Advances in the Treatment of Metastatic Colorectal Cancer

RICHARD M. GOLDBERG

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Key Words. Colorectal cancer • Metastatic • Irinotecan • Oxaliplatin • Fluorouracil • Bevacizumab • Quality of life

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify the advantages and disadvantages of the various chemotherapeutic regimens used to treat metastatic colorectal cancer.
2. Discuss the emerging role of new agents for the treatment of metastatic colorectal cancer.
3. Discuss the current status of trials of new combination therapies in the treatment of metastatic colorectal cancer.

ABSTRACT

The overall 5-year survival rate for patients with metastatic colorectal cancer (CRC) is less than 10%. Median survival with 5-fluorouracil (5-FU)/leucovorin (LV) therapy is approximately 12 months. Recent additions to the chemotherapy armamentarium for this disease have begun to prolong median survival times. In trials in which patients are exposed to all three approved chemotherapy agents, oxaliplatin, irinotecan, and 5-FU/LV, or capecitabine during the course of their disease, median survival has reached 20 months. The addition of oxaliplatin and irinotecan to 5-FU/LV regimens has also led to the maintenance of quality of life for longer intervals than were traditionally observed with 5-FU/LV alone. Current standard first-line regimens for metastatic CRC are FOLFOX (infusional 5-FU/LV with oxaliplatin) and FOLFIRI (infusional 5-FU/LV with irinotecan). The addition of bevacizumab to a two-drug regimen (irinotecan with 5-FU/LV) prolongs median survival to 20 months, with a modest amount of additional toxicity. Improvements in this median survival have not yet been realized with modifications to the current standard regimens; however, the oral agent capecitabine appears to be a reasonable substitute for infusional 5-FU/LV in combination regimens or as a single agent, with the advantage of reducing the inconvenience of the long infusion time. Ongoing investigations will identify a place for capecitabine, epidermal growth factor inhibitors, and new cytotoxics in the treatment of metastatic CRC. The Oncologist 2005;10(suppl 3):40–48

INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer in both men and women and accounts for 10% of all new cancer cases and cancer deaths [1]. Upon diagnosis, 19% of CRC cases are metastatic, and while the overall 5-year survival rate for patients with CRC is 63%, the rate drops to 10% or less in patients with metastatic disease [1].
5-Fluorouracil (5-FU) was introduced in 1957 and became a backbone of therapy for CRC. Subsequently, the addition of the biomodulator leucovorin (LV) was shown to improve outcomes [2]. Until recently, 5-FU/LV regimens were the standard of care, producing median survival times of approximately 12 months as first-line therapy for advanced CRC [3]. Starting in the mid-1990s, new cytotoxic chemotherapeutic agents became available that showed efficacy in CRC. In 1996, irinotecan (Camptosar®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com), a topoisomerase-I inhibitor, was introduced. Diarrhea and neutropenia are the most common grade 3–4 toxicities associated with this agent. In 1998, capecitabine (Xeloda®; Hoffmann-La Roche Inc., Nutley, NJ, http://www.rocheusa.com) was made available. This agent is an oral prodrug that is ultimately converted to 5-FU. Capecitabine mimics infusional 5-FU pharmacokinetics directed to the tumor and is associated with less neutropenia but a higher incidence of hand-foot syndrome than infusional 5-FU [4–6]. Finally, the platinum-based agent oxaliplatin (Eloxatin®; Sanofi-Synthelabo, Inc., New York, http://www.sanofi-synthelabo.us) was introduced in 2002; neuropathy and neutropenia are the most common toxicities associated with this agent.

New combination chemotherapy regimens designed with oxaliplatin and irinotecan have resulted in longer median survival times [7, 8]. This article reviews the current treatments and future directions in the management of metastatic CRC.

