Insulin-like Growth Factor Receptor Inhibition as Maintenance Therapy for Metastatic Ewing Sarcoma

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Summary: Despite the advances in oncology, the survival of children with Ewing Sarcoma metastatic at diagnosis continues to be 27% 3-year event-free survival and 34% 3-year overall survival. In other words, 7 of 10 children die within 3 years of their initial diagnosis despite intense chemotherapy, local treatment (radiation/surgery), and/or high dose busulfan-melphalan and autologous stem-cell transplantation. A chief contributor to this morbidity and mortality is the difficulty eradicating the tumor using present therapeutic modalities. Despite the extensive surgery, intensive chemotherapy and radiation, those left with a significant bulk of residual tumor relapse within a year of completing treatment. This case report suggests that in children left with a significant tumor burden after completing chemotherapy, a prolonged period of stability can be achieved with biological agents targeting the underlying molecular drivers. In this particular case we used figitumumab, an antibody targeting the insulin-like growth factor type 1 receptor pathway, a documented target in Ewing Sarcoma. Although not curative, these agents provide a better quality of life.

Key Words: (IGF-1R)—insulin-like growth factor type 1 receptor, Ewing Sarcoma, targeted therapies, autologous bone marrow transplant

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Patients with primary disseminated multifocal Ewing Sarcoma (ES) have a very poor prognosis despite very dose-intense treatment regimens. The disease, even though accounting for only 1% of all childhood cancers, accounts for a large proportion of morbidity and mortality.[1] Although it can occur at any age, it often accompanies the growth spurt of puberty. More than one third of the cases diagnosed in this age group are metastatic, most commonly to lungs and other sites of the skeleton. The realization that the presence of tumor cells in the bone marrow is associated with a very poor prognosis[2] has led to intensification of therapy.[3]

ES is consistently associated with chromosomal translocation and functional fusion of the ES gene (*EWS*) to any of several structurally related transcription factor genes. The most common translocation is t(11;22) present in our patient. The t(11;22) translocation produces an *EWS*/*Fli-1* fusion protein located upstream from the insulin-like growth factor receptor (IGFR) protein (Figs. 1A, B). The result is an upregulation of insulin-like growth factor type 1 receptor (IGF-1R) mRNA, present in 90% of neuroectodermal tumor cell lines with this translocation.[4–6] IGF-1R is a central component of a signal transduction pathway that is activated by the ligand insulin-like growth factor 1 (IGF-1) and which mediates a downstream intracellular cascade of events within the tumor cell that blocks apoptosis, enhances cell growth, and induces cell motility.[7] Preclinical as well as clinical data suggests that interrupting this autocrine loop by targeting IGF-1R effectively inhibits the growth of the tumor cell[8] and tumor xenografts,[9] and can sensitize tumors to chemotherapy.[10] This chemosensitization has been observed with many other biological response modifiers, and is thought to be due to the ability of these agents to strip both normal as well as cancer cells of their natural defense mechanisms. Unfortunately, this chemosensitization has also been one of the main reasons why many of these new agents fail in clinical trials designed to use maximum tolerated doses of chemotherapy.

Figitumumab is a human IgG_2 monoclonal antibody that targets IGF-1R and blocks IGF-1-induced autophosphorylation of IGF-1R through both receptor blockade and downregulation of IGF-1R and IGF-1R/1R heterodimers. Figitumumab was proven to be well-tolerated and safe as a single agent in pediatric patients with ES in a phase 1 expansion cohort.[11] A phase II expansion study[12] further supported the antitumor efficacy of figitumumab when used as a single agent in relapsed/refractory ES with an objective response rate (ORR) of 14.2% and median overall survival (OS) of 8.9 months.

Considering the risk of relapse in children presenting with a large burden of disease at diagnosis, and in those with only a partial response to intensive chemotherapy, surgery, and autologous bone marrow transplantation; consideration should be given to nontoxic maintenance therapy. The patient presented in this manuscript explores a case of using an IGF-1R inhibitor, figitumumab, as maintenance therapy to prevent recurrence in multifocal metastatic ES.

CASE PRESENTATION

A 13-year-old previously healthy girl presented with a 6-month history of progressive back pain, and 3 months of radicular pain in her legs. She had fatigue, weight loss, anorexia, severe constipation, and persistent headaches.

