ABSTRACT

Colorectal cancers are the second leading cause of cancer deaths worldwide. If detected early, surgical resection can result in a cure; however, often disease is only detected after metastasis. For decades the standard for chemotherapy was 5-fluorouracil (5-FU) plus leucovorin. In recent years these drugs have been joined by a host of others, including the cytotoxic drugs irinotecan and oxaliplatin, in addition to biological drugs that inhibit epidermal growth factor signaling (cetuximab and panitumumab) and vascular endothelial growth factor signaling (bevacizumab). Clinical trials have been performed to assess which combinations of these drugs might be most efficacious. The current standard regimens for metastatic disease include FOLFIRI (5-FU, leucovorin, and irinotecan) and FOLFOX (5-FU, leucovorin, and oxaliplatin). Patients who fail one of these regimens often benefit from the second regimen. Intermittent treatment does not seem to decrease survival and can decrease toxicity. Biologic agents are being combined with these cytotoxic agents with some success. Perhaps the most important role of these new chemotherapies is in the setting of potentially resectable metastatic disease, in which they cause sufficient regression of metastases to allow surgical resection in many more cases than was previously possible. It is clear that no one therapy will suit all patients. Instead, therapies will need to be tailored to the individual and prognostic tests will need to be devised that will assist in the process. (Adv Stud Med. 2007;7(2):39-44)

CURRENT APPROACHES AND MANAGEMENT OF ADVANCED COLORECTAL CANCER*

Daniel G. Haller, MD†

Early detection of a colon carcinoma allows for surgical resection with a high probability of cure. However, not all cancers are detected at such an early time point. Metastatic disease requires chemotherapy. With the advent of new drugs, new drug combinations have become possible leading to several questions which need to be addressed: Do all patients need all of these available drugs at once? Is the intent to cure the disease, or if the disease is too advanced, is the regimen intended to give the patient more time? Because the current chemotherapeutic options available all have associated toxicities, what are the best stop-and-go schedules and what therapies, if any, are best to administer during these treatment breaks? It is becoming apparent that there are now several useful endpoints that can be identified for these patients, and new clinical trials will need to choose among these endpoints during the trial design. It is also becoming apparent that different patients respond differently to various chemotherapeutic regimens indicating that treatment will have to become individualized in the future. To do this, better predictive tests will need to be developed.

CURRENT REGIMENS

Current chemotherapeutic agents widely used to treat metastatic colorectal cancer (MCRC) include the fluoropyrimidine analog 5-fluorouracil (5-FU), the
orally active 5-FU prodrug capecitabine, the 5-FU bio-
modulator leucovorin, the topoisomerase I inhibitor
irinotecan, and the third-generation platinum com-
pound oxaliplatin. Additionally, biologics, such as the
monoclonal epidermal growth factor receptor (EGFR)
antibodies, cetuximab and panitumumab, and the
monoclonal anti-vascular endothelial growth factor
(VEGF) antibody bevacizumab have been developed.
Several studies have been performed assessing the perfor-
mance of these drugs as monotherapies and in combina-
tion. A list of the currently used regimens is shown in
Table 1. Two clinical trials reported in 2000 looked at
irinotecan plus 5-FU/leucovorin, and on the basis of
these results the combination of IFL (irinotecan and 5-
FU/leucovorin) became the standard of care for a time.2,3
The IFL regimen was subsequently modified to become
the FOLFIRI (5-FU, leucovorin, and irinotecan) regi-
men. A third clinical trial looked at the combination of
FOLFOX4 (5-FU, leucovorin, and oxaliplatin); howev-
er, although progression-free survival was better than
with 5-FU/leucovorin alone (9 months vs 6.2 months, \( P = .0003 \)) the overall survival time (16 months vs 14.2
months, \( P = .12 \)) did not reach statistical significance.4
Several studies published in 2004 contested this view. A
crossover study was performed comparing IFL with
FOLFOX and with the combination of IROX (irino-
tecan and oxaliplatin).5 Time to progression was longer
with FOLFOX (8.7 months vs 6.9 months, \( P = .001 \)) as
was overall survival (19.5 months vs 15 months).
Results from the Multicenter International Study
of Oxaliplatin/5-FU/Leucovorin in the Adjuvant
Treatment of Colon Cancer study compared FOL-
FOX4 to a 5-FU/leucovorin regimen in patients with
resected stage II or stage III colon cancer.6 Again, dis-
ease-free survival was significantly improved with the
FOLFOX4 regimen. One important observation was
that bolus administration of 5-FU, although much
more convenient, leads to significantly worse toxicity
in combination regimens. A recent phase III random-
ized study directly compared FOLFOX4 with
FOLFIRI and found them to be indistinguishable in
terms of time to progression, overall survival, and
duration of response.7 Their differences mainly lay in
the toxicity profiles. Patients on the FOLFIRI arm
experienced relatively more nausea, diarrhea, mucositis, hair loss, and cholinergic syndrome whereas patients on the FOLFOX4 arm experienced relatively more thrombocytopenia and neurologic toxicities. Given these results, FOLFOX and
FOLFIRI can be considered equivalent as a first-line
treatment for colorectal cancer (CRC).

