

Anti-insulin growth factor receptor therapy in Ewing sarcoma

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Abstract

The insulin-like growth factor (IGF) signal transduction pathway appears to play a key role in the development and proliferation of the Ewing sarcoma family of tumors. Integration of anti-IGF-1 receptor therapy into the standard treatment for these patients is a novel approach that will likely be incorporated into future treatment to determine whether such agents will improve the outcome for patients with this malignancy.

Introduction and context

The Ewing sarcoma family of tumors, including Ewing sarcoma and the more differentiated counterpart, primitive neuroectodermal tumor, are the second most common primary malignancies of bone in childhood and adolescence [1] but can also occur in the soft tissues. These tumors are characterized by local destruction with the potential for distant metastatic spread. Treatment is multimodal and includes chemotherapy, surgery, and/or radiation therapy. Systemic chemotherapy is aimed at treating known or micrometastatic disease as well as improving local control of the cancer.

Historically, multiagent chemotherapy has been the standard of care for these patients. The Intergroup Ewing sarcoma study (INT-0091) demonstrated that a regimen of alternating cycles of vincristine-doxorubicin-cyclophosphamide and ifosfamide-etoposide was superior to vincristine-doxorubicin-cyclophosphamide alone, leading to a 5-year event-free survival of 69% versus 54% in the standard arm [2]. More recently, a randomized trial evaluated dose intensification by interval compression (administering cycles every 2 weeks) and found that approach to be superior, with a 4-year event-free survival of 76% in the dose-dense arm compared with 65% in the standard 3-week chemotherapy arm [3]. This is now considered by pediatric oncologists to be the

standard chemotherapy regimen for patients with Ewing sarcoma, although it has not been adequately evaluated in patients older than 18.

Although there have been improvements in the outcome for patients with localized disease, the outcome for patients with metastatic disease and for those who relapse is poor, with survival rates of 20% for those with metastases [2,4] and 10-20% following a recurrence [5]. Therefore, in addition to standard chemotherapeutics, future clinical trials will need to incorporate novel biologic agents in an effort to achieve further survival improvements.

The insulin-like growth factor pathway and cancer

The insulin-like growth factor (IGF) system has two principal ligands: IGF-1 and IGF-2. These ligands mediate their stimulatory effects via the IGF-1 receptor (IGF-1R), a transmembrane receptor tyrosine kinase [6]. Under normal physiologic circumstances, IGF-1 and IGF-2 are stimulated by growth hormone and function in a negative feedback loop to control growth hormone release. The insulin growth factor-binding proteins (IGFBPs) regulate the available free IGF proteins available for IGF-1R activation [7-9]. Upon ligand binding, autophosphorylation of the IGF-1R tyrosine kinase initiates activation of the mitogen-activated protein

kinase and phosphoinositide 3-kinase/AKT pathways, leading to proliferation, survival [10-13], and enhanced angiogenesis via downstream induction of vascular endothelial growth factor [14]. The IGF-2 receptor is a monomeric transmembrane protein with no kinase activity and has not been shown to play a role in the development of Ewing sarcoma [15]. Its role in binding IGF-2 has yet to be elucidated.

The IGF pathway is known to be a critical component of the endocrine system. Stimulation has effects on linear growth and bone formation. The pathway also has a role in promoting neuronal survival, myelination, and postnatal mammary development and lactation. In addition, metabolic pathways use the IGF system to help integrate signals from nutrition and stress in order to shift appropriately between anabolic and catabolic states [6].

High circulating levels of IGF-1 have been associated with the risk of developing prostate, breast, or colorectal cancer [16,17]. In addition, overexpression of IGF-1 has been shown to promote neoplastic transformation [18]. The IGF-1R is expressed at high levels in a wide variety of tumors [19,20]. In addition, IGF-1R expression is known to be necessary for cellular transformation and for signal transduction pathways stimulated by the IGF-1R to enhance tumor cell growth and proliferation [21,22]. Furthermore, IGF-1R gene expression is regulated by a number of tumor suppressors, including WT1, BRCA1, and p53 [20]. There are also data to suggest that signaling through the IGF-1R enhances resistance to cytotoxic chemotherapy [23]. Therefore, inhibition of the IGF-1R is a potentially important therapeutic target against a variety of tumors.

