

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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mTOR Inhibitors

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H&O What is mTOR?

EC Mammalian target of rapamycin (mTOR) is a protein with many functions. One of the first functional discoveries made about mTOR is that it is central to the growth of a cell (in terms of size, not proliferation). Initially, mTOR was thought to be a nutrition sensor because levels were observed to fluctuate with the amount of adenosine triphosphate present in the cell. Later, mTOR was also found to be important in cancer biology. This protein regulates two downstream proteins, P70 S6 kinase and 4EBP-1, both of which play key roles in a cell's ability to produce more protein. Many of the proteins that are dependent on that translational machinery are also important in proliferation.

H&O Why is mTOR a potential target for cancer therapy?

EC mTOR is a kinase, a class of proteins that has been successfully targeted with small molecule tyrosine kinase inhibitors in several cancer types. When targeting kinases, it is only necessary to inhibit their functions; the function does not need to be restored, as is the case with tumor suppressor genes such as *p53*. mTOR appears to be an important target in some cancers, although not all.

mTOR also seems to have a role in tuberous sclerosis, a family of cancer neoplastic syndromes. In this family of syndromes, there are mutations in the mTOR pathway that act as negative regulators, so that the protein is always switched on. It has been found that inhibiting mTOR in this setting can reverse the disease completely, at least in experimental models. This effect may also occur in Cowden syndrome, in which the PTEN protein is mutated, and Peutz-Jeghers syndrome, in which a different upstream protein is mutated. These are rare diseases, but demonstrate that mTOR can be important in neo-

plastic disease, and that it may play a particularly key role when the mTOR pathway is dysregulated.

H&O How was mTOR discovered?

EC Rapamycin, the agent that targets mTOR, was identified before the protein target, which explains why the protein is known as mTOR. It was identified in the mid-1970s as part of an effort to find new antibiotics, and was found to be produced by a particular fungal species. The name "rapamycin" comes from Rapa Nui (Easter Island), where the spores of this fungus grow. Rapamycin was originally thought to be similar to macrolide antibiotics such as erythromycin, and was therefore considered to be another antibiotic. However, preclinical studies demonstrated that in fact rapamycin in immunosuppressive. The target of rapamycin in yeast was found to be two specific proteins, and the human homolog has since been called mTOR.

H&O How has rapamycin been studied in the setting of cancer?

EC Actually, the first mTOR inhibitor to be studied in the treatment of cancer was not rapamycin but its analog, temsirolimus (CCI-779, Wyeth). Although rapamycin was initially studied in neoplastic diseases, it was developed for transplant rejection prophylaxis because of its immunosuppressive effects. During this time, as more was being learned about the biology of cancer, the interest in using rapamycin in the treatment of cancer began to grow. However, once the patent on rapamycin expired, it was no longer financially viable to develop it as a cancer therapeutic. Therefore, temsirolimus, the ester analog of rapamycin, was developed and is now being evaluated for cancer treatment.

There are two other mTOR-inhibiting compounds, although they are not prodrugs of rapamycin: everolimus (RAD001, Novartis) and AP23573 (Ariad).

H&O In what cancer types have rapamycin analogs been studied?

EC mTOR inhibitors have been found to be active in lymphomas, particularly mantle cell lymphoma. This

lymphoma subtype is unique in that it has a translocation involving the cyclin D1 gene, one of the proteins whose translation is dependent on mTOR. This mechanism may explain why mTOR inhibitors appear to be effective in this setting.

Other diseases in which mTOR inhibitors have shown activity include renal cell cancer and sarcomas. They may prolong stable disease in breast cancer, glioblastoma, and pancreatic cancer.

H&O Could you describe some of the clinical studies conducted thus far?

EC The largest study conducted to date was a randomized phase II trial of temsirolimus in renal cell cancer. In this three-arm dose-finding study, all arms demonstrated a response to therapy with temsirolimus. A phase III study in renal cell cancer is currently underway. Temsirolimus has also been studied in the phase II setting in breast cancer, glioblastoma, and sarcoma. RAD001 has been studied in phase II trials and AP23573 has just entered phase II testing, all in similar disease settings.

Rapamycin is also entering clinical trials. Once the analogs were found to have activity in the treatment of certain types of cancer, interest in rapamycin was renewed since it is already available and approved by the US Food and Drug Administration. Rapamycin is currently in phase I trials and there are several proposals for phase II trials, although none have yet been initiated.

H&O Might mTOR inhibitors become part of standard therapy for some cancer types?

EC Yes, this is certainly possible. As a single agent, mTOR inhibitors may be used in the treatment of lymphoma, renal cell carcinoma, and sarcomas.

Combining an mTOR inhibitor with chemotherapy or other targeted agents may prove to be effective in the treatment of cancers in which mTOR has been demonstrated to stabilize disease, such as breast cancer and pancreatic cancer, and possibly ovarian cancer.

In the setting of leukemia, there has been encouraging preclinical data and some signs of clinical activity. How-

ever, in general mTOR inhibitors tend to work slowly, and in acute leukemia it is necessary to have a fast-acting agent. Therefore, it may be that for this disease an mTOR inhibitor will be combined with chemotherapy, although this approach has yet to be explored.

H&O What side effects are associated with mTOR inhibitors?

EC These agents have metabolic, hematologic, and constitutional side effects. The metabolic side effects have been known for quite some time, since rapamycin first became available, and include increases in glucose and blood lipids (cholesterol and triglycerides). These increases are easily monitored and generally do not lead to clinical difficulty.

Hematologic side effects include lymphopenia, anemia, and neutropenia, and there is a theoretic concern about immunosuppression. Most mTOR inhibitors have been developed on intermittent schedules, and this approach appears to be associated with less immunosuppression than a daily regimen, which has been used with RAD001 and rapamycin.

Finally, mTOR inhibitors can also cause stomatitis and onycholysis. Rapamycin has been associated with rare interstitial lung disease, although it is difficult to determine whether this disease is due to the rapamycin itself or some other factor. In the phase I trials of rapamycin analogs, the dose-limiting toxicities were stomatitis and asthenia.

Suggested Reading

Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol.* 2004;22:909-918.

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