Trends in the Treatment of Colorectal Cancer

a report by
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DOI: 10.17925/OHR.2005.00.00.1d

Colorectal cancer is the third most frequently diagnosed cancer in the US and the third most common cause of cancer deaths in men and women. In 2004, an estimated 146,940 new cases of colorectal cancer will be diagnosed and 56,730 deaths will occur.[1] The stage of cancer at the time of diagnosis predicts overall survival. At presentation, 21% of patients will have stage IV disease, many pursuing chemotherapy to control disease and extend survival. The 37% of patients diagnosed with stage III disease and some of the 28% of patients with stage II disease will be offered chemotherapy to eradicate micrometastatic disease for cure. Approximately 85,000 people yearly will receive chemotherapy for colorectal cancer.

5-fluorouracil (5FU) has been the cornerstone of therapy for the treatment of colorectal cancer for more than 50 years. Within the past six years, two other cytotoxic drugs, irinotecan and oxaliplatin, and two monoclonal antibodies that target specific cancer-related proteins, bevacizumab and cetuximab, have proven efficacious in the treatment of colorectal cancer. Recent results of randomized clinical trials have changed the approach to the treatment of colorectal cancer.

Irinotecan was first shown as a single agent to improve survival and quality of life for patients who progressed on 5FU-based therapy.[2,3] Subsequently, two pivotal studies demonstrated a survival benefit of the combination of 5FU and leucovorin with irinotecan compared with 5FU and leucovorin alone. Different approaches in North America and Europe were pursued; in the North American study, 5FU, leucovorin, and irinotecan were administered on a weekly bolus schedule (IFL) and compared with bolus 5FU and leucovorin.[4] A median survival benefit was demonstrated (14.8 months compared with 12.6 months, p=0.04) and established IFL as the standard of care in the US. The European study gave an infusion schedule of 5FU with leucovorin and irinotecan and also showed a survival advantage when compared with an infusion schedule of 5FU and leucovorin (17.4 months compared with 14.1 months, p=0.031).[5] Subsequently, oxaliplatin with infusion 5FU and leucovorin (FOLFOX) was compared with infusion 5FU and leucovorin as first line treatment in a European study[6] and as second line therapy in a North American study after progression on IFL.[7] The European study again demonstrated an advantage to combination chemotherapy in the first line setting with an improvement in median progression-free survival (9.0 months versus 6.2 months, p=0.0003). The North American study demonstrated an advantage of the FOLFOX regimen compared with either infusion 5FU or single agent oxaliplatin in the second line setting in terms of response rate (9.9% versus 0% and 1.3%, respectively), time to tumor progression (4.6 months versus 2.7 months and 1.6 months, respectively), and improvement in tumor-related symptoms (33% versus 12% and 12%, respectively).

The randomized US Gastrointestinal Intergroup study was designed to determine the most effective therapy for the first-line treatment of advanced disease.[8] At the time this study was designed, bolus 5FU and leucovorin were the standard arm and oxaliplatin was not available commercially. The study was amended to reflect increased toxicity in some of the bolus combination schedules and the inferiority of 5FU and leucovorin as first-line therapy. It ultimately compared IFL with FOLFOX and a combination of irinotecan and oxaliplatin (IrOx). The final results demonstrated an improved survival for FOLFOX compared with either IFL or IrOx. There are three major factors that may have contributed to these results. Patients who were randomized to receive oxaliplatin in a first-line regimen had an active second-line agent available to them at the time of progression – either irinotecan or 5FU. This was not the case for patients randomized to receive IFL, as oxaliplatin was not available except in the setting of a second-line clinical trial. The role of infusion 5FU used in the FOLFOX regimen compared with bolus 5FU in the IFL regimen may have contributed to the difference in two ways: 5FU, when given as an infusion, has shown an increase in response rate compared with 5FU as a bolus injection, although no survival benefit has previously been demonstrated.[9,10] Furthermore, the incidence of treatment-related

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deaths was higher in the IFL regimen and is thought to be related to the use of bolus 5FU with irinotecan. This increase in mortality is not seen in infusion 5FU and irinotecan combinations.[5] Finally, the use of oxaliplatin compared with irinotecan in the first-line setting may actually account for the difference. This has not been proven, however, as subsequent studies using 5FU, leucovorin, oxaliplatin, and irinotecan have led to a median survival of 20–21 months for patients who have received all agents, regardless of the sequence.[8,11–13]

