Development of Therapies for Ewing Sarcoma: Strategies for Treating a Chemosensitive Pediatric Sarcoma

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1 Introduction

Ewing sarcoma was first described in the early twentieth century by James Ewing, who identified a small round cell malignancy that typically arose in the bones of adolescents and young adults (Ewing 1972). Over the years, many variations of this tumor have been appreciated, including differences in location of the primary tumor (bone vs. soft tissue) as well as the degree of histologic differentiation. However, despite these differences, the clinical course and response to therapy has been remarkably similar between these subtypes. One explanation for this similarity has been the consistent identification of translocations involving the EWS gene on chromosome 22 and members of the ETS oncogene family, suggesting the underlying biology of these malignancies is the same. These similar clinical and molecular findings have resulted in the previously described entities of classic Ewing sarcoma of bone, Askin tumors of the chest wall, and extraskeletal primitive neuroectodermal tumors all being now considered as part of the broader Ewing’s family of tumors (EFT) (Delattre, Zucman et al. 1994).

EFT has a reported incidence of 2.93 per million in the US population under 20 years, making it the second most common bone cancer in children and young adults behind osteosarcoma (Esiashvili, Goodman et al. 2008). There is a slight male predominance, and most patients are diagnosed in their teenage years or early twenties. Patients generally present with a mass or tumor-related pain. The pelvis and femur are the two most common locations for primary tumors, although virtually any area of the body can be affected. Metastases are evident at the time of diagnosis in approximately one-fourth of patients, with the lungs being the most common site followed by other bones and/or bone marrow.

Tissue biopsy is required to establish the diagnosis. Pathologic findings suggestive of EFT include sheets of small round blue cells which have membranous staining for CD99, a cell surface marker which is invariably expressed but not specific to this tumor type. Immunohistochemistry is used to distinguish these tumors from other small round blue cell malignancies of childhood, such as rhabdomyosarcoma. In most cases, the diagnosis is confirmed by identification of an EWS-containing translocation, such as the EWS-FLI-1 translocation that is seen in approximately 85% of Ewing sarcoma family of tumors (de Alava and Gerald 2000). There are multiple other partners for EWS that are seen at a much lower frequency. EWS is a RNA-binding protein that, when fused to the transcription factor FLI-1, results in upregulation or downregulation of target gene transcription, leading to malignant transformation (Erkizan, Uversky et al. 2010).

One critical feature of Ewing sarcoma is the high likelihood for patients to develop distant metastases even if they undergo complete surgical resection or radiotherapy of what appears to be a localized tumor. For example, only 10% of patients can be cured with surgery or irradiation alone, even in the absence of identifiable metastatic disease on imaging or conventional bone marrow analysis at the time of diagnosis (Johnson and Humphreys 1969). The cause of recurrence in this situation is felt to be occult tumor cells that are present in the blood or bone marrow at levels below the limits of routine detection. These residual tumor cells escape local therapies and eventually go on to form fatal lung metastases. Chemotherapy is now used to help eradicate this so-called micrometastatic disease, and since the use of systemic chemotherapy began in the 1970s, 5-year survival rates have steadily improved to the point that up to three-fourths of newly-diagnosed patients with localized tumors can be expected to be long-term survivors with current therapies (Balamuth and Womer 2010).

Because EFT is more responsive to chemotherapy than other adult-type bone or soft tissue sarcomas, the current treatment paradigm is that all patients receive a combination of systemic chemotherapy as well as local treatment with surgery and/or radiation. While this approach has been helpful for many
ESFT patients, treatment still fails in some cases, and cure rates remain low for those with recurrent or initially metastatic tumors. In the following sections, we outline the treatment philosophies and regimens that have been used in the past and are currently being employed. In addition, we discuss how the identification of new therapeutic targets can be exploited through the use of novel tumor-specific agents.

