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Position Paper

The challenge of very rare tumours in childhood: The Italian TREP project

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ABSTRACT

A national cooperative project on rare paediatric tumours (the TREP project) was launched in 2000 in Italy, with a view to improving the clinical management and the basic research on these 'orphan' tumours, defined as those childhood solid malignancies characterised by an annual incidence < 2/million and not considered in other clinical trials. This paper describes the process that the group developed and the problems it had to face, and aims to stimulate a debate on the rationale, scientific relevance and feasibility of running scientific research programs on rare childhood neoplasms. In the first phase of its activity, the project developed diagnostic and therapeutic recommendations for each rare tumour and established a collaborative network between 'experts' dedicated to each histotype and other specialists (i.e. adult oncologists, surgeons) involved in the management of these tumours. From 2000 to 2005, 297 patients have been registered from 35 Italian centres. This experience demonstrates the feasibility of a national multidisciplinary cooperation on rare paediatric malignancies and suggests that international studies could be realised.

1. Introduction

Malignant tumours are relatively uncommon in children, when one compares them to adult cancer. However, cancer is the main cause of death due to disease in adolescents and children more than 1 year old, and its incidence is comparable to the cumulative incidence of relatively common conditions – such as cerebral palsy, diabetes and bacteria meningitis – that affect quality of life and survival of the childhood population. The annual incidence of cancer is estimated to be around 1 in 7000 children younger than 15 years; more than 12,000 new cases of children and adolescents less than 20 years with malignancies are diagnosed every year in the United States of America[1] (and about 1800 new cases a year in Italy).

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Ever since the early Seventies, paediatric oncologists have put a lot of effort into developing research protocols and promoting multicentre, national and ultimately international cooperation schemes. Cooperative groups, clinical protocols and a growing body of basic research have enabled a progressive increase in our understanding of paediatric tumours and a consequent improvement in the outcome of treatment. This has not happened for the less common histotypes, however, on which there is still little knowledge and a shortage of clinical and biological research. Paediatric oncologists (even those working at major institutions) are often unfamiliar with the management of these uncommon tumours because they rarely or never encounter them in their daily activities, which is why these rare paediatric tumours deserve the name of 'orphan diseases'.

With a view to improving the management of rare paediatric tumours, and the clinical and basic research, a national study group was founded in Italy and a comprehensive project on *Rare Tumours in Paediatric Age*– called the TREP project – was launched in 2000. This paper describes the process that we developed and the problems we had to face.

2. Definitions and epidemiology

First of all, which entities should be included in the definition of '*rare paediatric tumours*'? Though cancer is the main cause of disease-related mortality in children, all paediatric tumours could be virtually defined as 'rare', in the sense generally attributed to the term 'rare disease' in Europe (i.e. a prevalence < 50/100,000). However, at the beginning of our project we arbitrarily defined as '*rare paediatric tumours*' any solid malignancies characterised by an annual incidence < 2/million and not considered in other clinical trials (renal rhabdoid tumours are registered in the national Wilms study; hepatoblastoma and malignant germ cell tumours have their own protocols; rare histotypes of soft part sarcomas are covered by the cooperative study on soft tissue sarcomas). Thus, our pragmatic definition includes: nasopharyngeal carcinoma, adrenocortical tumours, pleuro-pulmonary blastoma (and other lung tumours), carcinoid tumours, cutaneous melanoma, renal cell carcinoma, pancreatoblastoma (and other pancreatic exocrine tumours), gonadal non-germ-cell tumours (ovary/testis), pheochromocytoma and paraganglioma, thyroid carcinoma, salivary gland tumours, breast carcinoma, carcinoma of the gastrointestinal tract, and carcinoma of the thymus. This is a heterogeneous assortment of tumours with a different biology and clinical history, some of them rare at any age, others rare in children but more common in adults. Given this heterogeneity, and the particular rarity of each histotype, it is difficult to study these tumours together. The cumulative frequency of these tumours is nonetheless judged to be around 8–10% of all paediatric malignancies, which is higher than that of other childhood cancers that have been intensively studied in cooperative protocols over the years.

