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Pancreatoblastoma: A report from the European cooperative study group for paediatric rare tumours (EXPeRT)

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ABSTRACT

Background: Pancreatoblastoma is a very rare malignant tumour typically occurring in the early years of life. Due to its rarity, standardised diagnostic and therapeutic guidelines are not available for pancreatoblastoma.

Methods: The newborn cooperative group denominated EXPeRT – European cooperative study group for paediatric rare tumours – combined in a joint analysis of all cases registered between 2000 and 2009 by the national groups of Italy, France, United Kingdom, Poland and Germany.

Results: Twenty patients <18 years old (median age 4 years) were analysed: nine had distant metastases at diagnosis. Seventeen patients had tumour resection, at initial or delayed surgery. Eighteen received chemotherapy (response rate 73%), seven received radiotherapy. For the whole series, 5-year event-free survival and overall survival were 58.8% and 79.4%, respectively. Outcome did not correlate with tumour site and size, but was strongly influenced by the feasibility of tumour complete resection.

Conclusions: This international study confirms the rarity of the disease, the critical role of surgical resection both as therapy and as a prognostic variable, and the potential efficacy of chemotherapy. The adoption of an intensive multidisciplinary approach is required, as well as the referral to highly experienced centres. Further international cooperation is needed to collect larger series and stimulate biological studies to improve our understanding of the biology and the natural history of PBL.

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1. Introduction

Pancreatoblastoma (PBL) is the most typical paediatric malignancy of the pancreas, and usually occurs in young children. It is a malignant embryonal tumour that seems to recapitulate the embryogenesis of the pancreas, presumably because it originates from pluripotent pancreatic stem cells during foregut development.[1–3]

PBL is a very rare tumour and, similarly to other very rare paediatric neoplasms (i.e. childhood melanoma and gastrointestinal carcinoma, adrenocortical tumours, pleuropulmonary blastoma and others), it is considered an 'orphan' disease.[4,5] A Medline analysis of published cases collected 153 PBL cases,[6] with only a few published small series in the last decade, including cases treated over long periods: 10 cases of PBL (out of 58 pancreatic tumours in the paediatric age group) were registered in the North American population-based Surveillance, Epidemiology and End Results (SEER) database from 1973 to 2004[7]; seven PBL were reported in a French series over a 20-year period[8]; five PBL (out of 17 pancreatic tumours) were treated over a 35-year period at the Memorial Sloan-Kettering Cancer Center[9]; 11 PBL were recorded over a 30-year period in the United Kingdom National Registry of Childhood Tumours.[5,10] Very recently, the Italian TREP project (Tumori Rari in Età Pediatrica [*Rare Tumours in Paediatric Age*]) reported on four PBL (out of 21 pancreatic cases) seen over a 8-year period.[11]

As a consequence of its rarity, the clinical characteristics of PBL are generally unappreciated by most paediatric oncologists and surgeons, who rarely – if ever – encounter this tumour in their daily activities. Moreover, standardised diagnostic and therapeutic guidelines are not available for PBL.

Given the little experience that any single paediatric oncologist – or even any national paediatric oncology group – could have on PBL, as well as on other very rare paediatric cancers, the only way to improve our knowledge, promote dedicated research and produce guidelines for clinical management, is by the creation of an international network. In June 2008, the national groups dedicated to paediatric rare tumours in Italy, France, United Kingdom, Poland and Germany formed a new international cooperative group denominated EXPeRT – European cooperative study group for paediatric rare tumours.

PBL was chosen by the EXPeRT as one of the first tumour types to review. Data collected by the different national groups on clinical findings and treatment modalities were exchanged and hence this analysis.

2. Materials and methods

Inclusion criteria for the study were the following: age between 0 and 17 years, histologically confirmed diagnosis of PBL, diagnosis between 2000 and 2009. A relatively short study period was chosen in order to analyse the effect of more 'modern' treatment approaches, in particular the chemotherapy used. Data were extracted from the databases of the cooperating national paediatric working groups from Italy, France, United Kingdom, Poland and Germany. All patients, or their guardians, gave their informed consent for the data collection within the country specific rare tumour group and analysis. This study was approved by the institutional research ethics boards.

Specific forms for clinical findings (patient's age at diagnosis, gender, initial symptoms, site of disease, tumour size and stage), histopathology, therapy, and follow-up were used for data collection.