2 Evolution of Treatment Strategies for EFT

As mentioned, cure was quite uncommon for patients treated prior to the use of adjuvant chemotherapy (Johnson and Humphreys 1969). Beginning in the late 1960s, early reports of responses to single-agent chemotherapy in patients with metastatic EFT began to emerge. There were a limited number of chemotherapy agents available at that time, and their use was mainly empiric. Interestingly, many of those initial agents are still used today, including vinca alkaloids (vincristine), anthracyclines (doxorubicin), and alkylators (cyclophosphamide). Nevertheless, drug resistance to single agents developed rapidly, and survival rates were not consistently improved until the advent of multi-agent regimens (Rosen, Wollner et al. 1974; Jaffe, Paed et al. 1976). For example, in one small series, adjuvant combination chemotherapy using vincristine, dactinomycin, and cyclophosphamide (VAC) in addition to radiation for local control resulted in 7 of 9 patients with local disease surviving for more than four years after therapy, a dramatic increase from 27% survival in patients treated with single-agent chemotherapy and radiation (Jaffe, Paed et al. 1976). This study, and others like it, highlights the role of both local control and systemic multi-agent chemotherapy to eradicate micrometastatic disease and overcome drug resistance.

The advances in survival noted in small retrospective studies using historical controls led to more robust prospective studies using combination chemotherapy in the adjuvant setting. Because of the rarity of EFT, randomized studies to convincingly establish the efficacy of therapy required collaboration between multiple institutions. One of the first such trials was the Intergroup Ewing’s Sarcoma Study (IESS), which randomized patients with localized EFT following radiation to receive one of the following regimens: 1) VAC, 2) VAC plus doxorubicin (VACA), or 3) VACA plus bilateral pulmonary radiation (VACA + BPR). Patients treated with VACA had a 5-year relapse-free survival (RFS) rate of 60% and 5-year overall survival (OS) rate of 65%, which was significantly better than the other two arms (Nesbit, Gehan et al. 1990). These results highlighted the importance of including doxorubicin in the treatment regimen, and also showed that prophylactic lung irradiation did not help prevent fatal lung metastases in patients with localized disease. Based on the results of this study, VACA then became the standard chemotherapy regimen for non-metastatic EFT. The second intergroup study, IESS-2, demonstrated improved relapse-free and overall survival with higher intermittent doses of doxorubicin (5-year RFS 73%, OS 77%) versus lower continuous dosing (5-year RFS 56%, OS 63%), establishing that anthracycline dose intensity was important for optimizing treatment (Burgert, Nesbit et al. 1990).

The next logical step was to consider adding further agents as they became available, such as ifosfamide and etoposide (IE), to the VACA backbone. In the INT-0091 study conducted by the combined Children’s Cancer Group and Pediatric Oncology Group cooperative groups, VACA + IE demonstrated an 5-year event-free survival (EFS) of 69% and an OS 72% compared with the standard VACA (54% and 61%, respectively) (Grier, Krailo et al. 2003). Interestingly, patients with metastatic disease treated on this study showed no benefit to the addition of IE to the standard VACA backbone.

Attempts to further improve efficacy of standard cytotoxic regimens focused on escalating the intensity of therapy either by increasing the doses of the alkylating agents (cyclophosphamide and
ifosfamide), or by decreasing the interval between cycles. While increasing alkylator doses at set intervals of 3 weeks did not improve outcomes (Granowetter, Womer et al. 2009), the recently completed Children’s Oncology Group (COG) study AEWS0031 did show that compressing the intervals of standard-dose chemotherapy from 3 to 2 weeks improved the 3-year EFS to 76% compared to 65% with 3 week cycles (Womer, West et al. 2008). These encouraging results from AEWS0031 have helped to establish this regimen using interval compression as the current standard of care for localized EFT in North America.