The XELOX Study

5-fluorouracil is metabolized by dihydropyrimi-
dine dehydrogenase (DPD), and DPD activity levels
vary widely among the patient population. There is a
correlation between slow metabolizers and 5-FU toxici-
ity. Oral prodrugs, such as capecitabine, tend to be
converted to 5-FU in close proximity to the tumor,
thus resulting in theoretically higher concentrations.
Additionally, as 5-FU infusion over several days is
more efficacious and less toxic than administration of
a 5-FU bolus, it was thought that orally administered
capcitabine would mimic the infusion process.
However, there has been some difficulty in establishing
a protocol allowing for the safe administration of
capcitabine. Results of a study combining XELOX (also
known as CAPOX [capcitabine and oxaliplatin]) has
been promising; however, they have led to some inter-
esting observations.8 For example, this safety issue
appears to be most prevalent in the US patient popula-
tion. A multivariate analysis was performed on the
XELOX population comparing US patients as compared
to the rest of the world.9 As shown in Table 2,9 the rela-
tive risk for virtually all adverse events was greater for US
patients. The reason for this is unclear. Potential factors

### Table 1. Commonly Used Regimens for MCRC

<table>
<thead>
<tr>
<th>Biochemically modulated 5-FU only regimens</th>
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<tbody>
<tr>
<td>Mayo Clinic</td>
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<tr>
<td>Roswell Park</td>
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<td>LV5FU2</td>
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<tr>
<td><strong>Oxaliplatin-based regimens</strong></td>
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<tr>
<td>FOLFOX</td>
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<tr>
<td>FLOX</td>
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<tr>
<td>XELOX (or CAPOX)</td>
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<tr>
<td><strong>Irinotecan-based regimens</strong></td>
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<tr>
<td>IFL</td>
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<tr>
<td>FOLFIRI</td>
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<td>Capiri</td>
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*Also given qwk X 6 with 2-wk break.
5-FU = 5-fluorouracil; LV = leucovorin; MCRC = metastatic colorectal cancer.
may include methodology, baseline prognostic factors, diet, and culture. Of these, dietary folate has been given the greatest attention. Dietary folate intake has been inversely correlated with CRC risk. Folate plays an essential role in the biosynthesis of methyl group donors to DNA and is thought to decrease the extent of aberrant methylation associated with CRC. Surprisingly, a group has recently reported that the relationship between folate and CRC is more complex. Their observation of a bell-shaped curve describing the relationship between folate levels and CRC risk has led them to propose that there exists contexts in which low dietary folate may serve a protective role.

Should all patients receive all drugs? A study by Grothey et al looked at survival as a function of the presence of 3 chemotherapies: 5-FU/leucovorin, oxaliplatin, and irinotecan. Seven recent independent phase III trials were analyzed to assess the importance of the availability of these 3 agents. Strikingly, the authors found that overall survival correlated significantly with the presence of all 3 drugs during the course of their disease ($P = .0008$) but did not correlate with the percentage of patients who received any 1 second-line therapy ($P = .19$). Another study compared a 2-drug regimen, FOLFIRI, with a 3-drug regimen, FOLFOXIRI (5-FU/folinic acid, oxaliplatin, and irinotecan). The overall response rate for FOLFIRI was 34% as compared to 60% for FOLFOXIRI, again suggesting that 3 drugs are better than 2. Progression-free survival was extended by approximately 3 months (median 6.9 months vs 9.8 months) whereas overall survival was extended 6 months (median 16.7 months vs median 22.6 months).