Paediatric oncologists affiliated to the *Associazione Italiana Ematologia Oncologia Pediatrica* (AIEOP) and paediatric surgeons affiliated to the *Società Italiana Chirurgia Pediatrica* (SICP) conducted a retrospective study in Italy that collected clinical data on 259 patients up to 16 years old with these rare malignancies, treated between 1982 and 1998:[2] the limits and difficulties of the study emerged, relating to the variety of diagnostic and therapeutic approaches adopted and because the children were managed at different units (paediatric oncology, adult oncology, general surgery, endocrinology, gynaecology, and so on). Despite its limits, this study demonstrated the interest of Italian centres and the need for a more structured effort in favour of children with these tumours, as well as providing the groundwork that made a prospective study feasible.

3. The TREP project

The TREP project started in 2000 under the auspices of AIEOP and SICP.

The initial phase of the study was dedicated to organising the study's structure, and getting paediatric oncology and surgical centres all over the country involved in the project. The initial aims of the project were: 1) to develop diagnostic and therapeutic recommendations for each rare tumour; 2) to collect clinical data; 3) to identify one or two colleagues 'dedicated' to each histotype to serve as experts that clinicians at different institutions could contact in the event of problems with a patient affected by a rare tumour; 4) to establish a collaborative network with other specialists (i.e. adult oncologists, surgeons) involved in the management of these tumours; and 5) to establish pathological and biological studies.

The diagnostic-therapeutic recommendations were drafted by small appointed Working Groups including paediatric oncologists, surgeons, pathologists and, depending on the tumour, endocrinologists, dermatologists, radiotherapists, molecular biologists and adult specialists (mainly surgeons). The Working Group coordinators (one or two people) had to produce a preliminary document summarising the evidence of the literature (also from adult series) and previous Italian experience.[3–11] The drafts of the papers were revised by the TREP Scientific Committee and, after revision and approval, circulated to the AIEOP and SICP Directive Committees for endorsement. Revision by external experts, mainly adult surgeons, was requested in some cases (i.e. renal carcinoma, melanoma, salivary gland tumours).

All the final documents were combined into a single protocol and discussed openly at periodical AIEOP meetings, before circulating the protocol to the centres taking part.

The Working Group coordinators for each tumour were expected to re-evaluate the documents on the basis of new evidence and results obtained in the patients enrolled in the TREP project. These coordinators formed a network of 'experts' as paediatric oncology centres were expected to lack the necessary expertise for the multidisciplinary management of these particular tumours.

An important aspect of the project was the involvement of 'adult' specialists, as in the case of melanoma, for instance: childhood melanoma is a challenge even for clinicians who see pigmented skin lesions every day (and early diagnosis remains the most reliable way to cure these patients), so it is not so much a matter of paediatric oncologists needing to be able to make the diagnosis, but of their knowing that melanoma does occur in children and thus referring any suspected cases to expert physicians professionally dedicated to melanoma. So the aim of the TREP project was also to improve the collaboration between paediatric oncologists and

melanoma specialists (adult surgeons, dermatologists) at different centres all over the country.

Collaboration with the pathologist on the revision of the diagnosis and possible studies was considered right from the beginning of the TREP project and pathologists dedicated to the different rare tumours were identified. The same applied to the biological studies, where considered worthy of interest, e.g. when a pheocromocytoma is diagnosed, centres are asked to send their patient's blood samples to a reference laboratory to check for Von Hippel Lindau syndrome.

From 2000 to 2001, six guidelines were prepared and circulated on nasopharyngeal carcinoma, adrenocortical tumours, pleuro-pulmonary blastoma, carcinoid tumours, pancreatic tumours and gonadal non-germ-cell tumours (Table 1). Guidelines on pheochromocytoma, thyroid carcinoma, cutaneous melanoma and renal cell carcinoma were distributed in 2002–2003. The recommendations for salivary gland tumours and tumours of the thymus have recently been completed, while some of the first guidelines have been partially amended.