3 Current Therapeutic Strategies

3.1 Localized Disease

The presence of identifiable metastatic disease at initial diagnosis is one of the strongest prognostic factors in EFT. For example, roughly 3 in 4 patients with localized tumors can be long-term survivors, compared to approximately 1 in 4 patients with identifiable metastases (Balamuth and Womer 2010). Therefore, current clinical trials generally stratify patients based on this important risk factor. The usual strategy for incorporation of new agents is to first demonstrate activity in the relapsed setting, and then add these drugs onto a standard therapeutic backbone so as not to compromise the efficacy for newly-diagnosed patients with potentially curable tumors. Current strategies in North America for localized EFT build on the backbone of vincristine/doxorubicin/cyclophosphamide alternating with ifosfamide/etoposide, using interval compression as discussed above. The Children’s Oncology Group is now performing a randomized Phase III trial comparing this standard treatment with the same regimen + cassettes of cyclophosphamide/topotecan, based on two studies showing responses in approximately one-third of patients with recurrent EFT who were treated with this drug pair (Saylors, Stine et al. 2001; Hunold, Weddeling et al. 2006). Topotecan is a camptothecin agent which poisons the topoisomerase I enzyme that relieves torsional strain in DNA, and has shown activity against other “small round blue cell tumors” of childhood such as neuroblastoma (London, Frantz et al. 2010). The activity of camptothecins is enhanced when using DNA-damaging agents like cyclophosphamide, which is an important observation given that topotecan alone had insufficient activity to be developed as a single agent (Blaney, Needle et al. 1998). Children and young adults treated on this international COG Phase III study undergo 6 cycles of induction chemotherapy, followed by local control of the primary tumor with either surgery and/or radiotherapy. Patients then go on to complete 11 remaining cycles of chemotherapy.

In Europe, the treatment strategy also factors in other known risk factors, such as the size of the primary tumor and the histologic response of the primary tumor to induction chemotherapy. A four-drug combination of vincristine/ifosfamide/doxorubicin/etoposide (VIDE regimen) is administered in three-week cycles, followed by local control of the primary tumor site. Patients with smaller tumors and favorable histologic response to induction chemotherapy go on to receive maintenance therapy with either VAC, or with vincristine/actinomycin/ifosfamide (VAI). No randomized trials have directly compared these two similar but somewhat different cooperative group chemotherapy strategies.

3.2 Metastatic Disease

Unfortunately, progress has lagged behind in the treatment of patients with metastatic disease, with long-term cure rates being frustratingly stable over the decades. Interventions that improve survival in patients
with localized disease, such as the addition of ifosfamide and etoposide, do not have proven benefit in metastatic patients (Grier, Krailo et al. 2003), presumably because of inherent biological differences in metastatic tumors that make them less responsive to conventional therapy. Interestingly, the site of metastases has impact on the prognosis, as patients with metastases limited to the lungs have improved outcomes compared to those with bone or bone marrow metastases, who rarely survive (Pinkerton, Bataillard et al. 2001). This difference in prognosis is likely not just related to tumor burden, but also reflects underlying biological differences between these patients.

Because alkylating agents have a steep dose-response curve, there has been investigation of very high-dose, myeloablative chemotherapy followed by rescue with peripheral blood stem cells as a way to further intensify treatment. This so-called “megatherapy” with alkylating drugs like busulfan and melphalan has theoretical appeal, but has not consistently showed improvement in the highest-risk patients such as those with bone or bone marrow metastases (Ladenstein, Lasset et al. 1995; Meyers, Krailo et al. 2001). The ongoing European EuroEWING-99 study is the first to address the issue of autologous transplantation in a prospective randomized fashion, comparing megatherapy after local control with continued standard-dose chemotherapy in patients with unfavorable histologic response to induction or lung metastases.

In the US, new trials are being developed that will likely incorporate targeted agents described in detail below, as well as a different alkylator/camptothecin combination. In the same way the drug pair of cyclophosphamide/topotecan showed activity in relapsed patients and is now being incorporated into front-line trials, the combination of the alkylating agent temozolomide and the camptothecin irinotecan has also shown responses in patients with recurrent disease, including those resistant to topotecan (Wagner, McAllister et al. 2007; Casey, Wexler et al. 2009; Wagner 2011).

It is for this high-risk population of patients with metastatic disease that new therapies are most needed. Over the past two decades, at least a dozen other conventional chemotherapy agents apart have been studied in Phase II trials, including cytarabine, vinorelbine, pemetrexed, ixabepilone, oxaliplatin, vinblastine, and the combination of gemcitabine and docetaxel. While occasional responses have been seen, in general the results are disappointing and suggest that further benefit is unlikely to come from either conventional cytotoxic agents or additional manipulation of dose intensity or dose density. Thus, interest has now turned to so-called “targeted therapies,” which in contrast to conventional cytotoxics that indiscriminately kill rapidly dividing cells, are purported to selectively interfere with key pathways that are uniquely activated in tumor cells. The promise of targeted therapies is that they can more effectively eradicate tumor cells, while reducing life-affecting or life-threatening toxicities associated with conventional therapies such as severe infection, cardiomyopathy, or secondary cancers. In the following section, we present some examples of targeted therapies and their potential application for EFT.

