Ewing sarcoma treatment

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Ewing sarcoma (ES) is the second most common primary malignant bone tumour in children and adolescents following osteosarcoma. The annual incidence approximates 3 per million, with a male predominance of 1.2:1 and a median age of 15 years. All bones can be affected. The most common primary sites are the pelvis followed by the femur, tibia and the remainder of both the long bones of the extremities and flat bones of the axial skeleton. Approximately 25% of all patients present with visible metastasis at diagnosis affecting the lungs, other bones or multiple systems.

The histological appearance is a monotonous population of small blue round cells with relatively low mitotic activity in the range of 15–20%. Cytoplasmic glycogen is usually present in abundance. Also characteristic is a strong expression of the cell surface glycoprotein CD99. In addition, ES is positive for vimentin and immunohistochemical evidence of neural differentiation is demonstrable in approximately one third of all cases [1].

Genetically, ES is most commonly characterised by a reciprocal chromosomal translocation between chromosomes 11 and 22; t(11;22)(q24;q12) as present in about 85% of these tumours is considered pathognomonic for this disease. In addition, other structural changes may be present. The chromosomal rearrangement results in a fusion of the 5′ portion of the *EWSR1* gene on chromosome 22 encoding the EWS protein with the 3′ portion of the *FLI1* (Friend leukaemia virus integration site 1) gene on chromosome 11 or in the case of different translocations involving the *EWSR1* gene on chromosome 22 in a fusion with other members of the *ETS* gene family. The chimeric gene product is likely crucial to the malignant transformation in ES. The resulting fusion protein is a potent transcriptional factor, which is considered to exert much of the oncogenic activity via the inappropriate activation of target genes. Thus, ES represents a paradigm for understanding and investigating sarcoma biology and the search for the identification of tumour-specific therapeutic targets is the focus of current research activities [2–5].

Prior to the era of chemotherapy, survival in ES was less than 10%, although the radiosensitivity of this tumour was well known. With the application of modern multimodal therapeutic regimens including induction chemotherapy and local control with surgery, radiotherapy or a combination of both modalities, cure rates of approximately 70% can be achieved in patients with localised disease. The prognosis of patients with metastasis at diagnosis, however, has remained inferior, indicating the limitations of current treatment strategies. Intensity of chemotherapy is of significant importance. Most combination chemotherapy regimens are based on alkylating agents, primarily ifosfamide and cyclophosphamide, and anthracyclines, with the addition of vinca alkaloids and actinomycin D and etoposide. The value of the addition of high-dose chemotherapy regimens followed by autologous haematopoietic stem cell rescue is the subject of current, ongoing trials. The current standard is an ifosfamide- and doxorubicin-based, four- to five-drug combination chemotherapy schema initiated following biopsy-proven diagnosis, prior to definitive local control and continued following local treatment for a total duration of 10–12 months. The rationale for primary chemotherapy is to allow shrinkage of the primary tumour to facilitate local control, in particular limb salvage surgery, which is easier to perform once an initial bulky soft-tissue mass has disappeared under initial intense combination chemotherapy. With respect to the modality of local control, there is good evidence from various groups regarding the better control with surgical or combined surgical and radiotherapy modalities compared with definitive radiotherapy with a higher risk of local recurrence. As a result of current intense combination chemotherapy regimens and careful interdisciplinary local therapy planning, with a preference for surgery or combined modality local control, long-term disease-free survival in extremity tumours is approximately 80%. The most difficult primary site, however, remains the pelvis, given the usually extensive bulk of disease at diagnosis and the difficulties regarding appropriate surgery and radiation [6–8].

The presence of metastatic disease at diagnosis has remained the most important adverse prognostic factor. In patients with lung metastasis, lung irradiation appears to improve the outcome. Patients with multiple osseous metastases at diagnosis have an expected long-term survival of less than 10%, correlating with the extent of disease within the skeletal system [9–11].

In summary, Ewing sarcoma has become a model of a curable sarcoma as a result of combined multidisciplinary efforts. The hope is that the therapeutic arsenal may be complemented by targeted therapies directed against targets that will be visualised by applying modern molecular techniques that clarify the impact of the initial, molecularly associated downstream events. The family of growth factors and tumour immunological studies both have the potential to complement the therapeutic arsenal and contribute to the cure, and there is hope that the current translational research activities may eventually result in clinical benefit [12,13].

Conflict of interest statement

The authors have no conflict of interest to report.

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