**Developing the Current Standard of Care**

With the availability of new effective agents for CRC came a host of new combination chemotherapy regimens, detailed in Table 1 unless otherwise specified [7–20]. Three key trials were conducted in metastatic CRC and published in 2000 [9–11]. Based on these trials, the irinotecan–5-FU/LV (IFL) regimen became the standard of care in the U.S. as a result of its significant albeit modest superiority over 5-FU/LV in terms of important clinical end points. Patients in a trial conducted by Saltz et al. [10] received bolus 5-FU/LV either alone or combined with irinotecan (IFL). Compared with 5-FU/LV alone, patients receiving IFL had longer overall survival (median, 14.8 months vs. 12.6 months; \( p = .04 \)) and progression-free survival (PFS) (median, 7 months vs. 4.3 months; \( p = .004 \)) times [10]. Similarly, in a trial reported by Douillard et al. [9], patients received bolus and infusional 5-FU/LV alone or with irinotecan (Douillard regimen). Those receiving the Douillard regimen had a longer overall survival time (median, 17.4 months vs. 14.1 months; \( p = .03 \)), longer time to progression (TTP) (median, 6.7 months vs. 4.4 months; \( p < .001 \)), and higher response rate (35% vs. 22%; \( p < .005 \)) than those receiving 5-FU/LV alone [9]. The third key trial reported during the same year compared 5-FU/LV with the same regimen with the addition of oxaliplatin [11]. This oxaliplatin-based regimen is now known as FOLFOX4. Compared with 5-FU/LV, FOLFOX4 provided a longer PFS time (median, 9 months vs. 6.2 months; \( p = .0003 \)) and higher overall response rate (50.7% vs. 22.3%; \( p = .0001 \)) than 5-FU/LV, but the longer survival time in the FOLFOX4 group did not reach statistical significance (median, 16.2 months vs. 14.7 months; \( p = .12 \)) [11]. Although a subsequent study did establish a survival advantage for oxaliplatin when added to 5-FU/LV [14], the results of these three key trials were considered by the Oncologic Drug Advisory Committee (ODAC) of the U.S. Food and Drug Administration (FDA) and led to the recommendation that IFL become the preferred and reference regimen for first-line therapy of advanced disease in 2000.

The role of IFL, however, was challenged in the N9741 intergroup trial [7]. That trial, the results of which were published in 2004, compared IFL with FOLFOX4 and with IROX (irinotecan plus oxaliplatin). Compared with IFL patients, patients on FOLFOX4 had a significantly longer TTP (median, 8.7 months vs. 6.9 months; \( p = .001 \)), overall survival time (19.5 months vs. 15 months; \( p = .0001 \)), and greater response rate (45% vs. 31%; \( p = .002 \)). Survival with IROX was intermediate (17.4 months; \( p = .04 \) vs. IFL). It should be emphasized here that the IFL regimen employs a bolus 5-FU/LV schedule. While continuous infusion 5-FU/LV alone, compared with bolus 5-FU/LV, was known to confer benefits in terms of toxicity and survival [3], these benefits were modest, and the inconvenience of an ambulatory pump led to the bolus regimen being preferred in the U.S. However, the results of the N9741 trial demonstrate that bolus 5-FU/LV in the combination setting is associated with additional toxicity. That trial led to both FDA approval of the FOLFOX regimen as indicated for the treatment of metastatic CRC and to a widespread adoption of this regimen as the preferred first-line treatment for patients with metastatic CRC in the U.S.