Recent advances

Targeting insulin-like growth factor I receptor in Ewing sarcoma

The IGF signaling pathway and, in particular, the IGF-1R play a major role in the development and proliferation of Ewing sarcoma. Early studies documented the major autocrine role of the IGF-1 and IGF-1R pathways in Ewing sarcoma [24,25], and expression of IGF-1R has been shown to be a requirement for EWS/FLI-1 transformation in fibroblasts [26]. A variety of approaches *in vitro* and in animal models have been undertaken to disrupt the IGF-1R signaling pathway, including the development of small-molecule tyrosine kinase inhibitors (TKIs) and anti-IGF-1R antibodies. In preclinical testing, there was an initial difficulty in obtaining specific small-molecule kinase inhibitors of the IGF-1R due to a very-high-sequence homology with

kinase and ATP-binding domains of the insulin receptor [27]. Thus, major progress was initially slowed due to toxicity concerns. After initial attempts, the TKI NVP-AEW541 was shown to have a 27-fold increased selectivity for the IGF-1R over the insulin receptor [28]. This small-molecule TKI has shown promise in preclinical models, where inhibition of migration, metastasis, and angiogenesis was seen *in vitro* and a significant reduction in tumor growth was seen in xenograft models [29]. Further elucidation of the metabolic alterations related to the use of TKIs will be necessary prior to entry into clinical trials.

More recently, targeted antibodies have been shown not only to disrupt ligand-receptor binding, but also to decrease surface IGF-1R expression by internalization and degradation of the antibody-bound receptor [30,31]. Human monoclonal anti-IGF-1R antibodies have been produced by many pharmaceutical companies: IMC-A12 (ImClone Systems, New York, NY, USA), AMG 479 (Amgen, Thousand Oaks, CA, USA), R1507 (Roche, Basel, Switzerland), CP-751,871 (Pfizer Inc, New York, NY, USA), SCH717454 (Schering-Plough Corporation, Kenilworth, NJ, USA), MK-0646 (Merck), and AVE1642 (ImmunoGen, Inc, Waltham, MA, USA/Sanofi-Aventis, Paris, France). These antibodies have been tested in preclinical settings and ongoing early-phase adult studies [30,32-36]. However, few of these have been tested in patients with Ewing sarcoma.

The SCH717454 IGF-1R antibody was tested against a panel of pediatric tumors by the Pediatric Preclinical Testing Program, a comprehensive program to systematically evaluate new agents against childhood solid tumor and leukemia models. Intermediate or high activity was demonstrated in two of five Ewing sarcoma xenografts, including one complete response [36]. In addition, the IMC-A12 antibody is currently under investigation in a phase II Children's Oncology Group (COG) trial, with a stratum available for patients with Ewing sarcoma. Through the Sarcoma Alliance for Research through Collaboration (SARC), the R1507 antibody has been tested in two phase I studies in adults [37,38]. The first study assessed the administration of the antibody on a 3-week basis and was well tolerated, without any dose-limiting toxicity or serious adverse events; 11 of 26 patients were found to have stable disease, although none had Ewing sarcoma [38]. In the second study, four of eight heavily pretreated patients with Ewing sarcoma demonstrated stable disease, with two of eight patients demonstrating durable partial responses [37].

Implications for clinical practice

Human monoclonal antibody therapy directed against the IGF-1R holds great promise for improving the prognosis for children, adolescents, and adults with Ewing sarcoma. The recent data demonstrating responses in heavily pretreated patients with refractory Ewing sarcoma bring a wave of excitement to move these therapies to the forefront. Clinical trials are under way to assess the feasibility and efficacy of combining anti-IGF-1R therapy with multiagent chemotherapy. Over the next 5 years, feasibility testing will be completed, and if successful, phase III studies will assess whether the addition of these new agents will result in therapeutic improvements.

Abbreviations

BRCA1, breast cancer 1, early onset; COG, Children's Oncology Group; EWS, Ewing sarcoma protein; FLI-1, Friend leukemia integration 1; IGF, insulin-like growth factor; IGFBP, insulin growth factor-binding protein; IGF-1R, insulin-like growth factor 1 receptor; SARC, Sarcoma Alliance for Research through Collaboration; TKI, tyrosine kinase inhibitor; WT1, Wilms tumor 1.

Competing interests

The authors declare that they have no competing interests.

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