Computed tomography (CT) of the chest, abdomen, and pelvis showed disseminated disease (Figs. 2A, C, E, G), with a large heterogenous soft tissue mass arising from the right ilium, displacing the right common and external iliac vessels, compressing the right internal iliac vein, and cystic changes along the right iliac bone with associated periosteal reaction and bony destruction. She had metastatic lesions in the sacrum, L4, T8, and T12 vertebrae, with an associated compression fracture in T12. There was

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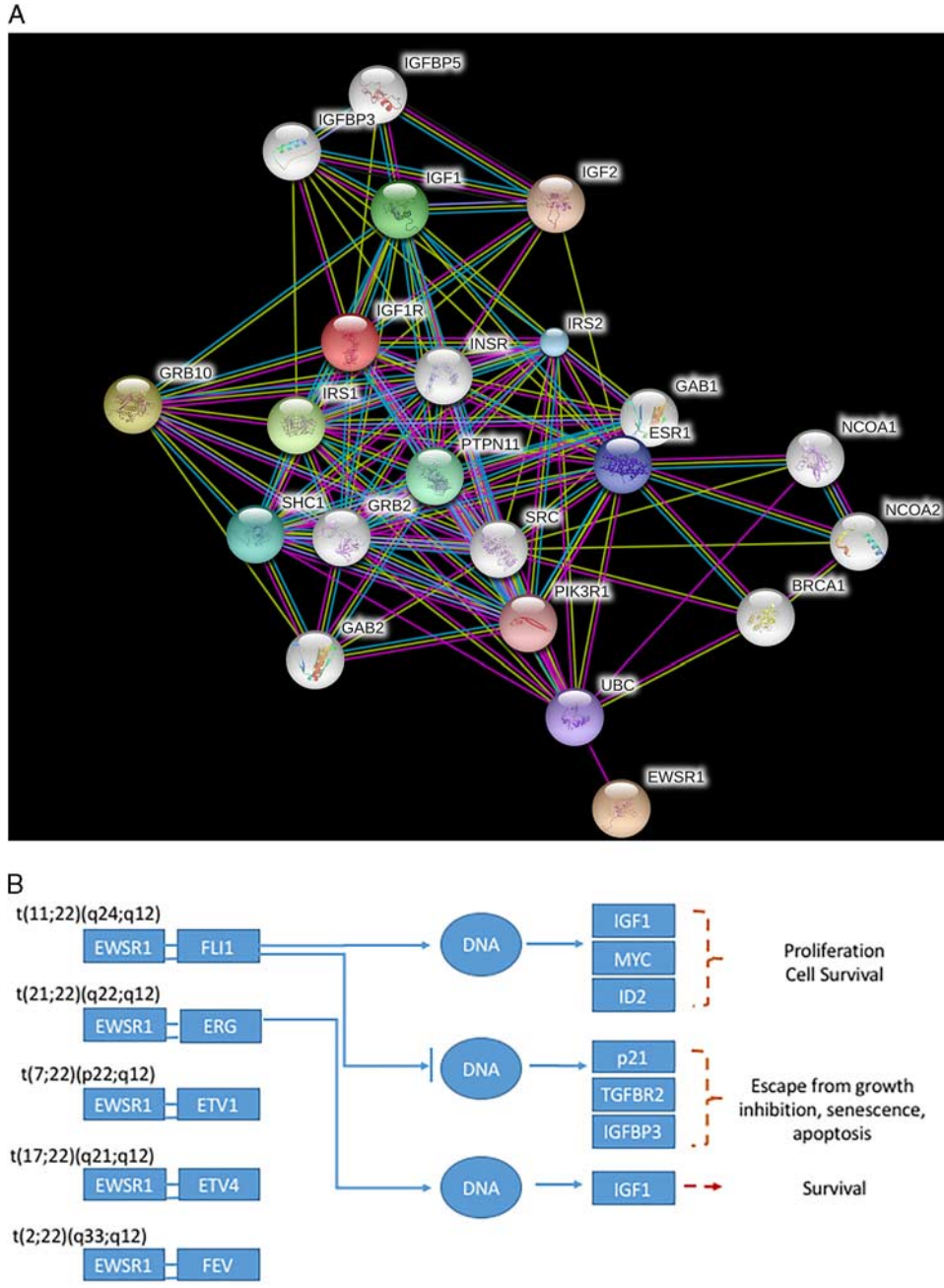