Also presented in 2004 were the results of a crossover trial that evaluated sequential FOLFOX6 followed by infusional 5-FU/LV with irinotecan (FOLFIRI) or the reverse sequence [8]. In that trial, patients who progressed on one regimen were then transferred to the alternate regimen. Although not the primary end point of the study, the results of each regimen as first-line therapy suggest that no difference exists between the two regimens in terms of efficacy. Response rates for FOLFIRI and FOLFOX6 were 56% and 54%, respectively, while median PFS times were 8.5 months...
Table 1. Components of chemotherapy regimens used in colorectal cancer

<table>
<thead>
<tr>
<th>Regimen name and frequency</th>
<th>Saltz 5-FU/LV (bolus)</th>
<th>de Gramont - A 5-FU/LV (infusional)</th>
<th>de Gramont - B 5-FU/LV (infusional)</th>
<th>AIO 5-FU/LV infusional</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Capcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douillard regimen [9], every 2 weeks</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFL [8, 10], weekly × 4 every 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX4 [8, 11], every 2 weeks</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX6 [8, 12], every 2 weeks</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI [8], every 2 weeks</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUFOX [13–14], weekly × 4 every 5 weeks</td>
<td>X</td>
<td>(5-FU; 2,000)</td>
<td></td>
<td></td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUFOXIRI [15], weekly × 4 every 5 weeks</td>
<td>X</td>
<td>(5-FU; 2,000)</td>
<td></td>
<td></td>
<td>50</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>FAFOXIRI [16], every 4 weeks</td>
<td>X (modified, see text)</td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td>125</td>
<td>days 1 and 8</td>
</tr>
<tr>
<td>XELOX [12, 17–18], every 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>130</td>
<td></td>
<td>days 1–14</td>
</tr>
<tr>
<td>CAPOX [13, 19], every 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
<td></td>
<td>days 1 and 8</td>
</tr>
<tr>
<td>XELIRI [20], every 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>240</td>
<td></td>
<td>days 1–14</td>
</tr>
<tr>
<td>CAPIRI [19], every 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td></td>
<td>days 1 and 8</td>
</tr>
<tr>
<td>IROX [7], every 3 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

*All doses in mg/m^2*.

*Saltz: LV, 20 on day 1; 5-FU, 500 on day 1, weekly.*
*De Gramont-A: LV, 200 on days 1 and 2; 5-FU, 400 bolus, 600 over 22 hours on days 1 and 2, biweekly.*
*De Gramont-B: LV, 200 or 400 on day 1; 5-FU, 400 bolus, 2,400–3,000 over 48 hours on day 2, biweekly.*
*AIO: LV, 500; 5-FU, 2,300 over 24 hours, weekly.*

Abbreviations: BID, twice a day; 5-FU, 5-fluorouracil; LV, leucovorin.
three drugs at some point during the course of their disease (Table 2) [7–11, 14, 21–23].

Most recently, the role of sequential single agents was compared with initial combination therapy in a large, randomized trial of five treatment arms in the United Kingdom (the FOCUS trial; Fig. 1) [22]. In that trial, only the difference between the combination of 5-FU/LV with irinotecan (arm C-Iri) and sequential 5-FU/LV and irinotecan (arm A) approached statistical significance in favor of the combination ($p = .04$; the significance level for the trial was set at $0.01$). However, toxicities were greater with the combination, and quality of life was not better despite superior response rates and longer PFS. The median survival times in the trial were low, all below 17 months, which may be explained by two factors. First, patients who were eligible for liver resection and downstaging were not eligible. Second, a low percentage of patients in each arm received salvage therapy with a third agent (14% of those in the sequential arms and 26% of those in the combination arms).

From these data, the following conclusions can be made. First, exposure to all three active agents during the course of disease improves survival to the current benchmark of approximately 20 months. Second, the use of sequential therapy versus first-line combination therapy yields similar survival times and poorer response rates and PFS times but less toxicity and a similar quality of life. While subject to the hazards of cross-study comparison, the fact that patients in the Tournigand et al. [8] trial had a median survival duration exceeding 20 months and those in the FOCUS trial had a median survival time of 17 months suggests that combination therapy should remain the first-line standard of care. Finally, first-line combination regimens that use oxaliplatin rather than irinotecan are similar in efficacy in the setting of advanced disease. Specifically, while FOLFOX4 is superior to bolus IFL, FOLFIRI is likely equivalent in efficacy to FOLFOX6 and hence, FOLFOX or FOLFIRI are both currently considered acceptable first-line treatment strategies for metastatic CRC.

