New Advances in the Chemotherapy of Metastatic Colorectal Cancer

a report by
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Introduction

Colorectal cancer (CRC) is a major public health problem in the US.[1] In terms of cancer-related mortality in the US, CRC ranks second only to lung cancer. In 2004, an estimated 147,500 new cases of CRC are expected to occur in the US, and about 57,000 patients will die of the disease.[2] Worldwide, nearly 800,000 new cases are diagnosed each year, resulting in approximately 500,000 annual deaths.

Chemotherapy for Advanced CRC

When advanced metastatic disease (stage IV) is diagnosed, the prognosis is poor with five-year survival in the 5% to 8% range. This survival rate has remained essentially unchanged over the past 35–40 years. However, over the past five years, significant advances have been made in the treatment options for this disease, such that dramatic improvements in two-year survival are now being observed. Chemotherapy is generally considered the standard treatment approach for patients with advanced CRC. The three main agents used in the systemic treatment of CRC include a fluoropyrimidine, either 5-fluorouracil (5-FU) or capecitabine, irinotecan, and oxaliplatin. It is now well-established that clinical efficacy is improved with the use of combination therapy, and studies are now in progress to determine the optimal sequencing of these combination regimens.

5-Fluorouracil

5-Fluorouracil (5-FU) is a fluoropyrimidine analog that is inactive in its parent form, and requires metabolic activation to generate the active metabolites responsible for cytotoxicity. The cytotoxic metabolites of 5-FU are incorporated into ribonucleic acid (RNA) and DNA, respectively, and they interfere with the processes of RNA and DNA biosynthesis. In addition, the 5-FU metabolite, FdUMP, is a potent inhibitor of *de novo* thymidylate synthesis, and inhibition of this process causes an eventual loss of thymidine triphosphate, which is a necessary constituent for DNA synthesis.

For nearly 40 years, 5-FU was the only active chemotherapy available to treat advanced CRC in the first-line setting.[4] However, response rates to 5-FU in patients with advanced disease were generally in the 10% to 15% range. To improve the clinical efficacy of 5-FU, the addition of certain biomodulation agents such as the reduced folate leucovorin (LV) and/or a change in the schedule of administration of 5-FU from bolus to continuous infusion were investigated.[5,6] While response rates have significantly increased with these maneuvers, overall survival has not been substantively altered.

Capecitabine

Capecitabine is a third-generation oral prodrug of 5-FU that was rationally designed to closely simulate infusional administration of 5-FU.[7] It is rapidly and nearly completely absorbed from the intestine and is then activated by a series of three enzymatic steps to generate 5-FU and its cytotoxic metabolites. The unique localization of activating enzymes results in the selective generation of 5-FU in tumor cells after the oral administration of capecitabine, and this fact has been confirmed in preclinical human cancer xenograft models and in patients with CRC.[8,9]

A randomized Phase II study of patients with advanced CRC helped to establish the efficacy and safety of capecitabine and identified the most appropriate monotherapy regimen for evaluation in Phase III trials.[10] The optimal regimen was shown to be an oral dose of 1,250mg/m^2 twice-daily (bid) for 14 days, followed by a seven-day rest period. This dosing regimen was subsequently used in two randomized Phase III trials comparing capecitabine with bolus 5-FU/LV (Mayo Clinic regimen).[11,12] Both Phase III studies showed that capecitabine significantly increased overall response rates in comparison with bolus 5-FU/LV, with equivalent median overall survival and time to tumor progression. Of note, the incidence of diarrhea, stomatitis, nausea, alopecia, and grade 3/4 neutropenia was significantly lower in patients treated with capecitabine, whereas the incidence of hand–foot syndrome was higher. Treatment with capecitabine also resulted in a reduced incidence of hospitalizations for adverse events in comparison with treatment with bolus 5-FU/LV. An integrated analysis revealed that the response rate was significantly greater with capecitabine than with 5-FU/LV (25.7% versus

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16.7%; P<0.0002), while secondary measures of time-to-tumor progression (TTP) and survival were equivalent.[13]