All patients under 18 years of age with a diagnosis of '*rare paediatric tumours*' were centrally registered at the Data Centre (Clinical Trials and Biostatistic Unit, Istituto Oncologico Veneto, Padova, Italy). Specific paper forms (diagnostic work-up, therapy, follow-up) were created for data collection purposes.

Data have been checked on a regular basis for completeness and consistency. A 6-month periodical follow up of registered patients has been requested, and the completeness of patient registration has also been checked, comparing against the general AIEOP registry.

4. Preliminary results

Since the TREP project started, 297 patients (age 1–18 years, median 12) have been registered from 35 Italian centres. Table 2 shows the different tumours involved: thyroid carcinoma was the most frequent histotype, followed by carcinoid tumours, cutaneous tumours and nasopharyngeal carcinoma.

Table 1 – Therapeutic recommendations

Adrenocortical tumours
- Group I (complete resection *and* tumour volume < 200 cm^3 *and* negative markers after surgery) → no further therapy
- Group II (micro residues or N1 *or* volume > 200 cm^3 *or* positive markers after surgery) → adjuvant mitotane
- Group III (macro residues *or* biopsy) or Group IV (M+) → mitotane + EDP

Pleuro-pulmonary blastoma
- Group I (complete resection, favourable histotype = type 1, *and* no pleural involvement) → no further therapy
- Group I (complete resection, unfavourable histotype = type 2–3, *or* pleural involvement) → VAIA × 6
- Group II (micro residues) → VAIA × 6
- Group III (macro residues *or* biopsy) → VAIA × 3 → delayed surgery - VAIA × 6

Nasopharyngeal carcinoma
Cisplatin + 5 fluorouracil × 3 courses – RT on T (60–65 Gy) and N (45–65 Gy)

Pancreatoblastoma
- Group I (complete resection) → PLADO × 4
- Group II (micro residues) → PLADO × 6
- Group III (macro residues *or* biopsy) → PLADO × 4 – surgery – PLADO × 2
- Group IV (M+) → PLADO × 4 – surgery – PLADO × 2

Pheochromocytoma
doxorubicin, etoposide, cisplatin in case of unresectable disease and, in an adjuvant setting, in case of residual disease after surgery

Non germ cell gonadal tumours
- Stromal ovarian tumours: Stage I (POG/CCG staging system) → only surgery
  Stage II → PEB × 3 courses
  Stage III → PEB × 4 (+ delayed surgery)
  Stage IV → PEB × 4 + delayed surgery
- Epithelial ovarian tumours: Stage II–III–IV → carboplatin × 6
- Testicular tumours: Stage I (POG/CCG staging system) → only surgery
  Stage II →PEB × 3 courses
  Stage III →PEB × 3 (+ delayed surgery)
  Stage IV →PEB × 4+delayed surgery

Thyroid carcinoma
- One lobe involvement, no nodal involvement
  →hemithyroidectomy → TSH-suppressive therapy
- Bilateral or multifocal tumour, bilateral N+, M+
  → total thyroidectomy → TSH-suppressive therapy or radioactive iodine ablation according to residual disease at scintigraphy and thyreoglobulin value
- One lobe involvement with monolateral N+, minimal multifocal tumour, capsule involvement
  →two options: hemithyroidectomy or total thyroidectomy (according to physician's decision)

T = tumour, N = nodal, M = metastases, RT = radiotherapy, CT = chemotherapy, EDP = etoposide, doxorubicin, cisplatin, VAIA = vincristine, actinomycin, ifosfamide, adriamycin, PLADO = cisplatin, doxorubicin, PEB = cisplatin, etoposide, bleomycin, POG/CCG staging system = Paediatric Oncology Group/Children Cancer Group staging system.

