ABSTRACT

Until the late 1990s, fluorouracil (FU) plus leucovorin (LV) was the standard adjuvant therapy for stage III colorectal cancer (CRC). Since then, 6 new agents (capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab) have been approved for the treatment of CRC. When added, either singly or in various combinations, to FU/LV these agents have produced varying degrees of improvement in clinical outcomes, with FU/LV plus irinotecan setting a new survival standard for metastatic CRC in 2001 and FU/LV plus oxaliplatin becoming the new standard of care for stage III CRC in 2004. This article reviews recent studies examining the impact of these drugs on outcomes and presents data from ongoing trials evaluating various combination regimens as first-, second-, and third-line therapy. Per-protocol variations in dose size, scheduling, and sequence of drug administration for several of these combination regimens are also addressed.

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ADJUVANT THERAPY IN STAGE II
COLORECTAL CANCER

Surgery alone cures 75% of patients with stage II disease. Surgery alone cures 75% of patients with stage II disease.1 This substantial cure rate calls into question whether these patients should receive adjuvant therapy as a matter of course. Based on a literature meta-analysis, which included 37 trials, 11 meta-analyses, and 20,317 patients and found a 5% to 10% improvement in disease-free survival but no improvement in overall survival with adjuvant therapy, an expert panel convened by the American Society of Clinical Oncology concluded that routine administration of adjuvant therapy is not warranted in stage II disease.1,2

However, the panel also indicated that adjuvant therapy could be reasonably offered to high-risk patients with stage II disease, who typically have a 5-year survival rate of 50%.1,3 High-risk patients include those with T4 lesions, poorly differentiated tumors, the presence of lymphatic, neural, and/or vascular invasion, and less than 12 lymph nodes sampled.

ADJUVANT THERAPY IN STAGE III
COLORECTAL CANCER

Recent studies evaluating adjuvant therapy with the newer agents in stage III CRC have yielded divergent results. Whereas 2 trials have shown that the addition of oxaliplatin significantly improved disease-free survival and 2 studies suggested that capecitabine may be more effective than FU/LV in terms of disease-free and overall survival, 3 trials have shown that the addition of irinotecan did not improve overall survival.4-11

It is important to emphasize that both the National Surgical Adjuvant Breast and Bowel Project Protocol C-07 and the Multicenter International Study of Oxaliplatin/5-FU/L in the Adjuvant Treatment of Colon Cancer (MOSAIC) study demonstrated a significant improvement in 3-year disease-free survival when oxaliplatin was added to either infusional or weekly bolus FU/LV.4,6 Accordingly, infusional or bolus FU/LV plus oxaliplatin, a platinum alkylating agent, became the new standard of care for stage III disease in 2004. It is also worth noting that one of the arms in the MOSAIC trial, the FOLFOX-4 regimen (infusional FU), significantly improved the 4-year disease-free survival rate by 6.8%.5,6

In contrast, investigators involved in the Cancer and Leukemia Group B study, the Pan-European Trials in Adjuvant Colorectal Cancer-3, and the ACCORD trial conducted in France declined to recommend irinotecan for adjuvant therapy in stage III CRC because of the absence of any benefit in overall survival.9-11

Ongoing studies comparing the monoclonal antibodies cetuximab and bevacizumab with FOLFOX regimens in stage III CRC are outlined in Table 1. Studies evaluating combinations of capecitabine and oxaliplatin in stage III disease are also ongoing.

ADVANCES IN METASTATIC
COLORECTAL CANCER THERAPY

The approval of irinotecan, capecitabine, oxaliplatin, cetuximab, bevacizumab, and panitumumab has led to significant advances in the treatment of metastatic CRC.

