Therapy for Metastatic Colorectal Cancer

RICHARD M. GOLDBERG

Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

Key Words. FOLFOX • FOLFIRI • Bevacizumab • N9741 • PTK 787 • Cetuximab

Abstract

Median overall survival of metastatic colorectal cancer patients treated with first- and second-line combination chemotherapy now extends to more than 20 months in some studies. Chemotherapy alone, particularly when oxaliplatin is included, may allow potentially curative resection of advanced disease. There is evidence that the addition of antibodies targeted against vascular endothelial growth factor or the epidermal growth factor receptor will further improve prospects for patients with advanced and metastatic disease. However, the optimum sequencing of chemo- and biological therapies remains to be established, as does the potential contribution of numerous agents in development. The Oncologist 2006;11:981–987

Introduction

Compared with the limited survival impact during the simple days when 5-fluorouracil (5-FU) was essentially the only chemotherapy choice, the therapy of metastatic colorectal cancer (CRC) is now in a state of creative chaos. This era of proliferating possibilities has spawned any number of algorithms suggesting how patients should be guided through first, second, and subsequent lines of therapy. For the most part, these algorithms suggest first-line use of a chemotherapy combination (such as oxaliplatin/5-FU/leucovorin [FOLFOX] or irinotecan/5-FU/leucovorin [FOLFIRI]) coupled with bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), followed by alternative chemotherapy combinations and other novel agents.

However, a broad conclusion can clearly be drawn from the mass of trial evidence: choice of first-line regimen does indeed matter, and the use of combination regimens is preferable to use of single agents.

A review of the literature suggests that the leucovorin (LV)-modulated single-agent 5-FU regimens of Saltz, Douillard, and de Gramont achieved a median overall survival (OS) of 15 months or less (Fig. 1) [1–5]. Combination...
The regimens of FOLFOX and FOLFIRI consistently lead to median survivals in the 15- to 20-month range. The combination of irinotecan/bolus fluorouracil/LV (IFL) plus bevacizumab seems at least to have matched this and raises the probability of even better statistics when optimized combination regimens delivering the 5-FU via infusion are combined with bevacizumab [6–7]. Overall, combinations seem to confer a 5- to 6-month advantage in median OS when compared with single-agent chemotherapy.

This conclusion has not been altered by the recent FOCUS trial. Initial data [8] suggested that there was no statistically significant difference in outcome between the strategy of using serial single agents and that of using doublets in 2,135 previously untreated stage IV patients. Median OS with serial agents was 13.7 months, and that with FOLFIRI was 16.2 months. However, a more recent report suggests that the advantage of using doublets, though modest, has become statistically significant [9].

**Figure 1.** Median overall survival of selected regimens. Abbreviations: 5-FU/LV, 5-fluorouracil/leucovorin; FOLFIRI, irinotecan/5-fluorouracil/leucovorin; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; IFL, irinotecan/bolus 5-fluorouracil/leucovorin; OS, overall survival.

**Areas of Uncertainty**

**Tolerability in Poor-Risk Patients**
The emphasis on doublets raises the question of the tolerability of FOLFOX or FOLFIRI in poor-risk or elderly patients. Data suggest that OPTIMOX is active (response rate [RR], 56%) and well tolerated in patients with raised alkaline phosphatase, 75% of whom were performance status (PS) 1–2 [10, 11]. Also, Tournigand et al. reported that patients aged over 70 had the same RR as younger patients in their trial of FOLFOX and tolerated the regimen equally well [12]. However, there are few published data on the tolerability and efficacy of first-line irinotecan-based regimens in the elderly or poor PS group.

**Bolus or Infusion?**
A second issue concerns the optimum means of delivering 5-FU: should this be by bolus or infusion, or as an oral prodrug?

Four studies have compared investigational regimens against a Mayo Clinic (Rochester, MN) regimen control arm [13–16]. In each case, the median OS was not significantly different from control. However, the trial reported by de Gramont et al. clearly showed that the infusion-based LV5-FU2 is a better-tolerated regimen than the bolus-based program developed at the Mayo Clinic [13]. There is a substantially lower frequency of diarrhea and neutropenia. Importantly, the comparisons involving capecitabine at the recommended doses suggested by the package insert of 1,250 mg/m² twice daily showed an overall incidence of grade 3–4 adverse events of nearly 40%, i.e., comparable with that reported with the Mayo regimen [15, 16].