Given the relative similarity in outcomes between the FOLFOX and FOLFIRI regimens, the initial choice is largely governed by patient and physician preference. Differential toxicities between the two were observed in the trial by Tournigand et al. [8] and are important considerations (Table 3). In general, neurotoxicity, neutropenia, and thrombocytopenia were more frequent with FOLFOX6, while febrile neutropenia, nausea/vomiting, mucositis, alopecia, and fatigue were more frequent with FOLFIRI. A decision based on overall severity of toxicity is difficult. Grade 3–4 toxicities were more common with FOLFOX6 (74% vs. 53% of patients; $p = .001$); however, serious adverse events were more frequent with FOLFIRI (14% vs. 5% of patients; $p = .03$).

An important additional consideration when choosing an initial regimen is the inclusion of the anti–vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com). In the pivotal trial that compared IFL alone with IFL plus bevacizumab, the median survival time

### Table 2. Survival according to the percentage of patients receiving both oxaliplatin and irinotecan in addition to 5-Fluorouracil

<table>
<thead>
<tr>
<th>Trial</th>
<th>Percentage of patients on three drugs</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltz et al. [10]</td>
<td>5%</td>
<td>14.8</td>
</tr>
<tr>
<td>Seymour [22]</td>
<td>12%</td>
<td>14.8</td>
</tr>
<tr>
<td>Seymour [22]</td>
<td>13%</td>
<td>13.9</td>
</tr>
<tr>
<td>Seymour [22]</td>
<td>17%</td>
<td>15.2</td>
</tr>
<tr>
<td>Douillard et al. [9]</td>
<td>16%</td>
<td>17.4</td>
</tr>
<tr>
<td>Goldberg et al. [7]</td>
<td>24%</td>
<td>14.8</td>
</tr>
<tr>
<td>Seymour [22]</td>
<td>26%</td>
<td>15.2</td>
</tr>
<tr>
<td>Seymour [22]</td>
<td>27%</td>
<td>16.3</td>
</tr>
<tr>
<td>de Gramont et al. [11]</td>
<td>30%</td>
<td>16.2</td>
</tr>
<tr>
<td>Grotthey et al. [14]</td>
<td>31%</td>
<td>16.1</td>
</tr>
<tr>
<td>Goldberg et al. [7]</td>
<td>50%</td>
<td>17.4</td>
</tr>
<tr>
<td>Kohne et al. [23]</td>
<td>54%</td>
<td>20.1</td>
</tr>
<tr>
<td>Goldberg et al. [7]</td>
<td>60%</td>
<td>19.5</td>
</tr>
<tr>
<td>Tournigand et al. [8]</td>
<td>62%</td>
<td>20.6</td>
</tr>
<tr>
<td>Grotthey et al. [14]</td>
<td>68%</td>
<td>19.7</td>
</tr>
<tr>
<td>Tournigand et al. [8]</td>
<td>74%</td>
<td>21.5</td>
</tr>
</tbody>
</table>

Duplicate entries indicate different arms of the study.

### Figure 1. Trial schema and median survival times in the FOCUS trial that compared sequential therapy with combination therapy for metastatic colorectal cancer. Abbreviations: 5-FU, 5-Fluorouracil; Iri, irinotecan; LV, leucovorin; Ox, oxaliplatin. From [22].
in the bevacizumab arm was 20.3 months, consistent with results found with exposure to three active cytotoxic agents [24]. This median survival time was longer than that experienced by patients receiving IFL alone (15.6 months), and the difference in overall survival was significant. The longer survival time was achieved with modest additional toxicities.

