The term Ewing sarcoma family of tumors (ESFT) defines a group of small round cell neoplasms of neuroectodermal origin that manifests as a continuum of neurogenic differentiation, with Ewing sarcoma of bone representing the least differentiated, and primitive neuroectodermal tumor and peripheral neuroepithelioma the most differentiated forms. Since its first description by James Ewing in 1921, the histogenesis and cell of origin of this sarcoma have been a matter of much debate; while originally described as an angio-endothelioma of bone by Ewing, several different hypotheses on the cell of origin have been proposed over subsequent decades. The existence of either a mesenchymal stem cell or an early primitive neuroectodermal cell that has retained its ability for multilineage differentiation is the currently accepted hypothesis. It is now well accepted that the ESFT constitute a single group of neurally derived neoplasms that share unique immunocytochemical, cytogenetic, and molecular markers (1). Molecularly, the ESFT are characterized by the presence of a chimeric transcript that results from the fusion of the $EWS$ gene with genes that encode structurally related transcription factors, usually $FLI1$ or $ERG$ (2).

The majority of patients with ESFT have localized disease at diagnosis, as defined by current imaging techniques. However, as diagnostic techniques are refined, it is evident that a significant proportion of patients with apparently localized disease have micrometastatic involvement in the bone marrow when molecular techniques are applied (3). Thus, all patients require systemic therapy, and upfront treatment must be aggressive since outcome after recurrence is very poor (4). Despite the aggressive nature of this malignancy, the last several decades have witnessed major improvements in the survival rates of these patients. This has been the result of a coordinated effort that integrated multiple disciplines and many cooperative groups in Europe and North America. Optimization of local control, design of more rational chemotherapeutic regimens, and development of risk-adapted approaches have all contributed to the current landscape, where more than two-thirds of patients can be cured. But this has been a long journey that has taught us the importance of well-designed prospective clinical trials, always trying to ask the appropriate questions at the appropriate time. Cooperative studies first showed the importance of performing early aggressive cytoreduction with high doses of alkylators and early dose-intensification of doxorubicin, as well as the importance of the addition of etoposide to a high-dose alkylator regimen (1). This approach evolved in North America to the current standard, which is based in alternating cycles of vincristine, cyclophosphamide and doxorubicin (VCD) with ifosfamide and etoposide (IE) with the goal of maximizing therapy intensification (5). An alternative approach to increasing dose intensity is decreasing the intervals between cycles while maintaining the same dose-per-cycle with the use of G-CSF. This interval compression has the potential advantages of allowing dose-intensification of all agents and limiting the time of recovery of partially resistant cells. In the US, this was the approach taken by the recently completed Children’s Oncology Group AEWS-0031 study, in which patients were randomized to receive alternating cycles VCD and IE every three weeks (standard arm) or two weeks (dose-compression arm). Importantly, this randomized trial showed a significant survival advantage to the use of dose-compressed therapy; this is now the standard of care in the management of ESFT in North America (6). It is, therefore, feasible to intensify the administration of alkylating agents, anthracyclines, and topoisomerase-II inhibitors, and this may result in an improved outcome for some patients. However, it is also important to understand that not all patients require the same intensified approach. Risk factors such as age, tumor size and site, pattern of metastatic disease, and histologic response to preoperative chemotherapy may be combined to define risk categories that will allow risk-adapted therapies, by which the cumulative doses of alkylating agents and etoposide can be tailored (7). The protocol that has best interpreted these concepts was the Euro-Ewing-99, in which patients were stratified into three risk groups based on tumor volume, presence and pattern of metastatic disease, and histologic response to induction therapy (8).

Despite the progress made in the management of patients with localized ESFT, patients with recurrent or metastatic disease have a very poor outcome (4, 7).
Treatment intensification, often including consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue has not proven to improve over standard chemotherapeutic regimens; (9) clearly, new treatments are needed.

Over the last years several drugs and combinations have been reported to result in remarkable responses in patients with refractory ESFT; this includes mostly combinations of topoisomerase I inhibitors with alkylators, such as cyclophosphamide with topotecan (10–12), or temozolomide with irinotecan (13, 14). Some of these combinations are currently being moved to the front line, and ongoing studies at the Children’s Oncology Group are exploring the incorporation of the cyclophosphamide/topotecan combination to the standard VCD/IE dose-compressed regimen for patients with localized disease. However, it is unlikely that modifications to standard chemotherapy approaches will result in a substantial impact in outcome; a better understanding of the pathogenesis of ESFT is needed for the identification of potential targets for antitumor therapy. Fortunately, our knowledge of ESFT biology has grown exponentially in the two decades since the key discovery that defined its molecular signature, and it is now for us to build on this knowledge and identify actionable pathways that would facilitate the incorporation of new agents (15).