Bolus 5-FU was used in three arms of study N9741 [17, 18]. It is important to note that all had to be modified or closed because of toxicity and the risk of treatment-related mortality (death within 60 days) (Tables 1, 2), including the IFL arm, which delivered the U.S. standard of care at the time. This exceeded 8% in both the irinotecan plus bolus 5-FU/LV and oxaliplatin plus bolus 5-FU/LV arms.

Delivering 5-FU by infusion rather than by bolus is associated with substantially less risk of early death (3%–4%) in the FOLFOX arm of N9741 and in the FOLFOX and FOLFIRI arms of the Tournigand trial. The infusional 5-FU in FOLFOX is also associated with substantially less febrile neutropenia than its delivery by bolus. Overall, such data make a powerful case for the use of European-style 5-FU regimens. The possible role of capecitabine, with the potential advantages of oral administration, is extensively considered elsewhere in this volume [19].

**Choosing a Combination**

**First Line**
For several commonly used first-line regimens (notably FOLFOX or FOLFIRI plus bevacizumab), supportive data from phase III studies are being collected but have not yet been reported. This is also true of combinations of FOLFOX or FOLFIRI plus cetuximab. Community oncologists in the U.S. are frequently inclined to favor capecitabine plus oxaliplatin or irinotecan, again without evidence of improved outcome from mature trials.
The first-line combinations that have proven superior to comparators in phase III trials are FOLFOX, FOLFIRI, and IFL plus bevacizumab [1, 6, 20–26]. Second line, FOLFOX plus bevacizumab has also shown significant additional benefit in a randomized trial over FOLFOX alone [27].

Comparisons across trials must be accompanied by the usual caveats. Nevertheless, it is interesting that the N9741 trial and that of Tournigand et al., though differing in complexity and hence in number of patients accrued, had a remarkably similar outcome in their common FOLFOX arms (Fig. 2, Table 3) [17, 18, 22]. The RRs were 54% and 45%, respectively; the median times to progression (TTPs) were 8 and 8.7 months, and the median OS times were 21 and 20 months.

In N9741, the fact that the 20-month OS with FOLFOX was highly significantly longer than the 15 months seen with IFL (accompanied by the greater toxicity of the latter regimen) has relegated IFL to the history books in the opinion of many leading investigators. However, in the study of Tournigand et al., outcome with FOLFOX was virtually identical to that with FOLFIRI. In this comparison, FOLFOX was associated with markedly higher risk of grade 3 or greater paresthesia (Fig. 3). This was counterbalanced by a reduced incidence of febrile neutropenia and nausea and vomiting.

### Table 1. N9741: Bolus-based regimens [17, 18]

<table>
<thead>
<tr>
<th></th>
<th>IFL</th>
<th>Irino day 1, F/L days 2-5</th>
<th>Oxali day 1, F/L days 2-5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>264</td>
<td>61</td>
<td>47</td>
</tr>
<tr>
<td>Response rate</td>
<td>31%</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Time to progression</td>
<td>6.9 months</td>
<td>6.4 months</td>
<td>8.2 months</td>
</tr>
<tr>
<td>Overall survival</td>
<td>15 months</td>
<td>15.9 months</td>
<td>13.7 months</td>
</tr>
</tbody>
</table>

Abbreviations: F, 5-fluorouracil; IFL, irinotecan/bolus 5-fluorouracil/leucovorin; Irino, irinotecan; L, leucovorin; Oxali, oxaliplatin.

### Table 2. N9741: Deaths and grade 4-4 toxicity [17, 18]

<table>
<thead>
<tr>
<th></th>
<th>IFL</th>
<th>I + F/L</th>
<th>O + F/L</th>
<th>FOLFOX</th>
<th>IROX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 60 days</td>
<td>4.5%</td>
<td>8.2%</td>
<td>8.5%</td>
<td>2.6%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28%</td>
<td>26%</td>
<td>20%</td>
<td>12%</td>
<td>24%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>15%</td>
<td>16%</td>
<td>2%</td>
<td>4%</td>
<td>11%</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>3%</td>
<td>0%</td>
<td>13%</td>
<td>18%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Abbreviations: F, 5-fluorouracil; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; IFL, irinotecan/bolus 5-fluorouracil/leucovorin; Irino, irinotecan; L, leucovorin; Oxali, oxaliplatin.

