Metastatic colorectal cancer: integrating irinotecan into combination and sequential chemotherapy

J.-Y. Douillard1,*, A. Sobrero2, C. Carnaghi3, P. Comella4, E. Díaz-Rubio5, A. Santoro3 & E. Van Cutsem6

1Centre R Gauducheau, Nantes, France; 2Ospedale S. Martino, Genova; 3Istituto Clinico Humanitas, Rozzano; 4Istituto Nazionale Tumori, Napoli, Italy; 5Hospital Clínico Universitario San Carlos, Madrid, Spain; 6University Hospital Gasthuisberg, Leuven, Belgium

The chemotherapy of metastatic colorectal cancer (CRC) has undergone a succession of refinements. Through the biochemical modulation of 5-fluorouracil (5-FU) with folinic acid (FA), the use of infusional rather than bolus regimens and the combination of 5-FU/FA with other active agents (notably irinotecan), first-line response rates (RRs) of 40% can be achieved, with patients surviving up to 17 months. Significant benefits on survival are also seen with second-line chemotherapy. The question of how best to sequence combination chemotherapy was addressed in a recent trial in which patients were randomized to receive either an irinotecan-based combination with 5-FU/FA (FOLFIRI) followed by an oxaliplatin-based combination (FOLFOX), or the two regimens in the reverse order. In both arms, RRs were greater than 50% and median survival exceeded 20 months. The primary end point was time to progression after two lines of treatment, and this was not significantly different. However, the sequence FOLFIRI followed by FOLFOX appears preferable because of the better tolerability of FOLFIRI in first-line use. Use of the sequence FOLFIRI/FOLFOX is also supported by the greater chance of a second-line response with FOLFOX. Concern has been expressed about the safety of irinotecan combined with bolus 5-FU/FA. Infusional regimens have a better risk/benefit ratio than bolus regimens. However, the adverse event profile with both approaches is manageable, and irinotecan plus 5-FU/FA can be considered one standard of care in metastatic CRC.

Introduction

First-line single-agent chemotherapy is beneficial to patients with advanced colorectal cancer (CRC) in terms of both quality and quantity of life. This has been shown in individual studies and confirmed by meta-analysis [1, 2]. The pooled analysis by Jonker et al. [2], which incorporated the results of eight studies of 5-fluorouracil (5-FU)-based chemotherapy compared with best supportive care alone, found that active treatment was associated with an approximate doubling of median survival.

In first-line treatment of advanced CRC, response rates (RRs) are 40% to 56% with time to progression (TTP) ∼6–8 months, and in second-line, RRs are 10% to 20%, with 40% of patients experiencing stable disease and a 3-month TTP [3–7].

Treatment benefits patients, and timing of treatment is important. This was first demonstrated a decade ago by the Nordic group, who randomized 183 asymptomatic stage IV patients to immediate or deferred chemotherapy [8]. The period of symptom-free survival was three times longer in the immediate therapy group.

The more recent findings of an Australian study by Ackland et al. [9] suggest that the position may not be entirely settled. In their study, the median survival was 12 months. The overall survival was not significantly better with early treatment compared with those patients whose treatment was delayed (median 13 versus 11 months; P = 0.5).

In the mid-1990s, second-line chemotherapy in metastatic CRC was unusual. Yet, to the credit of their investigators, such studies were undertaken. In two randomized second-line trials, irinotecan was shown to have a significant benefit on survival compared with best supportive care alone and compared with 5-FU [10, 11].

