

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Targeting the Insulin-like Growth Factor Receptor

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H&O What is the insulin growth factor (IGF) receptor pathway and how can we disrupt IGF signaling?

DY The insulin-like growth factor (IGF) receptor plays numerous roles in several cancers. The IGF pathway is composed of several growth factors, including IGF1 and IGF2—potent mitogens for many tumor cell lines. IGF1 is secreted by the liver following growth hormone stimulation, whereas IGF2 is less dependent on growth hormone and functions during fetal development. Its function in the adult is unknown, but it can bind some insulin receptor isoforms. Elevated circulating levels of IGF1 are associated with increased risk of breast, colon, and prostate cancers. Basically, this is a signaling system that allows cells to receive external signals and then process those signals resulting in a specific phenotype.

There are 2 types of IGF receptors—type I and type II. IGF type I receptor, which is highly homologous to the insulin receptor, binds insulin, IGF1, and IGF2. This receptor is composed of 2 α chains and 2 β chains. The β chains have a tyrosine kinase activity that is activated at the time of ligand binding. IGF type II receptor also binds IGF1 (with low affinity) and IGF2, and is mainly involved in clearance and degradation of IGF2.

There are also hybrid receptors, composed of a chain of insulin receptor and a chain of IGF receptor, which bind IGF1 and IGF2. Insulin action is well known: we eat a meal, our pancreas makes insulin, the insulin stimulates receptors on cell surfaces, and these receptors have intracellular domains that trigger a host of signaling events.

In the case of insulin, its receptor has an important role in glucose metabolism and utilization. The IGF receptor has very similar biochemical signaling events, but at the same time it regulates the growth and survival of cells more through pathways other than strictly metabolism. Developing inhibitors of the IGF pathway has to account for this system's role in the growth and development of normal cells. Developing this pathway is much like the development of the estrogen receptor in breast cancer as a pathway. The estrogen receptor is a molecule and signaling system that is very important in normal growth and development of the mammary gland. It is not so much an oncogene in the way we think of HER2, RAS, or RAF, but nonetheless, targeting that pathway—particularly in breast cancer—has led to very important therapeutic advances. I view IGF signaling in a very similar fashion to the estrogen receptor pathway.

H&O What types of tumors are affected by IGF?

DY Many cells express IGF receptors. Cells that are solely dependent on IGF receptors include pediatric tumors. There is very good evidence that diseases such as Ewing's sarcoma and some embryonal tumors, like rhabdomyosarcoma or Wilms' tumor, are very dependent on IGF signaling. Early clinical trials have suggested that a proportion of patients with a disease like Ewing's sarcoma can respond to the IGF receptor antibody as a single agent. Beyond that, almost every common malignancy—lung, colon, breast, prostate—expresses IGF receptors, and it is possible that some of these cancers will respond to IGF

receptor inhibition. The data that are furthest along are for non-small cell lung cancer. These data, which have been published, evaluated figitumumab, a monoclonal antibody to the IGF receptor manufactured by Pfizer. The results from this study by Karp and colleagues showed that giving the antibody with chemotherapy enhances the response rate and progression-free survival in patients with non-small cell lung cancer.¹ So, rather than trying to define which tumors are most responsive to IGF receptor signaling, we might be better served in defining which subsets of those tumors have IGF receptor activation. Taking breast cancer for example: anti-HER2 drugs are not very good for the vast majority of breast cancers because they do not express the target. The same goes for IGF receptors—only a subset of tumors within a given cancer type will be responsive to that pathway, and our challenge is to figure out what kind of tumors those are.

H&O What types of drugs target IGF signaling?

DY The second class of drugs that is furthest along in development is small molecule inhibitors of the IGF receptor tyrosine kinase domain. Several molecules, mostly ATP analogs, have been developed and are in clinical trials, including drugs from Bristol-Myers Squibb (BMS 754807) and OSI Pharmaceuticals (OSI-906). The one thing about these drugs that is both an advantage and disadvantage is that they are not very selective for the insulin receptor that they also inhibit. This is a disadvantage because insulin receptor inhibition leads to glucose intolerance. However, it might be advantageous because there is a lot of preclinical evidence suggesting that the insulin receptor on cancer cells also conveys some important survival signals. There are 2 other approaches to targeting IGF receptors that are being developed. One of these is the inhibition of the expression of the growth factors. IGF1 and IGF2 are both circulated in the serum, and one of the ways to block IGF action is to lower circulating IGF1. A drug called pegvisomant (Somavert, Pfizer), which inhibits growth hormone receptor, functions by lowering IGF1 levels. Within the next year or so, pegvisomant will be tested in cancer patients, along with an IGF receptor antibody (figitumumab), to determine whether there is any evidence of activity. There is also ongoing development of a neutralizing antibody to both IGF1 and IGF2; this drug is in very early phase clinical trials.² The hope is to develop a drug like bevacizumab for the IGF ligands—a neutralization strategy rather than a receptor-targeted strategy.