In all national groups, diagnostic investigations at the onset included the assay of serum markers (carcinoembryonic antigen, alpha-fetoprotein [aFP], cancer antigen [CA 125, and Ca 19-9]); computed tomography (CT) scanning and/or magnetic resonance imaging (MRI) to assess local tumour extent; and chest X-rays or chest CT scan for staging (few cases were submitted also to bone scan).

Since a tailored shared staging system did not exist for PBL, we arbitrarily decided to retrospectively classify patients according to a surgical staging system based on the results of initial surgery, as follows: stage I – completely-excised tumours with negative microscopic margins; stage II – grossly-resected tumours with suspected microscopic residual disease; stage III – gross residual disease after initial incomplete resection or biopsy; stage IV – distant metastases.

There were no specific guidelines for treatment but surgery tended to be primary excision if complete resection was considered feasible; if not, a biopsy was required and chemotherapy was administered prior to subsequent surgery, aiming again for complete resection. In the case of a tumour arising at the head of the pancreas, pancreaticoduodenectomy (Whipple's procedure or its 'modifications') was suggested.

There were no strict recommendations for chemotherapy: however, most national groups suggested a chemotherapy regimen with cisplatin 80 mg/m^2 in continuous 24-h intravenous infusions followed by doxorubicin 60 mg/m^2 over 48 h (the PLADO regimen), for 4–6 cycles.

In patients with measurable disease, response to chemotherapy was recorded after 2–3 cycles, according to the radiologically-assessed reduction in tumour volume, and defined as follows: complete response (CR) = complete disappearance of disease; very good partial remission (VGPR) = tumour reduction >90%; partial response (PR) = tumour reduction >66%; minor response (MR) = volume reduction between 33% and 66%. Stable disease, or a reduction <33% was classified as no response, while an increase in tumour size or the detection of new lesions was called progression of disease.

There were no defined recommendations for radiotherapy, i.e. it was generally suggested for selected inoperable tumours.

Event-free survival (EFS) and overall survival (OS) were estimated according to the Kaplan–Meier method.[12] Patients were evaluated from the date of pathological diagnosis to latest uneventful follow-up, disease progression, relapse or death of any cause, for EFS, and to death for OS. The log-rank test was used to compare in univariate analysis the survival curves for the different subgroups of patients to establish the potential value of prognostic factors. Multivariate analysis was not performed because of the low number of cases.

3. Results

3.1. Clinical findings

Twenty patients younger than 18 years old (median age 4 years) with PBL were registered in the Italian, French, Polish and German study groups, and for the United Kingdom in the National Registry of Childhood Cancer, between 2000 and 2009 for all patients.

In most patients initial symptoms comprised of abdominal pain, palpable mass in epigastrium, vomiting, jaundice and weight loss. One patient with Beckwith–Wiedemann syndrome was diagnosed with prenatal neuroblastoma and PBL simultaneously (this case has already been reported in the Italian TREP series).[11]

The tumours arose in different anatomical parts of the pancreas with similar frequency: five cases in the head of pancreas, four in the body, four tail (in seven cases it was difficult to identify one single pancreatic part as site of origin due to the huge tumour dimension). In 17 cases, tumour size was over 5 cm (and over 10 cm in 10 of them). Patients were classified as stage I in six cases, stage III in five and stage IV in nine (none was classified as stage II). Distant metastases were located in the liver in two children, lungs in two, distant lymph nodes in two and in subcutaneous tissue in one (in two children the data on the metastases' localisation were missing) (Table 1).

The initial serum levels of aFP were available in 18 out of 20 patients: they were normal (according to patient's age) in four cases and elevated in 14 (ranging from a 64 to 43,000 UI/ml, median level 658 UI/ml, mean level 7,620 UI/ml). Level of aFP seemed to correlate with primary tumour size, e.g. it was normal in 3/3 patients with tumour size <5 cm, high (range 64–24,030 UI/ml, median 328 UI/ml) in 5/6 patients with tumour of 5–10 cm (one not performed), and high (range 66–43,000 UI/ml, median 1,034 UI/ml) in 9/9 patients with tumour >10 cm (one not performed). However, aFP serum levels were normal in two of the seven metastatic cases with available data. Monitoring of the serum aFP during therapy was not always performed; however, in two cases a reduction of the aFP level was seen concomitantly to tumour shrinkage induced by chemotherapy.