Combination chemotherapy

When used first-line, the combination of irinotecan with 5-FU/folinic acid (FA) increases RR, TTP and overall survival compared with both modulated infusional [12] and bolus [13] 5-FU. In addition, when overall survival was not affected, the combination arm produced a better outcome for the subset of patients not receiving second-line treatment for whatever reason [14]. As reported in the European registration trial [15], the addition of oxaliplatin to 5-FU/FA improves RR and TTP. Survival with this combination is not prolonged compared with infusional 5-FU; however, compared indirectly with historical controls (i.e. bolus 5-FU alone) infusional 5-FU plus weekly oxaliplatin produced a longer survival [15]. Phase II/III studies of chemotherapy in advanced CRC are now achieving median survival times of ∼20 months [3]. Importantly, ∼10% of first-line patients initially judged inoperable may be amenable to potentially curative resection following downstaging. The toxic death rate associated with chemotherapy is believed to be in the region of 1%.
Whether all groups of patients stand to gain equally from combination chemotherapy remains an important question. Although the results of subgroup analyses must be treated with caution, and numbers may be too small to be definitive, the work of Knight et al. [16] demonstrated that there is a real benefit for all patients of adding irinotecan to 5-FU/FA in patients <65 years, and subgroup analyses have shown a similar benefit for both the >65 and <65 years age groups, for those with a performance status (PS) of 0, and those without abnormal serum chemistry (lactate dehydrogenase at or below the upper limit of normal).

Data from the German group of Grothey et al. [17] showed recently that the Mayo 5-FU/FA regimen, versus weekly high-dose 24-h 5-FU/FA and oxaliplatin, used as front-line control group achieved a median overall survival of almost 17 months.

Prognostic factors and choice of treatment

Another important advancement is the availability of oral chemotherapy. Patients clearly prefer oral rather than intravenous agents [18, 19]. Treatment can be given at home, and cancer centers are freed for other therapies. However, 70% of patients would not sacrifice efficacy to attain their preference for oral drugs [18].

Oral chemotherapy has produced efficacy results as good as those obtained with modulated bolus 5-FU, which makes this form of treatment a good option for combination chemotherapy.

Given that second-, and even third-line, chemotherapy is a reality for a significant proportion of patients, the question of how best to sequence regimens assumes importance.

When individualizing chemotherapy in a population that is very heterogeneous, there is a case for adjusting treatment according to the characteristics of the patient. Excluding the 10% of patients in whom downstaging is possible, outcome can be predicted using four factors: PS, white blood cell count, number of metastatic sites and alkaline phosphatase level [20].

On this basis, three sets of patients can be identified: those likely to have a poor median survival of 6 months; those with the prospect of surviving 15 months; and those with an expected intermediate median survival of ~10 months [20].

Patients with an anticipated survival of 6 months or less may elect for single-agent chemotherapy or no chemotherapy at all [20]. For those with a survival expectation of 15 months or more, combination chemotherapy is appropriate [20]. For around half the patient population, whose life expectancy is intermediate, it is appropriate to explore patient preference. Taking this into account along with the patient’s condition, a choice can be made between no chemotherapy, single-agent chemotherapy, and the use of chemotherapy combinations, possibly in sequence.

Optimizing sequential chemotherapy: the V-308 study

Given the choice of first-line regimens now available, it is important to establish whether there is an optimum sequence for their use. This question was addressed in the randomized study V-308 [3].

Design and treatment

In this randomized, multicenter, phase III trial, patients with previously untreated metastatic CRC were randomized to receive either FOLFIRI (irinotecan/5-FU/leucovorin) followed by FOLFOX6 (oxaliplatin/5-FU/leucovorin) on progression (arm A) or the reverse sequence of regimens (arm B). In FOLFIRI, irinotecan was given at 180 mg/m² i.v. over 2 h. In FOLFOX, the oxaliplatin dose was 100 mg/m² i.v.

In both regimens, 5-FU/FA was administered according to a simplified de Gramont schedule: L-FA 200 mg/m² given over 2 h followed by bolus 5-FU 400 mg/m², and then continuous infusion 5-FU over 46 h, starting at 2.4 g/m² for cycles 1–2, increasing to 3 g/m² for subsequent cycles if well tolerated. Cycles were repeated every 2 weeks until progression.