**IMPROVING THE CURRENT STANDARD OF CARE**

Subsequent investigations seek to improve outcomes, tolerability, and convenience of the current standard regimens. One strategy is to replace 5-FU with the oral agent, capecitabine. The efficacy of capecitabine combined with either irinotecan (XELIRI) or oxaliplatin (XELOX) has been demonstrated in a multitude of phase II trials, with response rates of 55% (XELOX) and 44% (XELIRI) and median TTP of 7.6 months (XELOX) and 6.7 months (XELIRI) [17, 20]. A phase III comparison trial of the two similar regimens, CAPOX and CAPIRI, is under way [19]. Trials comparing capecitabine with 5-FU–containing regimens with either oxaliplatin or irinotecan are also ongoing. A preliminary safety analysis of a trial comparing XELOX with FOLFOX6 showed more grade 1–2 hand-foot syndrome with XELOX, but less grade 3–4 neutropenia, stomatitis, neuropathy, and parasthesias [12]. Preliminary results from two separate trials comparing capecitabine plus oxaliplatin with 5-FU plus oxaliplatin suggest that the regimens are comparable in efficacy and toxicity with response rates of 47%–54% [13, 18]. Results of one trial were mature enough to report median survival times, which were 16.3 months with CAPOX and 17.2 months with 5-FU/LV plus oxaliplatin (FUFOX) [13]. A trial that was to evaluate capecitabine or 5-FU with irinotecan (XELIRI [250 mg/m^2 of irinotecan] versus the Douillard regimen) with or without celecoxib (Celebrex®; Pfizer Pharmaceuticals, New York, http://www.pfizer.com) was stopped early because of excess deaths in the XELIRI arm [25]. A new trial will evaluate reduced-dose XELIRI versus the Douillard regimen, with bevacizumab added to each arm. Hence, the role of capecitabine is still under investigation, but preliminary data suggest that it can be substituted for 5-FU in oxaliplatin-containing regimens with similar efficacy and comparable tolerability.

Two unique regimens were compared in the FIRE trial by Schalhorn et al. [26]. That study investigated irinotecan plus oxaliplatin versus 5-FU plus irinotecan with regimens that differ from the IROX regimen used in the N9741 trial and the FOLFIRI regimen used in the Tournigand et al. [8] study. The 5-FU/LV dosing was the same as the FUXOIR regimen, with irinotecan at a dose of 80 mg/m^2 weekly for 6 weeks. In the irinotecan–oxaliplatin arm, the regimen was irinotecan (80 mg/m^2) weekly for 6 weeks and oxaliplatin (85 mg/m^2) on days 1, 15, and 29. This large, multicenter trial demonstrated similar median survival times in the two arms (19.3 months with irinotecan plus oxaliplatin vs. 21.5 months with 5-FU plus irinotecan) and comparable toxicity, although delayed diarrhea, neurotoxicity, leukopenia, and thrombocytopenia occurred more frequently in the irinotecan–oxaliplatin arm. Although disease control rates were greater in the 5-FU–irinotecan arm, PFS was not significantly different between arms (8.2 months for 5-FU plus irinotecan vs. 7 months for irinotecan plus oxaliplatin).

Finally, in order to decrease the toxicity associated with using 5-FU/LV, oxaliplatin, and irinotecan together, other triplet regimens have been tested. A weekly regimen was evaluated in 14 patients (FUFeroxIRI) [15]. The overall response rate was 58%, median PFS was 8.5 months, and median survival time was 15.5 months. No grade 4 toxicities occurred, but over half the patients required dose reductions. A sequential regimen of irinotecan and 5-FU/LV followed by oxaliplatin (FAFOXIRI) was evaluated in 52 patients. The overall response rate was 48%, and the median TTP was 10.3 months [16]. Therapy was very well tolerated, with grade 3 neutropenia in 6% and no therapy discontinuations for adverse events. It is likely that new agents will be required to further improve outcomes in metastatic CRC.