Irinotecan

Irinotecan is a semisynthetic derivative of camptothecin, a natural alkaloid first extracted from the *Camptotheca acuminata* tree. Irinotecan is a member of the TOP-I inhibitor class of antineoplastic compounds.[14] TOP-I is an enzyme that interacts with DNA and facilitates DNA recombination, replication, and transcription by catalyzing the formation of a transient single-stranded DNA break, thereby allowing the torsionally strained DNA duplex to relax, separate, and reanneal.[14,15] Irinotecan is converted *in vivo* to its active metabolite, SN-38, by a carboxylesterase enzyme in the liver. This metabolite forms a stable, covalent complex with DNA and TOP-I, which then interrupts the breakage–reunion cycle associated with TOP-I activity – a process that eventually leads to cell death.

Second-line Monotherapy

The efficacy of irinotecan as second-line monotherapy in patients with metastatic CRC was established in two randomized Phase III clinical trials conducted in Europe. Cunningham et al reported that treatment with irinotecan and supportive care resulted in significantly greater overall survival than supportive care alone in patients who progressed while on 5-FU therapy or who progressed within six months after the last 5-FU infusion (one-year survival with irinotecan of 36.2% versus 13.8% with supportive care only; P=0.0001).[16] Patients in the irinotecan group did significantly better in terms of survival without performance status deterioration (P=0.0001), survival without weight loss of more than 5% (P=0.018), and pain-free survival (P=0.003). Rougier et al compared treatment with irinotecan or continuous infusion of 5-FU in patients with metastatic CRC whose disease had progressed while they were on first-line bolus 5-FU therapy.[17] Irinotecan monotherapy significantly improved overall survival in comparison with infusional 5-FU (P=0.035). Median survival was 10.8 months with irinotecan and 8.5 months with 5-FU. Survival at one year was 45% in the irinotecan group and 32% in the 5-FU group. Based on these two clinical studies, irinotecan was initially approved in the US as second-line monotherapy for the treatment of advanced CRC.

First-line Combination Therapy with 5-FU/LV

Two Phase III studies in patients with metastatic CRC provided evidence that first-line irinotecan–5-FU/LV (IFL) therapy is associated with a higher response rate and greater overall and progression-free survival than 5-FU/LV. Douillard et al used an infusional schedule of IFL and reported a response rate of 35% in the IFL group and 22% in the 5-FU/LV group for the intention-to-treat analysis (P=0.005). Overall survival times were 17.4 months and 14.2 months, respectively (P=0.031).[18] Time to treatment failure or progression was a median of 6.7 months with IFL and 4.4 months with 5-FU/LV (P<0.001). Using a bolus weekly regimen of IFL, Saltz et al reported similar results, with response rates of 39% versus 21% (P<0.001), overall survival times of 14.8 versus 12.6 months (P=0.04), and median progression-free survival times of 7.0 months versus 4.3 months (P=0.004) for the IFL and 5-FU/LV treatment groups, respectively.[19] In the Saltz study, irinotecan monotherapy was included as a third treatment, and results for these patients were similar to those treated with 5-FU/LV. These studies demonstrated the superiority of IFL over 5-FU/LV and established IFL as a new standard in the first-line treatment of metastatic CRC.

Irinotecan in Combination with Capecitabine

The combination of irinotecan-capecitabine (XELIRI) is being actively investigated in an attempt to replace the more complicated and potentially more toxic 5-FU/LV regimens with the oral fluoropyrimidine. Borner et al presented the clinical results of a Phase II trial comparing weekly irinotecan 70mg/m^2 (days one, eight, 15, 22, and 29) with every three week irinotecan 300/240mg/m^2 (day one and 22) in combination with capecitabine 1,000mg/m^2 bid (days one to 14 and 22 to 35) in 75 patients with good performance status.[20] Preliminary response rates were 42% and 41%, respectively, and median TTP was 7.2 months and 9.9 months. The most common grade 3/4 toxicity was diarrhea, at rates of 32% and 19% respectively.

