Good Drug, Bad Luck: Business, Regulatory Issues Can Create Obstacles for Drug Development

Anybody involved with cancer knows that bad things happen to good people. Sometimes bad things happen to good cancer drugs, too, for reasons ranging from regulatory red tape to intellectual property constraints. The stories of two drugs—one an oral chemotherapy, the other a bone-seeking radiopharmaceutical—show how regulatory or licensing barriers can block a promising compound’s path.

UFT: When One Plus One Equals Zero

At the annual meeting of the American Society for Clinical Oncology (ASCO) in June 2004, Norman Wolmark, M.D., had good news: results from a large trial of several years’ duration, in which an oral chemotherapy drug called UFT (uracil/tegafur) was tested in some 1,600 patients with colorectal cancer whose primary tumors had been removed. Wolmark, chairman of the Department of Human Oncology Allegheny General Hospital in Pittsburgh and the study’s lead investigator, reported that an oral regimen of UFT plus another drug, leucovorin, was as effective as the existing standard treatment—intravenous 5-fluorouracil plus leucovorin (5-FU/LV)—when the trials were begun in 1997. The two regimens were about equally toxic.

Given the advantage of taking a pill at home instead of visiting the doctor 30 times for an intravenous infusion, the trial’s results should have left Wolmark ecstatic. Instead, he wryly announced to his audience at the ASCO meeting that “the real question,” said Richard Schilsky, M.D., associate dean for clinical research at the University of Chicago, “should have been, how much theoretical potential for a loss of survival are the physician and patient willing to tolerate in exchange for a treatment that is less toxic and more convenient?”—a question, Schilsky said, “that has been shown to be safe at much higher doses when given to patients with bone metastases.

Quadramet: the Patients Versus the Patents

Even an established drug can run into obstacles that have little to do with the value of the drug itself. Quadramet (153-samarium lexidronam), licensed to Cytogen (Princeton, N.J.) has been approved since 1997 at low doses for bone pain palliation arising from bone metastases.

Quadramet is a radiopharmaceutical that has been shown to be safe at much higher doses when given to patients with bone metastases.
pediatric oncologist Peter Anderson, M.D., Ph.D., who pioneered human trials of high-dose Quadramet, said, “I’ve followed some of these patients for 5 years. They’re doing fine.”

A known side effect of bone-targeted radiopharmaceuticals—myeloablation (bone marrow destruction)—may be beneficial in bone marrow cancers. One treatment for multiple myeloma is to remove and preserve a sample of a patient’s bone marrow stem cells, and then, using chemicals or radiation, destroy the remaining marrow and transplant the stored stem cells to the patient. But typically the disease returns—probably, it is thought, because of incomplete killing of myeloma cells in the marrow.

Anderson co-authored a report of an uncontrolled phase II study last year led by Mayo Clinic hematologist/oncologist Angela Dispensieri, M.D., in which high-dose Quadramet was added to the bone marrow destruction regimen. At 100 days post-transplant, about half of the patients showed an absence, or near-absence, of a characteristic protein myeloma cells produce. These results trumped historical outcomes, and, importantly, toxicity was minimal.

While that is all highly encouraging, a contractual prohibition effectively stops Cytogen from sponsoring a multiyear, large-scale clinical trial that could examine whether Quadramet enhances long-term survival. Dow Chemical has licensed Quadramet to Cytogen only for bone-pain palliation, giving another company—Seattle-based NeoRx—myeloablation rights to a new radiopharmaceutical, STR (166-holmium DOTMP).

“Dow offered us rights to STR for myeloablation,” said Cytogen’s senior vice president of operations, William Goeckeler, Ph.D. “We told them we wanted to do that with Quadramet. We didn’t see [the] sense of developing a new compound to do what we could do with a compound already nearing registration.” For business reasons of its own, Dow elected not to license Quadramet for this purpose.

Goeckeler’s name appears on the patents for both compounds (as a University of Missouri graduate student, he had played a key role in working out their chemistry), so he knew that the bone-binding avidity of Quadramet’s chelating molecule exceeds that of STR. More than half of Quadramet’s samarium, but only about one-quarter of STR’s radioactive holmium, adheres to patients’ skeletons, so a bigger initial STR dose is needed to yield an equivalent skeletal radiation effect, and a lot more radioisotope gets excreted. Moreover, a given amount of holmium unleashes much more radiation during its 6-hour transit through the excretory system than samarium does.

Nor is there any evidence yet that 166-holmium’s more energetic emissions, by penetrating deeper into tissues than 153-samarium, make STR a better cancer-cell killer than Quadramet. In a three-center dose-escalation trial completed last year, STR at high doses yielded patient response rates no better than those in the Mayo Clinic Quadramet study, while causing serious delayed kidney and bladder damage—and several deaths.

Early this year, NeoRx initiated a phase III trial of STR plus melphalan or melphalan alone in refractory multiple myeloma. Based on analysis of a 10-patient subset from the earlier STR trial, patients’ marrow will receive less than two-thirds the effective radiation dose delivered safely in the Mayo Clinic’s Quadramet study, and all subjects will receive continuous bladder irrigation, which involves catheterization with attendant inconvenience and infection risk. Thus far, only eight centers are on board, and no patients have yet been recruited for the trial.

“Holmium’s radiation physics makes it more difficult than samarium,” said hematologist/oncologist Leonard Sender, M.D., deputy director for clinical affairs at the Chao Family Comprehensive Cancer Center at the University of California at Irvine, whose institution has been invited to be a study site. “When you’re talking about something potentially toxic not only to patients but to doctors and nurses and everybody else, you have to be careful. It will be a good 3 months before we start soliciting our first patients because we’re waiting for a safety report’s completion before we take the protocol to our institutional review board.”

Sender said he would have no qualms about submitting a high-dose Quadramet protocol to his IRB in parallel, rather than in series, with a radiation physics study. “I would feel more comfortable straightforward with Quadramet because there’s more data. It’s been given safely at high doses. The physicists and nuclear-medicine people understand it better.”

Common Sense

UFT and Quadramet are far from the only drugs to get tied up in red tape. And innocents in one case may be perpetrators in another. UFT sponsor BMS, for example, used a legal loophole to fend off generic competition against Taxol (paclitaxel) for 30 months (see News, Vol. 94, No. 5, p. 324).

FDA’s delayed approval of Sanofi-Synthelabo’s Eloxatine (oxaliplatin) was due not to regulatory nitpicking but rather to the European drugmaker’s initial attempt to win approval based on European phase III trials whose endpoints were time to progression (acceptable by European regulatory agencies) instead of survival (see News, Vol. 94, No. 16, p. 1191).

All of these examples point to the difficulty of generalizing when it comes to drug development. When patents, investors, decades of research, and—most importantly—patients’ lives are at stake, a one-size-fits-all approach simply will not work. For example, Schilsky said of the FDA’s interpretation of its “fixed combination” regulation regarding UFT, “Regulations like this one may well be extremely appropriate for some situations and nearly irrelevant for others.”

—Bruce Goldman