Ewing sarcoma cell lines express several tyrosine kinases, including c-kit and PDGFR, that could be targeted with the new tyrosine kinase inhibitors (16). Immunohistochemical studies performed in primary ESFT tumors have shown that approximately 70% of tumors express c-kit, although the staining is strong and diffuse only in 30% of the cases, although there appears to be no association with the outcome (17). Despite these interesting preliminary data, in vitro studies have shown the limited effect of imatinib mesylate on the growth and proliferation of Ewing sarcoma cell lines (17), and a phase II study of imatinib mesylate failed to show any responses in children with recurrent ESFT (18). Despite these disappointing results, other tyrosine kinase inhibitors with broader spectrum of action should continue to be explored.

Inhibition of histone deacetylation has proven to result in the antitumor effect in preclinical and clinical models. Acetylation and deacetylation of histones alter the higher order chromatin structure by influencing histone interaction with DNA. Deacetylated histones are associated with cell growth, whereas acetylated histones are associated with cell growth arrest, differentiation, and apoptosis. Transcription factors may also be acetylated, and the acetylation status influences their interaction with DNA. In this regard, chimeric transcription factors present in a variety of tumor systems might cause transcriptional repression of growth regulatory target genes by recruitment of transcriptional corepressors and their associated histone deacetylase (HDAC) activity (19). This is particularly relevant in ESFT; since it is a transcription factor driven disease, agents that target chromatin structure would be expected to be active, through the restoration of TGFβ-RII transcription, or indirectly by altering the expression of other genes (20, 15).

In the xenograft model, the HDAC inhibitor MS-27-275 was able to induce an increase in TGFβ-RII mRNA and restore TGFβ signaling, and this correlated with growth inhibition (21). Moreover, in the same model, p21WAF1/CIP1 was induced in most cell lines irrespective of the p53 status. Finally, HDAC inhibitors appear to interfere with angiogenesis, an effect that deserves further investigation (21). Unfortunately, clinical data supporting the use of HDAC inhibitors in ESFT is still lacking.

Another promising agent on which hopes have been placed is eteineasadin 743 (ET-743, trabectedin). This agent is a natural product isolated from the sea squirt Ecteinascidia turbinata, with a well-documented effect in L-type sarcomas (leiomyosarcoma and myxoid liposarcoma) and synovial sarcoma (22). The excellent responses seen in FUS-CHOP positive myxoid liposarcoma suggested that this drug could act against translocation-positive sarcomas, and in fact preclinical data showed interference with the EWS-FLI1 transcriptional activity. However, a phase II study in children with refractory disease failed to show any responses (23).

Very recently, data have shown that Ewing sarcoma cells are exquisitely sensitive to poly ADP ribose polymerase (PARP) inhibition, to levels of sensitivity similar to the inhibition of BCR-ABL by imatinib (24). Also interesting is the synergistic effect seen in preclinical models when the PARP inhibitor olaparib was combined with temozolomide (25). Clinical data is still being generated, but this is certainly a pathway that should be explored further.

The most promising actionable pathway seems to be the insulin-like growth factor–I pathway (IGF-1/IGF-1R). This pathway is actively involved in the cell transformation induced by EWS-FLI1 and in the inhibition of apoptosis induced by chemotherapy (26). Studies have shown that the inhibition of the IGF-1R or of some downstream elements such as MAPK, PI3-K, mTOR or Akt may provide effective antitumor activity and potentiate the effects of chemotherapeutic agents (27). Rapamycin and its derivatives such as CCI-779 (temsirolimus) or RAD001 (everolimus) might have a role in the treatment of ESFT; in vitro studies have shown that rapamycin may block cell line proliferation by promoting cell cycle arrest at the G1 phase, downregulation of EWS-FLI1 proteins, and concomitant restoration of expression of TGFβ–RII in ESFT cells (28).

A different approach is the inhibition of the IGF-1R via monoclonal antibodies directed at the receptor, and three phase II studies have recently reported using different monoclonal antibodies as single agents (29–31). Response rates using conventional imaging criteria were around 10–15%; however, a clinical benefit could be seen in up to 30% of the patients, suggesting that further evaluation of this pathway should be considered (29). A novel approach could include the double inhibition of the IGF-1 pathway using the combination of a monoclonal antibody against IGF-1R with an mTOR inhibitor; this regimen is currently being explored by the Children’s Oncology Group.

Finally, because the EWS-FLI1 fusion product that characterizes ESFT may induce a cytotoxic T lymphocyte response, the generation of specific immune therapeutic approaches might play a role in the near future, and should be investigated (32).
In summary, the advances of the last two decades have defined the basic guidelines for the multidisciplinary treatment of patients with ESFT, including a better characterization of the active drugs and local control measures. The intensification of alkylating agents, antracyclines, and topoisomerase-II inhibitors is feasible and may result in some improvement in the outcome for patients with ESFT. However, this benefit seems to be restricted to patients with localized disease. For the subgroup of patients with advanced metastatic disease, and for those with recurrent disease, new approaches must be investigated. Advances in our understanding of the biology of this neoplasm hopefully will open the door to new approaches to therapy. Many years have passed since James Ewing first described this sarcoma, and we have come a long way in characterizing it; the biology is now better understood, and many actionable pathways have been identified. Is it finally the time to find a cure?

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