The bolus IFL regimen has fallen out of favor as a result of associated toxicity demonstrated in two large randomized studies. In the Intergroup study for advanced disease, 14 patients died within 60 days of starting therapy compared with five patients on the FOLFOX arm and five patients on the IrOx arm.[14] Meanwhile, an adjuvant study for patients with stage III colon cancer randomized patients to receive the bolus IFL regimen or the standard weekly bolus 5FU and leucovorin regimen following surgical resection. Again, an increased and unacceptable rate of treatment-related deaths was demonstrated in the IFL arm (14 compared with five).[15] Subsequently, this regimen was not shown to offer a survival advantage compared with the standard 5FU and leucovorin in the final analysis recently reported.[16]

Prior to this toxicity being recognized, enrollment was progressing in a randomized study comparing IFL with IFL with the monoclonal antibody bevacizumab. Bevacizumab inhibits circulating vascular endothelial growth factor (VEGF), preventing its binding to the VEGF receptor tyrosine kinase. A median survival benefit was demonstrated for the combination of IFL with bevacizumab, compared with IFL (20.3 months compared with 15.6 months, p value less than 0.001).[17] When added to 5FU and leucovorin alone, the addition of bevacizumab was also shown to improve survival.[18] This led to the approval of bevacizumab for the first-line treatment of advanced colorectal cancer with 5FU-based chemotherapy. The actual median survival of IFL with bevacizumab was comparable with the median survival demonstrated in the Intergroup study for FOLFOX.[8,17] Whether the addition of bevacizumab to FOLFOX will result in further prolongation of survival remains to be seen when the results of the Eastern Cooperative Oncology Group study of FOLFOX compared with FOFLOX with bevacizumab as second-line therapy becomes available. In these first studies demonstrating activity of one of the angiogenesis inhibitors, some unique toxicities were shown. The patients randomized to receive bevacizumab had a higher incidence of hypertension, asymptomatic proteinuria, and minor bleeding. Although infrequent, of greater concern was the increased incidence of arterial thrombosis and bowel perforation. With widespread use of this agent, the significance of these serious complications will become apparent.

The importance of second-line therapy in the treatment of advanced colorectal cancer is clear, and recently third-line therapy has been evaluated with the addition of the monoclonal antibody cetuximab. Cetuximab targets the epithelial growth factor receptor (EGFR) over-expressed in many colorectal cancers. Patients with irinotecan refractory disease may benefit from irinotecan with cetuximab. A response rate of more than 20% was reported in two studies, although a survival benefit was not evaluated.[19–21] A recent report demonstrated a comparable benefit for patients with irinotecan and oxaliplatin refractory disease.[22] The mechanism is not clear, but down-regulating EGFR may resensitize cells to irinotecan. Both studies only enrolled patients whose tumors expressed EGFR by immuno-histochemical staining, although neither extent nor intensity of staining correlated with response. It is feasible that cetuximab may be active in tumors that do not over-express EGFR as determined by these staining methods. Future studies will evaluate cetuximab in EGFR-negative tumors.

Bevacizumab was also evaluated as third-line therapy after progression on irinotecan and oxaliplatin.[23] Unlike as first-line therapy, preliminary results have demonstrated no significant response in refractory disease. There is a suggestion of prolonged disease stabilization, however, and further analysis is needed. Similar to the situation with cetuximab and EGFR, neither VEGF levels or expression of VEGF predict response to therapy.

New schedules and combinations of chemotherapy have been explored in the adjuvant treatment of local disease. Infusion 5FU with leucovorin on the LV5FU2 schedule was shown to have an equivalent survival and an improved toxicity profile compared with bolus 5FU and leucovorin for adjuvant therapy.[24] The addition of oxaliplatin to the infusion 5FU and leucovorin schedule (FOLFOX) was compared with the LV5FU2 regimen for patients with resected stage II or III colon cancer. A three-year disease-free survival benefit was shown by the addition of oxaliplatin for stage II (87% versus 84.3%) and stage III (72.2% versus 65.3%) colon cancer.[25] The incidence of NCI common toxicity criteria (CTC) grade 3 peripheral neuropathy was reported as 12.4% during therapy, however for most patients it resolved within one year. The use of three-year disease-free survival as a predictor and surrogate end-point for

benefit from adjuvant therapy was recently defended.[26] As a result, the Oncology Drug Advisory Committee of the US Food and Drug Administration (FDA) has recommended acceptance of three-year disease-free as an appropriate end-point for adjuvant colorectal cancer clinical trials.

