Editorial Commentary

Results from the Children's Oncology Group phase III trial of a monoclonal antibody against the insulin-like growth factor-1 receptor in patients with newly diagnosed metastatic Ewing sarcoma

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Ewing sarcoma is one of the most aggressive bone and soft tissue malignancies of children and young adults (1). The pathognomonic genetic aberration of this type of cancer is a fusion gene encoding Ewing sarcoma RNA binding protein 1 (*EWSR1*) with a gene member of the erythroblast transformation-specific (*ETS*) transcription factor family, usually (85%) Friend leukemia virus integration 1 proto-oncogene (*FLI1*; fusion *EWSR1-FLI1*) and less commonly (10%) ETS-related gene (*ERG*; fusion *EWSR1-ERG*) (2). At diagnosis, around 20–30% of patients with Ewing sarcoma have metastases, which indicates the presence of a high-risk disease. Around 90% of these patients achieve complete remission after treatment with high-dose chemotherapy including cyclophosphamide, doxorubicin, and vincristine, among other drugs, in combination with radiotherapy and surgery (3). Unfortunately, a majority (around 80%) of patients diagnosed with metastatic disease experience relapse or progression during long-term follow-up (3,4). After relapse, curative options are low, due to acquired chemo-resistance (5). In the absence of chemotherapeutic options for these patients, there is a need to develop new targeted therapies with biologic rationale (6).

One of the pathways found deregulated in Ewing sarcoma was the insulin-like growth factor-1 receptor (IGF-1R), thus offering a new molecular target for treatment (7). The insulin-like growth factor receptor family has high pro-oncogenic relevance (8). The seminal work from Sell *et al.* discovered that important oncogenes require IGF-1R for their transforming action (9). IGF-1R is a member of the tyrosine kinase class of membrane receptors, and interacts with the ligands insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2). Both ligands are widely expressed by several cell types, including cancer cells. They are both hormones and growth factors, because they act on cells locally at the extracellular fluid, or distantly upon systemic distribution. In the extracellular fluids, these ligands interact with at least six IGF-binding proteins (IGFBP), such as IGFBP-3, which neutralize their binding to the receptor IGF-1R (8). Soon after the discovery of IGF signaling in cancers, inhibiting the pathway was considered a potentially relevant therapy. Blockade could be done by one of the following three approaches: monoclonal

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antibodies against IGF-1R, small molecules inhibiting the tyrosine kinase activity of IGF-1R, and neutralizing antibodies against IGF-1 or IGF-2 ligands circulating in the blood. The biomarkers that predict the activity of therapies targeting IGF signaling remain unclear, after studies failed to find a correlation of the expression of IGF-1R and treatment activity (10). Serum concentration of ligands IGF-1 and IGF-2 or their binding proteins could be additional biomarkers to explore.

To improve the upfront treatment of patients with high-risk Ewing sarcoma, the phase III clinical trial by DuBois *et al.* (ClinicalTrials.gov identifier: NCT02306161) evaluated ganitumab, a monoclonal antibody against IGF-1R, added to high-dose chemotherapy, in around 300 patients with newly diagnosed metastatic Ewing sarcoma (11). Participation of the Children's Oncology Group (COG, United States) allowed to recruit a sufficiently high number of patients in a relatively short period of 4–5 years, even though the incidence of this disease is very low [1 case per 1.5 million population (1)]. This COG study was timely and necessary, because data from initial clinical trials in patients with refractory or relapsed Ewing sarcoma indicated that anti-IGF-1R antibodies induced clinical responses in around 10–14% of patients, with good tolerability (12,13). In the early phase II trial of ganitumab in patients with refractory or relapsed Ewing sarcoma, published in 2012, the overall response rate was 6% and there was clinical benefit for another 11% of patients, whose disease was stabilized for at least half year (14).

The results of the phase III COG study are clear and showed no proof of clinical benefit for the patients in the experimental arm of the study (11). They achieved a 3-year event-free survival and overall survival of 39% and 57%, respectively, compared to values of 37% and 60% in the patients of the control group, who did not receive the antibody. Because ganitumab-treated patients had a slightly higher probability of having pneumonitis after radiation, the trial was closed prematurely (11). Before this trial started, several other anti-IGF-1R programs, including one of ganitumab, were discontinued in diseases such as small cell lung cancer and breast cancer, due to not achieving the expected clinical efficacy (15). Recently, another phase 2 trial of ganitumab and palbociclib in patients with relapsed Ewing sarcoma showed no significant activity (16).

Many factors could be involved in the lack of efficacy of ganitumab in the COG study, but the first relevant question is whether this antibody had shown relevant efficacy against preclinical Ewing sarcoma models. The public data, published in 2011 by the owner of the drug, Amgen (Thousand Oaks, CA, USA), show that the *in vivo* anticancer activity of the antibody was not sufficiently powerful (17). For the two Ewing sarcoma xenografts that were considered "responders" in the preclinical article, tumor response was actually "disease in progression" according to criteria defined as "<50% regression from initial volume during the study period and >25% increase in initial volume at the end of study period" (18). Researchers treated the mice twice per week intravenously during the extension of the experiment and tumors progressed clearly during treatment, even though they grew at a significantly slower pace than untreated controls (and therefore they were considered "responders") (17). It is thus arguable that such activity was strong enough to justify clinical trials. Geier *et al.* summarized preclinical data of three anti-IGF-1R agents in a large panel of pediatric sarcoma xenografts, showing very minor evidence of efficacy in Ewing sarcoma (19).

Despite the unclear activity of ganitumab in animal models, the clinical response of a small proportion of patients with relapsed Ewing sarcoma in the initial clinical studies of ganitumab justified sufficiently the subsequent phase III trial. In this regard, another important point of the COG study is that the patients were not selected based on any suitable biomarker, and the disease diagnosis had not been confirmed molecularly in 14% of patients. The justification for the lack of patient enrichment was that there were not validated biomarkers for anti-IGF-1R therapies.

To conclude, the important study by DuBois *et al.* (11) provides unequivocal evidence of the lack of efficacy of one anti-IGF-1R therapy in Ewing sarcoma, adding to similar evidence of dozens of clinical trials on anti-IGF signaling therapies in cancer. Whether this pathway could be relevant in the future for the treatment of this or other cancers remains unknown. In any case, such possibility should be substantiated by strong preclinical data in a sufficient number of cancer models, such as patient-derived xenografts (20), and by preclinical studies of suitable biomarkers (21), to enrich the population of patients likely to obtain a clinical benefit.

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