No major differences were observed as regards patient's clinical characteristics between the different countries.

3.2. Treatment

Resection of the primary tumour at diagnosis was undertaken in nine of 20 patients and was complete (R0) in eight (six with localised disease, two with distant metastases) and microscopically incomplete (R1) in one case with stage IV disease.

The surgical procedures involved distal pancreatectomy in five children, pancreaticoduodenectomy (Whipple's procedure) in three and tumour enucleation in one (defined as R1). Delayed surgery (after chemotherapy) was undertaken in nine patients: eight patients initially submitted to biopsy and one who had had an R0 primary resection (the second-look procedure was a physician's decision although the patient was without evidence of disease). Delayed surgery in the eight cases initially submitted to biopsy was defined as complete in six and macroscopically incomplete (R2) in two cases. Three patients had no definitive surgery – neither primary nor delayed – during their course of disease. The delayed operation was a corporeocaudal pancreatectomy in four cases, Whipple's operation in three and distal pancreatectomy in two. One patient received also regional hyperthermia. All six Whipple's operations were able to achieve R0 resections and were not associated with significant complications. Three patients also had surgical removal of their metastases (Table 2).

Chemotherapy was used in 18/20 patients (two stage I patients did not receive chemotherapy). The PLADO regimen was used in 13 cases (in nine cases PLADO alone, in four PLADO plus other drugs, i.e. vincristine, actnomycin D and cyclophosphamide, gemcitabine or ifosfamide, carboplatin and etoposide), while the other five patients received different schemes including vincristine, cyclophosphamide, doxorubicin, ifosfamide, etoposide, vinblastine, carboplatin, bleomycin and cisplatin. The number of administered cycles ranged from 2 to 9, median six. One patient with metastatic disease received high-dose chemotherapy with autologous peripheral blood stem cell rescue (after no response to standard chemotherapy). Radiological response to chemotherapy in the 11 cases with measurable disease was VGPR in one patient, PR in four, MR in three, no response in two and disease progression in one (Table 2).

Radiotherapy (total dose of 30–45 Gy) was administered in six patients, in one case because surgery was considered unfeasible, in five cases after resection (two initial R0 resection, two delayed R0 resection, one R2 delayed resection). One case received also radiotherapy on metastatic sites.

3.3. Outcome

At the time of the analysis, 13 patients were alive in first complete remission, with a follow-up of 6–88 months from diagnosis. Most of them (12/13) were able to achieve a complete resection, at primary or at delayed surgery. One had a delayed R2 resection followed by radiotherapy.

Table 1 – Clinical characteristics of the patients series.

Clinical findings	
Age	1 month–17 years (median 4 years 9)
Gender	females – 7, males – 13
Tumour site within pancreas	head – 5, body – 4, tail – 4, body/tail – 4, head/body/tail – 3
Tumour size	<5 cm – 3, 5–10 cm – 7, >10 cm – 10
Stage	I – 6, II – 0, III – 5, IV – 9
Distant metastases	liver – 2, lungs – 2, distant lymph nodes – 2, subcutaneous tissue – 1 missing data – 2

Table 2 – Treatment modalities and outcome according to stage group.