FIGURE 1. Insulin-like growth factor type 1 receptor (IGF-1R) signaling Pathway. IGF-1R pathway is one most vital pathways and its regulation is maintained through interaction with numerous growth factor pathways (A). The fusion proteins generated by the Ewing-specific translocations (B) function as aberrant transcription factors that lead to altered transcriptional profiles of both upregulated and downregulated transcripts. The images of the signaling pathways have been adapted from String, and the Kyoto Encyclopedia of Genes and Genomes.

mediastinal, right hilar, and subcarinal lymphadenopathy with compression of the right main pulmonary artery (Fig. 2G) and numerous nodular opacities in the lower lobes of the lungs bilaterally with pleural-based masses on the right. Bone scan identified additional lesions in T4, T9, the ninth rib, left acetabulum, and right manubrium.

The histology was typical, with primitive round blue cells positive for CD99, S-100, synaptophysin, and fluorescence in situ hybridization positive for t(11; 22), consistent with ES.

The patient was enrolled in the Children's Oncology Group protocol AEWS0331 and completed 6 cycles of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) with an additional cycle of vincristine, dactinomycin, and ifosfamide (VAI).

She had good response with marked improvement in hilar and subcarinal adenopathy, and near complete resolution of the right subpleural and right pericardial tumor. However, a large tumor bulk remained in the pelvis, and her case was discussed at a multidisciplinary tumor board conference. The benefit of further