As in stage III disease, FU has been the standard of care in stage IV metastatic CRC for nearly half a century. Even with the addition of synergistic LV in the early 1990s, response rates remained low, approximately 15% to 20%, and the combination had little impact on overall survival.12,13 However, randomized trials comparing continuous infusion with bolus administration have found that overall response rates increased to approximately 30% when FU/LV was infused continuously.12,13

<table>
<thead>
<tr>
<th>Table 1. Ongoing Studies of Monoclonal Antibodies in Stage III Disease</th>
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<tr>
<td>NSABP-08 Patients randomized to:</td>
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<tr>
<td>FOLFOX-6 ( ^* ) x 24 weeks vs</td>
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<td>FOLFOX-6 + bevacizumab x 24 weeks ( \rightarrow ) bevacizumab</td>
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<td>Intergroup NO147Patients randomized to:</td>
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<td>FOLFOX-6 + cetuximab x 24 weeks</td>
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<td>PETACC-8 Patients randomized to:</td>
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<tr>
<td>FOLFOX-4 ( ^* ) x 24 weeks vs</td>
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<td>( ^* )Oxaliplatin dose: 100 mg/m².</td>
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<td>( ^* )Oxaliplatin dose: 85 mg/m².</td>
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<tr>
<td>FOLFOX = fluorouracil plus leucovorin plus oxaliplatin; NSABP = National Surgical Adjuvant Breast and Bowel Project; PETACC = Pan-European Trials in Adjuvant Colorectal Cancer.</td>
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Findings from several studies evaluating regimens of FU/LV plus 1 or more of the agents approved since 1997 in metastatic CRC are discussed later in this article.

**IRINOTECAN**

Two phase II trials evaluating irinotecan, a topoisomerase I inhibitor also known as CPT-11, as a single agent for second-line therapy in patients with recurrent or metastatic CRC following FU-based therapy found that 125 mg/m²/week for 4 of 6 weeks produced an overall response rate of 13% to 23%. In one of these studies, the survival rate 1 year after recurrence was 46%. Studies have established a synergistic effect between irinotecan and FU. Two pivotal phase III trials comparing irinotecan combinations with standard of care regimens (and reported in a single paper by Saltz et al) demonstrated that the combination of irinotecan and FU/LV (IFL) was superior to FU/LV alone as first-line therapy in patients with metastatic CRC, with consistently improved tumor control and prolonged survival. In study 1, which utilized bolus FU/LV, the confirmed response rate was 39% for IFL versus 21% for FU/LV alone. Median overall survival time was 14.8 months for IFL versus 12.6 months for FU/LV alone. In study 2, which was previously reported by Douillard et al, FU/LV was given by infusion. Response rates were 35% for IFL versus 22% for FU/LV alone. Median overall survival time was 17.4 months for IFL versus 14.1 months for FU/LV alone. Thus, IFL set a new survival standard for metastatic CRC.

On the basis of these results, the Oncology Drug Advisory Committee of the US Food and Drug Administration approved the IFL regimen for first-line therapy of advanced CRC in 2000 and recommended that it be the regulatory standard to which new regimens would be compared. The IFL regimen remained the standard until 2002, when oxaliplatin was approved for metastatic CRC refractory to FU/LV.

**OXALIPLATIN**

Oxaliplatin, a platinum alkylating agent and a component of all FOLFOX regimens, has been studied as second-line therapy in recurrent disease in patients previously treated with FU/LV and as first-line therapy in untreated stage IV disease in trials employing several FOLFOX regimens and/or other combinations.

A phase II study evaluating oxaliplatin as second-line therapy found that oxaliplatin alone, at a dose of 85 mg/m² intravenously every 3 weeks, resulted in overall response rates of 10% to 24%, a median progression-free survival time of 5.1 months, and median overall survival time of 11 months. When the same dose of oxaliplatin was administered with FU/LV in another phase II study, overall response rates were 23% to 58% and median overall survival time was 12 to 17 months.

Phase III studies comparing FOLFOX-4 (oxaliplatin 85 mg/m² and FU/LV) with FU/LV alone and with IFL demonstrated even better results, with similar or higher response rates and further increases in median overall survival.