In a Phase II study conducted by Patt et al in the US, patients under age 65 received capecitabine 1,000 mg/m^2 bid (days one–14) plus irinotecan 250mg/m^2 (day 1) in a 21-day cycle; those over age 65 received capecitabine 750mg/m^2 bid plus irinotecan 200 mg/m^2.[21] Treatment with XELIRI yielded a 42% overall response rate, and median TTP was 7.1 months. Disease control (i.e. complete response/partial response plus stable disease) was achieved in 71% of evaluable patients. XELIRI demonstrated a predictable and manageable safety profile. The most common grade 3/4 toxicities included diarrhea (20%) and neutropenia (18%). These results suggest that capecitabine may be a reasonable alternative to bolus or infusional schedules of 5-FU/LV in combination with irinotecan in the metastatic setting.

Oxaliplatin

Oxaliplatin is a third-generation platinum compound that exerts its cytotoxic effects through the formation of

intrastrand and interstrand DNA cross-links. It is the only platinum drug effective against CRC, and it exhibits a different spectrum of toxicity when compared with other platinum compounds. In particular, it does not cause the nephrotoxicity associated with cisplatin, or the degree of myelosuppression and alopecia observed with carboplatin. The main dose-limiting toxicity of this agent is neurotoxicity, and this particular adverse event presents as both an acute and chronic sensory neuropathy. The acute form is exhibited by nearly all patients, and typically presents as transient paresthesias that are exacerbated upon exposure to cold. In addition, about 3% to 4% of patients experience laryngopharyngeal spasms. In contrast, the chronic form is a cumulative sensory neuropathy that develops in up to 12% to 15% of patients. *In vitro* and *in vivo* tumor models indicate that combining oxaliplatin with 5-FU or SN-38 (the active metabolite of irinotecan) results in additive or synergistic cytotoxicity.

Second-line Therapy with 5-FU/LV

Several Phase II clinical trials evaluated different dosing schedules of oxaliplatin plus infusional 5-FU/LV (FOLFOX) as second-line treatment for patients with metastatic CRC resistant to 5-FU/LV.[22–25] Early trials suggested that a higher dose intensity of oxaliplatin might be associated with a higher response rate without increasing toxicities to an unacceptable level. In 2000, Maindrault-Gœbel et al retrospectively analyzed data from regimens combining oxaliplatin with different schedules of 5-FU and leucovorin (FOLFOX-2, -3, and -6). They reported that objective responses occurred in a significantly higher percentage of patients treated with high-dose (>85mg/m^2 for two weeks) than with low-dose (≤85mg/m^2 for two weeks) oxaliplatin (39% versus 19%, respectively; P=0.03).[25] They also concluded that a greater proportion of patients treated with high-dose oxaliplatin demonstrated progression-free survival at six months (52% versus 36%; P=0.02) and that improvements in efficacy were not associated with increased neurotoxicity or other toxicities.

A Phase III trial by Rothenberg et al led to the US approval of FOLFOX4 as second-line therapy for metastatic CRC.[26] FOLFOX4 was initially approved in Europe in 1999 as first-line treatment in this patient population. A total of 463 North American patients with IFL treatment-resistant metastatic CRC were randomized to receive one of three treatment regimens:

- bolus and infusional 5-FU plus LV (the de Gramont regimen);
- oxaliplatin alone (85mg/m^2 intravenously) for 120 minutes, administered on day one of a 14-day treatment cycle); or
- oxaliplatin plus 5-FU/LV (FOLFOX4).

Compared with 5-FU/LV alone, FOLFOX-4 was associated with a significantly higher response rate (9.9% versus 0%; P<0.0001), a longer median TTP (4.6 months versus 2.7 months; P<0.0001), and a greater proportion of patients experiencing relief from tumor-related symptoms (33% versus 12%; P<0.001). Treatment with oxaliplatin monotherapy was similar to that with 5-FU/LV. The incidence of clinically significant toxicities was higher with FOLFOX4 than with 5-FU/LV – including grade 3/4 diarrhea, grade 3/4 hematologic toxicity (neutropenia), and peripheral neuropathy (with either FOLFOX4 or oxaliplatin alone) – but these side-effects did not result in a higher rate of treatment discontinuation or 60-day mortality. The final results, which include data from 821 patients, confirmed the earlier findings with regard to response rate and TTP, but examination of the survival data, which had previously been unavailable, indicated no significant differences between treatment groups with regard to overall survival.[27]