5FU and irinotecan schedules have also been explored as adjuvant therapy. Unlike oxaliplatin, irinotecan dose does not have cumulative toxicity. The adjuvant study randomizing patients to weekly bolus 5FU and leucovorin or IFL failed to demonstrate an advantage with the addition of irinotecan.[16] The toxicity profile was significantly different with a greater percentage of NCI CTC grade 3 or 4 neutropenia (42% versus 5%, $p<0.00001$), febrile neutropenia (4% versus 1%, $p=0.0005$), and patient deaths (2.8% versus 1%, $p=0.008$) on the IFL arm. Irinotecan is currently undergoing evaluation as adjuvant therapy using the infusion 5FU schedule with leucovorin and bolus 5FU (FOLFIRI) compared with 5FU and leucovorin. In the first line study for advanced disease, the irinotecan-containing group experienced more frequent NCI CTC grade 3 or 4 neutropenia (9.3% versus 0.7%) and diarrhea (31.5% versus 11.6% for the weekly regimen and 11% versus 1.4% for the every two week regimen), however, the excessive treatment-related mortality seen with the IFL schedule has not been demonstrated with the FOLFIRI schedule.[14] The results of this study should better define the role of irinotecan as adjuvant therapy.

It has become clear that 5FU given as a continuous infusion is associated with lower toxicity and possible improved efficacy.[9,10] The disadvantage of infusion 5FU is the need for a central indwelling line, infusion pump, and 24-hour support in case of pump malfunction. One alternative to infusion therapy being investigated is the use of oral fluoropyrimidines to mimic the continuous exposure to 5FU. The oral fluoropyrimidine capecitabine has demonstrated equivalent efficacy and a superior toxicity profile to the bolus schedule of 5FU and leucovorin for the treatment of advanced disease.[27,28] Recent reports also demonstrate equivalency for the adjuvant treatment of early-stage disease.[29,30] Capecitabine clinical trials conducted in Europe seem to achieve a higher dose intensity than in the US. One mechanism proposed to explain this phenomenon relates to the high level of folate in the US food supply, which acts as a 5FU modulator. The dose generally used in practice in the US (2,000mg/m^2 daily for 14 days) has not been compared with either standard bolus 5FU and leucovorin or infusion 5FU. Capecitabine is being investigated in combination regimens with irinotecan or oxaliplatin as treatment for both advanced and early-stage disease, as well as with radiation for the treatment of rectal cancer.

The plethora of options for the treatment of colorectal cancer is a welcome dilemma. Well-designed clinical trials have advanced the field of cancer therapy and provided much needed evidence on which to base treatment decisions. Many questions remain. It is clear that infusion 5FU has a preferred toxicity profile compared with bolus schedules and allows for tolerable combinations. The resources needed to support infusion schedules may not be available to all patients, however. Many physicians have moved to using capecitabine in place of the infusion 5FU without the data to support it. While this is probably acceptable and may be necessary if resources are not available, it is important to realize that the dose intensity is not the same. When infusion 5FU is administered in combination with either irinotecan or oxaliplatin, an efficacious single agent dose is used. This is not the case with capecitabine, as a dose substantially less than the tolerable single agent dose is required. Early studies have demonstrated efficacy, but the phase III studies comparing oral therapy with intravenous therapy are premature.

The sequence of therapy and the development of cross-resistance have been evaluated in few studies.[13] As of yet, there is no evidence of sequence dependency when using oxaliplatin and irinotecan. Future studies will explore this concept further. The use of molecular markers may predict response to therapy or excessive toxicity. Trials are being designed incorporating predictive markers in a prospective evaluation. Until this information is available, the side effect profile associated with each drug and regimen may drive the treatment decision.

There is a great deal yet to be learned about the molecular abnormalities that influence cancer growth, metastasis, and resistance. Bevacizumab has been shown to be beneficial as first-line therapy, but early reports demonstrate little or no benefit in refractory disease. Cetuximab has demonstrated efficacy in refractory disease, but results are not yet available demonstrating activity in untreated disease. The marker used to predict response to cetuximab has not been validated as a predictive marker, yet identification of the marker is recommended prior to initiating therapy. Especially given the cost of these complex agents, it is imperative that treatment decisions be based on the results of well-designed clinical trials with clinically relevant end-points.[31] An important component of these trials will be the prospective evaluation of markers that predict response to therapy and identify patients who may not need or benefit from therapy.[32] ■

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