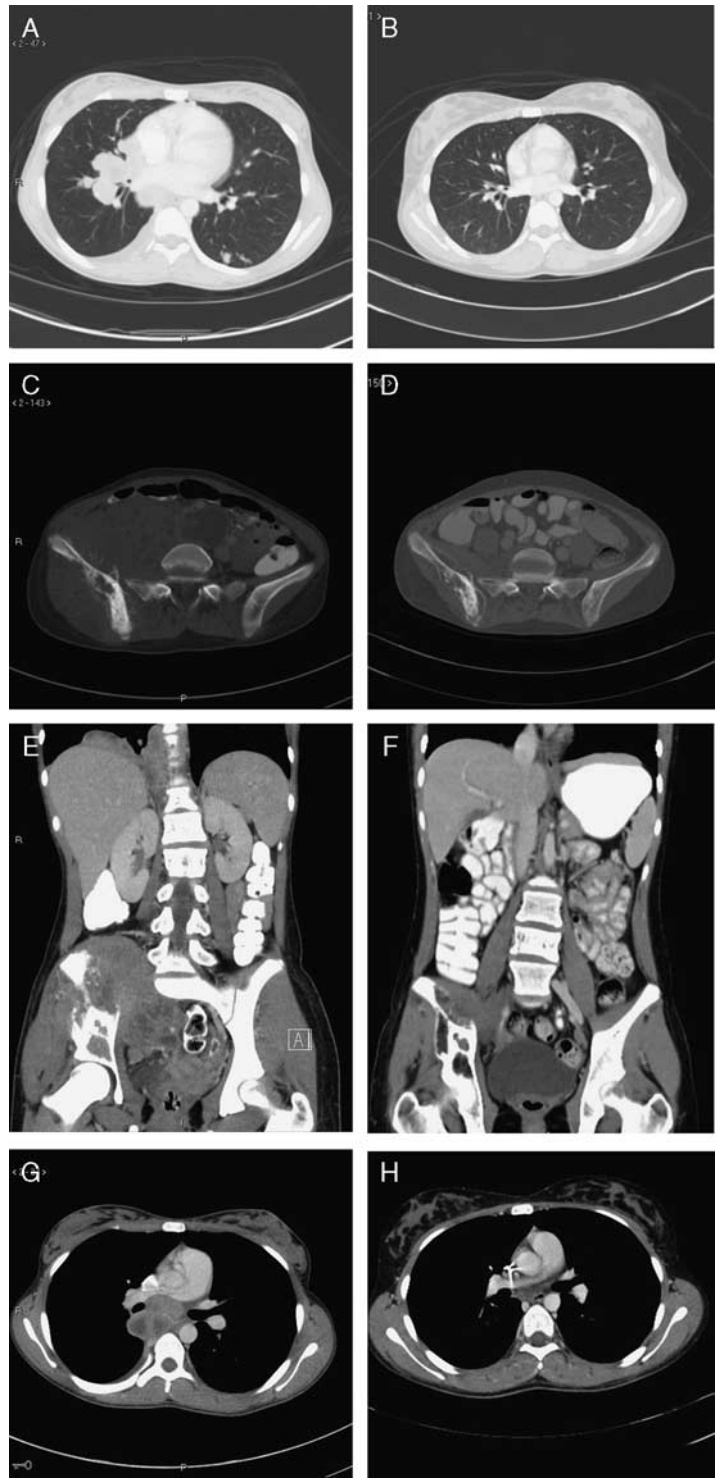

FIGURE 2. Response to Standard Chemotherapy. Following the standard of care regimen with maximum tolerated chemotherapy using multimodal therapy of vincristine, ifosfamide, doxorubicin, etoposide (VIDE); vincristine, dactinomycin, ifosfamide (VAI); and busulphan/melphalan with peripheral stem cell rescue, only a partial response was achieved. The pulmonary parenchymal lesions (pre treatment panel A, post treatment panel B), abdominal lesions (panels C & D), iliac bone primary (panel E & F) as well as the pulmonary artery lesions (panel G & H) significantly decreased in size, but eradication could not be achieved. While with localized disease, surgical resection can be curative, in dissminated disease such was this case, cure is not possible.

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chemotherapy versus stem cell transplant was discussed at length, and the decision to give high dose busulphan/melphalan with autologous stem cell rescue was made, even though there was no evidence of superiority for either approach. She experienced substantial toxicities with myelosuppression, infections, and severe venoocclusive disease requiring treatment with defibrotide. Although liver function returned to baseline, her bone marrow function never recovered (Figs. 3A, B).

The positron emission tomography scan after the stem cell transplant showed no areas of abnormal fluorodeoxyglucose uptake, even the tumor was originally fluorodeoxyglucose avid. The magnetic resonance imaging scans continued to show residual tumor in the right ilium, diaphragm, T8, T12, L4, subcarinal mediastinum, and the pleura of the right lower lung lobe (Figs. 2B, D, F, H). Because of the high risk of recurrence she was started on figitumumab at 20 mg/kg intravenously every 3 weeks. She did well on this therapy with no side effects or pain and returned to school, completing 17 doses (51 wk). She had a radiologic progression in the medial right iliac bone at the margin of the original tumor, and a biopsy confirmed a recurrence. Unfortunately, at the time, due to the toxicities seen in early clinical trials where figitumumab was used in combination with standard doses of chemotherapy, figitumumab could not be used in combination. It had to be discontinued, and the child was changed to a combination of pazopanib, thalidomide and low-dose metronomic topotecan. She had a transient stabilization of disease, but developed intraabdominal abscesses and the therapy had to be stopped. The child ultimately succumbed to the disease exactly 4 years from diagnosis.

DISCUSSION

Our patient presented with extensive disease at diagnosis, and completion of a standard chemotherapeutic regimen did not lead to disease eradication. For diseases where upfront tumor eradication is not possible, the rates of recurrence are high, and the risk of recurrence with chemotherapy-resistant tumor is even higher. Most traditional chemotherapeutic agents target DNA synthesis or proliferating cells, and they have limited efficacy in slow growing indolent cancers such as sarcomas where a large percentage of cancer cells is quiescent and chemotherapy resistant. Although the goal of high-dose chemotherapy with stem cell rescue is the eradication of these chemotherapy-resistant fractions, not even these extremely toxic approaches can overcome the intrinsic chemotherapy resistance of these cells.

The standard therapy for ES metastatic disease consists of 6 cycles of VIDE chemotherapy and a seventh cycle of VAI, local therapy (either surgery or radiation) after cycle 6, followed with high-dose busulfan and melphalan and stem cell rescue. The regimen, despite its toxicity, leads to only a 27% 3-year event-free survival and a 34% 3-year OS.[3] Although some of the drug doses, namely etoposide and ifosfamide, had to be reduced in the case of our patient due to a severe exfoliating rash, she completed 7 cycles of VIDE/VAI chemotherapy as well as the autologous stem cell transplant. There was only a partial reduction in the tumor size (compare Figs. 2A/B, C/D, E/F, G/H). Although the use and efficacy of bone marrow transplant in ES remains controversial, most pediatric oncologists are at a loss for better options, and continue to justify the toxicity of the therapy.

