

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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VEGFR-Targeted Therapy

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H&O What is the role of the vascular endothelial growth factor receptor in the growth and proliferation of tumor cells?

KF The vascular endothelial growth factor receptor (VEGFR) appears to play a relatively small role in direct tumor cell growth. VEGF also does not appear to trigger tumor cell multiplication, division, etc. Their major role is in relation to endothelial cells, which line blood vessels.

Endothelial cells are normally present in nonmalignant tissues. Even in tumors, the endothelial cells themselves are still normal. However, in order for tumor cells to grow beyond a certain point, they have to recruit normal cells into their structure, including endothelial cells. According to research findings, VEGF and VEGFR exert their major effect on endothelial cells, and through this effect are able to facilitate tumor cell growth.

H&O Why do tumor cells need endothelial cells?

KF When cancer cells form, one of the first hindrances to their growth is a shortage of oxygen and nutrients. Early in their development, tumor cells are frequently located far away from a blood vessel. One of the mechanisms by which tumor cells obtain oxygen and nutrients is by secreting growth factors, such as VEGF. Nearly all cells have this growth factor secretion mechanism, but usually it is dormant. Cancer cells develop mutations that enable activation of this signaling mechanism. This mutation is frequently seen in kidney cancer, the disease setting in which the majority of VEGF research has been done.

It has been known for some time that VEGF exerts its most direct effect on endothelial cells by causing them to multiply, divide, and migrate. VEGF exerts this effect by binding to the VEGFR, which is expressed at fairly high levels on the surface of endothelial cells. This observation

has been known for a long time in cancer research and in other disciplines as well.

H&O How do VEGFR inhibitors work?

KF Anti-VEGFR agents block the function of VEGFR and prevent VEGF from inducing its signal in endothelial cells. By blocking this mechanism, endothelial cells are prevented from multiplying, dividing, and migrating, regardless of how much VEGF is present. Thus the mechanism of action of VEGFR-targeted agents is not really anticancer but rather antiendothelial.

H&O Why don't VEGFR inhibitors completely eradicate tumors?

KF There are other cells involved in blood vessel formation aside from endothelial cells that do not seem to be activated or triggered by VEGF, and so VEGFR is not central to their function. Also, VEGF and its receptor are not the only mechanisms by which endothelial cells multiply, divide, and migrate; there are other growth factors involved. This aspect is most likely why VEGFR-targeted therapy does not completely cure cancer. Most likely, there are secondary and tertiary mechanisms by which this same process can happen, although perhaps not as vigorously as with VEGF-triggered growth.

H&O Could you describe the various VEGFR inhibitors currently being studied?

KF The oldest VEGFR inhibitor is SU5416, a small-molecule agent that inhibits the receptor from inside the cell. This drug failed to demonstrate significant efficacy in clinical studies. Interestingly, headaches proved to be the most problematic side effect and prevented an increase in dose level. The dose level that was causing headaches was not enough to prevent blood vessel formation in humans, even though this effect was shown in laboratory studies.

When SU5416 was found to not be an effective VEGFR inhibitor, many clinicians wondered whether this class of drugs would prove successful. However, the second generation of these agents has generated much more enthusiasm. SU11248 (sunitinib, Sutent, Pfizer), BAY 43-9006 (sorafenib, Bayer), PTK787 (vatalanib, Novartis), and AG013736 (Agouron/Pfizer) are all potent

inhibitors of VEGFR. However, what distinguishes them most strongly from SU5416 is that they also inhibit other kinases.

H&O How do these agents inhibit other kinases, and what is the significance of this activity?

KF The VEGFR lies across the membrane of the cell, and so has both an intracellular and extracellular domain. The binding of VEGF to the extracellular domain triggers the activation of the inside part of the receptor, where there is a kinase domain (kinase indicates an enzyme that puts phosphate residues on other proteins). It is this enzymatic function on the intracellular domain of the receptor that VEGFR inhibitors block. The enzymes are prevented from consuming adenosine triphosphate.

As it turns out, the part of the protein that anti-VEGFR agents block is fairly similar to that same entity in other enzymes. There are approximately 200 different kinases known to be present in human cells. The structures of these enzymes do not completely overlap, but there are some striking similarities. Each of the drugs mentioned above blocks the function of VEGFR as well as other enzymes. Some of these other enzymes are also receptor kinases, and some are kinases that live inside cells but are not attached to the membrane.

The VEGFR inhibitors each inhibit different enzymes, with potent inhibition of VEGFR as their commonality. The significance of this characteristic is not completely understood. Each agent has a different side effect profile, with some but not complete overlap. It may be that the differences in side effects are related to how these drugs affect other targets besides VEGFR. Of the 200 known kinases, the function of only 20 or so is well understood. There is still a great deal that is not known about these agents.

H&O In what diseases have these agents been studied?

KF As mentioned earlier, kidney cancer is somewhat biologically unique among cancers in that it produces more VEGF than any other type, a result of a mutation in the cancer cells themselves. Thus this disease setting is a useful one in which to study VEGFR inhibitors. Each of the 4 agents mentioned above has shown remarkable efficacy for kidney cancer patients with metastatic or advanced disease. Each agent has been found to stabilize disease, and to cause at least partial regression of tumors in some percentage of patients.

Each agent has also been tested in other types of cancers. Because blood vessel formation occurs in all can-

cers, it makes sense that VEGFR inhibitors should elicit some effect in other disease settings, though perhaps with activity that is not quite as striking as that seen in kidney cancer. This level of activity is exactly what has been seen in clinical trials. The percentage of patients who experience disease stabilization or regression is highest among kidney cancer patients, but the drugs do still show efficacy in other settings.

H&O When may these agents become widely available?

KF The clinical trials being conducted for each of these agents are all on different timelines. SU11248 will likely be the first to reach approval by the US Food and Drug Administration (FDA), although that is not yet confirmed. However, the first indication would be for the treatment of gastrointestinal stromal tumors, not kidney cancer. If BAY 43-9006 is approved by the FDA, the indication would be for kidney cancer, based on interim results of a phase III trial. Other trials still underway with BAY 43-9006 include one in the setting of melanoma and another in the setting of hepatocellular carcinoma.

PTK787 has been most heavily studied in colon cancer. In this setting, recent data have shown that it may not have sufficient activity to warrant approval. Other trials underway may show efficacy in other tumor types, but it is too soon to know for sure. PTK787 has shown efficacy in the treatment of kidney cancer, but it has not been extensively researched in this setting, and there are no ongoing trials that would lead to its approval for the treatment of kidney cancer.

Lastly, AG013736 has been tested in a variety of cancer types and has shown efficacy in kidney cancer. However, an indication in kidney cancer for AG013736 is not being pursued right now. Several trials are ongoing that might lead to its approval, but results are at least a couple of years away.

Suggested Reading

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