**NEWER AGENTS**

Newer agents for the treatment of metastatic CRC can broadly be categorized into three classes: anti-VEGF agents, anti-epidermal growth factor (EGF) agents, and new cytotoxic agents. The only commercially available anti-VEGF agent is bevacizumab. Thus far, this is the only newer agent to demonstrate a survival advantage in metastatic CRC.
Bevacizumab
As noted earlier, the addition of bevacizumab to IFL produced a median survival time comparable with that achieved with three active cytotoxics, with minimal additional toxicity [24]. Additional trials are under way to evaluate bevacizumab with other cytotoxic combinations. When bevacizumab was added to reduced-dose XELOX (oxaliplatin, 85 mg/m², and capecitabine on days 1–5 and 8–12 only), the median TTP reached 11.9 months in a preliminary analysis [27]. When added to each of several oxaliplatin-containing regimens (in combination with either 5-FU/LV or capecitabine), bevacizumab produced greater response rates than those reported with the regimens alone; the analysis of that trial was too early to provide a comparison of median TTP or survival [28]. In both these trials, dose reduction of capecitabine to 850 mg twice daily was required to reduce diarrhea and hand-foot syndrome. An ongoing trial is evaluating the addition of bevacizumab to each of two irinotecan plus 5-FU/LV regimens [29]. Further investigations are required to determine the optimal use of bevacizumab with the current standard regimens. However, it is clear that the antiangiogenic strategy is beneficial in advanced CRC.

Anti-EGF Agents
The EGF-targeted agents have thus far primarily been studied in the setting of therapy for patients with disease that is refractory to one or more lines of chemotherapy. Available first-line trials are nonrandomized and include cetuximab (Erbitux®; Imclone Systems, Inc., New York, http://www.imclone.com), an anti-EGF monoclonal antibody, with FOLFOX4 [30] and gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE, http://www.astrazeneca-us.com), an anti-EGF receptor tyrosine kinase inhibitor, with FOLFOX4 [31] or a modified FOLFOX6 regimen [32]. The combination of cetuximab and FOLFOX4 yielded a response rate of 72% and a median PFS time of 10.2 months [30]. Gefitinib with FOLFOX4 yielded a response rate of 78% and, with modified FOLFOX6, a response rate of 74%; however, survival data with the gefitinib trials were immature at the time of presentation [31, 32].

In the salvage setting, trials of EGF inhibitors as monotherapy have shown response rates of 8%–11% and median TTP of 1.5–2.5 months [33–35]. Only one randomized phase II trial has been completed, which evaluated cetuximab versus cetuximab and irinotecan in irinotecan-refractory disease [33]. That trial demonstrated a response rate of 23% with the combination, versus 11% with cetuximab alone (p = .007). TTP was significantly longer in the combination group as well (median, 4.1 months vs. 1.5 months; p < .001). Some have criticized the application of p values to this analysis (Erlichman and Sargent in the editorial that accompanied the paper). However, that trial did not answer the important question of how effective the addition of cetuximab is compared with irinotecan alone, a study that is currently ongoing [36]. The incidences of grade 3–4 toxicities with cetuximab are low, consisting primarily of dyspnea and asthenia [33]. Approximately 80% of patients develop an acne-like rash characteristic of EGF blockade, but the majority are grade 1–2 in severity [33]. There is also a low incidence of severe but potentially life-threatening anaphylactic reactions to this murine monoclonal antibody.

Given the relatively low toxicities of bevacizumab and cetuximab and their differing mechanisms of action, an intriguing strategy is to combine them. Such a study was conducted in irinotecan-refractory patients [37]. In this comparison of cetuximab, bevacizumab, and irinotecan (CBI) versus cetuximab and bevacizumab (CB) alone, the response rate and median TTP in the CBI arm were impressive for this population of patients with chemotherapy-refractory tumors (37% and 7.9 months, respectively). The trial included only bevacizumab-naïve patients. Because of the large number of patients now receiving bevacizumab, subsequent investigations will evaluate this combination in patients who have manifested progression of disease while receiving both chemotherapy and bevacizumab. It is also uncertain whether these patients have disease that is resistant to or remains sensitive to continued exposure to bevacizumab [37].