Patients

Of the total of 226 patients accrued, 113 were randomized to first-line FOLFIRI followed by FOLFOX. One hundred and nine patients received the allocated first-line treatment. Eleven had no second-line therapy; a total of 88 received second-line FOLFOX (81 on study and seven off study). In the FOLFOX followed by FOLFIRI group, 113 patients were randomized and 111 were actually treated first-line. Eighteen had no second-line therapy; 69 had FOLFIRI on study and 13 off study (a total of 82 treated).

There was some imbalance between the two arms of the study in demographic and prognostic factors. A higher proportion of patients in arm A were women (72% versus 57%). Whereas 17% of patients in arm A had PS 2, only 6% of patients had PS 2 in arm B. These differences may have implications for toxicity. The two groups were reasonably well matched on prior adjuvant treatment (19% in arm A and 23% in arm B had received chemotherapy, and 21% and 17% radiotherapy, respectively) and in the number and distribution of metastatic sites (59% in both arms had only one site of secondary disease).

Treatments administered

The median number of cycles administered in first-line was similar (13 in arm A, 12 in arm B). However, the two groups differed substantially in the proportion of patients who stopped first-line treatment for reasons other than progression. In arm B, 36% of patients withdrew from first-line FOLFOX while only 2% of arm A patients withdrew from first-line FOLFIRI. Second-line, 10% of patients receiving FOLFOX and 3% of patients receiving FOLFIRI decided to discontinue therapy.

Efficacy

TTP was the primary end point of the study. The difference was not statistically significant (14.4 months in arm A and 11.5 months in arm B; \( P = 0.65 \)). The TTPs of the two regimens in first-line use were similar (8.5 months in arm A and 8.1 months in arm B). However, when used second-line, FOLFOX appeared to delay progression for longer than FOLFIRI (4.1 and 2.5 months, respectively).
This greater second-line efficacy is supported by the RRs. When used second-line, the RR with FOLFOX was 15%, but second-line FOLFIRI achieved only a 4% RR. In terms of overall control of disease (overall RR plus stable disease), the figure for second-line FOLFOX is 63% and that for second-line FOLFIRI 35%. These data showing the greater efficacy of second-line FOLFOX argue for using the combinations in the sequence FOLFOX followed by FOLFIRI.

Although this was not a primary end point of the study, the high RRs seen with both regimens first-line suggest the possibility of potentially curative resection. Among the 109 patients randomized to first-line FOLFIRI, eight were resected (seven R0). Among the 111 first-line FOLFOX patients, 21 patients were resected (but only 13 were R0).

Overall survival in the two arms of the study was almost identical, and in both cases exceeded 20 months (20.4 months in arm A and 21.5 months in arm B; \( P = 0.90 \)). These are the longest median survivals ever achieved in phase III trials in metastatic CRC.

### Tolerability

Given the lack of statistically significant difference on the primary efficacy end points of the study, attention focuses on factors such as tolerability, which may provide an important guide as to which combination to use first.

The rate of grade 3/4 neutropenia among patients receiving first-line FOLFIRI was 25% (Table 1). This represents an appreciable reduction on the 45% rate seen in the DOUILLARD regimen involving a day 1 and 2 bolus of 5-FU. The incidence of grade 3/4 neutropenia with first-line FOLFOX was 44%.

In this study, appropriate use of loperamide appears largely to have eliminated the problem of grade 3/4 diarrhea, which occurred in only 14% of first-line FOLFIRI patients. This incidence was not significantly greater than the 11% rate seen with FOLFOX.

Grade 3 neurotoxicity (using the modified Levy scale) was reported in 34% of first-line FOLFIRI patients but in none of the patients randomized to first-line FOLFOX. As expected, the rate of alopecia was higher with FOLFIRI than with FOLFOX, as was the incidence of nausea and stomatitis.

Overall grade 3/4 toxicities were more frequent when FOLFOX was used first-line than with first-line FOLFIRI (74% versus 53%; \( P = 0.001 \)).

### Conclusion

Study V-308 shows that the majority of patients with metastatic CRC can receive at least two lines of chemotherapy, in the expectation of a median survival >20 months. Based on evidence of greater second-line efficacy with FOLFOX, the sequence FOLFOX followed by FOLFIRI appears to be preferable. This view is supported by the fact that first-line FOLFIRI appears to be better tolerated than first-line FOLFOX and is associated with less likelihood of treatment discontinuation.