Combination studies with conventional chemotherapy have been published, but combination studies with other signaling agents, such as IGF receptor antibodies in combination with mammalian target of rapamycin

(mTOR) inhibitors (eg, everolimus, temsirolimus), are currently ongoing. To date, I do not think anyone has combined an IGF receptor antibody with an IGF receptor tyrosine kinase inhibitor. These are some of the combinations moving through the pipeline.

H&O Are there any known toxicities seen with these drugs?

Some of the early clinical trials have suggested that there may be some cytopenias associated with this particular class of compounds. Cytopenia and neutropenia have been reported with AMG 479. However, overall, the side effect profile has been favorable. Very few trials have defined a maximum tolerated dose because of the small percentage of grade 3 and 4 toxicities observed. Most trials have also demonstrated some level of insulin resistance. Frank hyperglycemia has been observed, but many of those observations were in combination with glucocorticoids given in conjunction with taxanes.

H&O Is there any updated information on AMG 479?

DY Phase I studies of AMG 479, Amgen's fully human monoclonal antibody antagonist of IGF1 receptor, have been reported last year. At this year's American Society of Clinical Oncology (ASCO) meeting, McCaffery and colleagues presented phase I biomarker data.³ The study, which analyzed biomarkers during early phase development of AMG 479, suggested that KRAS mutation was not a predictive factor for response. At this time, researchers are trying to determine the best way to use monoclonal antibodies in various trials, and AMG 479 is expected to move forward in various solid tumor malignancies.

H&O Does the IGF receptor play a prognostic role in any tumors?

DY There seems to be some controversy in this area. Analogous to the estrogen receptor, the IGF receptor has been identified as a favorable prognostic factor in certain diseases. Conversely, there has also been some evidence that IGF receptor expression is a negative predictive factor. Previously published data suggested that after radiation therapy for breast cancer, patients that have IGF receptor expression have more frequent recurrences.⁴ It remains to be seen whether the IGF receptor is more predictive versus prognostic, and whether the level of discussion should focus on the receptor level or the demonstration of activation of the pathway. A paper published last year by Creighton and colleagues demonstrated that activation of the IGF receptor pathway signaling measured by gene expression profiling is a poor prognostic factor.⁵ I believe the

next step in IGF research, and all oncology in general, is not just assaying the level of the receptor, but assaying the level of the receptor's activation pathway.

H&O What are the future directions for therapies targeting the IGF receptor?

DY Like many other targeted therapies, we need to obtain more robust predictive factors. It is necessary to identify patients either before or immediately after treatment to see who will or will not benefit. Ideally, we would like to discover a biomarker like HER2, ER, or KRAS, which would help us identify both negative and positive predictive values. Another issue that researchers need to address is determining the resistance pathway to the drug. Because IGF receptors are part of the endocrine system, when an IGF receptor antibody is given to patients, they upregulate expression of the ligand and have increased blood levels of IGF1 and insulin. We need to understand whether this is significant, whether it has a biologic function, and whether it should be blocked. We also need to identify the rational drug combinations—how do we combine anti-IGF receptor antibodies with both conventional cytotoxic chemotherapy and with other targeted therapies? There are a lot of preclinical data suggesting that drugs such as HER2 and IGF receptors could interact with each other, so inhibiting both pathways may be beneficial. There is also a level of concern regarding the sequencing of IGF receptors with cytotoxic chemotherapy. My colleagues and I published a paper in

which we showed that giving a cytotoxic in sequence with IGF receptor inhibition produced better responses, and determined that sequencing of anti-IGF1 receptor therapies is an important consideration in clinical trials.⁶ If the treatments were administered one way, there was enhanced cell kill, if they were administered another way, there was less cell kill. Thus, just like with other targeted therapies, once we have the drugs and understand how they work, we really are challenged by how to use them in combination to optimize their benefit.

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