Agents in Development for Colorectal Cancer

Colorectal cancer remains a deadly and prevalent disease, with approximately 150,000 new cases estimated to be diagnosed in 2007. Last year, more than 55,000 Americans died of colorectal cancer, accounting for 10% of all cancer deaths and ranking second only to lung cancer. Age is a major risk factor for colorectal cancer, with a lifetime incidence of 5% among average risk individuals and with more than 90% of cases developing after age 50.

Treatment of early-stage colorectal cancer centers around surgery, with the use of adjuvant chemotherapy common in patients with local lymph node involvement. Chemotherapy regimens have been built on a foundation of 5-fluorouracil, given as an intravenous (IV) bolus, by continuous IV infusion, and now by oral administration as capcitabine. The approval of irinotecan, a topoisomerase-1 inhibitor, in 1995 and oxaliplatin, a platinum alkylator, in 2002, both for refractory colon cancer, has quickly led to new front-line and adjuvant chemotherapy regimens that have greatly improved outcomes for colorectal cancer patients. Treatments with FOLFOX (oxaliplatin and infusional 5-FU) and FOLFIRI (irinotecan and infusional 5-FU) are now commonly administered to stage III and IV cancer patients after well-conducted phase 3 clinical trials.

Incorporation of targeted agents has occurred quickly in the treatment of this malignancy. The initial FDA approval of the exciting anti-angiogenesis monoclonal antibody bevacizumab (AVASTIN, Genentech) was for the first-line treatment of colon cancer in combination with chemotherapy, demonstrating improvements in median survival as well as tumor response rates and time to tumor progression (TTP). Furthermore, the first monoclonal antibody targeting the epidermal growth factor (EGFR-1), cetuximab (ERBITUX, Bristol-Myers Squibb/Imclone), received approval after demonstrating a benefit in response rate and TTP alone and in combination with irinotecan in refractory colon cancer patients. Both AVASTIN and ERBITUX are being developed in a variety of scenarios in colorectal cancer, including the adjuvant treatment of surgically resected stage 3 patients, hopefully leading to more long-term survivors and cures. More recently, a human monoclonal antibody against EGFR has come to clinical practice, panitumumab (VECTIBIX, Amgen), with rapid expansion of clinical trials underway.
Anti-angiogenesis remains an important area of drug development in colorectal cancer. Inhibiting tumor blood vessel growth and expansion, interfering with the formation of metastases and disrupting tumor vasculature and theoretically leading to greater chemotherapy penetration and thus response rates, has been the observed preclinical effect for many of these new agents. While AVASTIN remains the only intravenous monoclonal antibody targeting vascular endothelial growth factor (VEGF), a number of oral small molecules are in late-stage clinical trials. These include, but are not limited to, sunitinib, sorafenib, AMG706, AZ2171, AZ6474, PTK787, and pazopanib. A broader spectrum of effect on the VEGF-Rs and greater potency are just part of the cause for enthusiasm in testing these agents clinically. In addition to ERBITUX and VECTIBIX, oral EGFRs such as erlotinib (TARCEVA, Genentech/OSI) are being studied in colorectal trials, including large phase 3 adjuvant populations. It is clear from the initial trials in refractory populations that this class of targeted therapies has a role in treating colon cancer.

A very novel approach to colon cancer treatment focuses on the human tumor necrosis factor (TNF)-related apoptosis-inducing ligand receptors 1 and 2 (TRAIL-R1, DR4 and TRAIL-R2, DR5), which activate the extrinsic apoptosis pathway. TRAIL-Rs are a member of the TNF superfamily consisting of 18 ligands and 28 receptors. The normal biologic role for these receptors is regulation of cell survival, making them ideal targets for anticancer therapies. Mapatumumab (HGS-ETR1, TRM-1, Human Genome Sciences) is a fully human monoclonal antibody that has completed phase 1 trials with an excellent safety profile and evidence of antitumor activity; a follow-on compound, HGS-ETR2, has also entered clinical trials. AMG 655 (Amgen) is a fully human monoclonal agonist antibody that binds human TRAIL-R2 (TR2/DR5) and activates caspases and induces apoptosis. Tumor shrinkage has been observed in the initial phase 1 studies. Finally, initial reports have been made of delivering actual recombinant human Apo2L/TRAIL, (Genentech/Amgen), the ligand against the pro-apoptotic receptors DR4 and DR5, alone and in combination with other agents. Targeting and inducing apoptosis holds great promise for anticancer activity, particularly in combination with other cytotoxics and biologics.

Another exciting advancement in the use of targeted biologics is the development of cytotoxic monoclonal antibodies. RAV-12 is a high-affinity chimeric IgG1 monoclonal antibody that binds RAAG-12, a novel epitope present on multiple cell-surface proteins, particularly those of gastrointestinal origin, such as stomach, pancreas, and colorectal adenocarcinomas. Initial trials have demonstrated objective responses in refractory colon cancer, and phase 2 trials in pancreas cancer are being initiated.

In addition to the enthusiasm around biologics, both small molecules and monoclonal antibodies, there are a number of unique cytotoxic chemotherapies being evaluated in colorectal cancer. The aurora kinase inhibitors and the naturally occurring epothilones are in this class, as well as a number of camptothecin analogues. This year we will see the introduction of nanoparticulate, liposomal, lyophilized, and vitamin E-emulsion camptothecins that inhibit topoisomerase-1, hopefully with greater potency and less toxicity.

Advances in the treatment of colorectal cancer are coming steadily, and the continued development of novel regimens utilizing cytotoxics and biologics should further improve outcomes for these patients.

Howard A. “Skip” Burris III, MD, is currently serving as Director of Drug Development at The Sarah Cannon Research Institute in Nashville, TN, where he is also an Associate with Tennessee Oncology, PLLC. He currently serves on the ASCO Board of Directors and is a member of the ASCO Ethics Committee.