Clearly, there is a great difference in the outcomes of localized and metastatic ES, and the improvements in survival of patients with localized ES at diagnosis have not been reproduced in metastatic disease. Although the 5-year survival and 10-year survival rates for localized ES have risen from 44% and 39%, respectively, to 68% and 63%, this had not been the case with ES metastatic at diagnosis. For the 30% of these ES patients with metastatic disease at diagnosis, the outcomes are much worse, and the 5-year survival rate remains only 39%.[1] Similarly, the recurrence rate with localized disease following standard therapy is 30% to 40%, but 60% to 80% in those with metastatic disease.[13–15] This high recurrence rate is one of the important determinants of the low survival rate. Regardless of treatment modality, the 5-year OS is 7% for those who recur within the first 2 years after initial diagnosis, and 29% for those who recur 2 years after completing therapy.[14]

The localized and metastatic ES treatments differ mainly in intensity and in the capability to eradicate residual disease. For localized disease a 5-drug alternating combination of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide with interval compression (3 wk cycles) leads to 73% 5-year event-free survival, and 83% 5-year OS.[16] The treatment of disseminated ES is much more challenging, and the 6 cycles of VIDE, and a seventh cycle of VAI lead to only a 27% 3-year event-free survival and a 34% 3-year OS.[3] The optimal treatment regimen for recurrent ES or disseminated ES at diagnosis remains an area of active investigation; no studies in

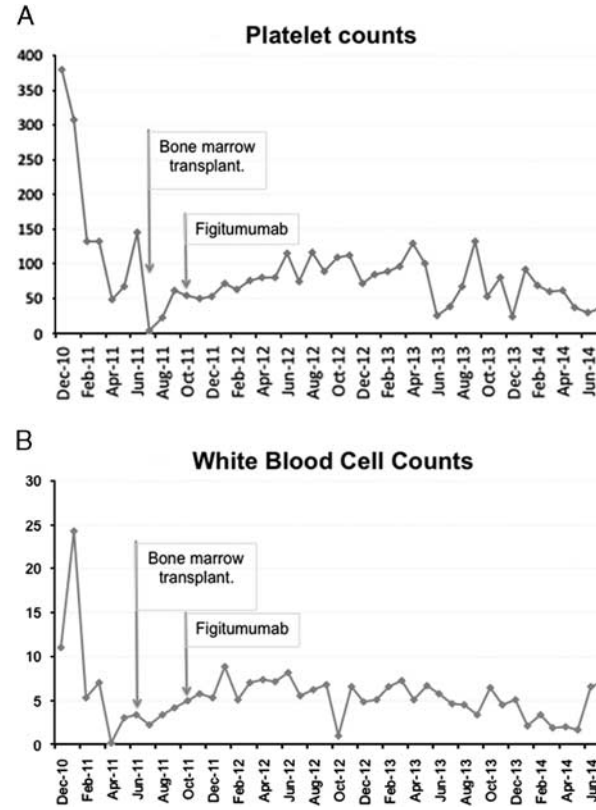

FIGURE 3. Toxicity of standard of care chemotherapy. The toxicity of standard of care chemotherapeutic regimen often leads to permanently altered bone marrow function making further chemotherapy or radiation-based approaches impossible and increasing the risk for myelodysplasia and secondary malignancies. Our patient was left with severe thrombocytopenia (Panel A) and neutropenia (Panel B) and never recovered.

recurrent ES have shown survival benefit. A combination of cyclophosphamide and topotecan had shown a 36% combined complete/partial response rate in 17 patients,[17] and represented the standard retrieval therapy for recurrent ES in 2001 despite its low survival rates. Early exploration of whether the addition of bevacizumab (then a novel angiogenesis inhibitor) to the standard of vincristine, topotecan, and cyclophosphamide would lead to improvements in response rates did not warrant further study, and the results were unfortunately never reported. In a larger cohort,[18] reinduction therapy using ifosfamide, carboplatin, and etoposide led to an ORR of 48% and 2-year survival of 33%, and despite the low survival rates, remains a frequently used regimen. The AEWS0621, a phase II trial, showed no objective responses to cytarabine as a single agent.[19] Similarly, a retrospective analysis of 22 patients treated with vincristine, irinotecan, and temozolomide may have demonstrated a 68% ORR, but the 2-year survival remained low at 26%.[20] The use of high-dose ifosfamide for recurrent disease felt to be resistant to standard doses of chemotherapy revealed an ORR of 34% and a 2-year survival of only 29%.[21] The combination of gemcitabine and docetaxel, while promising at first, yielded mixed results at the end. The initial study of 10 pediatric patients with ES showed an ORR of 50% with median progression free survival of 10.5 months,[22] but these results were not reproduced in a subsequent, also retrospective, study,[23] or in a phase II study closed early for lack of benefit.[24] Likewise, a trial of trabectedin (also called Yondelis or ecteinascidin 743), which had shown some efficacy in breast, prostate and some soft tissue sarcomas, did not meet adequate response rates to warrant further investigation in children.[25] All in all, the salvage rates of children with ES following recurrence average 20% to 30%, and while the lack of therapeutic efficacy may be due, at least in part, to low power in these studies, there is no evidence that the response rate corresponds to survival benefit in ES.