Table 2 – Paediatric rare tumours treated by AIEOP and SICP centres: comparison between the retrospective series and the prospective TREP study

	Retrospective series 1982–1998	TREP project Jan 2000–Dec 2005
Thyroid carcinoma	53	65
Nasopharyngeal carcinoma	45	28
Non-germ-cell tumours (ovary/testis)	37	28
Adrenocortical tumours	19	16
Carcinoid tumours	15	48
Renal cell carcinoma	25	19
Pheochromocytoma/paraganglioma	13	12
Lung tumours (including PPB)	12	11
Pancreatic tumours	11	12
Cutaneous tumours	11	36
Salivary-glands tumours	7	3
Carcinoma of the thymus	3	3
Gastro-intestinal carcinoma	3	6
Others	5	10
Total	259	297
	15/year	49/year

AIEOP = Associazione Italiana Ematologia Oncologia; SICP = Società Italiana Chirurgia Pediatrica; TREP = Pediatric Rare Tumours; PPB = pleuro-pulmonary blastoma.

Only seven centres have enrolled more than ten cases, and only one has had more than ten cases a year. Annual recruitment rates were: 39 in 2000, 50 in 2001, 44 in 2002, 46 in 2003, 57 in 2004, and 61 in 2005.

An attempt at a population-based analysis has been done. It is quite difficult to estimate the registration completeness of the incident '*rare paediatric tumours*' cases that occurred during the study period. We do not have concurrent incidence data from 'population-based' cancer registries in Italy. Updated epidemiological data from 12 Italian registries, from the Automated Childhood Information System (ACCIS) database, was however available for the 1995–1998 period.[12] From this data, it is possible to estimate in Italy an annual incidence of about 1400 cases of malignancies in patients 0–18 years old (amongst a population of about 10,500,000 individuals in this age bracket) (S. Guzzinati, Registro Tumori Veneto, personal communication). ACCIS data confirmed that the relative frequency of '*rare paediatric tumours*' is about 8–10%, that is to say 100 to 140 cases per year. The TREP project enrolled about 50 cases per year. In particular, comparing our data with the ACCIS data and focusing on some particular histotype, we can see that we have been able to register almost all the cases of renal carcinoma, but only one quarter of the expected melanoma cases, one third of the thyroid carcinoma cases and 60% of the nasopharyngeal carcinoma cases.

Preliminary analyses have shown that the guidelines have been widely accepted and used, improving the quality of the patients' diagnostic work up. It's too early, of course, to think in terms of improving survival rates – something far more difficult to achieve. The systematic study of children with rare tumours has prompted initial reports summarising our experience of the single histotypes.

5. Discussion

After 5 years of activity, we believe the TREP project has improved our knowledge and, to some degree, the quality of care for paediatric patients with rare tumours. The participation of the Italian paediatric oncologists and surgeons in this project has repaid the TREP Committee's efforts and we much appreciated the cooperative spirit of the other specialists (adult surgeons, endocrinologists, dermatologists, gastroenterologists, etc) actively involved as experts, each in their own field, to create a fruitful advisory network. However, the comparison with Italian population-based cancer registries showed a discrepancy between the expected cases and the registered cases. Why the TREP project, despite the large participation of paediatric oncology/surgery centres all over the country, was able to collect less than half of the expected cases is a matter of analysis and debate. We have seen that we have been able to register almost all the cases of renal carcinoma, but only one quarter of the expected melanoma cases, one third of the thyroid carcinoma cases and 60% of the nasopharyngeal carcinoma cases. We may suppose that a quite large percentage of cases occurring in adolescents are managed by adult centres, in particular for those malignancy that are typical of adulthood (i.e. thyroid carcinoma by otorhinolaryngologists, melanoma by dermatologists). In fact, the majority of 'TREP' histotypes are adult tumours, but the median age of our patients cohort is 12 years. May be, on the other hand, renal carcinoma cases are fully registered because renal masses in children are usually supposed to be Wilms' tumour, and therefore addressed to paediatric surgeons or paediatric oncolgists. More efforts should be done in the direction of improving the collaborations with adult specialists.