First-line Therapy of Oxaliplatin in Combination with 5-FU/LV

It is now widely established that FOLFOX4 is effective as first-line treatment for patients with metastatic CRC. In a Phase III study by de Gramont et al, oxaliplatin (85mg/m^2 as a two-hour infusion on day one, every two weeks) plus 5-FU/LV (de Gramont regimen) was compared with the de Gramont regimen of 5-FU–LV alone in 420 patients with previously untreated advanced CRC.[28] FOLFOX was associated with significantly longer median progression-free survival times (nine versus 6.2 months; P=0.0003) and improved response rates (50.7% versus 22.3%; P=0.0001), although the two treatment groups did not differ significantly with regard to overall survival (16.2 versus 14.7 months; P=0.12). Grade 3/4 neutropenia, diarrhea, and neurosensory toxicity were more frequent with FOLFOX than with 5-FU/LV alone, although measures of quality of life did not differ between the groups. Some studies have suggested that chronomodulated infusion of oxaliplatin and/or 5-FU/LV as first-line therapy in patients with metastatic CRC may reduce toxicity while improving efficacy.[29,30] In addition, there are now a growing number of studies of first-line chronomodulated 5-FU/LV and oxaliplatin that showed that surgical resection of metastatic disease was possible after chemotherapy in a subset of patients (13%) with initially unresectable colorectal metastases, with approximate five-year survival rates of 30%.

Intergroup Trial N9741 was a randomized Phase III trial in the first-line therapy for metastatic CRC with the bolus, weekly IFL regimen as the control arm.[31] The two experimental arms of this trial included FOLFOX4 and a

non-fluoropyrimidine-containing arm of irinotecan and oxaliplatin (IROX). This pivotal study demonstrated that FOLFOX4 had significantly greater clinical efficacy in terms of response rate (45% versus 31%), TTP (8.7 versus 6.9 months; P=0.0001), and median overall survival (19.5 versus 14.8 months; P=0.0001). In addition, when compared with IFL or IROX, FOLFOX4 was associated with a markedly lower incidence of febrile neutropenia and fewer gastrointestinal side-effects in terms of nausea/vomiting, diarrhea, and dehydration. However, peripheral sensory neuropathy and myelosuppression were more common with both FOLFOX4 and IROX when compared with IFL. Based on the results from this large Phase III clinical trial, in Janurary 2004, FOLFOX4 was approved for use in the US as first-line treatment of patients with advanced CRC.

Various Phase I/II clinical studies, conducted mostly in Europe, have been exploring the use of combination therapy with oxaliplatin, irinotecan, and 5-FU/lLV ('triplet therapy') as either first-line[32–34] or second-line treatment[35,36] in patients with metastatic CRC. The different mechanisms of action and generally divergent dose-limiting toxicities of the various agents form part of the rationale for this combination, and bi-weekly administration is being explored as a means to lower peak drug concentrations and improve tolerance.

Oxaliplatin is also being studied as a component of non-fluoropyrimidine combination therapy. For example, oxaliplatin is being investigated in combination with gemcitabine (GEMOX), which is an agent with minimal activity in CRC. The preliminary results of a Phase II study evaluating this GEMOX regimen in the second-line treatment of 31 patients with advanced CRC has been reported.[37] After a median follow-up period of five months, one-year survival was 45.9%, and no grade 4 toxicity was observed. Grade 3 toxicities included febrile neutropenia (19.4%), thrombocytopenia (12.9%), anemia (3.2%), and nausea (3.2%). The combination of pemetrexed–oxaliplatin in patients with previously untreated metastatic colorectal cancer has been reported to be well tolerated and to have clinical activity in advanced CRC.[38]

