Optimizing the Use of Irinotecan in Colorectal Cancer

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ABSTRACT

The introduction of new agents with novel mechanisms of action has led to considerable changes in the management of colorectal cancer in recent years. One of these novel agents, irinotecan, has been shown to offer survival benefits in both the first- and second-line treatment of advanced/metastatic colorectal cancer. Irinotecan monotherapy improves survival compared with both best supportive care and infused 5-fluorouracil (5-FU) in patients with 5-FU-pretreated disease, without impacting negatively on patients' quality of life. As a result, irinotecan monotherapy is now considered to be the standard treatment in this setting. Irinotecan in combination with 5-FU/leucovorin (LV) was subsequently evaluated as first-line therapy for metastatic colorectal cancer in two randomized, phase III studies. Both trials confirmed that irinotecan plus infused or bolus 5-FU/LV provide a modest survival benefit without compromising patients' quality of life. Combined irinotecan/5-FU/LV represents a new standard in the first-line treatment of metastatic colorectal cancer.

In an attempt to further improve efficacy and tolerability, recent studies have investigated irinotecan in combination with capecitabine as first-line treatment for colorectal cancer. The replacement of infused 5-FU with oral capecitabine provides a more convenient treatment option. A phase I study was conducted to establish the maximum tolerated dose, and demonstrated encouraging antitumor activity and a manageable safety profile with the combination. This article provides a brief overview of the pivotal clinical trial data for irinotecan and discusses how irinotecan-based therapy may be improved in the future. It also discusses potential optimization of irinotecan use through identification of patient subpopulations most likely to benefit from combination or sequential strategies, and the potential of new, oral agents such as capecitabine to replace i.v. 5-FU as a combination partner for irinotecan.

The Oncologist 2001;6(suppl 4):17-23

INTRODUCTION

In recent years, there have been important advances in the management of colorectal cancer. These include the identification of effective adjuvant therapies and the introduction of new agents with mechanisms of action other than thymidylate synthase inhibition. Until recently, there was no established standard of care in patients with advanced/metastatic colorectal cancer unresponsive or resistant to 5-fluorouracil (5-FU)-based chemotherapy. However, the introduction of irinotecan, a semisynthetic camptothecin derivative with a novel mechanism of action, has provided a new and effective treatment option in this setting [1]. Following i.v. administration, irinotecan is converted by carboxylesterase in the liver and in plasma to SN-38. This active metabolite is a potent inhibitor of topoisomerase I, an enzyme with an essential role in DNA replication and cell division [2].

SECOND-LINE IRINOTECAN MONOTHERAPY

A series of phase II studies in Japan [3], Europe [4, 5], and the U.S. [6, 7] demonstrated that irinotecan monotherapy results in objective tumor response rates of 16%-27%, with disease stabilization occurring in a further 40%-60% of patients. Median duration of response was 6.0-9.1 months and median overall survival was 8.3-10.0 months. One trial demonstrated that similar response rates could be
achieved in 5-FU-pretreated and chemotherapy-naïve patients (18% versus 19%, respectively), suggesting lack of cross-resistance [5]. In patients with stringently defined 5-FU-resistant colorectal cancer, irinotecan achieved an objective response rate of 14%, with a median duration of response of 8.5 months and a median overall survival of 10.4 months [8].

The promising results of the phase II trials led to the initiation of two European, randomized, phase III studies to evaluate further the overall benefit of irinotecan as second-line therapy for colorectal cancer. The primary endpoint in both trials was survival. In one of these trials, 279 5-FU-pretreated patients were randomized to best supportive care with or without i.v. irinotecan 350 mg/m² administered every 3 weeks [9]. Baseline characteristics and prognostic factors were well balanced in the two treatment arms. The trial demonstrated that the addition of irinotecan to best supportive care provided a significant survival benefit compared with best supportive care alone (median survival 9.2 months versus 6.5 months, respectively; \( p = 0.001 \)). The 1-year survival rate was 36% versus 14%, respectively (\( p = 0.0001 \)).