Stage	No.	1° surgery	CT	CT response	2° surgery	RT	Event	Status
Stage I	1	R0	–	–	–	–	–	1° CR
	2	R0	–	–	–	Yes	–	1° CR
	3	R0	PLADO	Not evaluable	R0	–	–	1° CR
	4	R0	PLADO	Not evaluable	–	–	–	1° CR
	5	R0	PLADO	Not evaluable	–	–	–	1° CR
	6	R0	other regimen	Not evaluable	–	Yes	Local relapse	2° CR
Summary	Six patients	Six R0 resection	Four adjuvant CT	Not evaluable	–	Two RT	1/6 relapse	5/6 1° CR 1/6 2° CR
Stage III	7	Biopsy	PLADO	PR	R0	–	–	1° CR
	8	Biopsy	PLADO + other drugs	PR	R0	–	–	1° CR
	9	Biopsy	Other regimen	MR	R2	yes	–	1° CR
	10	Biopsy	PLADO	VGPR	–	–	Regional relapse	DOD
	11	Biopsy	PLADO	PD	–	–	PD	DOD
Summary	5 Patients	No initial resection	Five primary CT	Four response 1 PD	Three resection (2 R0, 1 R2)	One RT	2/5 relapse/PD	3/5 1° CR 2/5 DOD
Stage IV	12	Biopsy	other regimen	SD	–	yes	toxic death	toxic death
	13	Biopsy	PLADO + other drugs	PR	R0	yes	–	1° CR
	14	Biopsy	PLADO + other drugs	SD	R2	–	PD	DOD
	15	R0	Other regimen	Not available	Met	–	–	1° CR
	16	Biopsy	Other regimen	MR	R0 + Met	–	–	1° CR
	17	Biopsy	PLADO + other drugs	MR	R0 + Met	yes	–	1° CR
	18	R1	PLADO	Not available	–	–	PD	Lost at follow up
	19	R0	PLADO	Not available	–	–	PD	DOD
	20	Biopsy	PLADO	PR	R0	RT on M	–	1° CR
Summary	Nine patients	Three initial resection (2 R0, 1 R1)	Nine primary CT	Four response 2 SD	Five resection (4 R0, 1 R2) 3 Met	Three RT + 1 on M	One toxic death 3 PD	5/9 alive in 1° CR

CT, chemotherapy; RT, radiotherapy; R0, complete resection; R1, microscopically incomplete resection; R2, macroscopically incomplete resection; PLADO, cisplatin + doxorubicin chemotherapy; VGPR, very good partial remission; PR, partial response; MR, minor response; SD, stable disease; PD, progression of disease; Met, metastasectomy; M, metastases; CR, complete remission; DOD, dead of disease.

Table 3 – Univariate analysis for 5-year event-free survival (EFS).

		EFS (%)
	Whole series	58.8%
Tumour size	<10 cm	56.0%
	>10 cm	64.8%
	P (test log-rank)	*0.405*
Tumour location	Head of the pancreas	50.0%
	Other sites	60.5%
	P (test log-rank)	*0.481*
Stage	Stage I	75.0%
	Stage III–IV	52.9%
	P (test log-rank)	*0.390*
Surgery	R0 (initial or delayed resection)	75.0%
	other	28.6%
	P (test log-rank)	*0.0141*

Six patients had either tumour progression (two cases) or relapse (four cases), at 3–27 months from initial diagnosis. All of them had large tumours (between 5 and 10 cm in two and >10 cm in three cases) and elevated serum aFP levels. Only one of them achieved a second remission and was alive at the time of the analysis. Four died of disease (4–77 months after initial diagnosis) and one was lost at follow-up. One child with metastatic disease died due to treatment toxicity (interstitial pneumonia).

For the whole series, 5-year EFS and OS were 58.8% (±12.5) and 79.4% (±9.2), respectively. Table 3 shows the results of the univariate analysis. EFS did not correlate with tumour site and, but was influenced by the feasibility of complete resection (at initial or delayed surgery). As for tumour stage, there was a favourable trend in EFS for stage I as compared to stage III–IV patients; however, all six stage I patients were alive in remission (five first remission, one second remission) at the time of the report.

Considering the nine patients with stage IV, five were alive in disease remission at the time of the analysis, 22–53 months (median 28) after initial diagnosis: all of them had objective response to chemotherapy and underwent complete resection (R0) of the primary tumour. The remission of metastatic disease was achieved in three cases with surgical resection of metastases, in one with chemotherapy plus radiotherapy and in one with chemotherapy alone (Table 2).

4. Discussion

The current paper represents the first report of the EXPeRT group, a new European network dedicated to paediatric rare tumours with the aim of promoting collaboration between the different national groups dedicated to rare tumours, to exchange experience and data, prospectively register cases on an international level, promote research, provide shared guidelines and, therefore, assist clinicians in clinical management.

As an initial initiative, the EXPeRT group decided to combine the data collected by each national group on some tumour entities included in the list of very rare paediatric tumours.[4] PBL was selected as the first tumour type to be analysed.

Firstly, our study enhanced once again the rarity of this tumour: in a 10 year-period, 20 cases only were collected from Italy, France, United Kingdom, Poland and Germany. Even at European level, PBL is too rare to allow the recruitment of sufficient number of cases to conduct clinical trials leading to evidence-based treatment guidelines.