The persistently poor responses and lack of improvement in survival rates despite high-dose, intensive regimens in relapsed disease has turned attention toward agents that target specific biological processes in the tumor. These agents, while not free of toxicities, have different types of side effects and can be used even in heavily pretreated patients such as ours. Examples of such targeted agents include monoclonal antibodies against tyrosine kinase receptors or other growth factor pathways. In the case of ES, which engages the mammalian Target of Rapamycin (mTOR)/IGF-1R pathway, the focus has been on inhibitors of IGF-1R/IGF signaling.[10–12,26–28] There are a number of agents including R1507 (Hoffman-La Roche), cixutumumab (IMC-A12, Eli Lilly), ganitumab (AMG 479, Amgen), and figitumumab (CP-751871, Pfizer), and it will be very important to understand the mechanism of action of these agents if a successful trial is to be designed. Each of these agents has been tried in monotherapy settings for recurrent solid tumors including ES, and even though phase 1 trials are not geared to document efficacy, all have shown signals of activity. Even in the monotherapy setting, ganitumab has shown a 6% ORR when used in adult patients with recurrent Ewing family tumors or desmoplastic small round tumors,[28] figitumumab has shown modest antitumor activity in recurrent ES (ORR 14%, median survival 8.9 mo),[12] and even though R1507 and cixutumumab had no effect as single agents,[26,27] their efficacy as chemotherapy sensitizers has not been investigated.

As mentioned above, the IGF signaling pathway is intimately involved in the pathogenesis of ES. IGF-1R is a plasma-membrane receptor belonging to the insulin growth factor receptor family. It has 2 alpha subunits and 2 beta subunits. Binding of a ligand (IGF-1 and IGF-2) to the alpha subunits induces activation of tyrosine kinases (beta subunits), phosphorylation, and activation of the intracellular pathways. The normally quiescent mTOR pathway is activated, leading to upregulation of protein synthesis and induction of cellular proliferation due to an increase in downstream signaling through the Raf-1/MEK/ERK pathway. The activation of Raf-1/MEK/ERK pathway leads to simultaneous inhibition of apoptotic pathways, more specifically inactivation of the Bad pathway and Bcl-X and Bcl2 facilitated dysregulation of apoptosis. The PI-3K/Akt and/or ERK pathways lead to cell-cycle progression, making the IGF system a complex but very valid target for cancer growth modulation.[29]

However, the likelihood that a single agent is going to cure this complex cancer is very low. There is a built in redundancy for most pathways associated with cell survival and proliferation, and this is true for the IGF-1R system as well. A major mechanism of resistance to the highly selective inhibition of IGF-1R involves enhanced insulin receptor-A homodimer formation and IGF-2 production. Cells become resistant by switching from IGF-1/IGF-1R stimulation to IGF-2/insulin receptor-A dependency, and continue to maintain sustained activation of AKT and ERK1/2, leading to continued proliferation, migration, and metastasis.[30] Yet, the overexpression of IGF-1R mRNA seen in the vast majority of tumor cells with the t(11;22) translocation provides an explanation for the dysregulation of cellular proliferation and suggests that IGF-1R is a valid target for therapy. It is our belief that if we were able to combine figitumumab with low-dose chemotherapy and an mTOR pathway inhibitor such as sirolimus or everolimus, we would have been able to further stall progression.