Side effects were more frequent in patients treated with irinotecan than in the control arm (grade 3/4 events, 79% versus 67%, respectively), and, in particular, diarrhea and nausea were more common in patients receiving irinotecan. However, asthenia, initially thought to be a key toxicity of irinotecan, was less common in the irinotecan group (grade 3/4 events, 15% versus 19% in the control arm). Subsequent clinical experience has indicated that the safety profile of irinotecan can be improved with careful patient monitoring, routine administration of antiemetics prior to irinotecan infusion, and prompt, aggressive treatment of delayed-onset diarrhea. Such measures result in lower incidences of severe/life-threatening adverse events, with fewer patients requiring hospitalizations for complications such as febrile neutropenia/sepsis [8]. Global quality of life (European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30 questionnaire) was significantly superior in patients receiving irinotecan (\( p < 0.01 \)).

In the other second-line, randomized, phase III trial [10], i.v. irinotecan (300-350 mg/m² once every 3 weeks) was compared with continuously infused 5-FU with or without leucovorin (LV) (de Gramont [27%], German AIO [43%], or Lokich [30%] regimens) [11-13]. Survival was significantly superior in patients treated with irinotecan compared with infused 5-FU-based therapy, with a median overall survival approximately 2 months longer in patients receiving irinotecan (Fig. 1). In addition, progression-free survival was significantly superior with irinotecan (median, 4.2 months versus 2.9 months with 5-FU; \( p = 0.03 \)). Grade 3/4 side effects were more frequent with irinotecan (69%) compared with 5-FU (54%), particularly diarrhea, pain, nausea/vomiting, myelosuppression, and alopecia. However, there was no difference in the incidence of asthenia between groups (13% versus 12%, respectively), and quality-of-life scores were similar in both treatment arms.

The results of these two trials have established irinotecan monotherapy as the new standard of care in the second-line treatment of 5-FU-pretreated colorectal cancer.

**First-Line Irinotecan: Improving Survival**

The different mechanism of action of irinotecan, together with the survival benefit observed with second-line irinotecan monotherapy [9-10], provided the rationale for evaluating irinotecan in combination with 5-FU/LV as first-line therapy for metastatic colorectal cancer. Consequently, two randomized, phase III trials were conducted, one in Europe (with tumor response rate as the primary endpoint) [14] and one in the U.S. (with progression-free survival as the primary endpoint) [15]. Secondary endpoints were survival, safety, and quality of life (EORTC QLQ-C30 questionnaire) in both trials. Patients had received no previous chemotherapy for metastatic disease, but prior adjuvant therapy was permissible (completed >12 months and >6 months prior to enrollment in the American and European trials, respectively). In the European trial, patients received an infused 5-FU/LV regimen (de Gramont regimen [11] in 288 patients; German AIO regimen [12] in 97 patients) with or without irinotecan (180 mg/m² every 2 weeks with the de Gramont regimen; 80 mg/m² weekly with the German AIO regimen). The American study, which included three treatment arms, compared irinotecan 125 mg/m² plus i.v. bolus 5-FU 500 mg/m² and LV 20 mg/m² weekly for 4 of 6 weeks versus irinotecan alone versus the Mayo Clinic regimen [16].

![Figure 1. Overall survival: irinotecan versus infused 5-FU in pretreated patients. Reprinted with permission [10].](http://theoncologist.alphamedpress.org/Downloaded from http://theoncologist.alphamedpress.org/)
In both studies, the addition of irinotecan to bolus or infused 5-FU/LV resulted in significantly superior tumor response rate, time to disease progression, and overall survival. An analysis of the combined data from both trials confirmed these results: the response rate of 37% in patients receiving irinotecan/5-FU/LV combination therapy was almost double that in patients treated with 5-FU/LV (21%; \( p < 0.05 \)) [17]. The progression-free survival was 6.9 months with 5-FU/LV/irinotecan versus 4.3 months with 5-FU/LV alone (\( p < 0.05 \)) in this analysis, and median overall survival was 15.9 months versus 13.3 months, respectively (\( p < 0.05 \)). Global health status scores confirmed that in both trials, the survival benefit was achieved without compromising patients’ quality of life (global health status). Moreover, in the European trial, deterioration in quality of life occurred consistently later in patients receiving combination therapy.