4 Potential Molecular Targets for Therapy

4.1 Direct Inhibition of the EWS-FLI1 Fusion Protein

Perhaps the most appealing target in Ewing’s sarcoma is the oncogenic fusion protein EWS-FLI1 which results from the t(11:22) translocation seen in 85% of EFTs. Oncogenic fusion proteins are attractive targets due to their presence in tumor cells and absence in normal tissues. In fact, the age of targeted therapy was ushered in with the development of imatinib and related compounds, which target the t(9;22) translocation that characterizes chronic myelogenous leukemia (Yeung and Hughes 2012).
EWS-FLI1 is a dysregulated transcriptional protein which can transform mesenchymal stem cells so they produce colonies with morphological, immunohistochemical and gene expression profiles similar to Ewing sarcoma tumors (Erkizan, Uversky et al. 2010). Historically, transcription factors have been considered “undruggable,” but new strategies using anti-sense DNA and siRNA targeting EWS-FLI1 have shown promise in cell lines and xenografts (Takigami, Ohno et al. 2011). However, while the delivery of anti-sense DNA and siRNAs is an excellent way to demonstrate proof of principle, clinical application of this strategy has been limited by feasibility. Recently, high through-put screening of chemical libraries have identified small molecule inhibitors of the EWS-FLI1 protein, including the antitumor antibiotic mithramycin and the DNA-modulating agent trabectidin (Erkizan, Kong et al. 2009; Grohar, Griffin et al. 2011; Grohar, Woldemichael et al. 2011). Of note, mithramycin is an older agent used in the 1960s to treat testicular cancer and malignancy-associated hypercalcemia, and it is now being currently investigated in clinical trials for EFT based on these preclinical findings. On the other hand, a Phase II trial of trabectidin has recently been completed by the Children’s Oncology Group, and showed very little activity despite the encouraging preclinical results (Baruchel, Pappo et al. 2012). A similar experience has been seen with cytarabine, a nucleoside analogue used to treat leukemia. A signature-based small molecule screening process suggested that this agent may have activity against EFT, and preclinical studies showed that cytarabine downregulated EWS-FLI1 protein expression in vitro, producing gene expression patterns similar to when EFT cells are treated with RNA interference to knock down EWS-FLI1 (Stegmaier, Wong et al. 2007). Further, those investigators showed that use of cytarabine to treat mouse xenografts harboring human EFT resulted in significant growth inhibition. However, despite this strong preclinical rationale, a recent Phase II trial also showed disappointing results for this agent (DuBois, Krailo et al. 2009). These examples demonstrate that compelling rationale and activity seen in the laboratory does not always translate into clinical effectiveness.

4.2 PARP Inhibition

Leveraging the power of high-throughput cell line screening against genomic analysis has identified heretofore unappreciated targets. This functional genomics approach recently identified Poly (ADP-ribose) polymerase (PARP) as a target for inhibition in Ewing’s cell lines that harbor the EWS-FLI1 translocation. In one screen, 630 cells lines from adult and pediatric cancers were tested against 130 compounds, including traditional cytotoxic chemotherapeutics and molecularly targeted agents which were both approved drugs and experimental agents. In total, over 48,000 drug/cell line combinations were tested. Genomic characterization of the 630 cells lines was performed, including exon sequencing of 64 known cancer-causing genes, copy number analysis by Affymetrix SNP6.0 microarrays, and expression profiling using Affymetrix HT-U133A microarrays. Of note, cell lines containing the EWS-FLI1 translocation were sensitive to PARP inhibition with experimental agents such as olaparib and AG-014699 (Garnett, Edelman et al. 2012). PARP inhibitors interfere with the ability of cells to repair single-stranded breaks in their DNA, which lead to double-stranded breaks during DNA replication. Cells with deficient homologous recombination repair pathways, like those with BRCA mutations, are particularly sensitive to PARP inhibition, because they accumulate irreparable double-stranded breaks that lead to cell death. PARP inhibitor activity had been identified in BRCA1 and BRCA2 deficient cancers, but not previously in Ewing sarcoma cells, which were thought to have intact homologous recombination repair pathways. In a separate study, PARP inhibition with the investigational agent olaparib was shown to disrupt survival and invasion capacity of multiple Ewing sarcoma cell lines harboring the EWS-FLI1 translocation. Additionally,
EFT xenografts showed significant growth delay with olaparib monotherapy, and synergy with sustained complete responses for 30 days with combined temozolomide treatment (Brenner, Feng et al. 2012). In this study, olaparib appears to function by both potentiating DNA damage and by inhibiting transcription of the EWS-FLI1 fusion gene by interfering with a PARP1: EWS-FLI1 positive feedback loop. These results show the promise of a functional genomics approach where high-throughput drug screening is coupled with genomic analysis to identify novel targets in specific tumor types, although these results have not yet been confirmed in the clinic.

