

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Development of Rapamycin as an Orphan Drug

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H&O What is the background of the development of rapamycin as an orphan drug?

MH This case is unique because the new cancer target, mammalian target of rapamycin (mTOR), was discovered after the drug which targets it, rapamycin, was already known. It is an orphan drug because no one was researching and developing rapamycin as an anticancer agent due to its patent expiring. Initially, it was thought that due to specific pharmacologic properties, such as low solubility and oral dosing, rapamycin was not going to be effective as an anticancer agent. However, none of these concerns has been relevant. Our group became interested in the target and the agent in pancreatic cancer—what is considered an orphan disease—because there is no treatment for it and because less than 200,000 cases exist in the US population. For such diseases, there are mechanisms to fund clinical trials for drugs already approved in other indications, and that is the program we are using. Our work was funded by the National Cancer Institute and the US Food and Drug Administration, rather than by industry. This model could be applied to other agents in the setting of cancer, such as statins, and in the past, thalidomide as an anticancer agent was developed in this way.

H&O For what other indication is rapamycin used?

MH Rapamycin is approved as an immunosuppressant to prevent rejection in organ transplantation. Like many drugs approved for other indications, rapamycin was found to have anticancer properties.

H&O What is the drug's mechanism of action in cancer?

MH Rapamycin is a macrolide antibiotic and an immunosuppressor. It was initially identified in the 1970s during a search for new antibiotics. It is derived from a fungus that is found on Easter Island, in the Pacific Ocean. The name “rapamycin” comes from “Rapa Nui,” which is the native name for Easter Island. Initially, the analog of rapamycin, temsirolimus (CCI-779, Wyeth), was evaluated for the treatment of cancer. As anticancer therapy, rapamycin inhibits the mTOR kinase (also called RAFT and FRAP), which is involved in the regulation of cell growth, survival, and response to nutrients. Essentially, it regulates translational control of different mRNAs and proteins. mTOR regulates two downstream proteins, P70 S6 kinase and 4EBP-1, which are both important to a cell's ability to produce more protein, and thus, are important to cell proliferation.

H&O What have been the results of your research into rapamycin in pancreatic cancer?

MH The phase I trial was completed and presented at the American Society of Clinical Oncology annual meeting in 2006. We enrolled 10 patients, who received doses of 2, 3, or 6 mg/day. We concluded that the recommended dose of rapamycin is 6 mg/day based on toxicity, pharmacodynamic, and pharmacokinetic data gathered. Though these data were limited, there were no specific problems or concerns relating to pharmacokinetics of the drug. Based on

positron emission tomography, there is some evidence of reductive response in the tumor types treated, and therefore we considered rapamycin an attractive agent in this setting. We thus began a phase II trial, which has enrolled 15–20 patients, but we have not presented any data yet. A single flat dose of 5 mg/day is being used in this trial, but it is as yet unclear whether it will be effective in pancreatic cancer. We plan to enroll 15 additional patients.

Suggested Readings

Abraham RT. Mammalian target of rapamycin: immunosuppressive drugs uncover a novel pathway of cytokine receptor signaling. *Curr Opin Immunol.* 1998;10: 330-336.

Cohen E. mTOR inhibitors. *Clin Adv Hematol Oncol.* 2006;4:38-39.

Jimeno J, Kulesza P, Cusatis G, et al. Pharmacodynamic-guided, modified continuous reassessment method (mCRM)-based, dose finding study of rapamycin in adult patients with solid tumors. *J Clin Oncol.* 2006;24(18S): Abstract 3020.

Hidalgo M, Rubio-Viqueira B, Weekes C, et al. In vivo platform for translational drug development and biomarker discovery in pancreatic cancer. *J Clin Oncol.* 2006;24(18S): Abstract 4000.



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