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Targeting IGF-1R: at a Crossroads

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In this issue of *ONCOLOGY*, Golan and Javle provide an excellent update on targeting the insulin growth factor (IGF-1R) in gastrointestinal cancers. The review opens with the statement “IGF-1–directed therapy is currently at a crossroads”; this truly sums up the current status of the field. Decades of laboratory and preclincial research have shown a role for IGF-1R in many cancers; however, this hypothesis is now being tested directly in clinical trials. The crossroads the authors refer to, which several other targeted therapies have previously arrived at, is a dangerous one. The requirement for rapid clinical development of therapeutics demanded by both the pharmaceutical industry and patient advocates results in the risk that several therapies will be abandoned simply because trials have been performed in unselected populations. In this commentary, we will not dwell on the large literature implicating IGF-IR in cancer, but rather focus on the road forward for development of IGF-1R inhibitors.

Early clinical data from anti–IGF-1R trials were awaited with bated breath—and they did not disappoint. In a phase 1 trial of AMG 479, a patient with chemo-refractory Ewing sarcoma had a complete remission, a result that sent ripples of excitement throughout the field. A doubling of progression-free survival in a phase 2 trial of figitumumab in combination with cytotoxic chemotherapy for the treatment of non–small-cell lung cancer continued the fervor. However, while the road was initially fairly straight and clear (and at times resembled a freeway), two years later we stand at a crossroads. Two large phase 3 trials of figitumumab were closed due to futility or potential futility, major toxicities have become apparent, and several drug companies have curtailed or totally eliminated their anti–IGF-1R programs. Golan and Javle suggest that the road ahead lies in the “identification and validation of biomarkers of IGF-I pathway activation in clinical samples.” We wholeheartedly agree with this assessment.

Breast cancer provides an excellent example of the need for biomarkers—and a possible roadmap. The first two targeted therapies used in breast cancer (targeting the estrogen receptor [ER] and HER2) both have biomarkers for response. Indeed, the first trials of trastuzumab (Herceptin) were in a selected group of patients with HER2-positive disease. Since only 20% of patients have HER2-positive disease, and of these only 30% respond to trastuzumab alone, this is equivalent to a response rate of ~7% in an unselected population, a number that would not have encouraged further development of the drug. One has to wonder why it is, given the large literature on the absolute requirement of IGF-1R for mitogenesis and tumorigenesis,[1] that IGF-IR positivity is not used as an enrollment criteria for all anti–IGF-1R trials (similar to the restriction to HER2-positive disease in the development of trastuzumab). For example, Golan et al comment on a pre-clinical study that found that low

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IGF-1R levels showed excellent negative predictive value for lack of response (with 95% specificity). Importantly, IGF-1R by itself had only a 28% positive predictive value; however, several groups have shown that incorporation of other downstream pathways can improve specificity. To this end, recent reports have identified gene expression[2, 3] and an integrated genomic classifier that are associated with response to IGF-1R inhibitors.[4]

In addition to the need for biomarkers, the review discusses mechanisms of resistance to IGF-IR inhibitors. The review is relatively comprehensive, but its coverage of one of the most obvious aspects of the topic—the role of the highly similar insulin receptor—is scant. The authors clearly outline the endocrine effects of blocking IGF-1R with monoclonal antibodies: elevated growth hormone levels and increased levels of both glucose and insulin. While the authors discount these endocrine effects by stating that “to date there is no evidence of a deleterious effect on the cancers,” this is not entirely accurate. In many cancers, patients with elevated insulin levels have poor outcomes and receive less benefit from chemotherapy.[5] When tumors are carefully examined, many cancers have substantial expression of insulin receptor,[6] and experimental models have shown that inhibition of insulin receptor and IGF-1R together might improve tumor inhibition.[7, 8]

In addition, the authors comment on the need to combine anti–IGF-1R therapies with chemotherapy, but there are several important nuances to this approach that deserve mention. Effects from sequencing cytotoxic chemotherapy after IGF-1R blockade have been observed.[9] Blockade of IGF-1R prior to the cytotoxic insult results in a worse outcome because IGF-1R blockade can downregulate expression of the cytotoxic agent’s therapeutic target. Similar considerations are also important with regard to the ability of IGF-1R inhibition to affect progression through the cell cycle. IGF-I was initially described as a factor that allowed competent cells to progress through the cell cycle.[10] If cell cycle progression is disrupted by IGF-1R monoclonal antibodies, then cell cycle–specific chemotherapy could become less effective in a fashion analogous to tamoxifen’s ability to reduce benefit from cytotoxic chemotherapy.[11]

Thus, there is potential for IGF-1R blockade to actually do harm in the treatment of cancer. If a patient’s tumor has a substantial number of insulin receptors, then the hyperinsulinemia associated with IGF-1R monoclonal antibodies could enhance tumor growth or protect cells from apoptotic cell death. In this scenario, the antibodies to IGF-1R do not block insulin receptor but in fact induce insulin receptor signaling by elevating host insulin levels. IGF-2 can also act through insulin receptor, and this important mitogen may not be disrupted by anti–IGF-1R drugs.[12] Thus, insulin receptor can mediate cell survival, metabolism, motility, and proliferation by interacting with insulin or IGF-2, even in the absence of functioning IGF-1Rs. Furthermore, if IGF-1R affects progression through the cell cycle, some cytotoxics might be less effective.

Does this mean that blockade of IGF-1R should not be pursued as a cancer therapy? The authors point out the multiple lines of evidence implicating the IGF system in cancer. However, to date, only the clinical results of anti–IGF-1R antibodies have been described, and this strategy might be insufficient to block all of the effectors of the IGF system. Certainly, IGF-1R tyrosine kinase inhibitors disrupt the kinase function of both the insulin and the IGF receptor. Ligand-lowering or neutralization strategies have been under-explored. Combining anti–IGF-1R strategies with insulin-sensitizing agents (metformin, peroxisome proliferator-activated receptor [PPAR] agonists) might result in improved insulin control and avoid antibody-induced hyperinsulinemia. IGF-1R monoclonal antibodies could be combined with other pathway signaling molecules to improve therapeutic response. For example, multiple trials are underway testing IGF-1R monoclonal antibodies in combination with rapamycin analogs. Finally, only brief inhibition of IGF-1R

might be necessary when used in combination with cytotoxic chemotherapy; the tyrosine kinase inhibitors could be used in this setting.

We are in the adolescence of anti–IGF-1R therapies for cancer, and it is a troubled adolescence at best! Further development of appropriate clinical strategies that incorporate meaningful biomarkers will be needed to determine whether this receptor signaling system is a genuine target for cancer therapy.

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