### The OPTIMOX Study Series

Whereas increasing the number of drugs certainly increases the response rate and extends survival, it also increases toxicity and cost of treatment. One way to manage cost along with toxicity is to limit the patients’ exposure to the regimens. Oxaliplatin is a case in point. Unlike earlier platinum compounds, oxaliplatin is not associated with significant nephrotoxicity or ototoxicity. Rather, its toxicity profile includes hypersensitivity and neuropathy. Neuropathic toxicities can be divided into 2 classes. Perhaps 85% to 95% of toxic reactions are acute and consist of a mild transitory paresthesia. The remaining toxicities are cumulative, dose dependent, and consist of grade 3 paresthesia, dysesthesia, and sensory ataxia. Deterioration is progressive and leads to functional impairment. However, after discontinuation of the therapy, the symptoms gradually reverse. In the OPTIMOX study, a continuous FOLFOX4 regimen (in which the patient was treated until progression or treatment failure) was compared to an intermittent FOLFOX7 regimen (6 cycles) with maintenance 5-FU/leucovorin (12 cycles) and reintroduction of FOLFOX7 (6 cycles). The duration of disease control and overall survival curves were virtually identical. Importantly, the number of grade 3/4 neurotoxicities was significant reduced. On the FOLFOX4 arm approximately 16% of patients developed neurotoxicity by cycle 13 whereas only 7% of patients on the maintenance arm developed a similar toxicity. These data indicate that the patient does not need to be on all 3 drugs all the time for the best outcome. In the OPTIMOX study patients were managed with a chemotherapy break or “holiday.” The OPTIMOX-2 study is currently looking at whether chemotherapy-free intervals have any deleterious effect on survival. The data support the hypothesis that patients with good prognoses after first-line therapy are potential candidates for chemotherapy-free intervals. In a similar fashion, the COIN study is examining the effects of intermittent chemotherapy in Great Britain. Finally, the OPTIMOX-3 trial will be looking at the use of biologic agents during the chemotherapeutic “holiday”—specifically bevacizumab in the presence or

<table>
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<th>Table 2. Logistic Regression of XELOX (or CAPOX) Patients: US vs RoW</th>
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<tr>
<td><strong>Adjusted Relative Risk (95% CI)</strong></td>
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<tr>
<td>Grade 3/4</td>
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<tr>
<td>AEs</td>
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<td>First-line MCRC data</td>
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<td>• US vs non-US</td>
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<td>Adjuvant colon cancer</td>
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<td>• RoW vs Asia</td>
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AE = adverse events; CI = confidence interval; GI = gastrointestinal; MCRC = metastatic colorectal cancer; RoW = rest of world; XELOX (or CAPOX) = capecitabine and oxaliplatin.

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absence of the small-molecule EGFR kinase inhibitor, erlotinib.

**Predictive Markers: The ECOG 5204 Study**

Given that it is clear that the population of patients with advanced CRC is heterogeneous, it is likely that individualized chemotherapies could greatly increase survival. The question is how to associate the appropriate chemotherapies with the appropriate patients. Considering the metabolism of 5-FU, several correlations have been made. Fluoropyrimidines work by inhibiting thymidylate synthase (TS) thus causing cell death in rapidly dividing cells. Tandem repeat polymorphisms have been identified in the TS promoter that have been shown to affect TS expression. For example, 3 copies of the tandem repeat TS enhancer region (TSER*3) result in a 2.6-fold increase in TS expression in vitro. This is relevant as approximately 30% of Caucasian patients with CRC have the TSER*3/TSER*3 genotype and respond poorly to 5-FU treatment. The topoisomerase I inhibitor, irinotecan, is a prodrug that is converted by liver carboxylesterase to form the active compound 7-ethyl-10-hydroxycamptothecin (SN-38). SN-38 is then further metabolized to an inactive glucuronide by 1 of several UDP-glucuronosyltransferases (UGT) including UGT1A1, UGT1A6, UGT1A9, and extrahepatic UGT1A7. As with metabolism of 5-FU, a tandem repeat within the UGT1A1 promoter has been associated with irinotecan toxicity, most notably neutropenia. Recently, UGT1A7 and UGT1A9 polymorphisms also have been shown to have predictive value. These data have led to the design of clinical trials to assess the use of these predictive markers. ECOG (Eastern Cooperative Oncology Group) 5204, for example, is comparing high and low TS expressers, placing the low expressers on a FOLFOX regimen whereas the high expressers are placed on a FOLFOX regimen or an IROX regimen that dispenses with 5-FU. The results from this trial will be quite informative.