Another phase III study compared FOLFOX-6 (oxaliplatin 100 mg/m² and FU/LV) with a FOLFIRI regimen (irinotecan 180 mg/m² and FU/LV). Previously untreated patients with advanced CRC were randomized to receive FOLFIRI followed by FOLFOX-6 (n = 109) or FOLFOX-6 followed by FOLFIRI (n = 111). Both regimens were infused over 48 hours every 2 weeks. Thus, the investigators were able to assess both regimens as first- and second-line therapy and to determine whether one sequence was better than the other.

Overall response rates were similar for both regimens when used as first-line therapy (56% for FOLFIRI and 54% for FOLFOX-6). However, the overall response rate was higher (15% vs 4%) when FOLFOX-6 was used as second-line therapy. Progression-free survival with both regimens for first- and second-line therapy is shown in Figure 1. There was no difference in overall survival between the regimens when used as first-line therapy (21.5 months for FOLFOX-6 and 20.6 months for FOLFIRI). However, there were differences in toxicity, with 34% of patients receiving FOLFOX-6 first developing grade 3 neuropathy and 14% of patients receiving FOLFIRI first developing grade 3 diarrhea.

A data analysis of 7 phase III trials evaluating 3-drug combinations with oxaliplatin, irinotecan, and FU/LV in patients with advanced CRC has shown that median overall survival time was higher in patients who received all 3 drugs than in those who received only 2 (21 months vs 12 months). Therefore, the investigators involved in the analysis have recommended that all 3 agents be made available to patients with advanced CRC to maximize overall survival.
A recent phase III study comparing this 3-drug combination, which has been designated FOLFOXIRI, to FOLFIRI has shown that FOLFOXIRI produced the highest response rate seen to date in metastatic CRC (66% vs 41% for FOLFIRI), in addition to an increase in median overall survival time (22.6 months vs 16.7 months for FOLFIRI). The study also investigated whether either regimen would permit liver resection in patients with liver metastasis. Among patients who received the FOLFOXIRI regimen, 36% were able to undergo liver resection versus 12% of those who received FOLFIRI.

CAPECITABINE

Phase III studies of capecitabine, an oral fluoropyrimidine, have shown that it is superior to bolus FU/LV in terms of overall response rate (26% vs 17%) and activity at sites of metastatic disease. As shown in Figure 2, lung and liver metastases had a significantly better response to capecitabine than to FU/LV, and the response was not affected by prior adjuvant therapy or the number of sites of metastasis.

However, capecitabine was associated with a significantly higher incidence of all grades of hand-foot syndrome and a slightly higher incidence of grade 3/4 diarrhea than FU/LV. By comparison, FU/LV had a significantly higher incidence of diarrhea, stomatitis, nausea, and alopecia (all grades) and grade 3/4 stomatitis and neutropenic fever and sepsis.

The combination of capecitabine and irinotecan has been shown to have at least additive activity, and was highly curative in tumor xenograft models. Phase II studies of capecitabine and irinotecan (Capiri regimens) have demonstrated a 31% to 61% response rate in untreated metastatic CRC and a median survival time of 15.6 months. In a study involving patients with previously treated metastatic disease, the overall response rate in intent-to-treat was 33.3%, including 1 complete response. The median time to progression was 6.7 months, and the median overall survival time was 13.4 months (95% confidence interval, 11.0–15.8 months), with a 1-year survival rate of 55.4%.

Capecitabine is also synergistic when combined with oxaliplatin. A phase II study of the combination (CapeOx) reported a partial remission rate of 50%. However, a recent randomized trial of Capiri versus FOLFIRI found that Capiri was inferior in efficacy and more toxic, but equivalent to CapeOx.