First- or Second-line Oxaliplatin Combinations with Capecitabine

FOLFOX regimens typically require infusional therapy over two days every two weeks, whereas XELOX regimens involve one two-hour infusion every three weeks. There is growing evidence that the oral fluoropyrimidine capecitabine can effectively substitute for bolus or infusional schedules of 5-FU/LV in combination with oxaliplatin in the metastatic setting. Borner and colleagues reported objective response rates of 49% and 15% in first- and second-line treatment, respectively, and median overall survival rates of 17.5 months and 11.5 months, respectively.[39] The main side-effect was grade 3/4 diarrhea (35% in first-line and 50% in second-line treatment), which resulted in 26% and 50% dose reductions, respectively. Of note, this toxicity was largely prevented in cycles two through four through appropriate dose reductions. Scheithauer et al. conducted a study in 89 patients with advanced CRC using a dose-intensified bi-monthly schedule for capecitabine (3,500mg/m^2 days one to seven and 14-21) plus oxaliplatin (85mg/m^2 days one and 14) every four weeks versus a conventional dose regimen.[40] Patients receiving high-dose therapy had a higher response rate (54.5% versus 42.2%) and a significantly longer median progression-free survival time than those receiving the conventional dose (10.5 versus 6.0 months; P=00013). The safety profile was similar to that observed with the lower-intensity regimen – diarrhea was the most frequent side-effect, but in general, it was well controlled.

van Cutsem et al. conducted a large Phase II multicenter international study investigating the XELOX regimen.[41] The dosing regimen of capecitabine 1,000mg/m^2 bid (days one to 14), plus 130mg/m^2 intravenously (day one) every three weeks, yielded an overall response rate of 55% – similar to that observed with infusional 5-FU/LV plus oxaliplatin. Importantly, median overall survival was compelling at 19.5 months. The adverse events most frequently leading to dose reductions were gastrointestinal side-effects, myelo-suppression, and neurotoxicity. The findings from this study, together with those previously summarized, indicate that the XELOX regimen is effective and well tolerated as first-line treatment for patients with metastatic CRC.

XELOX Versus XELIRI

In a Phase II randomized setting, Grothey et al directly compared XELOX with XELIRI as first- and second-line therapy in patients with advanced CRC.[42] Preliminary efficacy data presented at ASCO 2003 and updated at ASCO 2004 showed a slightly higher response rate with first-line XELOX than with XELIRI (51.3% versus 42.6%), and progression-free survival of 7.9 months in both arms. In the first phase of the study, an unexpected number of early deaths in the XELIRI arm led to a reduction of the irinotecan dose. However, reduction of the irinotecan dose from 100mg/m^2 to 80mg/m^2 did not impair the clinical efficacy of the XELIRI combination (response rate, 41.7% before and 43.8% after dose reduction). Grade 3/4 hematologic and non-hematologic toxicities were generally similar with XELOX and XELIRI therapy. Diarrhea was the most frequently reported grade 3/4 toxicity in both groups, occurring in 12.7% and 13.6% of XELOX- and XELIRI-treated

patients, respectively. Grade 2 alopecia occurred more frequently in XELIRI-treated patients (13.9% versus 7.4%), and grade 2/3 sensory neuropathy occurred more frequently in XELOX-treated patients (6.2% versus 1.3%). As second-line therapy, response rates were slightly higher with XELIRI when compared with XELOX (19% versus 12%).

Novel Targeted Agents in the Treatment of Advanced CRC

The significant advances in molecular oncology have generated tremendous interest in the development of targeted therapies for solid tumors. Such agents are designed to modulate, inhibit, and interfere with the function of specific molecular targets that are essential to the malignancy of tumors. The agents with the greatest interest in CRC are the monoclonal antibodies bevacizumab and cetuximab.

Cetuximab

Cetuximab is a chimeric monoclonal antibody directed against the external cell surface of the epidermal growth factor receptor (EGFR). It has been shown that the EGFR is over-expressed in up to 8% of colorectal tumors, and its expression has been correlated with metastatic disease and poor prognosis. Activation of the EGFR signaling pathway results in activation of cellular processes involved in cellular growth and proliferation, invasion and metastasis, and angiogenesis. Moreover, this pathway inhibits the cytotoxic activity of various anticancer agents and radiation therapy, thereby leading to the development of cellular drug resistance.

