

# What's New in ...

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## ... COLORECTAL CANCER

### Meaningful progress in therapy options

Colorectal cancer (CRC) is the second most common cancer, with Americans carrying a lifetime risk of 5.29%.<sup>1</sup> In its most recent report, the National Cancer Institute (NCI) reveals a steady improvement in 5-year survival rates. Released in 2007, the report shows that of patients with all stages of CRC diagnosed in 1999, the 5-year survival rate was 65.5% compared with 49.39% in 1975.<sup>2</sup> The number of new CRC cases predicted for 2008 was 148,810, and the number of predicted CRC-related deaths in 2008 was 49,960.<sup>1</sup> Fortunately, several new drugs have been approved by the FDA for the treatment of CRC in recent years. Moreover, in the past few years, innumerable clinical trials have revealed higher response rates for several new treatment options. These new options are resulting in better survival not yet reflected in NCI statistics.

#### ADVANCES IN CRC THERAPY

Until the mid-1990s, mean survival for patients with metastatic CRC was less than 12 months, and 5-fluorouracil (5-FU) was the only chemotherapy agent approved by the FDA for this disease. Capecitabine, an oral fluoropyrimidine that is converted to the active form of 5-FU, was later found to be noninferior to 5-FU for treatment of stage III CRC. Capecitabine has also been used in combination with other cytotoxic drugs, although 5-FU remains the primary fluoropyrimidine for CRC.

In September 1996, after demonstrating a modest response rate and survival benefit in patients who had previously been treated with 5-FU, irinotecan received fast-track FDA approval for use in patients who had CRC progression following 5-FU therapy. By March 2000, irinotecan received FDA approval for use as first-line therapy in combination with 5-FU after that combination was found to be more effective than either agent alone. With the availability of irinotecan, modest but important survival benefits were realized; median survival increased to a range of 14 to 16 months,<sup>3,4</sup> although the 5-year survival rate remained at less than 10%.

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At the dawn of the new millennium, advances in drug development resulted in more effective treatment options for patients with CRC. The chemotherapeutic agent oxaliplatin, a third-generation platinum analog, demonstrated synergistic effects with 5-FU, improving survival in patients with metastatic disease compared with 5-FU alone (16.2 versus 14.7 months,  $P = .12$ )<sup>5</sup> and leading to FDA approval in August 2002. In January 2004, the FDA announced the approval of oxaliplatin as first-line treatment for metastatic disease when it was shown to be superior to irinotecan-containing regimens for newly diagnosed disease, resulting in median survival of 19.5 months.<sup>6</sup> By November 2004, the role of oxaliplatin (in combination with 5-FU) as adjuvant therapy for patients with resected stage II or III CRC was also established, leading to improvement in disease-free survival.<sup>7</sup>

Not only have irinotecan and oxaliplatin played a role in improving overall survival of patients with metastatic CRC, these agents have also impacted resectability rates for hepatic metastasis; in tumors initially considered to be unresectable, the rate of resectability has increased from 12% to 22%.<sup>8</sup> This is quite meaningful given that patients who are able to undergo resection may see a 5-year survival rate of 30% to 58%.<sup>8,9</sup>

Although improvements in survival of patients with metastatic CRC and in hepatic resectability rates were promising, the era of molecular targets introduced new ways to manage CRC, turning it from an incurable disease to a chronic disease for many patients. The most exciting breakthrough undoubtedly occurred in 2003 when the first anti-angiogenic agent, the recombinant humanized monoclonal antibody bevacizumab, was shown to improve survival in combination with chemotherapy by binding vascular

#### TAKE-HOME POINTS

- CRC screening is essential for those older than 50 years and for younger persons at increased risk, to prevent or provide for earlier diagnosis.
- More effective treatment options are available to patients with CRC whether their disease is diagnosed at an earlier stage (localized) or when more advanced (metastatic).
- Several new chemotherapy options are available for treatment of metastatic disease, resulting in longer survival not yet fully recognized in existing data.
- Individualized therapies may be increasingly available to patients, resulting in increasing efficacy, reduced side effects, and cost containment.
- The United States will see a rapid increase in cancer survivors, including those with active disease and those cured following extensive therapy, with the need for all health care providers to stay abreast of the needs of this unique population.

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endothelial growth factor.<sup>10</sup> By February 2004, bevacizumab had received fast-track approval by the FDA.

During the same month, another molecular targeted agent, cetuximab, a monoclonal antibody to epithelial growth factor receptor (EGFR), was approved. Unlike bevacizumab, cetuximab has some modest activity when used alone, but it is more effective when combined with chemotherapy.<sup>11</sup> Most recently, in February 2006, an additional monoclonal antibody to EGFR, panitumumab, was approved for use as a single agent to treat CRC that had progressed on chemotherapy.<sup>12</sup>

Since 2004, much work has been done to determine the best combinations and sequence in which to use these various agents. Questions still remain, but there is a clear consensus that utilization of all agents over time in various combinations results in prolonged survival of CRC patients. With the development of more effective drugs for metastatic CRC, the role of surgical resection is changing, and further improvement of resectability rates and 5-year survival rates with the addition of targeted therapies are still being realized.<sup>13</sup> There has also been progress in diagnostic imaging, interventional radiology, radiation oncology, and surgical oncology that allows for more appropriate selection of patients and more effective treatment options.

The development of more treatment options will increase the importance of identifying which are most effective while limiting the risk of side effects and controlling cost. Researchers have found that when patients with a mutant form of the gene *KRAS* are treated with cetuximab or panitumumab, the benefit is no greater than if they were treated with chemotherapy alone.<sup>14</sup> *KRAS* testing is now recommended for all tumors to determine if these anti-EGFR antibodies should be used, as a means of *personalizing* cancer care while reducing costs.<sup>15,16</sup> Enhanced options invite new challenges to develop effective treatment strategies that improve odds of cure and, when cure is not possible, prolong survival while maintaining quality of life.

### ►PREVENTION IS STILL THE BEST MEDICINE

As exciting as these advances are, we know that prevention (and early detection) of CRC is the best medicine. From 1987 to 2005, CRC screening doubled to nearly 50% for those older than 50 years, with most of the increase occurring after 2000. On January 1, 1998, Medicare began reimbursing for screening colonoscopies, likely impacting the availability of this technique to reduce CRC incidence while also resulting in earlier diagnosis. Since 5-year overall survival rates are significantly better for those patients whose disease is diagnosed at an early stage (more than 90% for stage I disease), increased rates of screening should also impact survival for those with CRC. Incidence rates have declined nearly 25% since 1985,<sup>2</sup> presumably a result of the increase in CRC screening noted during the same time period. Further improvements in cancer screening rates for CRC are clearly needed.

Presently, cancer care in the United States is predominately addressed by specialists, including medical oncologists. However, with cancer affecting approximately 40% of the US population and the prediction that cancer will become the primary cause of death worldwide by 2010, new models of care will be needed. In addition, there will be an estimated 20 million cancer survivors in this country by 2020 (the current number of CRC survivors is 1 million). Therefore, we can no longer think of cancer as a disease that can simply be referred to specialists. It is essential that all health care providers, particularly those in primary care, remain apprised of trends in diagnosis and treatment and understand the unique needs of cancer survivors. **JAAPA**

### DRUGS MENTIONED

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|-----------------------|------------------------|
| Bevacizumab (Avastin) | Irinotecan (Camptosar) |
| Capecitabine (Xeloda) | Oxaliplatin (Eloxatin) |
| Cetuximab (Erbix)     | Panitumumab (Vectibix) |
| 5-Fluorouracil        |                        |

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