The addition of irinotecan to infused 5-FU/LV resulted in significantly (\( p < 0.05 \)) more grade 3/4 diarrhea, asthenia, neutropenia, and leukopenia [14]. Dose reductions due to toxicities were also more frequent in patients receiving irinotecan: 30% versus 19% in the German AIO arm and 21% versus 5% in the de Gramont arm [14]. Similarly, the addition of irinotecan to bolus 5-FU/LV was associated with a higher incidence of grade 3 diarrhea and grade 3/4 vomiting [15]. The incidence of grade 4 diarrhea was similar in the irinotecan and irinotecan plus bolus 5-FU/LV arms, and patients receiving irinotecan plus bolus 5-FU/LV experienced a lower incidence of grade 3/4 mucositis, grade 4 neutropenia, and neutropenic fever compared with bolus 5-FU/LV alone. This may have been because of the lower dose intensity of 5-FU administered in patients receiving irinotecan (median relative intensity of 5-FU: 71% versus 86% in patients receiving 5-FU/LV alone). Furthermore, less than half of the patients in the irinotecan group received the full dose of irinotecan on day 1 of cycles 2 and 3, owing to toxicities in previous cycles. As mentioned previously, clinical experience has shown that the safety profile of irinotecan can be improved with careful patient monitoring, routine administration of antiemetics prior to irinotecan infusion, and prompt, aggressive treatment of delayed-onset diarrhea and neutropenia with its complications.

These two phase III studies have therefore demonstrated that the addition of irinotecan to bolus or infused 5-FU/LV provides a modest but statistically significant survival benefit in the first-line treatment of colorectal cancer, thus setting a new standard in the care of colorectal cancer.

**Sequential Therapy Versus Combination Therapy**

The phase III studies described above raised two important questions for oncologists: first, should all patients be treated with combination therapy or can subpopulations of patients who benefit particularly from combination therapy be identified? And second, can sequential therapy be as effective as combination therapy and are there subpopulations of patients that benefit particularly from sequential therapy? Two trials are being planned and conducted by the Colorectal Cancer Group of the Medical Research Council in the United Kingdom and the EORTC to address the issue of sequential versus combination therapy. Further analysis of these data from the phase III trials of irinotecan described above also provides interesting insights into these questions.

**The Case for Combination Therapy**

First-line irinotecan/5-FU/LV significantly improved overall survival compared with standard 5-FU/LV, and this survival advantage was maintained despite effective second-line therapy in several patients in the control arm [14, 15]. Of note, the trial by Saltz et al. was not designed with survival as a primary endpoint, but nevertheless demonstrated a statistically significant survival benefit [15]. Administration of combination therapy in the first-line setting means that all patients can potentially benefit from combination therapy, whereas after first-line therapy 20%-40% of patients are not eligible for second-line therapy.

A recent analysis of data from 3,825 patients with colorectal cancer using mathematical modeling also supports combination therapy [18]. It was found that first-line therapy has the most significant impact on survival, that response rate is an independent prognostic factor, and that the most substantial survival benefit is achieved through increased response rates. In addition, effective second-line therapy did not compensate for differences in response rates to first-line therapy if these differences were large or if the use of second-line therapy was limited.

In terms of safety, the addition of irinotecan to 5-FU/LV did not result in unacceptable toxicity. Irinotecan/5-FU/LV was associated with a higher incidence of grade 3 diarrhea compared with bolus or infused 5-FU/LV [14, 15], but it also resulted in lower incidences of some key 5-FU toxicities (neutropenia, neutropenic fever/sepsis, and mucositis) due to the lower doses of 5-FU administered in combination [15]. Furthermore, addition of irinotecan to 5-FU/LV did not compromise patients’ quality of life.

