Targeting Insulin-Like Growth Factor Signaling: Rational Combination Strategies

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Activation of the insulin-like growth factor (IGF) pathway, by binding of the growth factors IGF-I and IGF-II to the receptors IGF-IR and insulin receptor (IR), triggers complex signaling cascades that regulate cell growth, survival, proliferation, and differentiation. There has been intense interest in targeting the IGF axis as an anticancer strategy, following the identification that its dysregulation contributes to malignant transformation (1) and resistance to established anticancer treatments (2). Moreover, knockout of IGF-IR was reported to render nonmalignant cells highly resistant to oncogenic transformation (3). The IGF pathway has been implicated in the pathogenesis of numerous tumors, including Ewing’s sarcoma, breast cancer, non–small cell lung cancer, adenocortical cancer, and prostate cancer. Epidemiologic studies have also related higher circulating IGF ligand levels and polymorphic variants of IGF pathway regulatory genes to cancer risk and prognosis (2). Overall, these data have led to multiple approaches to abrogate IGF-IR signaling, including antisense oligonucleotides, small interference RNA, small-molecule tyrosine kinase inhibitors (TKI), and IGF-IR blocking antibodies (4). Many of these agents reverse transformation in tumor cell lines and increase sensitivity to chemotherapy and irradiation in vitro, inhibiting tumor cell growth and metastasis (2). Clinically, credence for therapeutic IGF-IR blockade has also been strengthened by the reports on tumor responses, for example, with IGF-IR monoclonal antibodies (mAb) in patients with Ewing’s sarcoma (5).

Nevertheless, recent clinical trials examining IGF-IR–targeting antibodies have raised concerns about the likely success of this monotherapy strategy. Two recently reported phase II studies have shown that two different human IGF-IR mAbs in Ewing’s sarcoma patients as monotherapy, R1507 (Roche) and AMG479 (Amgen), have disappointing progression-free survival at 2.2 and 2.3 months, respectively. Moreover, two other phase III trials investigating the addition of the fully human mAb to IGF-IR, figitumumab (CP-751,871, Pfizer), to either carboplatin and paclitaxel (ADVIGO 1016) or to the epidermal growth factor receptor TKI erlotinib (ADVIGO 1018) in patients with advanced non–small cell lung cancer have been suspended, as planned interim analyses by independent data safety monitoring committees indicated that the addition of figitumumab would be unlikely to meet the primary end point of improving overall survival (6).

Conversely, a phase I clinical trial evaluating a combination of the humanized IGF-IR mAb dalotuzumab with the mammalian target of rapamycin (mTOR) inhibitor ri盼forolimus (7) has shown antitumor activity in patients with estrogen receptor–positive metastatic breast cancer. Other combination strategies to block this pathway have focused on blocking both IGF-I and IGF-II signaling. This strategy has arisen from preclinical studies indicating that there are different binding epitopes on IGF-IR that have differing biological activities (8, 9). In this issue of Molecular Cancer Therapeutics, Dong and colleagues (10) elegantly describe the antitumor effects of combining two inhibitory IGF-IR antibodies with distinct mechanisms of action, BIIB4 and BIIB5, which block the binding of IGF-I and IGF-II to IGF-IR by competitive and allosteric means, respectively. They show, first biochemically, then in cell-based assays, and finally in xenograft models that combined blockade by these two antibodies results in enhanced inhibition of intracellular signaling through the IGF-IR axis with increased antitumor efficacy in vitro and in vivo when compared with the activity of either single antibody alone. This enhanced reduction in ligand-driven growth was shown to be at least partly due to an accelerated downregulation of IGF-IR following dual targeting by both antibodies. Significantly, however, the enhanced antitumor activity with the two antibodies was most evident at high ligand concentrations, where efficacy of monotherapy was considerably reduced. The combination of BIIB4 and BIIB5 also improved the antitumor efficacy of the epidermal growth factor receptor TKI erlotinib and the mTOR inhibitor rapamycin. These results are timely as combinations of two HER2 targeting therapeutic antibodies against distinct epitopes on HER2, trastuzumab, and pertuzumab have improved response rates in HER2 positive metastatic breast cancer patients in a recent Phase II trial (11), providing a clinically relevant paradigm for dual targeting approaches against different extracellular regions of a cell surface receptor.