Figure 1. Progression-Free Survival with FOLFIRI Versus FOLFOX-6 in First-Line and Second-Line Therapy

Figure 2. Response Rates of Metastases to Treatment with Capecitabine Versus Fluorouracil/Leucovorin

- FU = fluorouracil
- *P < .05
- †Predominant site of metastases.
**BEVACIZUMAB**

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), which is overexpressed in many tumor types, including CRC. When used as third-line therapy—after FU, irinotecan, and oxaliplatin—it has virtually no activity. However, when added to FU/LV in a phase II study, it produced a 40% response rate, delayed time to disease progression, and increased overall survival by 8 months.35

The first large study evaluating bevacizumab compared bolus IFL plus placebo versus bolus IFL plus bevacizumab versus FU/LV plus bevacizumab in a total of 925 patients with previously untreated metastatic CRC.36 Irinotecan 125 mg/m² was administered for 4 weeks out of 6, and bevacizumab 5 mg/kg was administered every 2 weeks. IFL plus bevacizumab was significantly better than IFL plus placebo with respect to response (partial remission) rate (45% vs 35%; P = .001), duration of response (10.4 months vs 7.1 months; P = .0014), median progression-free survival (10.6 months vs 6.2 months; P = .00001), and median overall survival time (20.3 months vs 15.6 months; P = .00003). These encouraging findings represent an alternative for patients with disease recurrence after IFL.

A more recent study (NO 16966) utilized a 2 x 2 placebo-controlled design to evaluate CapeOx and FOLFOX-4 regimens with and without bevacizumab.37 Although the addition of bevacizumab to either CapeOx or FOLFOX-4 had little effect on response rates, there was a statistically significant increase in progression-free survival time of 1.5 months in patients receiving CapeOx plus bevacizumab versus CapeOx plus placebo and 2 months in those receiving FOLFOX-4 plus bevacizumab versus FOLFOX-4 plus placebo. In addition, fewer patients receiving bevacizumab (vs placebo) discontinued treatment because of disease progression, but more patients receiving bevacizumab (vs placebo) discontinued treatment because of adverse events.

**CETUXIMAB**

Cetuximab, a chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR), is typically administered with irinotecan, which increases the time to disease progression from 1.5 months to 2.9 to 4.0 months.38

The most frequently reported toxicities (all grades and grade 3/4) with cetuximab are malaise, diarrhea, nausea, vomiting, leukopenia, acneiform rash, and infusion reactions.39 With the exception of the rash and infusion reactions, which occurred with about the same frequency in patients receiving cetuximab only and cetuximab plus irinotecan, adverse events were more common in those receiving combination therapy and were attributed to irinotecan.

**PANITUMUMAB**

Panitumumab is a fully human monoclonal antibody targeting EGFR, which is overexpressed in many tumor types, including CRC.

Dose escalation studies in patients with different tumor types demonstrated that the principal toxicity was an acneiform rash in most patients receiving at least 3 doses of panitumumab 1.0, 1.5, 2.0, or 2.5 mg/kg/week.40 All patients receiving the highest dose developed the rash, which reached maximal intensity between weeks 3 and 5, but then steadily abated with continued treatment. In contrast, a study examining a wider range of dosing schedules found a lower incidence of skin toxicity.41 The study also found that pharmacokinetics were stable over the range of dosing schedules and that 5 of the 39 patients with CRC (57 additional patients had other forms of cancer) achieved a partial remission.

Two studies of panitumumab monotherapy in patients with metastatic CRC who were refractory to prior chemotherapy with fluoropyridimines, irinotecan, and/or oxaliplatin have shown favorable results.42,43 In a phase II, open-label study, patients with 10% or more 1+ EGFR staining by immunohistochemistry were stratified into 2 cohorts by high (n = 105) or low (n = 43) staining intensity and treated with intravenous panitumumab 2.5 mg/kg for 8 of every 9 weeks until disease progression or unacceptable toxicity.42 Overall response by central review was 9% and was similar between the cohorts. An additional 29% of patients had stable disease. Median progression-free survival time was 14 weeks and median overall survival time was 9 months. No antibody formation was detected, and the single patient who experienced an infusion reaction was able to continue therapy. Although skin toxicity was common (95%), it was rarely severe (5%).

A more recent study of 203 patients who had low (1%–9%) or negative (<1%) levels of EGFR expression on tumor membranes found that monotherapy with
Panitumumab (6 mg/kg every 2 weeks) had antitumor activity and produced similar rates of objective response in both groups. Duration of response ranged from 12 to 46 weeks in nonexpressers who responded to panitumumab and from 8 to 28 weeks in low expressers. Median progression-free survival time was 11 weeks in nonexpressers and 7.9 weeks in low expressers.