Angiogenesis is another case in point. Although the importance of angiogenesis in cancer is undisputed, blockade of VEGF signaling (which has been shown to block angiogenesis) did not enhance survival in the Colorectal Oral Novel Therapy for the Inhibition of Angiogenesis and Retarding of Metastases (CONFIRM) 1 trial. Here patients were treated with FOLFOX4 plus vatalinib (an experimental small-molecule multi-VEGF receptor inhibitor) or placebo. Overall response rate was 42% for the vatalinib arm and 46% for the placebo arm, respectively. The hazard ratio (HR) was not significant for the 2 arms (HR = 0.88, P = .118). However, when a meta-analysis was performed on several trials including CONFIRM 1, it was established that patients who express high levels of lactate dehydrogenase (LDH) did show increased survival with vatalinib (HR = 0.68, P = .012). A correlation between LDH and survival in operable CRC also has been observed. Because LDH is responsible for the anaerobic conversion of pyruvate to lactate, the logic is that high LDH levels indicate a hypoxic state which strongly correlates with an activated VEGF pathway.

**Studies Considering the Biologic Therapies**

Careful consideration of the benefits of the biologics in CRC is especially important given their expense (Figure). In a randomized phase III trial, bevacizumab, when combined with irinotecan plus bolus 5-FU/leucovorin in the first-line treatment of MCRC, led to an increased median survival, progression-free survival, and response rate compared with the cytotoxic chemotherapy alone. As just described, VEGF inhibition can be beneficially combined with FOLFOX4.
in a subset of patients. Unlike bevacizumab, cetuximab is active in irinotecan-refractory CRC. Cetuximab also is being examined in combination with FOLFOX or FOLFIRI regimens and with VEGF inhibition through bevacizumab in the CALGB/SWOG (Cancer and Leukemia Group B/Southwest Oncology Group) 80405 trial, however the data is not yet available. In the CALGB 80203 trial, previously untreated patients with MCRC were given FOLFOX or FOLFIRI regimens in the absence or presence of cetuximab. Although the numbers of patients are small, it appears that the addition of cetuximab improves the response rate as a whole (Table 3; \( P = 0.029 \) for upper row). Interestingly, as shown in Table 4, if this is broken down into FOLFOX and FOLFIRI treatments, it appears that cetuximab may interact more beneficially with oxaliplatin-based therapies (ie, FOLFOX) than irinotecan-based therapies (ie, FOLFIRI).

Perhaps the most important aspect of how treatment for MCRC has changed in recent years is that with improved surgical techniques for metastatic disease coupled with the above mentioned improvements in chemotherapy, many more patients can be offered potential therapy. In this regard the added expense of the biologics is not wasted resources. However, it is not the case that a single adjuvant chemotherapy will prove to be the perfect solution. Each patient will need an individualized treatment plan depending on a multiplicity of factors.

**CONCLUSIONS**

Adjuvant chemotherapies have been significantly improved with the introduction of the cytotoxic agents irinotecan and oxaliplatin, in addition to the biologic agents designed to inhibit EGFR and VEGF receptor signal transduction pathways. However, it has become apparent that the patient with MCRC will not be served with 1 therapeutic regimen. Clinical trials have established that 5-FU/leucovorin protocols can be improved by the introduction of irinotecan (ie, FOLFIRI) or oxaliplatin (ie, FOLFOX) and that continuous infusion is superior to bolus 5-FU administration in that toxicities are significantly reduced. Indeed FOLFOX and FOLFIRI regimens appear to be quite similar in terms of overall survival and time to progression, differing only in the toxicity profile. It is apparent that patients can benefit from regimens that include 5-FU, oxaliplatin, and irinotecan with the third agent supplied to patients that fail the first 3.

Finally, the biologic agents appear to have efficacy as single agents and in combination with the cytotoxic agents. Trials are currently under way to establish appropriate combinations. Perhaps the most interesting result thus far is the observation that the oxaliplatin/cetuximab combination may be superior to the irinotecan/cetuximab combination, however additional patient data are needed to confirm this. Whereas these newer therapies have tremendously increased treatment costs, they have also increased patient quality of life and life span. Indeed, with parallel improvements in surgical techniques, combination chemotherapy has greatly increased the number of instances in which CRC is resectable. In this regard, a cure has become possible for a much greater percentage of the population than ever before.

**REFERENCES**

2. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as