**The Case for Sequential Therapy**

When drugs are administered in combination, the dose of one or more of the agents is often lower than the standard monotherapy dose in order to avoid additive toxicity. In contrast, sequential therapy enables each drug to be prescribed at its optimal dose, thus avoiding any potential loss
of efficacy, with less toxicity and potential quality of life benefits compared with combination treatment.

Turning to the phase III data for irinotecan, both of the trials of second-line irinotecan monotherapy described above demonstrated that the survival benefit was confirmed across a heterogeneous patient population, including patients with poor performance status [9, 10]. In contrast, despite significantly improved response rates and progression-free survival with first-line irinotecan/5-FU/LV therapy, overall survival was only modestly improved [14, 15]. The difference in survival between groups may have been reduced by effective second-line therapy in 34%-56% of all patients, lending support to the sequential administration of effective treatments.

In contrast to the efficacy of second-line irinotecan demonstrated across a heterogeneous patient population, retrospective analyses of the phase III trials in the first-line setting have identified certain subgroups of patients who derive the most benefit from the addition of irinotecan to 5-FU/LV [15]. These subpopulations include patients with the following characteristics at baseline: age <65 years, Eastern Cooperative Oncology Group (ECOG) performance status 0, normal lactic dehydrogenase (LDH) and bilirubin concentrations, normal white cell count, hemoglobin ≥11 g/dl, no prior adjuvant therapy, and only one metastatic site (Table 1). LDH concentration appears to be a particularly important predictive factor. Patients with poor performance status, elevated serum LDH, prior adjuvant chemotherapy, or more than one metastatic site at baseline did not benefit from increased survival with irinotecan combination therapy. In fact, survival was diminished in a subgroup of patients with prior adjuvant therapy compared with the overall patient population treated with the irinotecan combination. Similar observations were seen in the trial evaluating irinotecan in combination with infused 5-FU/LV [14]. Therefore, in these patient subpopulations, sequential monotherapy may be as effective and better tolerated than combination therapy.

Another consideration is that first-line combination therapy exposes all patients to increased risk of toxicity while providing an increase in efficacy in only a proportion of the patients. In the study by Saltz et al. investigating first-line irinotecan plus bolus 5-FU/LV [15], the overall survival curves overlapped during the first 10 months of therapy (Fig. 2). This means that more than 40% of patients derived no survival benefit, but were at increased risk of toxicity, particularly diarrhea and neutropenia. Therefore, because of unacceptable levels of toxicity with no increase in efficacy, combination therapy may be inappropriate for these patients, and many oncologists would advocate sequential therapy. In this context, taking into account patient preference and the convenience of home-based oral therapy, capecitabine provides an attractive first-line treatment option.

**OPTIMIZING IRINOTECAN THERAPY**

It appears that in the future, the use of irinotecan may be optimized through identification of those patient subgroups most likely to benefit from aggressive combination therapy in the first-line setting and those patient subgroups which are more suitably treated with sequential use of an active 5-FU-based regimen followed by irinotecan monotherapy at disease progression. Neither strategy is most suitable for all patients. Therefore, a number of factors besides disease characteristics, treatment history, and patient preference and social situation must be taken into consideration when choosing, in consultation with the individual patient, the most appropriate treatment.

**CAPECITABINE PLUS IRINOTECAN**

Another important option in the future may be the use of an oral fluoropyrimidine instead of 5-FU/LV as a combination partner for irinotecan. The oral fluoropyrimidine capecitabine, which has confirmed single-agent efficacy and a favorable safety profile as first-line treatment in patients with colorectal cancer [19], is an attractive agent for combination with irinotecan. As an oral agent that generates