A study evaluating a combination of panitumumab and IFL as first-line therapy in patients with metastatic CRC required all patients to have EGFR expression of 1+, 2+, or 3+ in 10% or more of cells by immunohistochemistry. Although the first 19 patients received panitumumab and bolus IFL weekly for 4 weeks of each 6-week treatment cycle, the change in the standard of care from bolus IFL to infusional IFL led to an amendment to the study protocol to include the FOLFIRI regimen. The findings are encouraging.

In the first part of the trial, the partial response rate was 47%, with 5 additional patients (26%) having stable disease. Thus, the disease control rate (overall response plus stable disease) for panitumumab and bolus IFL was 74%. The median progression-free survival time was 5.6 months and overall survival time was 17 months.

Results in 24 patients from part 2 of the trial, in which panitumumab was combined with FOLFIRI, were similar to those seen in part 1. The disease control rate was 79%, with 33% of patients achieving a partial response and 46% exhibiting stable disease. The median progression-free survival time was 10.9 months. However, overall survival data are not yet mature.

A study comparing panitumumab with best supportive care in 463 patients with very advanced CRC has shown that treatment with panitumumab is clearly better, despite the lack of any difference in overall survival (Table 2). Using progression-free survival as the major outcome measure, the study allowed patients who had a relapse to cross over from best supportive care to panitumumab. Overall survival results were confounded by the crossover.

Although the Panitumumab Advanced Colorectal Cancer Evaluation Study comparing FOLFOX/bevacizumab and FOLFIRI/bevacizumab regimens with or without panitumumab was recently halted, an ongoing phase I study is evaluating concurrent therapy with panitumumab and AMG 706, an oral agent with activity against multiple tyrosine kinases, including VEGF. Another ongoing trial is evaluating panitumumab in combination with chemotherapy.

**CONCLUSIONS**

Treatment strategies for CRC include surgery for stages I, IIA, and IIB, surgery plus adjuvant chemotherapy for stages IIC and III, and palliation with chemotherapy rather than best supportive care for stage IV.

Adjuvant chemotherapy is not the standard of care for stage II CRC because surgery alone cures 75% of patients with stage II disease. However, adjuvant chemotherapy can be reasonably offered to high-risk patients with stage II disease with T4 lesions, poorly differentiated tumors, evidence of lymphatic, neural, and/or vascular invasion, and less than 12 lymph nodes sampled.

Until the late 1990s, FU/LV was the standard adjuvant therapy for stage III and stage IV metastatic CRC. Since then, 6 new agents (irinotecan, capecitabine, oxaliplatin, cetuximab, bevacizumab, and panitumumab) have been approved for CRC, leading to new combination regimens (eg, FOLFOX, FOLFIRI, FOLFOXIRI, and others) and to new standards of care.

The approval of oral capecitabine led to regimens that combined this drug with irinotecan (Capiri) and **Table 2.** Progression-Free Survival and Other Outcomes with Panitumumab Versus Best Supportive Care

<table>
<thead>
<tr>
<th><strong>Primary analysis</strong></th>
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<tr>
<td>Powered to detect a 33% difference in PFS</td>
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<tr>
<td>463 patients: 231 receiving panitumumab, 232 receiving BSC</td>
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<tr>
<td>Risk reduction by panitumumab: 46% (P &lt; .0001)</td>
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<tr>
<td>Partial response at 12 months: 10% for panitumumab vs 0% for BSC</td>
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<tr>
<td>PFS at 6 months: 18% for panitumumab vs 5% for BSC</td>
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<tr>
<td>PFS at 8 months: 20% for panitumumab vs 4% for BSC</td>
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<tr>
<td>Overall survival: no difference</td>
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<tr>
<td>Hazard ratio for all events: 0.54 at 48 months</td>
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<th><strong>Crossover analysis</strong></th>
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<tr>
<td>174 BSC patients crossed over to panitumumab arm</td>
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<tr>
<td>Complete response: 1%</td>
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<tr>
<td>Partial response: 9%</td>
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<tr>
<td>Stable disease: 32%</td>
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BSC = best supportive care; PFS = progression-free survival.
Data from Van Cutsem et al. 45
oxaliplatin (CapeOx), both of which demonstrated efficacy. In addition, capecitabine has been found to be superior to FU/LV against lung and liver metastases. The addition of monoclonal antibodies to existing regimens has led to several studies evaluating these agents as monotherapy and second- and third-line therapy. Results from several recent and ongoing studies suggest that these agents provide additional improvements in clinical outcomes.