### Optimizing irinotecan regimens

#### Single-agent studies

Irinotecan was developed initially for use second-line in 5-FU-resistant CRC. In Europe, the drug was given at a dose of 350 mg/m² administered once every 3 weeks, while in the USA the favored schedule was 100–125 mg/m² weekly for 4 weeks every 6 weeks (with a 2 week rest). Pooling data from the phase II studies shows the two approaches to have similar efficacy [21, 22]. The RRs in 5-FU-resistant disease are 13% with both schedules, with stable disease seen in a further 40% or more of patients. The TTP is 4 months and median survival 9–9.5 months.

Subsequently, the two pivotal phase III second-line studies already mentioned showed that irinotecan improved overall survival, 1-year survival and quality of life when compared either with best supportive care or with an infusional 5-FU regimen (Table 2) [10, 11]. Data from the study against infusional 5-FU showed that the use of irinotecan was associated with greater adverse events (i.e. neutropenia, vomiting and diarrhea) (Figure 1) [11]. However, quality of life was not impaired.

In a phase II study by Van Cutsem et al. [23], patients with 5-FU-resistant CRC were randomized to fixed-dose treatment with irinotecan 350 mg/m² or to an individualized dose-optimization strategy in which the amount of drug administered was increased, in the absence of major toxicity, from 250 to 350 to 500 mg/m².
The latter approach appeared to reduce the incidence of neutropenia and diarrhea (Table 3).

Table 3. Randomized phase II trial with three regimens of irinotecan in 5-FU-resistant colorectal cancer [23]

<table>
<thead>
<tr>
<th>Irinotecan (n = 164): dose and regimen</th>
<th>Response rate (%)</th>
<th>Diarrhea (grade 3/4) (%)</th>
<th>Neutropenia (grade 3/4) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>350 mg/m² every 3 weeks</td>
<td>10</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>250 mg/m² every 3 weeks increased to 350-500 according to toxicity</td>
<td>17</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>250 or 500 mg/m² every 3 weeks according to risk factor analysis</td>
<td>7</td>
<td>28</td>
<td>45</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil.

The latter approach appeared to reduce the incidence of neutropenia and diarrhea (Table 3).

Irinotecan in combination

In parallel with attempts to minimize single-agent toxicity, phase I studies of irinotecan plus 5-FU/FA were in progress. In Europe, the emphasis was on infusional 5-FU, using either the biweekly 48 h (LV5FU2) regimen or the weekly 24 h regimen of the Arbeitsgemeinschaft Interniste Onkologie (AIO). In the USA, attention focused on the weekly 4 bolus regimens of Saltz et al. [13].

Experience in the phase III trial of Douillard et al. [12] showed that the addition of irinotecan to infusional 5-FU/FA increased the incidence of grade 3/4 diarrhea, leukopenia and neutropenia, with the proportion of patients affected being at least twice that in the control arm. However, given the experience with single-agent irinotecan, the toxicity was actually lower than had been expected, and the rate of febrile neutropenia was only 6%.

In the study by Saltz et al. [13], the incidence of grade 3/4 mucositis, neutropenia and febrile neutropenia were actually lower in the irinotecan combination than when the Mayo Clinic 5-FU/FA bolus regimen was used alone. With bolus 5-FU, fully 66% of patients experienced grade 3/4 neutropenia, compared with 54% in the irinotecan plus 5-FU/FA arm. However, the addition of irinotecan to bolus 5-FU/FA was associated with a higher incidence of vomiting and diarrhea.

In the study by Comella et al. [14], a biweekly regimen of irinotecan on day 1 and leucovorin-modulated 5-FU i.v. bolus on day 2 (IRIFAFU) caused a greater occurrence of grade 3 or 4 neutropenia (40%) in comparison with 5-FU modulated by methotrexate and leucovorin (MTXFAFU) (9%), but the incidence of severe stomatitis was lower (3% versus 12%). Grade ≥3 diarrhea affected 13% of patients in the combination arm, compared with 4% in the control arm.