The promise of monoclonal antibodies or small molecules directed at IGF-1R is undeniable. However, in the present clinical trial setting where most trials occur in heavily pretreated, disseminated or relapsed disease, testing a new agent as monotherapy is an exercise in futility. We had therefore considered monotherapy only after completion of intensive cytoreduction that included maximal doses of chemotherapy and stem cell rescue. The child had significant inoperable residual pelvic disease and her risk of recurrence was increased by the presence of multiple areas of metastatic and bone marrow involvement. When she relapsed, the best course of action would have been IGF-1R inhibition combined with inhibitors of the alternative PI3K pathway and low-dose continuous chemotherapy.

Finally, resistant or recurrent metastatic ES carries a poor prognosis, and the treatment options are limited. Although toxicity may be justified in acute lymphoblastic leukemia where the survival rates are over 90%, quality of life should warrant a greater consideration in poor prognosis cancers. In situations where the likelihood of progression or relapse is over 60% to 80%, the readiness to engage promising novel therapeutics should be higher. Our patient had no significant side effects with figitimumab maintenance therapy, and received all of her therapy as an outpatient. She was able to resume going to school, work a part time job, and enjoy her family and friends.

CONCLUSIONS

Despite aggressive multimodal therapy and advancements in surgery, radiation, and chemotherapy, 30% of

patients with localized ES at diagnosis and 75% to 80% of patients who present with metastases die of their disease. The case presented in this report suggests that changing strategies is the most appropriate approach. We have exposed a number of issues with the use of targeted agents in the present clinical oncology setting. One is the structure of the clinical trials, which demands single agent use even though most biological agents are chemotherapy sensitizers and their selectiveness and anti-tumor effect is enhanced by low dose chemotherapy.

The second consideration is that children with ES left with a large tumor bulk should not be exposed to further toxicity unless there is clear evidence of therapeutic efficacy in that setting. One should instead consider the importance of outpatient, minimally toxic targeted therapies which can be combined with low dose chemotherapy for maximum efficacy. These options, in addition to providing potential therapeutic benefit, will maintain better quality of life and function. There are a number of potential therapeutic strategies with solid rationale now in ES. They include growth factor receptor blockade with IGF-1R inhibitory antibodies, intracellular signal inhibition with tyrosine kinase inhibitors, epigenetic modulation with vorinostat or poly ADP ribose polymerase inhibitors, immune clearance enhancement with lexatumumab or chimeric antigen receptor cells, and manipulation of the EWS-Fli1 transcriptional signature with RNA interference by YK-4-279.[31] If the cost of these therapies is a concern, one should account for the cost-savings achieved by keeping the child from repeated admissions for high dose chemotherapy management, and for the repeated palliative surgeries or radiation. This case should encourage pediatric oncologists to consider biological agents for patients with all poor prognosis cancers as it represents a viable, less toxic, quality of life improving, and costneutral therapeutic option for patients with poor prognoses. In the not too distant a future, as more and more evidence supports the use of these agents we believe most therapies will be guided by the molecular signature of the tumor.