4.3 Insulin-like Growth Factor Type 1 Receptor Antibodies

The insulin-like growth factor type 1 Receptor (IGF-1R) has long been considered a promising target for the treatment of EFT. IGF-1R is a transmembrane tyrosine kinase receptor that when bound to either of its two ligands, IGF-1 or IGF-2, activates pathways involved in proliferation (Ras/Raf/MAPK) and survival (PI3K/AKT/mTOR) (Olmos, Tan et al. 2010). EFT cell lines and primary tumors strongly express IGF-1R as well as both ligands, suggesting there may be an autocrine stimulation driving tumor growth (Scotlandi, Benini et al. 1996). Preclinical studies targeting IGF-1R with either monoclonal antibodies or small molecule inhibitors have shown activity in cell lines and xenograft models (Scotlandi, Manara et al. 2005). Early small molecule inhibitors to IGF-1R also had substantial inhibition of the insulin receptor, which can impair glucose control. Therefore, monoclonal antibodies reached clinical development first, and impressive tumor reduction and prolonged stable disease was seen in these early trials (Tolcher, Sarantopoulos et al. 2009; Olmos, Postel-Vinay et al. 2010; Malempati, Weigel et al. 2012). These responses, as well as the presence of IGF-1R expression in a wide variety of solid tumors other than sarcoma, led to the clinical development of at least 8 different IGF-1R antibodies. Unfortunately, larger Phase II trials did not confirm high response rates in relapsed EFT patients in the three studies reported to date. For example, response rates have ranged from 6-14%, with median progression-free survival of 1.9-7.9 months (Juergens, Daw et al. 2011; Pappo, Patel et al. 2011; Tap, Demetri et al. 2012). These results have dampened enthusiasm for the use of IGF-1R antibodies as a single-agent, but it remains possible that they might be useful in the right clinical context, such as in combination with other agents, or in the setting of very low tumor burden.

5 Role of Biomarkers to Predict Response

The clinical experience with IGF-1R has been a good demonstration of how rational targets can be identified through basic science research, evaluated preclinically in xenograft models through translational research, and then tested in patients through clinical research. The development of this class of agents also highlights the difficulties in determining the optimal application of a drug. For example, although some striking and durable clinical responses have been achieved with IGF-1R antibodies, the overall activity in larger studies has been relatively low, and does not justify further investigation as a single agent to treat patient with bulky tumors. However, it is possible that such a drug could be synergistic with other chemotherapies, or could be beneficial as maintenance therapy in high-risk patients who appear to be in remission and have completed all of planned conventional chemotherapy. More importantly, if there was a way to prospectively identify the 10 – 15% of patients with recurrent Ewing sarcoma who benefit from this treatment, then clinical trials could be “enriched” for these patients and it would be predicted that response rates would be much higher. Such a strategy has been seen with other targeted therapies used in
adult cancers (Sequist, Bell et al. 2007), although this usually involves identification of a mutation in the therapeutic target, which has not been described with IGF-1R in Ewing sarcoma. Thus, there is a focused effort to identify other potential predictive biomarkers that could suggest a response to this therapy.