**Discussion Highlights**

**Community Versus Specialty Pharmacy Issues**

*Dr Waddell:* Now that we have oral agents such as capecitabine, my concern is that patients who are filling their prescriptions at their community pharmacy may forget about the drug-free interval and perhaps the community pharmacist won’t pick up on that when the patient comes in for a refill. I teach my pharmacy students that many oral chemotherapy drugs have these intervals and why it is essential for the patient to understand that.

*Dr Iacovelli:* It also raises a concern about compliance. When patients have reactions to an intravenous bolus or infusion in your clinic, you know the medicine went in. But it’s another story when they have reactions to oral medications. When asked, patients often say, “Everything’s fine.” Meanwhile, they’ve discarded half the bottle because of side effects.

We had a patient whose pharmacist filled the capecitabine prescriptions for a long period of time without instructing him about the drug break. He continued to take the drug daily for approximately 6 weeks and wound up in the hospital with bad hand-foot syndrome.

*Dr Ignoffo:* There really is a need in the pharmacy school curriculum and in our continuing education programs to address the role of the pharmacist in the community setting with regard to oral chemotherapy.

Another important issue is drug interactions. For example, capecitabine enhances the effects of warfarin and there are many patients with epithelial cancers who are at risk for clotting disorders and are also receiving warfarin. Pharmacists should advise these patients to monitor their INRs (international normalized ratios) a little more closely during the time they are on capecitabine.

*Dr Heaton:* In the managed care environment, we’re increasingly taking that out of the hands of the community pharmacists. Oral targeted agents are not a community pharmacy issue. They are specialty pharmacy drugs. We have different systems set up to guarantee persistence, with refill reminders and gap reminders.

As for drug interactions, we learned that, in most cases, they sail through pharmacy systems. However, community pharmacists don’t have their computer systems tagged to the actual filling. We put in hard edits and stops to safeguard the system.

*Mr Solimando:* By taking it out of the community pharmacy, aren’t you concerned that you are fragmenting care and might not know what other medicines the patient is on? Aren’t you concerned that the community pharmacist may not know that the patient is on capecitabine or one of the tyrosine kinase inhibitors, and therefore won’t be able to do the proper screening for interactions?

*Dr Heaton:* No, because we use one common adjudication system and community pharmacists may have their system underneath that. We have a separate one that crosses all lines—mail order, community, specialty, you name it. It all goes on one platform that way.

*Mr Rutledge:* What about the opposite end of the spectrum, in which you’ve got a closed system? The prescription is going out to the specialty pharmacy, but the closed system doesn’t realize that.

*Dr Heaton:* Many of our oncology clinics have an existing pharmacy within. Although the existing pharmacy could bill us directly on-line, they have a tendency to bundle claims under J codes on the medical side and bill as a batched process. We’ve created some systems to sort that out. In some respects, we take the view that it’s easier to mandate than it is to educate because it’s difficult to give to everybody. However, if we can put a system in place that prevents it, that’s the best. Ironically, it’s the pharmacies within the oncology clinics that are the most resistant to that.

*Dr Ignoffo:* That works for your particular managed care system, but it may not work for all. Let’s say you have a patient on an oral agent that has a lot of drug interactions and the specialty pharmacy receiving that order may not have the patient’s entire list of medications.