Our series showed that PBL tends to be diagnosed at an advanced stage. More than half of all patients were diagnosed with large tumours that either locally extended beyond the pancreas or were metastatic. This observation illustrates the aggressive biology of this tumour. In addition, a diagnostic delay may occur as a result of the often unspecific clinical symptoms and the extreme rarity of this disease. Serum aFP (known to be a possible marker of tumour activity) was higher than the age-related reference level in more than 75% of cases, making this marker a valuable diagnostic tool in patients with pancreatic tumours.[13]

Nevertheless, the majority of cases underwent complete resection, either at diagnosis or following initial chemotherapy. Noteworthy, tumour size did not correlate with resectability (and did not predict outcome). Our series confirmed that surgical resection was clearly the mainstay of therapy; most patients alive in first CR at the time of the analysis had undergone complete resection. Therefore, the therapeutic strategy must primarily aim at a complete surgical therapy. Ideally, this may be obtained even in high stage tumours after up-front chemotherapy that may allow for down-staging of tumours and thus facilitate tumour resection. In the spectrum of possible surgical procedures, pancreaticoduodenectomy (Whipple's procedure) achieved local control of the disease in all cases when it was performed, and was not associated with higher incidence of major complications. This finding emphasises the importance of referring patients with PBL to centres experienced in paediatric hepatobiliary surgery. In addition, the results achieved with stage IV disease underline the role of aggressive surgery not only for the primary tumour, but also for the metastases.

Though there are few data from literature, PBL is generally considered a chemosensitive tumour. A variety of chemotherapeutic regimens (including cyclophosphamide, etoposide, cisplatin, doxorubicin) had shown to be active,[6,8,11,14–19] and also high-dose chemotherapy with peripheral blood stem cell rescue had been used in high-risk cases.[20,21] However, a standard regimen has yet to be defined. Based on the identification of some genetic similarities between pancreatoblastoma and hepatoblastoma (i.e. loss of heterozigosity at 11p15.5, over expression of IGF2, and beta-catenin mutations), suggests in principle a similar pathogenesis for these tumours,[22] recognising the PLADO regimen, usually adopted for hepatoblastoma, as an effective regimen for PBL. In our series, 73% of cases responded to primary chemotherapy, and its effectiveness was confirmed by the high rate of secondary R0 resections in cases initially considered as non-resectable tumours. This observation illustrates again that a strategy incorporating up-front chemotherapy prior to delayed, optimally planned and hopefully complete tumour resection presently constitutes the best option in PBL. If primary chemotherapy in initially unresected disease seems to be a keystone of treatment strategy, the role of adjuvant chemotherapy in patients initially submitted to complete resection is less clear: in our cohort, two cases did

not receive adjuvant systemic therapy (one treated with surgery alone, one with surgery plus post-operative irradiation).

Radiotherapy may have a role in PBL in the case of unresectable disease or after incomplete excision, though its potential morbidity is an important issue to consider and a possible limit for its use, since the majority of children with PBL are very young. In our series, the small number of patients who received radiotherapy limited any new hint on its role.

In conclusion, this report describes the first international joint series of this very rare tumour. Despite the biological aggressiveness of the tumour, the overall outcome of children with PBL seems relatively satisfactory because of the adoption of an intensive multidisciplinary approach, with chemotherapy and aggressive surgery. Due to the rarity of PBL and the need for multimodal therapy and specialist surgery, we believe that children with PBL should be referred for management to highly experienced centres. Though further studies are clearly needed to validate any formal guideline for this very rare tumour, the EXPeRT group would propose a sort of standard approach for PBL, including a surgical staging system, an initial conservative surgical approach, chemotherapy according to PLADO regimen, and a post-chemotherapy aggressive surgery, on both primary tumour and metastases, when present. The role of adjuvant chemotherapy after initial complete surgery as well as that of radiotherapy need to be clarified.

Finally, this study demonstrates that international cooperation in very rare tumours is feasible, and supports the benefit of the foundation of the EXPeRT group. International cooperative studies on rare entities may significantly help in advancing our clinical understanding and in improving our clinical care in these tumours. Further steps are needed to facilitate the collection of larger numbers of cases by creating a prospective international registry, and to set up a biorepository, to stimulate biological studies to improve our understanding of the molecular genetic basis and the natural history of PBL.

Conflict of interest statement

None declared.

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