It is important to underline that our experience developed in a context where little effort has gone into creating cooperative paediatric oncology groups to develop clinical studies. It is acknowledged that the extreme rarity of these malignancies makes clinical and biological research very difficult - but not impossible. Studies coordinated by the International Childhood Liver Tumour Strategy Group SIOPEL on paediatric liver tumours represent a successful model and demonstrate that worldwide cooperation between different specialists is

feasible even for such rare tumours.[13] Another approach to the study of rare tumours is represented by the creation of national and international registries dedicated to a particular histotype, such as the International Pediatric Adrenocortical Tumor Registry[14,15] or the registry on pleuro-pulmonary blastoma.[16,17] Previous attempts to create an international registry on the group of rare paediatric tumours as a whole were unsuccessful, however. As for cooperative multidisciplinary groups, the Children Oncology Group (COG) in North America has a scientific committee dedicated to rare tumours, with three subcommittees on germ cell tumours, liver tumours and other rare tumours. In Europe, several national groups are conducting studies on single histotypes, but there are very few formally-created national groups to have focused on all rare paediatric tumours (i.e. United Kingdom, Poland).[18]

We consequently believe our experience may well be of interest. The appeal of our model lies in that it has a dual aim, i.e. to promote research and to develop clinical guidelines (with the support of an expert advisory network) within a common framework.

One of the limits of the TREP project is that it is restricted to one country. Clearly, international cooperation is now warranted to improve the quality of studies on these rare tumours. More than to present our experience, therefore, the main purpose of this report is to stimulate a debate on the rationale, scientific relevance and feasibility of running scientific research programmes on rare childhood neoplasms in the light of our experience. The key questions are 'why' and 'how' an international research project on these tumours should be set up. As for the 'how' to actually run clinical research program on rare childhood tumours, the TREP experience suggests that the key ingredients should be: i) a solid network of paediatric oncology centres and paediatric surgical units, already used to the discipline required to take part in cooperative clinical trials; ii) accepted common treatment guidelines; iii) an effective data collection system shared by all participating institutions; iv) a central pathology review process (for most of the histotypes at least); and, of course, v) dedicated financial resources.

Indeed, we believe that most of these elements are available in Europe (and we hope that financial resources might also become available). One question to address is whether it would be better – because these tumours are, by definition, dispersed in 'time' and 'space' (different centres) - to adopt a centralised model for running the project (like the one used by the SIOPEL, for example) or a de-centralised one based on a sort of federation of TREP-like national networks.

As for the question 'why', we should understand which is the scientific driving force to inspire, justify and guide such a project. The need to make treatment recommendations available to the paediatric oncologists encountering a child suffering from a rare tumour (that they may have never seen before) is one of the reasons. When it comes to scientific research, however, we know that for almost all the tumours in the TREP project, prospective randomised clinical trials will never be accomplishable within a reasonable time span, not even with a worldwide cooperation. One wonders whether any relevant clinical information will ever be produced in a reasonable time, so is this clinical research worth pursuing, supporting and investing in, or is it simply an amateur's collection of rarities? The question is not easy to answer. One way to address this issue might be to select and prioritise those rare neoplasms that pose a scientific biological/clinical question, e.g. some of these rare neoplasms are indicators of possible relevant clinical conditions, such as adrenocortical carcinoma or pheocromocytoma, and there are already laboratories working on these neoplasms in many parts of the world, so a large-scale cooperation designed to stimulate translational research in this field would be justifiable. Of course, this raises the question of the need to collect biological material, which poses a further burden on the project.

The issue of international cooperative trials on rare paediatric tumours has been raised only too often in the past, however, to little effect. We think the time is now ripe for this issue to be addressed more effectively.

Conflict of interest statement

None declared

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