Cytotoxics
Several new cytotoxics have shown activity in metastatic CRC. These agents include pemetrexed (Alimta®; Eli Lilly and Company, Indianapolis, http://www.lilly.com), edotecarin (Pfizer Pharmaceuticals), and members of a newer class of nontaxane microtubule-stabilizing agents called epothilones. Thus far, data indicate that these agents will not replace the current standard of care, but studies have provided some intriguing results nonetheless.

Pemetrexed is a multitargeted antifolate that inhibits thymidylate synthase, among other folate-dependent enzymes involved in nucleotide synthesis. Three phase II trials in metastatic CRC have been reported. As first-line monotherapy at a dose of 500 mg/m² every 21 days, the response rate was 17% and median TTP was 3.3 months [38]. As first- or second-line monotherapy at a dose of 600 mg/m² every 21 days, the response rate was 15%, median TTP was 4.4 months, and median survival time was 16.2 months [39]. That trial was encouraging; however, 55% of patients experienced grade 3–4 neutropenia. It is possible that vitamin supplementation (B₁₂ and folic acid) could have attenuated the hematologic toxicity, as was noted in a mesothelioma study [40]. Finally, as first-line therapy...
(500 mg/m²) in combination with oxaliplatin (120 mg/m²), the response rate was 23% (TTP was not reported), and 23% of patients experienced grade 3–4 neutropenia [41]. This response rate is low compared with that of FOLFOX/FOLFIRI; however, vitamin supplementation was not employed, which was associated with better outcomes in the mesothelioma study [40].

Edotecarin is a novel synthetic indolocarbazole topoisomerase-I inhibitor that was evaluated in a phase II trial of second-line therapy in patients who were irinotecan-naïve [42]. The overall response rate was 13% and median TTP was an encouraging 7.1 months. Importantly, toxicity was favorable, with relatively low incidences of grade 3 diarrhea (4%) and grade 3–4 vomiting (17%) and neutropenia (21%). A conversation with Mark Gelder, Pfizer Pharmaceuticals, Inc. (2005), revealed that clinical development of this agent, however, has been suspended.

The epothilone class currently includes two compounds that have undergone phase II testing in CRC: epothilone B (EPO906) and ixabepilone (BMS-247550), an epothilone B analogue. Modest activity was shown in two trials of epothilone B, with response rates of 2% and 7% in refractory patients receiving the drug as second- or third-line therapy at two different dose schedules (2.5 mg/m² weekly for 3 weeks, followed by 1 week of rest, or 6 mg/m² every 3 weeks) [43]. Stable disease occurred in 13% and 2%, respectively. Similarly, a trial of ixabepilone in patients refractory to IFL showed no responses [44]. However, disease stabilization occurred in 56%. The median TTP was 11 weeks. The toxicity differs between the two agents, with epothilone B causing more diarrhea (29% grade 3–4) and ixabepilone causing more grade 3–4 neutropenia (48%) and peripheral neuropathy (20%) [43, 44].