REFERENCES

1. Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: surveillance epidemiology and end results data. *J Pediatr Hematol Oncol*. 2008;30:425–430.
2. Schleiermacher G, Peter M, Oberlin O, et al. Increased risk of systemic relapses associated with bone marrow micrometastasis and circulating tumor cells in localized ewing tumor. *J Clin Oncol*. 2003;21:85–91.
3. Ladenstein R, Potschger U, Le Deley MC, et al. Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010;28:3284–3291.
4. Yee D, Favoni RE, Lebovic GS, et al. Insulin-like growth factor I expression by tumors of neuroectodermal origin with the t(11;22) chromosomal translocation. A potential autocrine growth factor. *J Clin Invest*. 1990;86:1806–1814.
5. Bovee JV, Hogendoorn PC. Molecular pathology of sarcomas: concepts and clinical implications. *Virchows Archiv*. 2010;456: 193–199.
6. Osuna D, de Alava E. Molecular pathology of sarcomas. *Rev Recent Clin Trials*. 2009;4:12–26.
7. Janknecht R. EWS-ETS oncoproteins: the linchpins of Ewing tumors. *Gene*. 2005;363:1–14.
8. Maloney EK, McLaughlin JL, Dagdigian NE, et al. An anti-insulin-like growth factor I receptor antibody that is a potent inhibitor of cancer cell proliferation. *Cancer Res*. 2003;63: 5073–5083.
9. Gualberto A. Figitumumab (CP-751,871) for cancer therapy. *Expert Opin Biol Ther*. 2010;10:575–585.
10. Benini S, Manara MC, Baldini N, et al. Inhibition of insulin-like growth factor I receptor increases the antitumor activity of doxorubicin and vincristine against Ewing's sarcoma cells. *Clini Cancer Res*. 2001;7:1790–1797.
11. Olmos D, Postel-Vinay S, Molife LR, et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: a phase 1 expansion cohort study. *Lancet Oncol*. 2010;11:129–135.
12. Juergens H, Daw NC, Geoerger B, et al. Preliminary efficacy of the anti-insulin-like growth factor type 1 receptor antibody figitumumab in patients with refractory Ewing sarcoma. *J Clin Oncol*. 2011;29:4534–4540.
13. Leavey PJ, Mascarenhas L, Marina N, et al. Prognostic factors for patients with Ewing sarcoma (EWS) at first recurrence following multi-modality therapy: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2008;51:334–338.
14. Stahl M, Ranft A, Paulussen M, et al. Risk of recurrence and survival after relapse in patients with Ewing sarcoma. *Pediatr Blood Cancer*. 2011;57:549–553.
15. Leavey PJ, Collier AB. Ewing sarcoma: prognostic criteria, outcomes and future treatment. *Expert Rev Anticancer Ther*. 2008;8:617–624.
16. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30:4148–4154.
17. Saylors RL 3rd, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. *J Clin Oncol*. 2001;19:3463–3469.
18. Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. *Pediatr Blood Cancer*. 2005;44:338–347.
19. DuBois SG, Krailo MD, Lessnick SL, et al. Phase II study of intermediate-dose cytarabine in patients with relapsed or refractory Ewing sarcoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2009;52:324–327.
20. Raciborska A, Bilska K, Drabko K, et al. Vincristine, irinotecan, and temozolomide in patients with relapsed and refractory Ewing sarcoma. *Pediatr Blood Cancer*. 2013;60: 1621–1625.
21. Ferrari S, del Prever AB, Palmerini E, et al. Response to high-dose ifosfamide in patients with advanced/recurrent Ewing sarcoma. *Pediatr Blood Cancer*. 2009;52:581–584.
22. Mora J, Cruz CO, Parareda A, et al. Treatment of relapsed/refractory pediatric sarcomas with gemcitabine and docetaxel. *J Pediatr Hematol Oncol*. 2009;31:723–729.
23. Rapkin L, Qayed M, Brill P, et al. Gemcitabine and docetaxel (GEMDOX) for the treatment of relapsed and refractory pediatric sarcomas. *Pediatr Blood Cancer*. 2012;59: 854–858.
24. Fox E, Patel S, Wathen JK, et al. Phase II study of sequential gemcitabine followed by docetaxel for recurrent Ewing sarcoma, osteosarcoma, or unresectable or locally recurrent chondrosarcoma: results of Sarcoma Alliance for Research Through Collaboration Study 003. *Oncologist*. 2012;17:321.
25. Baruchel S, Pappo A, Krailo M, et al. A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas: a report from the Children's Oncology Group. *Eur J Cancer*. 2012;48:579–585.
26. Pappo AS, Patel SR, Crowley J, et al. R1507, a monoclonal antibody to the insulin-like growth factor 1 receptor, in patients with recurrent or refractory Ewing sarcoma family of tumors: results of a phase II Sarcoma Alliance for Research through Collaboration study. *J Clini Oncol*. 2011;29: 4541–4547.

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27. Malempati S, Weigel B, Ingle AM, et al. Phase I/II trial and pharmacokinetic study of cixutumumab in pediatric patients with refractory solid tumors and Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30:256–262.
28. Tap WD, Demetri G, Barnette P, et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. *J Clin Oncol*. 2012;30:1849–1856.
29. Samani AA, Yakar S, LeRoith D, et al. The role of the IGF system in cancer growth and metastasis: overview and recent insights. *Endocr Rev*. 2007;28:20–47.
30. Garofalo C, Manara MC, Nicoletti G, et al. Efficacy of and resistance to anti-IGF-1R therapies in Ewing's sarcoma is dependent on insulin receptor signaling. *Oncogene*. 2011;30: 2730–2740.
31. Arnaldez FI, Helman LJ. New strategies in ewing sarcoma: lost in translation? *Clin Cancer Res*. 2014;20:3050–3056.