Such an IGF-targeting combination approach is supported by other studies that have shown that different IGF-IR antibodies can behave differently in competitive binding assays with IGF-I and IGF-II (12, 13). The strategy...
suggested by Dong and colleagues—that is, targeting more than one epitope on IGF-IR to improve the blockade of this signaling axis—provides impetus for clinical evaluation of both this and other approaches, including the dual targeting of IGF-I and IGF-II, or using small molecule TKIs that cotarget IR and IGF-IR. Further support for such cotargeting strategies are supported by the reported increases in serum IGF-I levels in cancer patients following treatment with IGF-IR antibodies that may abrogate their therapeutic efficacy through bypass mechanisms (14). Whether IGF-IR blockade clinically also results in raised IGF-II levels requires further investigation. It is noteworthy that preliminary clinical data in adrenocortical cancer patients suggests that figitumumab monotherapy shows no significant activity in this disease, whereas the IGF-IR and IR small-molecule TKI OSI-906 has resulted in tumor responses (15, 16), supporting further investigation of this combined IGF-IR and IR blockade strategy. It is hypothesized that this finding in adrenocortical cancer may be a result of increased expression of IGF-II due to loss of imprinting; such a combination targeting strategy may also be critically important in other tumors with aberrant expression of IGF-II, including Wilms’ tumors, hepatocellular cancers, and rhabdomyosarcomas (17).

Overall, it is clear that we now need to consider how we can optimize our therapeutic strategies in light of our understanding of the intrinsic complexities of the IGF axis, which involves three ligands (IGF-I, IGF-II, and insulin) and at least four receptors (IGF-IR, IGF-IIR, IR, and hybrid receptors; ref. 18). Moreover, IR has two isoforms, IR-A and IR-B, as a result of alternative splicing. Whereas IGF-I and insulin are highly selective for binding IGF-IR and IR, respectively, IGF-II can bind IGF-IR as well as the IR-A isoform and IGF-IIR. IGF-IIR may not mediate intracellular signaling and may be a negative regulator of IGF-II. Increasing complexity also arises, however, from the fact that while both IGF-IR and IR function as homodimers, they can also form heteromultimers. These hybrid receptors are composed of both IGF-IR and IR and can be activated by both IGF-I and IGF-II. Signaling downstream of IGF-IR may therefore be activated by both IGF-I and IGF-II ligands through different functional IGF-IR epitopes but encompassing the same ligand-binding site (9, 10). Further studies supporting an important bypass role for IGF-II have arisen from a transgenic mouse model of pancreatic neuroendocrine cancer; this model is dependent on IGF-II signaling, with IR also directly promoting carcinogenesis and compromising the efficacy of strategies targeting IGF-IR alone (19). IR knockout in these tumors resulted in enhanced sensitivity to anti–IGF-IR therapies, implying that blockade of IGF-IR may be bypassed by IGF-II through IR. This may be especially important in malignancies in which IGF-II loss of imprinting is implicated to play a role, and in which direct targeting of IGF-II or use of TKIs with cross-reactivity against IGF-IR and IR may be more efficacious than targeting IGF-IR alone. Nonetheless, molecular events outside the IGF axis may be critical to codriving the growth and survival of tumor cells. Cotargeting strategies will need to also consider both sequential and parallel pathway blockade such as the parallel coinhibition of the erbB axis (20, 21). Sequential pathway inhibition also merits further careful evaluation as indicated by the preliminary results of clinical trials combining IGF-IR/mTOR inhibitors (7), which are consistent with the enhanced antitumor activity observed by such dual inhibition in preclinical models (22).

Finally, while the IGF axis clearly remains an important therapeutic target, increasing knowledge of the complexity of this pathway and its altered signaling in human malignancy must guide future studies of IGF pathway inhibitors to accelerate patient benefit and successful drug development. Moreover, there is a pressing need to identify a suite of analytically validated predictive biomarkers to better select the patients who will ultimately derive most benefit from such therapeutic strategies.

Disclosure of Potential Conflicts of Interest

Johann de Bono has served as a paid consultant for Pfizer, Genentech, Novartis, Astellas, Boehringer Ingleheim, Merck, and AstraZeneca.

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