom were stage IV. One of them died one month after diagnosis without receiving any treatment and the other two died of progressive

disease 6 and 30 months after the diagnosis, respectively. The patients treated with adjuvant therapy did not receive mitotane, as this drug is not available in our country.

Of 14 patients with lung tumour, four were diagnosed with pleuropulmonary blastoma. Two patients were classified as type I and the other two as type II. These latter patients received adjuvant therapy, one with CT only and the other CT combined with RDT. Both patients died due to disease progression 4 and 6 months after the diagnosis, respectively. Surgical resection was the only treatment used in type I blastomas achieving complete remission and both patients are alive and disease free after a median follow-up of 24 months (17 and 31 months). One patient developed a cystic nephroma 2 years after the initial diagnosis. Seven patients were diagnosed with inflammatory myofibroblastic tumour and treated with surgical resection only. Two patients presented with local relapse and both achieved remission after a second surgery. One patient died 3 months after diagnosis because of disease progression, two patients were lost to follow-up, and four patients (including those that relapsed) were disease free after a follow-up of more than 5 years after the initial diagnosis. Finally, three patients were diagnosed with carcinoma (epidermoid, myoepithelial, and adenoid cystic). The patient with myoepithelial carcinoma underwent surgery and was followed-up at our hospital, while the other two patients were referred to another institution. One of them (epidermoid carcinoma) underwent surgery followed by CT at another institution and died of disease progression 15 months after the diagnosis. The other two patients were alive and disease free 25 and 63 months after the diagnosis, respectively. Of 14 patients with melanoma, eight were alive and disease free, after a median follow-up of 26 months (range, 2-89 months). Four patients died of disease

progression 2, 4, 19, and 26 months after the diagnosis. Two patients were lost to follow-up.

Twelve patients who had carcinoid tumours (five of the lung and seven of the cecal appendix) only received surgical treatment. They were alive and disease free after a median follow-up of 35 months (range, 3-71 months).

Among eleven patients with salivary gland carcinoma, only the one who had poorly differentiated carcinoma developed metastasis and received adjuvant therapy with both CT and RDT. This patient died of disease progression 8 months after the diagnosis. One patient with mucoepidermoid carcinoma had a local relapse 55 months after the initial diagnosis. Surgical remission was again achieved. Nine patients were alive and disease free after a median follow-up of 29 months (range, 2-79 months). One patient was lost to follow-up.

All four patients with colon carcinoma had metastasis at diagnosis. All received CT; one was referred to another institution for this treatment. All of them died of disease progression with a median survival of 6.7 months (range, 5-11 months) after diagnosis.

The patients who were diagnosed with GIST (three patients) and GANT (one patient) underwent surgery only. One of the GIST patients had loco-regional recurrence 24 months after the initial diagnosis. The patient received Imatinib for two years resulting in stable disease and was alive at 79 months after the diagnosis. The remaining three patients were alive and disease free after a follow-up ranging between 5 and 20 months.

Seven patients with sex cord stromal tumours were classified after surgery as IRS I (three patients) and II (four patients). Only the small-cell carcinoma of the ovary was

metastatic. Five patients underwent treatment. Four received CT, of whom one relapsed, and only the patient with small-cell carcinoma of the ovary received CT and RDT. This latter patient died of disease progression 3 months after the diagnosis. The remaining patients are alive and disease free after a median follow-up of 18 months (range, 8-119 months).

Two histological subtypes of pancreas tumour were found. Solid pseudopapillary (Frantz) tumour was diagnosed in six patients, who underwent surgery only. Localized pancreatoblastoma was found in one patient who underwent CT (cisplatin/doxorubicin) and finished therapy in complete remission. The patient was alive and disease free 7 months after the diagnosis.

All of the six patients with renal carcinoma except one underwent nephrectomy. At diagnosis, three patients showed lymph-node involvement, but none of them had metastasis. Two of the patients received both CT and RDT, one received RDT, and the remaining patients underwent surgery only. One patient in whom a biopsy was performed did not receive treatment and died 21 months after diagnosis. One patient had a metastatic relapse 5 months after diagnosis and died 1 month later. The other four patients are alive and disease free after a median follow-up of 52 months (range, 18-86 months).

Of five patients with nasopharyngeal carcinoma, three had metastasis at the time of diagnosis. All underwent treatment (CT + RDT 4, one RDT only). Two patients had a metastatic relapse, one of whom died 33 months after the initial diagnosis. The remaining patients were alive and disease free after a median follow-up of 60 months (range, 26-105 months).

The patients that were diagnosed with pheochromocytoma-paraganglioma underwent surgery. One patient presented with metastasis at diagnosis and died 50 months after. Three patients were alive and disease free after a median follow-up of 60 months (range, 22-53 months) and one was lost to follow-up.

The patient with thymic carcinoma had metastasis at diagnosis. The surgically resected specimen showed positive margins. After the surgery, CT and RDT were performed; however, the patient died 7 months after the diagnosis due to disease progression.

None of the patients had breast carcinoma.