Recommendations aimed at reducing the toxicity of bolus regimens have been made [24]. In Europe, safety concerns with infusional regimens have been less pressing. Although close monitoring of patients remains mandatory, it appears that the infusional 5-FU/FA combination with irinotecan may have a better risk/benefit ratio than the weekly bolus approach (Figure 2) [12, 13, 25].

Toxic deaths in context

The US Intergroup study (NCCTG N9741) of irinotecan plus bolus 5-FU/FA versus oxaliplatin plus infusional 5-FU/FA versus irinotecan plus oxaliplatin in first-line metastatic CRC has been much discussed [24, 26]. The proportion of patients who died within 60 days, after the first administration of the study drug, was higher in the irinotecan/5-FU/FA arm (4.5%) than in either of the comparator arms (mortality rate 1.8% in both).

The study was halted pending the results of an independent review. The panel found that deaths had occurred primarily in the first cycle and that they were associated at least in part with inadequate monitoring and use of antibiotics. It was emphasized that patients should receive early antibiotic support and that 24 h free from diarrhea should precede each chemotherapy cycle [24].

In an attempt to provide a context for these figures, the ODAC of the FDA has reviewed mortality rates in a range of studies [27]. Among historical controls the 60 day mortality rate in the Mayo Clinic series was 6.1%, with the Roswell Park bolus regimen 7.6%, and with de Gramont’s LV5FU2 regimen 5.5%. Following drug approval, early death rates have been comparatively low (3.8% in the Saltz et al. [13] experience and 2.6% in that of Douillard et al. [12]).

Recently, data have been reported from the UK MRC CR08 FOCUS trial, in which irinotecan 180 mg/m² on day 1 was combined with day 1 bolus administration of 5-FU 400 mg/m², followed by a 46-h infusion of 5-FU 2.8 g/m² [28]. The occurrence of two deaths among the first four patients treated (due to neutropenia and diarrhea) prompted a reduction in 5-FU dose to...
Toxic Grade 4 neutropenia
Grade 3/4 diarrhea
Thromboembolism
Deaths
3/93
0/115
Combined adverse events
Adverse outcomes
FA 500 mg/m²
2/116
Discontinuous
1/96
Failure to complete cycle 1
Grade 3/4 vomiting
3/6
on 03 February 2018
FA, folinic acid; 5-FU, 5-fluorouracil.

2.6 g/m². At the time the data was reviewed, there have been no problems among 475 patients accrued.

The EORTC 40986 trial tells a similar story [25]. In the combination arm of this study, toxic deaths occurred in three of 93 patients treated with irinotecan 80 mg/m² plus 5-FU 2.3 g/m² over 24 h and one AIO. However, once the 5-FU dose was reduced to 2 g/m², there were no deaths among the 115 patients treated in arm B (Table 4).

Among many risk factors under consideration, the relationship of PS to adverse outcome has been extensively investigated. According to data from the Saltz study presented at the ODAC, patients with a PS of 2 are at significantly higher risk of neutropenic fever, hospitalization, death within 30–60 days of the start of treatment and failure to complete the first cycle [13].

The data from the Douillard et al. trial confirmed that poor PS was associated with a significantly increased risk of hospitalization and combined adverse events [12] (Table 5).

**Conclusions**

Over the past decades, improvements in chemotherapy for metastatic CRC have resulted in significant benefits in terms of RRs and survival. Further refinements addressed the best sequencing of combination chemotherapies, with FOLFIRI followed by FOLFOX appearing to be the preferable sequence in terms of tolerance.

**Acknowledgements**

J.-Y.D., A.S. and E.V.C. have received honoraria and medical research grants from Aventis Pharmaceuticals, Inc.

**References**


27. Presented at the ODAC meeting, held in the United States on December 6, 2001.