

NEW DRUG REVIEW

Perspectives on Recent FDA Drug Approvals in Hematology and Oncology

Temsirolimus for Advanced Renal Cell Carcinoma

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Temsirolimus (Torisel, Wyeth) targets the mammalian target of rapamycin (mTOR), which is important in angiogenesis and cell-cycle control. Based on tissue microarray research, mTOR is also now known to be important in cell proliferation in both clear- and nonclear-cell types of renal cell carcinoma (RCC). A clinical trial was developed using three arms in which patients received, on a randomized basis, either intravenous temsirolimus alone 25 mg weekly, interferon alfa subcutaneous at the standard dose of 3 million U (with an increase to 18 million U) thrice weekly, or a combination of the two. This trial, reported in the *New England Journal of Medicine* in May 2007, demonstrated a nearly 50% improvement in survival for patients who received temsirolimus alone. The importance of this finding is two-fold. First, this trial is the first in both the clear- and nonclear-cell types of kidney cancer in which a survival advantage, by any agent, has been demonstrated in a population of kidney cancer patients. Secondly, the population in which temsirolimus was tested included poor-prognosis patients, characterized as having at least three of six risk criteria for poor prognosis based on Memorial Sloan-Kettering Cancer Center guidelines. Poor-prognosis patients comprise approximately 40% of patients with metastatic previously untreated RCC. Therefore, temsirolimus offers a dramatic and unequivocal survival advantage and is a first-in-class drug in a population of patients to whom many clinicians have found difficulty offering any hope.

The intravenous dose of temsirolimus alone 25 mg weekly was determined in part by a prior study by Atkins and colleagues, published in the *Journal of Clinical Oncology*, which tested three different doses of temsirolimus and found that 25 mg weekly was comparable in target

inhibition and clinical activity to the other doses but had the best side-effect profile. It was generally thought that an intravenous dose of 15 mg or higher weekly was the targeted dose for mTOR inhibition, but 25 mg weekly is a sufficient dose and schedule to effect inhibition of cell proliferation while being tolerable to the patient. Clinicians should not escalate the dose outside the setting of a clinical trial. Dose reduction based upon known toxicities associated with temsirolimus should be done according to the guidelines in the drug's package insert.

Although the drug is generally well tolerated, the major side effects of temsirolimus of which clinicians should be aware are anemia, fatigue, cutaneous rash, diarrhea, nausea, and peripheral edema. Additionally, because mTOR inhibitors are associated with the glucose pathway, it is necessary to monitor patients for hyperglycemia, especially those with underlying diabetes, and hyperlipidemia, especially those with underlying cholesterol or lipid abnormalities. If such patients are followed on a regular basis with blood tests and physical examinations, the full dose can usually be tolerated during the time that a clinical benefit is the goal. This agent's toxicity profile differs from that of other agents used in the setting of kidney cancer that target the vascular endothelial growth factor (VEGF) pathway in that no hand-foot syndrome or hypertension is associated with administration of temsirolimus.

The future of temsirolimus appears promising, not only in the setting of kidney cancer but also in the settings of other solid tumors, because this pathway is so important to angiogenesis and cancer-cell proliferation. A series of trials are planned to examine combinations of temsirolimus and other active agents in patients with RCC. One planned trial will compare temsirolimus to sorafenib (Nexavar, Bayer) in patients with kidney cancer who have previously received sunitinib (Sutent, Pfizer) in an effort to understand the magnitude of the benefit temsirolimus might offer in the population of patients who have failed frontline therapy with sunitinib. Current trials are combining temsirolimus with other agents in the setting of kidney cancer; the most promising combination, although very early in its development, is that of temsirolimus and bevacizumab (Avastin, Genentech), a VEGF ligand inhibitor shown in phase I trials to be easily combined with temsirolimus. Additionally, the Eastern Cooperative Oncology Group randomized phase II BeST trial is testing temsirolimus in combination with sorafenib or bevacizumab for the treatment of kidney cancer.