The initial clinical studies with cetuximab were performed in the US. Saltz et al reported a 17% response rate in patients with irinotecan-refractory, metastatic colorectal cancer, who were treated with the combination of cetuximab and irinotecan.[43] An additional 31% of patients had stable disease giving a disease control rate of 48%. A subsequent study evaluated the clinical activity of cetuximab monotherapy in patients with refractory CRC whose tumors expressed EGFR.[44] Cetuximab was administered intravenously on a weekly schedule. A total of 57 patients were evaluated, and the overall response rate was 9% with a median survival of 6.4 months. In general, this treatment was well tolerated, and the most common side-effects were acne-like skin rash presenting mainly on the face and upper torso and a composite of asthenia, fatigue, malaise, and/or lethargy. At the ASCO 2004 meeting, Lenz and colleagues reported the results of a large (n=346) Phase II study of single-agent cetuximab in heavily pretreated patients who had previously failed both irinotecan and oxaliplatin.[45] The response rate in this trial was 12%, and the median overall survival was 6.7 months, which exactly paralleled the results previously reported by Saltz et al in irinotecan-refractory patients. Cunningham et al presented the results of the Bowel Oncology with Cetuximab Antibody (BOND) randomized Phase II study in heavily pretreated patients with advanced CRC. This study enrolled 329 patients with EGFR-positive metastatic CRC who had failed to respond to irinotecan (progressing on or within 30 days).[46] Patients were randomized in a 2:1 ratio to cetuximab 400mg/m^2 infusion, followed by weekly cetuximab 250mg/m^2, plus irinotecan at the same dose and schedule on which they had been progressing, or cetuximab monotherapy. The objective response rate (22.9% versus 10.8; P=0.0074), TTP (4.1 versus 1.5 months; P<0.0001), and disease control rate (55.5% versus 32.4%; P=0.0001) were significantly higher in the combination therapy group. There was a trend towards improvement in median survival in patients treated with the combination of cetuximab and irinotecan when compared with cetuximab monotherapy (8.6 versus 6.9 months; P=0.48), although this difference did not reach statistical significance. Of note, cetuximab treatment did not worsen the toxicities normally associated with irinotecan chemotherapy. The most frequent grade 3/4 events in patients receiving combination therapy were diarrhea (21.2%), asthenia (13.7%), neutropenia (9.5%), acne-like rash (9.4%), and vomiting (6.1%). Patients receiving cetuximab alone had fewer adverse effects, including asthenia (10.4%), acne-like rash (5.2%), and abdominal pain (5.2%). Based on the results of this randomized study as well as Phase II clinical studies conducted in the US, cetuximab was approved for use in combination with irinotecan for the treatment of EGR-expressing, metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy. This agent was also granted approval for use as a single agent for the treatment of EGFR-expressing, recurrent metastatic colorectal cancer in patients who are intolerant to irinotecan-based chemotherapy.

Bevacizumab

The vascular endothelial growth factor (VEGF) is established to be one of the most important angiogenic growth factors known to regulate angiogenesis. Since the growth of primary tumors, as well as metastatic disease, requires an intact vasculature, VEGF and the VEGF-signaling pathway represents an attractive target for chemotherapy. Several approaches have been taken to inhibit VEG signaling, and they include inhibition of VEGF/VEGF receptor interactions by targeting either the VEGF ligand with antibodies or soluble chimeric receptors, or by direct inhibition of the VEGF receptor-associated tyrosine kinase activity by small molecule inhibitors.

Bevacizumab is a recombinant humanized monoclonal antibody targeted against all splice variants and post-

translationally modified forms of VEGF-A. It binds to and prevents VEGF-A from interacting with their target VEGF receptors. A randomized Phase II trial (AVF0780) investigated the safety and efficacy of two dose levels of BV in combination with 5-FU/LV in patients with metastatic CRC.47 The two treatment arms that included BV (at doses of 5mg/kg or 10mg/kg, respectively) resulted in higher response rates (40% and 24%) and a longer median time to disease progression (nine and 7.2 months) and median survival (21.5 and 16.1 months) compared with the control arm consisting of 5-FU/LV alone (17%; 5.2 months; 13.6 months). Because higher clinical efficacy was observed in the 5mg/kg arm compared with the 10mg/kg arm, the 5mg/kg dose of BV was chosen for further clinical study. Although BV was generally well-tolerated, this trial identified a number of important safety signals associated with BV therapy, including an increased incidence of thromboembolic complications, hypertension, proteinuria, bleeding complications in the form of epistaxis, headache, fever, and rash. In general, however, these adverse events were either clinically insignificant or easily manageable.

