Prognosis and therapeutic targets in the Ewing family of tumours

Keywords
Ewing’s sarcoma, EWS/FLI1, CD99, insulin-like growth factor, microarrays

Summary
The project through collaborative studies will define prognostic markers and new therapeutic targets in the Ewing’s sarcoma family of tumours (ESFT) to provide rigorous scientific justifications for the development of clinical trials for this rare disease, which is mainly manifested in children. The main objective of this project is to evaluate the prognostic relevance of selected markers (EWS/FLI-1, secondary genetic alterations, CD99, IGF-IR, NOVH, erbB-2 and TTF1) and the effectiveness of therapeutic approaches targeting some of these molecules. Another major goal of the project is the construction of ESFT c-DNA microarrays and tissue arrays, which will be used for the analysis of different histologic subtypes of ESFT, primary and metastatic tumours and poor and good responders to chemotherapy. This will lead to: 1) the definition of forthcoming risk-adapted strategies and targeted molecular treatments to be advantageously combined with established therapies; 2) improved quality of life and survival for ESFT patients; 3) prevention of risk in groups at risk.

Problem
The Ewing’s sarcoma family of tumours (ESFT) includes: Ewing’s sarcoma; primitive neuroectodermal tumour; Askin’s tumour; paravertebral small-cell tumour; atypical Ewing’s sarcoma. ESFT represents a peculiar entity in oncology. In spite of its absolute rarity (about 300-400 cases per year in Europe), ESFT is one of the most frequent solid neoplasms in paediatric age groups. Due to this fact, its impact on the health system is particularly important. The adoption of multimodal treatments with very aggressive chemotherapeutic regimens have significantly improved the chance of survival of ESFT non-metastatic patients, shifting the five-year survival rates to around 60%. Despite these important clinical results, which are usually difficult to obtain in rare diseases, several problems related to histogenesis, prognosis and treatment response are still open. In particular:

a. The histogenesis of ESFT is still uncertain and the normal counterpart of ESFT cells is still unknown.
b. The lack of prognostic factors obliges the use of non-differentiated treatments for all patients, leading to over-treatment of those patients who could benefit from less toxic therapies. The reduction of delayed side-effects is particularly important in this disease considering the young age of the patient and their long life expectancy.
c. In the current state of ESFT treatment there is a survival ‘plateau’ (around 60% for patients with localised disease and 25% for high-risk groups) due to the lack of new drugs and toxicity that impedes more intense use of existing drugs. The identification of new targets for innovative therapeutic strategies is, therefore, strongly needed for this tumour.

Progress is generally hampered by the rarity of the disease (in Europe about 400 cases/year) implying a limited number of cases for effective research. Moreover, because ESFT is an orphan disease, no private company will develop new therapeutic tools and take on the costs to conduct pre-clinical investigation.

Aim
The project will define prognostic markers and new therapeutic targets in the Ewing’s sarcoma family of tumours (ESFT) through collaborative studies to provide rigorous scientific justification for the development of new therapeutic strategies for this rare disease, which is manifested for the most part in children. Goals expected to be achieved:

1. With respect to the problem of toxicity, the project, by identifying the clinical relevance of a number of markers, may allow the differentiation of patients in terms of risk to recur. This will enable more aggressive treatments where these are justified, and avoid toxicity in cases where such treatments may be known to be unnecessary, with particularly significant consequences for the quality of life of the patients.
2. Successful treatment of therapy-resistant patients requires new strategies. Indeed, there is a desperate need for new therapeutic approaches in ESFT. A thorough study of the pre-clinical effectiveness of new targeted therapeutic strategies will be performed with the aim of the identification of the Achilles’ heel in this disease and the consequent development of a tailored biological therapy to be used in association with conventional chemotherapy.
3. By providing an organisational framework for collaboration the project will also allow multi-centre collection and analysis of cases as well as suitable collaborative research to allow genetic studies for the screening of high-risk patients and patients responding differently to chemotherapy.

**Expected results**

1. The identification of prognostic factors in ESFT as a basis for the definition of individual therapeutic regimens, which would limit the incidence of acute side-effects and long-term morbidity as well as the economic and social consequences of intensive chemotherapy.
2. The definition of patient selection criteria to be used as a basis for beginning a pivotal clinical trial.
3. The creation of new therapeutic bullets against ESFT. They will be available at the end of the project as new drugs for ESFT treatment, together with the required toxicological and pharmaco-kinetics studies. This is an important point because ESFT is an orphan disease and no private company will develop new therapeutic tools and take on the costs of conducting pre-clinical investigation.
4. New therapeutic strategies for oncologists to increase the survival rate of ESFT patients through the pre-clinical evaluation of new drugs and strategies based on an immunological approach.
5. New clues in the diagnosis and the screening of high-risk groups through the creation of an extensive tissue bank and the genetic profile analysis (cDNA microarray and tissue array analyses) of these samples.

**Potential applications**

Therefore the project, aiming to ameliorate treatment of ESFT, will have an impact on child health. In particular, the main objective of this project is to develop patient-oriented strategies for Ewing's sarcoma patients by: a) integrating different disciplines and advanced technologies to develop effective approaches or new tools for diagnosis, prognosis and treatment. b) elucidating the contribution of specific molecular and genetic factors to the histogenesis of the disease.

This work will unlock the potential of the individual studies carried out by each of the consortium partners, and it will define targeted therapeutic strategies of practical value in clinical settings and the clinical relevance of a number of markers that will allow the differentiation of patients in terms of risk of recurrence. It will also unlock the biological and clinical information potential behind multi-centre data collection and genetic analysis of patients, bringing basic knowledge to the application stage. Progress is generally hampered by the rarity of the disease, implying a limited number of cases for effective research. The creation of a multi-centre tissue bank and data collection will help to overcome a big obstacle. The application of new technology will be used to identify ESFT-related molecular mechanisms. The gene expression profile of ESFT will be analysed and new markers to be used for diagnostic, prognostic and therapeutic purposes will be identified.

The project made efforts in the integration of multi-disciplinary research capacities across Europe. The consortium includes pathologists, oncologists, immunologists, and molecular and cellular biologists. Moreover, PROTHETS lays emphasis on collaboration with small and medium-sized enterprises (SMEs), devoted to the development of specific tools for prognostic and therapeutic applications.

Finally, the development of evidence-based guidelines will ensure that the knowledge held and developed by and within the project will be distributed as widely as possible to have the highest possible impact on the biomedical world. Specified actions of the project are devoted to dissemination activities to ameliorate harmonious relations between cancer researchers and society, with particular regard to patient associations.

**Project website:** under construction (www.prothets.org).

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