New treatments offer better survival and fresh challenges in colorectal cancer

August 21 2009

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the Western world. Fortunately physicians today have an abundance of drug therapies available to improve survival length for more advanced cancer patients. Now the discovery of genetic biomarkers relevant to CRC means that targeted personalised medication is increasingly common.

CRC affects approximately 150,000 patients and leads to over 52,000 deaths every year in the US alone. In the early stages, CRC can often be cured by surgery. It is in the more advanced, palliative cases that the abundance of drug therapies comes into play, according to Mayo Clinic oncologist Axel Grothey, MD. In his paper Medical treatment of advanced colorectal cancer in 2009 published this week in the journal *Therapeutic Advances in Medical Oncology*, Grothey details the interplay of therapies currently on offer.

Oncologists now integrate conventional cytotoxic agents oxaliplatin and irinotecan (which directly fight tumour cells) with treatments such as bevacizumab and epidermal growth factor receptor (EGFR) antibodies, cetuximab and panitumumab, as novel targeted agents into standard medical therapy. The result is that median overall survival in metastatic CRC now exceeds two years for the first time.

For decades, standard first-line therapy consisted of the drugs fluorouracil (5-FU) plus leucovorin, which helped just a fifth of patients to survive a median of one year. In the late 1990s and early 2000s, the

addition of oxaliplatin and irinotecan to the backbone of 5-FU and leucovorin led to dramatic improvement in median survival to nearly 24 months. Most recently, biologic agents such as bevacizumab, cetuximab, and panitumumab, have yielded even better results for many patients.

"It cannot be overemphasized that these significant improvements in outcome of patients with CRC are closely linked to the number of active drugs available to treat this disease," says Grothey. However, he adds that this treatment abundance also provides oncologists with specific challenges for managing palliative medical therapy in advanced CRC, particularly when they use targeted agents.

One targeted agent is bevacizumab (a monoclonal antibody developed by Genentech under the trade name Avastin), which inhibits vascular endothelial growth factor (VEGF), a natural protein that the tumour uses to grow new blood vessels (angiogenesis). Bevacizumab was the first angiogenesis inhibitor available in the US, and has become established as a standard component of first-line chemotherapy.

To date, no researchers have identified a predictive marker for bevacizumab's activity in metastatic CRC. According to Grothey, key questions surrounding bevacizumab's use in the palliative setting are whether it provides clinical benefit beyond the stage of tumour progression, and which patient group is at higher risk for bevacizumab-related toxicities. Data from a large observational, non-randomised cohort study by Grothey and colleagues in 2008 suggests that patients may benefit from continued use of bevacizumab beyond tumour progression . Randomised phase III clinical trials are currently underway in Europe and the US to determine whether this should become standard practice.

Anti-epidermal growth factor receptor (EGFR) antibodies cetuximab (Erbitux) and panitumumab (Vectibix) are both targeted monoclonal

antibody treatments that have demonstrated efficacy both in combination with chemotherapy or, in contrast to bevacizumab, used alone. Trials on unselected patient groups show limited results. But clinical trials and translational studies now indicate that those patients with advanced CRC must have a tumour with specific genetic mutations (wild type KRAS and wild-type BRAF) for EGFR antibodies to be effective. Testing for BRAF and KRAS mutations now excludes about half of patients with CRC from an ineffective, but potentially harmful (and expensive) therapy with cetuximab and panitumumab.

Clinical decisions regarding whether the goal is to rapidly shrink a tumour, whether to attempt curative surgery or to rapidly boost short-term quality of life or survival, or instead aiming for a longer-term quality of life with minimum side effects will determine the physician's choice of approach.

"Although biomarkers will provide some guidance on which agents are potentially useful in a given setting, in particular with regard to the use of EGFR antibodies, the importance of individualizing therapy based on clinical parameters cannot be overemphasized," says Grothey.

Targeted agents have become an integral part of medical therapy for advanced CRC. The next challenge for oncologists is to develop a rationale and biomarker-based treatment algorithm to use all potentially active agents as individualized therapy.

More information: Medical treatment of advanced colorectal cancer in 2009 by A. Grothey is published this week (Friday 21st August 2009) in the launch issue of Therapeutic Advances in Medical Oncology. The article will be free online for a limited period from tam.sagepub.com/cgi/rapidpdf/1758834009343302v1

Source: SAGE Publications