Quality of Life

Although an important consideration, particularly in metastatic disease, few trials have evaluated quality-of-life end points. Of those studies that have, it appears that the addition of oxaliplatin and irinotecan to 5-FU/LV regimens leads to improvements in the maintenance of quality of life, as measured using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30). In comparison with 5-FU/LV alone, FOLFOX4 produced similar median quality of life scores; however, the time to 20% and 40% deterioration in global health status was significantly longer with FOLFOX4 (p = .004 and p = .0004, respectively) [11]. Similarly, the addition of irinotecan to 5-FU/LV resulted in a longer time to 40% deterioration (p = .04) [9]. When IFL was compared with 5-FU/LV or irinotecan alone, no significant difference occurred in the mean change-from-baseline scores [10]. However, on univariate analysis, there was a significantly smaller increase in the severity of fatigue, anorexia, pain, and function with IFL compared with the single-drug regimens (p < .05). Although the addition of bevacizumab to 5-FU/LV produced a significantly longer time to deterioration in quality of life as measured by the Functional Assessment of Cancer Therapy-Colorectal score (p = .02) and Trial Outcome Index (p = .048), no difference in time to deterioration was observed when bevacizumab was added to IFL in the phase III pivotal trial [45]. Finally, a noncomparative study of capecitabine monotherapy demonstrated improved or maintained quality of life in at least 60% of the patients in most domains, as measured by the EORTC QLQ C-30 and CR-38 questionnaires [46]. However, whether the replacement of 5-FU/LV with capecitabine in standard regimens improves quality of life has not been answered.

Summary

The modern era of chemotherapy for metastatic CRC involves FOLFOX or FOLFIRI as standard first-line regimens. Median survival has been improved to approximately 20 months with exposure to three active drugs (5-FU/LV, irinotecan, and oxaliplatin) during the entire course of disease as well as through the addition of bevacizumab, the latter contributing modest additional significant toxicity. The addition of oxaliplatin and irinotecan to 5-FU/LV regimens has also led to improvements in the maintenance of quality of life, with a longer median survival time than with single-agent therapy. Ongoing investigations seek to identify the optimal doses and schedules of current regimens and to incorporate new targeted agents and cytotoxics to further improve outcomes in metastatic CRC.

Disclosure of Potential Conflicts of Interest

Dr. Goldberg has acted as a consultant for Amgen, Pfizer, AstraZeneca, sanofi-aventis, and Genentech; performed contract work for sanofi-aventis, Pfizer, and Amgen; and has received support from sanofi-aventis.
REFERENCES


12 Seymour MT. Fluorouracil, oxaliplatin and CPT-11 (irinotecan), use and sequencing (MRC FOCUS): a 2135-patient randomized trial in advanced colorectal cancer (ACRC). J Clin Oncol 2005;23:252s. (Updated based on presentation.)


16 Schmoll H, Kubicka S, Schmid D et al. Randomized trial of capcitabine plus oxaliplatin (CapeOx) vs. infusional 5-FU/LV or oxaliplatin (FOLFOX-6) in stage II/III colon cancer. Proc ASCO 2005;24:45A. (Updated based on presentation.)

17 Harb A, Peinert S, Grothey A et al. Weekly administration of 5-fluorouracil (5-FU), folinic acid (FA), oxaliplatin (L-OHP) and irinotecan (CPT-11) (FOLFIRI) for patients with metastatic gastric or colorectal cancer. J Clin Oncol 2005;23:300s. (Updated based on presentation.)


19 Hochster HS, Harris JR, Wu K et al. Phase III trial of oral capcitabine for metastatic colorectal cancer: results of the randomized, placebo-controlled, multicenter CA06009 study. J Clin Oncol 2006;24:531s. (Updated based on presentation.)


21 Diaz-Rubio ED, Tabernero J, van Cutsem E et al. Erbitux in combination with oxaliplatin/5-fluorouracil (5-FU)/folinic acid (FA) (FOLFIRI) and irinotecan in the first-line treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer: an international phase II study. J Clin Oncol 2005;23:254s. (Updated based on presentation.)


35 Malik I, Hecht JR, Patnaik A et al. Safety and efficacy of panitumumab monotherapy in patients with metastatic colorectal cancer (mCRC). J Clin Oncol 2005;23:251s. (Updated based on presentation.)


45 Chawla A, Kabbinavar F, Holmgren E et al. Quality of life (QoL) impact of bevacizumab (BV) when combined with irinotecan + 5-FU/leucovorin (IFL) and 5-FU/leucovorin (FL) for metastatic colorectal cancer (mCRC). J Clin Oncol 2005;23:262s. (Updated based on presentation.)