

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Novel Agents and Targets for the Therapy of Advanced Colon Cancer

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H&O What spurred research into finding new targets for advanced colon cancer?

PH As in other tumor types, there are limited options for treatment of patients with advanced colon cancer. The traditional chemotherapeutic regimens, although improved in recent years, had reached what was thought to be a plateau in benefit, and it was thought that in order to further improve results, therapy needed to go in a different direction. The entire field of oncology was moving away from classic chemotherapeutic agents, in the direction of a more focused, molecular-targeted therapy—the so-called “magic bullet” concept that Dr. Paul Ehrlich had described near the turn of the 20th century. With colon cancer, researchers were fortunate to be able to discover a few effective molecular-targeted agents rapidly. The concept of molecular-targeted treatment for colon cancer was proven useful, and it became a model for treatment of other types of tumors. Once we had some success with the first agents and targets, it was only normal that we would extend the search for even more novel ways of treating the tumor.

H&O What successes have been seen with small molecules against targets in colon cancer?

PH Small molecules are relatively easy and cheap to manufacture, but even though they are directed against specific targets, they can also affect other unrelated targets, which is not necessarily a negative quality. For example,

imatinib (Gleevec, Novartis) is a small-molecule tyrosine kinase inhibitor directed against *BCR-ABL*, which also affects c-KIT and platelet-derived growth factor (PDGF). Additionally, many small molecules are administered orally, which improves compliance. In colon cancer, however, small molecules have not been as successful as may have been originally anticipated. Multiple small molecules targeting epidermal growth factor receptor (EGFR) or VEGF have been tried and there has not been great success. For example, erlotinib (Tarceva, Genentech/OSI), which is successful in treating lung cancer and may add to the treatment of pancreatic cancer, was investigated in combination with chemotherapy in colon cancer and found to be too toxic. Other small molecules, such as vatalanib (Novartis), have been considered promising against angiogenesis but have failed to improve the results obtained with chemotherapy so far.

Nevertheless, currently, there is a host of small molecules under investigation. Some agents, like AZD2171 (AstraZeneca), sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer/Onyx), and AMG706 (Amgen), are directed against established targets, such as VEGF and EGFR. There are other small molecules being designed to focus on novel targets, such as mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), and other pathways. It is likely that effective small molecules will be discovered in the future, but at present none has been proven effective in combination with chemotherapy in phase III trials in colon cancer.

H&O Could you discuss the use of monoclonal antibodies in colon cancer?

PH Monoclonal antibodies are relatively large molecules, which are more expensive and complicated to manufacture than the small molecules. These agents are typically given intravenously. Their value, however, derives from their specificity; these agents do not hit targets other than the one they have been designed to hit. One particularly successful monoclonal antibody is bevacizumab (Avastin, Genentech), which targets VEGF and is approved for use in non-small cell lung cancer and as a first- and second-line agent combined with 5-fluorouracil-based chemotherapy against metastatic colorectal cancer. Another nonclas-

tic antibody against VEGF is VEGF Trap (Regeneron), which is a construct that mimics a monoclonal antibody, and is currently under investigation in phase II trials.

H&O What is the status of cetuximab and panitumumab in the treatment of colon cancer?

PH Both of these agents are monoclonal antibodies as well. Cetuximab (Erbix, Bristol-Myers Squibb/Merck/ImClone) is approved for use in metastatic colorectal cancer. Like cetuximab, panitumumab (Vectibix, Amgen) also targets the EGFR and is approved for use in metastatic colorectal cancer. By blocking the EGFR, these agents inhibit cell growth, induce apoptosis, decrease interleukin-8 and VEGF production, and induce the internalization of the EGFR. Currently, both panitumumab and cetuximab have proven activity in patients who have been previously treated with chemotherapy. Both are being investigated in the first-line setting, but there are no published results thus far. Cetuximab has been investigated in previously untreated patients with metastatic colorectal cancer in the CRYSTAL trial, in which patients were randomized to receive irinotecan, leucovorin, and 5-fluorouracil (FOLFIRI) plus cetuximab or FOLFIRI alone. A press release from the manufacturer indicated that the trial achieved its primary endpoints but no details are available. Panitumumab has been investigated in the PACCE trial, in which patients were given either FOLFIRI or 5-fluorouracil, leucovorin, and oxaliplatin (Eloxatin, Sanofi-Aventis; FOLFOX) and randomized to receive either bevacizumab or a combination of bevacizumab and panitumumab. Surprisingly, a recent press release has indicated that the trial was negative, but no other information is available at this time.

H&O What is the status of TAS-102 with regard to treatment of colon cancer?

PH TAS-102 is an interesting compound. It is a fluoropyrimidine, which is considered a classic chemotherapy agent, combined with a thymidine phosphorylase inhibitor. Thymidine phosphorylase is a proangiogenic molecule that is commonly expressed by tumors; thus, TAS-102 could be potentially an antiangiogenic agent. This agent was designed as a combination of fluoropyrimidine and a thymidine phosphorylase inhibitor because the active chemotherapeutic agent fluoropyrimidine is destroyed by thymidine phosphorylase, which is blocked by the addition of the inhibitor of thymidine phosphorylase inhibitor. TAS-102 is currently entering phase II trials in several settings. There are data from phase I trials showing that it does have some antitumor activity.

H&O What is the status of vatalanib in colon cancer?

PH Vatalanib is a very efficient tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3, and also PDGF receptor. This agent was considered quite promising based on phase I results and it was rapidly entered into phase III trials in colorectal cancer. Vatalanib was added to FOLFOX and compared to FOLFOX alone in previously untreated patients in the CONFIRM 1 trial and in previously treated patients in the CONFIRM 2 trial. These trials were negative, but there was apparently a subgroup of patients with high lactate dehydrogenase (LDH) in whom the combination seemed to show some benefit. At this point it is unclear whether research will continue into the combination of FOLFOX and vatalanib in patients with high LDH.

H&O What other targets are being investigated in colorectal cancer?

PH EGFR and VEGF are the targets that have been proven, but in colorectal cancer, we need to assess new prospective targets. There are other truly novel targets worthy of investigation, such as mTOR and Src. Both are important to colon tumors, and there are inhibitors of both currently under investigation. Dasatinib (Sprycel, Bristol-Myers Squibb) blocks Src and everolimus (Novartis) and temsirolimus (Wyeth) block mTOR. Research with these agents will be closely watched in the future. I believe there will continue to be an effort to identify better drugs that target known targets, such as VEGF and EGFR, and an even bigger effort to find new medically treatable targets.

Suggested Readings

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