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<th>Table 1. A Cox regression analysis of U.S. study: predictive factors for time to disease progression and survival</th>
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5-FU preferentially in tumor tissue [20], capecitabine has the potential to further improve the efficacy and tolerability of fluoropyrimidine/irinotecan combination regimens. The distinct mechanisms of action of the two agents and the limited overlap of key toxicities make capecitabine a good candidate for combination therapy with irinotecan. In addition, preclinical studies have shown that sequential combination of low irinotecan doses plus capecitabine are highly curative in in vivo xenograft models of human colorectal cancer [21]. Therefore, capecitabine, which mimics continuous infusion 5-FU, is a logical combination partner for irinotecan. Together, these factors provided a clear rationale for investigating irinotecan in combination with capecitabine as first-line therapy for patients with metastatic colorectal cancer [22].

A phase I, dose-escalating study has investigated capecitabine in combination with a weekly irinotecan schedule in 37 patients with previously untreated, measurable metastatic colorectal cancer. The treatment schedule for the three dose levels explored is shown in Figure 3. The dose-limiting toxicities of this regimen were diarrhea and neutropenia, with diarrhea being the major toxicity after multiple cycles. To date, 13 of 29 patients evaluable for response treated at all three dose levels have achieved an objective response, including one complete remission, resulting in an overall response rate of 45% (95% confidence interval: 26%–63%). Based on the data from this study, capecitabine 1,000 mg/m² twice daily, administered on days 1-14 and 22-35 in combination with weekly irinotecan 70 mg/m² administered on weeks 1-6 every 7 weeks, appears to be feasible and has shown substantial antitumor efficacy.

Another phase II study evaluating capecitabine in combination with two irinotecan schedules has also demonstrated that this combination is active in patients with advanced colorectal cancer, achieving objective responses (not confirmed) in 13 of 18 evaluable patients (72%) [23]. The results of this study need to be confirmed in a larger trial.

CONCLUSIONS

Following demonstration of a survival benefit in 5-FU-pretreated patients in two randomized, phase III trials, irinotecan monotherapy has become an established second-line treatment for metastatic colorectal cancer. More recently, phase III trials have demonstrated that the addition of irinotecan to first-line 5-FU/LV significantly improves response rate and time to disease progression, with a modest but statistically significant improvement in overall survival. The incidence of toxicities was increased and did not negatively impact on patients’ quality of life. Irinotecan/5-FU/LV therefore offers an important new option for the first-line treatment of metastatic colorectal cancer.

The choice of when to administer irinotecan is causing some controversy, with some advocating aggressive, up-front combination therapy with irinotecan/5-FU/LV, and others preferring a sequential approach, with irinotecan administered only after disease has progressed with 5-FU-based therapy. The retrospective identification of subgroups deriving the greatest benefit from combination therapy has enabled oncologists to make treatment decisions based on

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**Figure 2.** Overall survival: irinotecan plus 5-FU/LV versus 5-FU/LV. A) U.S. study; reprinted with permission [15]. B) European study; reprinted with permission [14].

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**Figure 3.** Treatment schedule for capecitabine/irinotecan combination therapy [24].
patient characteristics, thus potentially optimizing irinotecan therapy. It is now generally accepted that for younger patients with good performance status, normal LDH, no prior adjuvant therapy, and only one metastatic site at baseline, combination therapy is probably the most appropriate strategy, whereas for older patients or those with poor performance status, elevated LDH, and more than one metastatic site at baseline, sequential therapy may be more suitable.

Another important step in the future use of irinotecan is the potential replacement of 5-FU/LV with an effective oral fluoropyrimidine, such as capecitabine. Capecitabine is an attractive combination partner for irinotecan, with a different mechanism of action, high single-agent activity, and partially overlapping toxicities. An extended phase I/II clinical trial has identified a feasible regimen for administration of capecitabine and irinotecan in combination, with promising antitumor activity. In the future, capecitabine may potentially replace 5-FU as a combination partner for irinotecan in the first-line treatment of colorectal cancer.

ACKNOWLEDGMENT

D.C. has received honoraria from Bristol-Myers Squibb, Roche, Aventis, Sanofi, and Zeneca during the past 3 years.

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