Expression of IGF-1R on tumor cells intuitively seems a necessary requirement for benefit from IGF-1R antibodies, but it is clear that this factor alone cannot be used to stratify patients. In fact, most Ewing sarcoma primary tumors express this target (Scotlandi, Benini et al. 1996), but responses are seen in only a minority. Assuming the receptor is effectively neutralized by the antibody, how then can growth of tumor cells be maintained? One possibility is redundant growth signaling through other cell surface receptors. Recent preclinical work has suggested that signaling of IGF-2 through the structurally similar insulin receptor (IR) is not abrogated using conventional anti-IGF-1R antibodies, and may serve as a mechanism of resistance to this therapy. For example, Garofalo et al. report that tumors with a low IGF-1R:IR ratio are unlikely to benefit from IGF-1R antibody therapy (Garofalo, Manara et al. 2011). When examining 109 archival Ewing sarcoma tumor samples by immunohistochemistry, 60% were determined to have high IGF-1R expression, while 81% had high expression of insulin receptor A, and an inverse correlation was present such that tumors with great expression of IR had less IGF-1R expression. These findings would be consistent with the relatively low rate of objective responses to single-agent IGF-1R antibodies. The clinical impact of insulin receptor expression in still unknown, but will be assessed prospectively in a study of an IGF-1R antibody combined with an inhibitor of mammalian target of rapamycin (mTOR) currently being conducted through the Children’s Oncology Group. That study will also use immunohistochemistry to assess for other potential signaling pathways that could contribute to resistance from IGF-1R antibodies, such as ERK (Subbiah, Naing et al. 2011) and RON (Potratz, Saunders et al. 2010). It is likely that identification of predictive biomarkers will be necessary for these agents to continue to be used in the clinic.

The trial mentioned above reflects the growing enthusiasm to combine targeted agents to maximize efficacy and circumvent tumor cell resistance. This can be done by targeting multiple cell surface receptors, using a so-called “horizontal inhibition” approach. For example, the small molecule OSI-906 is designed to inhibit both the IGF-1R as well as the insulin receptor, which theoretically may eliminate one mechanism of tumor cell resistance (Mulvihill, Cooke et al. 2009). Alternatively, one can inhibit two separate targets within the same pathway, using “vertical inhibition.” This strategy has been effective in preclinical testing which shows that upstream blockade of IGF-1R is synergistic with downstream inhibition of mTOR in preclinical models of Ewing sarcoma (Kurmasheva, Dudkin et al. 2009). Benefits have been seen with either simultaneous administration, or as demonstrated by Cao et al., the later addition of rapamycin to treat mice bearing rhabdomyosarcoma xenografts which were failing therapy with IGF-1R antibody (Cao, Yu et al. 2008). Similar findings were also seen in Ewing sarcoma patients, who benefited from the addition of an mTOR inhibitor following progression with single-agent IGF-1R antibody therapy (Subbiah, Naing et al. 2011). This synergy is presumably from either IGF-1R blockade working upstream of Akt, or mTOR inhibition working downstream of Akt, suggesting that these two agents function together to abrogate escape pathways that result from single-agent therapy. Promising activity in early adult clinical trials has now been reported with this combination (Naing, LoRusso et al. 2012; Schwartz, Tap et al. 2012), and will be further assessed by the ongoing COG study. Of note, one of the recently completed adult trials of an IGF-1R antibody and an mTOR inhibitor stratified patients based on the presence or absence of IGF-1R expression in tumor tissue. Rates of disease stabilization were similar between groups (Schwartz, Tap et al. 2012), again demonstrating the complexity of this process and that expression of the purported “target” is not the only factor which determines clinical benefit.
6 Conclusions

When compared to many adult-type sarcomas, EFT is different in both its tendency for metastatic disease to develop despite adequate local control, and its relative responsiveness to chemotherapy. These features have underscored the need for systemic therapy, and thoughtful clinical testing of well-formed hypotheses has resulted in up to three-fourths of patients with localized tumors remaining free of disease five years after diagnosis. However, patients with identifiable metastases at diagnosis, or those with recurrent tumors after initial therapy, generally have resistant tumors for which new therapies are necessary, as further modifications of conventional agents are unlikely to result in substantial improvement. Instead, the current focus is on identifying new molecular targets which can be therapeutically exploited, with the potential for improved efficacy and less toxicity. The examples offered here show not only the promise but also the complexity and frustrations of targeted therapy, and underscore our need for better understanding of the mechanisms of action and resistance of these drugs so that we can more effectively develop these agents and apply them to the specific population most likely to benefit.

References


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