Discussion

This is, to our knowledge, the first report on rare tumours from our country. The study was conducted at a single centre, but as this centre receives almost one-third of the patients with cancer and 50% of the solid tumours, the results may be considered representative for the Argentine population. The concept of representativeness is reinforced when comparing our cohort with patients registered in the ROHA[2] between 2 000 and 2 013. In the ROHA, a mean of 30 patients were registered per year, while in our 10-year study a mean of 16 new patients per year was found. As ours is a retrospective study including patients treated at different departments, the number of patients registered is probably lower than the actual number seen, which is one of the main weaknesses of the study. This finding is similar to that of the first report by the TREP[4], in which retrospectively between 1 982 and 1 998 a rate of 15 new patients per year was found, while prospectively between January 2 000 and December 2005 this number increased to 49 new patients per year. Another indication of patient subregistration is that, while by the Italian group and the COG rare tumours were

reported to account for 8% to 10% of all the tumours diagnosed in children[4,6], in our cohort of 4 100 cancer patients diagnosed in Garrahan Hospital, 164 (4%) had rare tumours. When considering only solid tumours, 10% of a total of 1 657 patients registered, had rare tumours.

According to the data of the SEER[9] (Surveillance Epidemiology and End Results Program), 75% of rare tumours occur in adolescents and young adults, while in our cohort patients older than 15 years accounted for 27%, a percentage similar to that reported by the Italian group that found that 22% of the patients was between 15 and 17 years old[4]. This discrepancy may explained by the fact that a high percentage of patients in whom these tumours are diagnosed in adolescence are followed at adult centres, especially those tumours that are more common in this age group.

In our series, the most commonly diagnosed tumours were thyroid carcinoma, adrenal carcinoma, and melanoma. If we break down the numbers by age groups, in children (0-14 years) the same order of frequency is found, while in adolescents (15-18 years) thyroid carcinoma continues being the most frequent followed by colon carcinoma. The remaining tumours in this age group have a distribution similar to that in children. It would be important to emphasize that, except for those known by the Department of Oncology because of a previous cancer, the remaining patients with thyroid carcinoma are only followed-up and treated at the Department of Endocrinology. Something similar happens with patients with melanoma, for whom the Department of Dermatology is the treating department and who are often not referred to the Department of Oncology. This is a “limiting factor” observed at the moment of registering the patients shared with international cooperative groups[4,6,10], as in some

cases were surgical tumour resection or follow-up and treatment at adult centres complicate the registration of these patients. At our centre, tumours that are surgically resolved are all evaluated and, if necessary, followed-up at the Department of Oncology. This analysis is essential for the planning of strategies to improve registration of these patients.

Some of these rare tumours are associated with specific molecular alterations. The knowledge of the presence of these alterations is fundamental for adequate genetic counselling and, in certain cases, have the opportunity to study the relatives of the index case for an eventual early diagnosis. In our study we found that only 43% of the patients with adrenal carcinoma were studied for the mutation in the p53 gene, which has been shown in 50% of the studied cases. Considering the higher incidence of this tumour in the south of Brazil due to a specific mutation[11] and the large number of patients from provinces bordering that country, evaluating the status of the p53 gene would be important.

Von Hippel-Lindau disease (VHL) is a familial cancer predisposition syndrome, associated with a variety of malignant and benign neoplasms, most frequently retinal and cerebellar tumours, spinal hemangioblastoma, and renal cell carcinoma and, less often, pheochromocytoma.[12] The disease of autosomal dominant inheritance is caused by a mutation inthe VHL gene, located on chromosome 3p25.3. Identification of this mutation in one of the patients with pheochromocytoma was not only useful for the genetic counselling, but also for the routine follow-up controls with the aim to rule out other tumours that more frequently occur in this disease.

Another mutation that should be ruled out, is the mutation in the DICER-1 gene on chromosome 14q32.13, is shared by two conditions. This mutation is associated with pleuropulmonary blastoma, ovarian sex-cord stromal tumours, and cystic nephroma, among others[13]. In our patients with pleuropulmonary blastoma, only those with type I were studied. One of them subsequently developed cystic nephroma but did not have the mutation, while for the other results of the genetic studies are pending. Among the gonadal non-germ cell tumours, a mutation in the DICER-1 gene was found in both patients with Sertoli-Leydig-cell tumour, which is the most common histological subtype associated with this mutation described in the literature.

Collecting the data regarding molecular alterations in our patients, we found the limiting factor that not in all patients these studies were performed, mainly because of the lack of availability of this type of study at the time of diagnosis.

An important finding of this study is that 10% of the patients with thyroid carcinoma had previously had another type of cancer. Four of them had received RDT (two specifically to the neck), which increases the risk of developing thyroid carcinoma by 17% as the thyroid gland is highly sensitive to the cancer-causing effect of radiation[14]. One of the patients received post-transplantation immunosuppressive treatment and in the other a mutation in the DICER-1gene was discovered. This finding supports the importance of the post-treatment follow-up of oncological patients.

When evaluating the post-treatment control of patients with rare tumours, we found that only 6% (10 patients) of our cohort were lost to follow-up.

Conclusion

This is, to our knowledge, the first report of rare tumours in childhood in Argentina. The main limit of our study is that, as in other collaborative studies, this was a retrospective analysis, leading to greater subregistration. These initial data allow us to propose new registration strategies and to establish interdisciplinary proposals for the diagnosis, treatment, and follow-up of these patients. Collecting this information at a multicentre and multinational level poses a future challenge.

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