*Mr Solimando:* What I see as a major problem with oral anticancer agents is the proliferation of different specialty pharmacies. Depending on your patient, you might have to deal with 4 or 5 specialty pharmacies and the different sets of standards for different drugs. At what point are we going to say these are counterproductive?

*Dr Heaton:* I have 2.8 million members nation-
wide. I deal with 4 specialty pharmacies and roughly 61,000 retail pharmacies. It’s a lot easier for me to deal with 4 than it is with 61,000, and I think many more plans are going to follow this route.

Mr. Bullard: I’m concerned about the edits and hard stops on oral therapies, especially when there is a need for some sort of clinical intervention at that point in therapy. Is it too pragmatic to allow a prescription to proceed if the patient has a requisite gap interval in drug therapy? Is the use of edits contrary to the goals of the chemotherapy? Does it create a rebellion among practitioners, and does it create too much of a barrier for patients who have to wait for somebody to make an extra phone call when they get to the pharmacy to fill or refill a prescription? What are your perceptions at the clinic level?

Dr. Iacovelli: It’s multifactorial. It’s a combination of all those things you just mentioned. If you go to a pharmacy that handles 100 prescriptions a day, it’s probably not an issue for the pharmacist to stop what he or she is doing and make a phone call. However, if you go to a chain pharmacy that is handling 100 prescriptions an hour, that might be a big issue.

Monitoring Liver Function

Dr. Waddell: There have been several reports in the literature linking oxaliplatin with veno-occlusive disease and some cases of liver failure. Although liver function tests may not be needed to adjust an oxaliplatin dose, should you monitor liver function occasionally for early signs of liver damage?

Dr. Ignoffo: In many practices, platinum compounds are often combined with taxanes, at least in my patient population, which was gynecologic oncology. We’d get a monthly chemistry panel, including liver function tests, because we had to know whether we needed to modify the taxane dosing. Liver function would be a natural monitoring parameter in CRC because many of these patients have metastatic disease in the liver. Serial chemistries should be done on a monthly basis, or at least every 6 weeks.

Mr. Solimando: We get a complete blood count and a chemistry panel at each cycle. If a patient has not had a problem in the past, we may treat him before we get the chemistry panel back, but it does get looked at. I can’t recall a single case of veno-occlusive disease with oxaliplatin, but I’d certainly wonder what was going on if the bilirubin or transaminase levels were elevated. In that case, I’d probably adjust the oxaliplatin dose.

FOLFOX Regimens and Dose Escalation

Dr. Waddell: It’s been interesting to follow the FOLFOX regimens. If I’m not mistaken, there was no FOLFOX-5.

Mr. Solimando: There was, but it was never published. It was an abstract only.

Dr. Waddell: What has your experience with the FOLFOX regimens been like? Do all patients in your clinic receive oxaliplatin 85 mg/m² or are they tolerating the higher doses?

Dr. Iacovelli: I believe there was a published trial that showed no difference in efficacy with any of the doses. However, it’s a fairly toxic drug and I’ve seen patients who developed neuropathies. If all 3 doses are the same in terms of efficacy, we opt for the lowest dose.

Dr. Ignoffo: The standard now is FOLFOX-4, 85 mg/m².

Mr. Solimando: I think we’re seeing a variation of FOLFOX-6 because our doctors and our patients especially like the single (46- to 48-hour) infusion rather than coming in the next day for the extra bolus. We’re using the lower dose of oxaliplatin and giving it as a single infusion.

Mr. Rutledge: I don’t recall the specific published study evaluating the modified version of FOLFOX-6, but this regimen is used frequently to eliminate the need for patients to return to the clinic on consecutive days, especially when they have to travel long distances.

Dr. Iacovelli: I’d like to mention an ongoing dose-escalation study with cetuximab, the EVEREST trial, in which the dose is being titrated to the rash. Most patients develop a rash after a loading dose of cetuximab, but it tends to abate when they go to the weekly dose.

Dr. Waddell: I’m glad you mentioned that. It’s a situation in which we want patients to get the rash because it relates to therapeutic efficacy.

REFERENCES