In the pivotal randomized Phase III study, previously untreated patients with metastatic CRC who received BV plus standard chemotherapy with the bolus weekly IFL regimen had longer progression-free survival (10.6 months versus 6.2 months, P<0.00001) and survived significantly longer (20.3 months versus 15.6 months; P=0.00003) than those receiving IFL chemotherapy plus placebo.[48] The only adverse event that occurred with greater frequency in the anti-VEGF regimen was grade 3 hypertension, which was managed effectively with oral medications. In contrast to the randomized Phase II study described above, no increases in thromboembolic events, bleeding complications, and proteinuria were observed. Based on the positive clinical results of this Phase III pivotal trial, BV received approval in February of 2004 from the US Food and Drug Administration (FDA) as a first-line treatment for metastatic colorectal cancer in combination with any intravenous fluoropyrimidine-containing regimen.

Trial AVF2192g was a randomized, double-blind, placebo-controlled, multicenter study in patients in the first-line setting, who were deemed to not be optimal candidates for irinotecan-based chemotherapy.[49] The primary objective of the trial was duration of survival. Secondary end-points included response rate (RR), progression-free survival (PFS), response duration, quality of life assessment, and safety. Patients were randomized to one of two treatment arms. In arm one, patients received the Roswell Park regimen of 5-FU/LV and BV 5mg/kg, while in the second arm, patients received the Roswell Park regimen of 5-FU/LV plus placebo. The preliminary results of this trial were presented by Kabbinavar et al at the recent 2004 ASCO meeting. The overall median survival was 12.9 months on the placebo arm compared with 16.6 months on the BV arm (P=0.159). Progression-free survival in the placebo arm was 5.5 months compared with 9.2 months in the BV arm (P=0.0002). The overall response rate was 15% in the placebo arm and 26% in the BV arm (P=0.0552), with all responses being partial responses in both arms. The toxicities most commonly associated with BV included bleeding, thromboembolic events, hypertension, and proteinuria. Hypertension (4.8% versus 32%) and proteinuria (19.2% versus 38%) were observed more frequently in patients treated with BV, and two patients in the BV arm experienced gastrointestinal perforations.

Summary

Significant advances have been made in the treatment of advanced CRC over the past four to five years. This progress has been made possible with the introduction of three novel cytotoxic agents, capecitabine, irinotecan, and oxaliplatin, and the development of two novel targeted therapies, BV and cetuximab. During this time period, the median survival of patients with stage IV disease has gone from 10-12 months to nearly 24 months. It is now well-established that all patients with advanced disease should have access to all of these active agents at some point in the course of their treatment.

Despite the development of active combination regimens, however, improvements in the actual cure rate have not yet been achieved. With this in mind, intense efforts have focused on identifying novel targeted therapies that target specific growth factor receptors, critical signal transduction pathways, and/or key pathways that mediate the process of angiogenesis. The recent clinical results with the anti-VEGF antibody, bevacizumab, in combination with the IFL bolus weekly regimen provide important validation for the process of angiogenesis being an important chemotherapeutic target for CRC. Similarly, the randomized Phase II study documenting the clinical activity of the combination of the anti-EGFR antibody cetuximab and irinotecan-based therapy and/or cetuximab monotherapy validate the role of the EGFR-signaling pathway as a key target for chemotherapy. Combination regimens incorporating standard chemotherapy with novel targeted agents with activity in advanced disease are now being evaluated in the adjuvant setting. Investigators continue to focus their efforts on identifying novel therapies that target specific growth factor receptors, critical signal transduction pathways, and/or key pathways that mediate the process of angiogenesis. The goal is to integrate these novel targeted therapies into standard chemotherapy regimens so as to advance the therapeutic options for the treatment of advanced CRC. ■

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