### Table 3. Efficacy results of the N9741 and Tournigand trials [17, 18, 22]

<table>
<thead>
<tr>
<th></th>
<th>IFL</th>
<th>FOLFOX</th>
<th>p value</th>
<th>IROX</th>
<th>FOLFIRI</th>
<th>p value</th>
<th>FOLFOX</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>31%</td>
<td>45</td>
<td>.03</td>
<td>35</td>
<td>56</td>
<td>.26</td>
<td>54</td>
<td>.26</td>
</tr>
<tr>
<td>Time to progression (months)</td>
<td>6.9</td>
<td>8.7</td>
<td>.009</td>
<td>6.5</td>
<td>8.5</td>
<td>.8</td>
<td>8.0</td>
<td>.26</td>
</tr>
<tr>
<td>Overall survival (months)</td>
<td>15</td>
<td>19.5</td>
<td>.0002</td>
<td>17.4</td>
<td>21.5</td>
<td>.99</td>
<td>20.6</td>
<td>.99</td>
</tr>
</tbody>
</table>

Abbreviations: FOLFIRI, irinotecan/5-fluorouracil/leucovorin; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; IFL, irinotecan/bolus 5-fluorouracil/leucovorin; IROX, irinotecan/oxaliplatin.
There has been considerable speculation about the role of oxaliplatin and irinotecan-based regimens in rendering patients with responsive disease suitable for resection and hence, prolonged survival and possible cure. These data must be treated with caution: resection was not mandated in either N9741 or the study of Tournigand et al., nor were any guidelines specified. Nevertheless, it is the case that 22 of the 24 patients resected in N9741 had had oxaliplatin-containing chemotherapy (and only two had IFL). Data from Tournigand et al. showed a 22% rate of resection in patients assigned initially to FOLFOX, compared with 9% in the FOLFIRI arm ($p = .02$).

Data from N9741 can also be compared (with appropriate caution) with data from the trial of Hurwitz et al., in which 925 patients were randomized to IFL, IFL plus bevacizumab 5 mg/kg, or 5-FU plus bevacizumab at the same dose [6, 24–26]. Interestingly, the 4.7-month difference in median OS when FOLFOX is compared against IFL is the same as the difference when IFL plus bevacizumab is compared against IFL alone (Table 4). It is therefore reasonable to hope that the addition of bevacizumab to FOLFOX will result in a median OS of up to 23 months. Such a prospect, while encouraging for patients and clinicians alike, has implications for the size and duration of future clinical trials of novel agents.

Two aspects of the Hurwitz et al. study should receive additional emphasis. The first is that the survival curve for patients receiving 5-FU/LV plus bevacizumab largely overlaps that of patients assigned to bevacizumab plus the irinotecan-containing regimen. Secondly, bevacizumab did add toxicity. While 74% of patients in the IFL plus placebo arm were classified as having a grade 3/4 event, this was true of 87% of patients treated with IFL plus bevacizumab. Concern centers on the increased risk of hypertension and arterial thrombosis, especially in older patients and those with a history of thrombotic events.

The CONFIRM-1 study of PTK 787 has aroused considerable interest [27]. One thousand and ninety previously untreated patients were randomized to either FOLFOX plus placebo or FOLFOX plus PTK 787. It appears that the addition of PTK 787 did not significantly increase OS, the primary endpoint of the trial. It remains to be seen whether a subset analysis examining those patients with high LDH (lactate dehydrogenase), and thus presumably with higher degrees of poorly perfused tumor, might preferentially benefit from this agent.

Figure 3. Toxicity of N9741 and Tournigand trials. Abbreviations: FOLFIRI, irinotecan/5-fluorouracil/leucovorin; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; IFL, irinotecan/bolus 5-fluorouracil/leucovorin; IROX, irinotecan/oxaliplatin.

Table 4. Efficacy of IFL, with or without bevacizumab, in the N9741 and Hurwitz trials [17, 18, 24]

<table>
<thead>
<tr>
<th></th>
<th>N9741 study</th>
<th>Hurwitz study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX N9742</td>
<td>IFL N9741</td>
</tr>
<tr>
<td>Overall survival</td>
<td>19.5 months$^a$</td>
<td>14.8 months</td>
</tr>
<tr>
<td>Time to progression</td>
<td>8.7 months$^a$</td>
<td>6.9 months</td>
</tr>
<tr>
<td>Response rate</td>
<td>45%$^a$</td>
<td>31%</td>
</tr>
</tbody>
</table>

$^a$ $p < .05$  
Abbreviations: BEV, bevacizumab; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; IFL, irinotecan/bolus 5-fluorouracil/leucovorin.
Second Line
In study E3200, 829 second-line stage IV patients who had proved refractory to IFL were randomized to FOLFOX4, FOLFOX4 plus bevacizumab 10 mg/kg, or bevacizumab 10 mg/kg alone [28]. The addition of bevacizumab to FOLFOX4 significantly extended median OS when compared with FOLFOX4 alone (12.5 vs. 10.7 months, \( p = .002 \)).

NEW DRUGS AND COMBINATIONS IN DEVELOPMENT
Also conducted in second-line patients (in this case refractory to 5-FU/irinotecan), the phase II BOND trial randomized 329 patients in the ratio of 2:1 to irinotecan plus cetuximab or cetuximab followed by irinotecan plus cetuximab [29]. Although the 23% RR in patients randomized to the up-front combination was twice that in the sequential arm, the median OS in the two groups was not significantly different (8.6 vs. 6.9 months, \( p = .48 \)). Some have questioned the validity of making a statistical comparison between two arms of the study, as it was a phase II trial [30]. As expected, grade 3–4 diarrhea was significantly more common with the combination of cetuximab plus irinotecan.

BOND2 was a relatively small trial, conducted in fewer than 80 patients refractory to first-line irinotecan-based chemotherapy, in which patients were randomized to cetuximab plus bevacizumab plus irinotecan or to cetuximab plus bevacizumab [31, 32]. Grade 2 or greater skin rash occurred in more than 50% of patients in both arms of the trial, but irinotecan-related toxicities were not exacerbated by combination with the antibodies. Among 39 patients randomized to the two antibodies plus irinotecan, the RR was 38% and median TTP was 8.5 months. This suggests median OS will be encouraging. In the control arm without irinotecan, the RR was 23% and the median TTP was 6.9 months. This in itself is sufficiently good to raise the possibility that with further refinement we may be treating metastatic CRC without chemotherapy.

According to data presented last year, the 10% RR and median 5-month OS seen with panitumumab are similar to those expected with single-agent cetuximab [33]. Data on panitumumab in combination from the Amgen Inc. (Thousand Oaks, CA)—sponsored PACCE (panitumumab advanced colorectal cancer evaluation) study are awaited. Currently, there is considerable interest in reports of phase II trials showing an 81% RR with FOLFOX combined with cetuximab [34]. High RRs (74%) have also been reported using chemotherapy in combination with gefitinib, although there appear to be problems with toxicity using this combination [35, 36].

Figure 4. Schema of C80405, Intergroup first-line study. Abbreviations: FOLFIRI, irinotecan/5-fluorouracil/leucovorin; FOLFOX, oxaliplatin/5-fluorouracil/leucovorin; FU, fluorouracil; XRT, radiotherapy.

DISCUSSION
Intergroup C80405, an important trial that opened in mid-September 2005, essentially merges two poorly accruing SWOG (Southwest Oncology Group) and CALGB (Cancer and Leukemia Group B) studies. By design, it permits physicians to choose between a chemotherapy platform of FOLFOX or FOLFIRI and then randomizes patients to the addition of bevacizumab alone, cetuximab alone, or both (Fig. 4). This study will answer one important current question, i.e., whether chemotherapy plus bevacizumab and/or cetuximab is today’s standard of care.

Another important question, concerning the possible merits of a “stop and go” strategy of intermittent therapy, will be answered by ongoing studies in Europe and the U.S. However, many questions remain to be fully addressed. These include optimum sequencing, the best strategy to use following adjuvant FOLFOX, and the possible integration into therapy of tyrosine kinase inhibitors and other small molecules. Individualizing therapy to the molecular characteristics of a specific patient’s tumor remains a goal. However, given the increasingly large number of mutations that appear to be involved in CRC, it is not clear that “tailor made” therapy will be possible in the near future.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The author indicates no potential conflicts of interest.
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