The Role of Irinotecan and Oxaliplatin in the Treatment of Advanced Colorectal Cancer

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By David Khayat, MD, PhD [2], Marian Gil-delgado, MD, PhD [3], Eric-charles Antoine, MD [4], Daniel Nizri, MD [5], and AndG&, 233:rad Bastian, PhD [6]

Colorectal carcinoma is one of the most common malignancies in the western world, and although fluorouracil (5-FU) has been used in its treatment for almost 40 years, new agents with significant activity have been introduced recently. Irinotecan (CPT-11, Camptosar), a topoisomerase I inhibitor, administered at 300 to 350 mg/m² every 3 weeks is significantly more active than continuous-infusion 5-FU in patients who have experienced disease progression after conventional therapy with 5-FU. In comparison to best supportive care, irinotecan improves survival and preserves quality of life despite treatment-related toxicity. Moreover, the combination of irinotecan and 5-FU has been explored in a number of different schedules. In previously untreated patients, overall response rates are high. Irinotecan can also be combined with mitomycin (mitomycin-C [Mutamycin]), oxaliplatin, or raltitrexed (Tomudex). Oxaliplatin is a new-generation platinum compound that has demonstrated activity against colorectal carcinoma in preclinical trials. It has been evaluated as a single agent against advanced colorectal carcinoma in the salvage setting and also in combination with 5-FU as initial therapy for metastatic disease (where it shows significant activity). The toxicity profile of oxaliplatin (chiefly characterized by neurotoxicity) differs from that of irinotecan (primarily producing diarrhea) and the potential, therefore, exists for combining these agents or for exploiting their possible synergy with 5-FU. The introduction of these two new active agents of different pharmacologic classes promises to enable significant improvements in the treatment of patients with colorectal carcinoma. [ONCOLOGY 15(4):415-434, 2001]

Introduction

Colorectal carcinoma is one of the most common malignancies in the western world, with over 300,000 new cases diagnosed in Europe and the United States each year. Surgery is the principal treatment for operable patients, but for patients who have relapsed following surgery or who present with metastatic disease, the prognosis is poor. Although systemic treatment is possible, the effect is mainly palliative. For almost 40 years, fluorouracil (5-FU) has been the mainstay of the treatment of patients with advanced colorectal cancer.

Over the past 15 years, several attempts have been made to increase the efficacy of 5-FU, either through modulation of its activity with compounds such as leucovorin, methotrexate, or interferon-alpha, or through techniques that increase tumor exposure to the drug by means of protracted continuous infusion. Although these methods have increased the efficacy of 5-FU by a factor of two to three in terms of response rate, survival of patients with advanced colorectal cancer remains relatively disappointing, rarely exceeding a median of 12 months.

Treatment options for these patients remained limited until recently, when the topoisomerase I inhibitor irinotecan (CPT-11, Camptosar) and the diaminocyclohexane (DACH) platinum compound oxaliplatin (E... N.: roxaliplatin is investigational in the United States and available as Eloxatin in France) were developed and approved for use in advanced colorectal carcinoma.

Irinotecan

Irinotecan is a water-soluble semisynthetic compound derived from the antineoplastic agent camptothecin, a natural alkaloid of the Chinese tree Camptotheca acuminata. It is a selective inhibitor of the DNA enzyme topoisomerase I. In preclinical studies, irinotecan and its active metabolite SN38 demonstrated significant antitumor activity against a variety of tumor cell lines in vitro and also showed activity in in vivo models, including tumors (such as colorectal cancer) that
express the p-glycoprotein-mediated, multidrug-resistant phenotype.[1]

**Single-Agent Trials**

Irinotecan has demonstrated activity as a single agent in several phase I and phase II trials conducted in Europe, Japan, and the United States. Initial phase I studies of irinotecan began in Japan in 1986, and the most common dose-limiting toxicities were found to be hematologic (neutropenia) and gastrointestinal (delayed diarrhea).[2] Early in its development, irinotecan was tested as a short infusion (30 to 90 min) using three different schedules: (1) 100 mg/m²/d over 3 days, repeated every week; (2) 100 to 125 mg/m²/d every week; and (3) 350 mg/m² every 3 weeks.

The most widely used schedule of irinotecan in European phase I studies was a single dose administered every 3 weeks. These studies led to the recommendation that a dose of 350 mg/m² every 3 weeks be evaluated in clinical phase II trials. Delayed diarrhea was countered by subsequent incorporation of high-dose loperamide.

In a multicenter phase II trial in 166 patients with previously treated colorectal cancer, Rothenberg et al administered irinotecan at 125 mg/m²/wk to the first 64 patients and at 100 mg/m² to the subsequent 102 patients.[3] Irinotecan was administered as a 90-minute infusion for 4 consecutive weeks followed by 2 weeks’ rest. There were no significant differences in grade 3/4 toxicities between those receiving 125 mg/m² and those receiving 100 mg/m², except for grade 3/4 emesis (22% vs 2%; *P* < .001).[3] Compared with younger patients, elderly patients (> 65 years old) were twice as likely (38.6% vs 18.8%, *P* < .008) to develop grade 3/4 diarrhea.

Objective responses to irinotecan were observed in 18 patients (1 complete response and 17 partial responses) for an overall response rate of 10.8% (95% confidence interval (CI) = 6.1%-15.6%). In addition, 67 patients (40.4%) had stable disease. The treatment response rates were 14.1% (9/64) for the 125-mg/m² arm and 8.8% (9/102) for the 100-mg/m² arm. This trial suggested a trend toward a higher response rate without substantially greater toxicity for the 125-mg/m² dose, while the overall median survival was 9.9 months (range: 0.3 to 38.8 months, Table 1).[3]

**Multicenter Phase III Trials:** Two important randomized multicenter phase III studies of irinotecan as a single agent were performed during its development in Europe. The first, conducted by Rougier et al, compared irinotecan with continuous-infusion 5-FU[4] in 267 advanced colorectal cancer patients who either did not respond or whose disease had progressed after first-line treatment with 5-FU. Patients were randomly assigned to receive a 90-minute infusion of irinotecan at 300 to 350 mg/m² every 3 weeks or a continuous infusion of 5-FU according to three different schedules (Table 2).[4] Both treatments were given until the development of disease progression or unacceptable toxicity.

As second-line therapy, irinotecan improved survival and median time to disease progression compared to continuous-infusion 5-FU, with relative outcomes of 10.8 vs 8.5 months (*P* = .035) and 4.2 vs 2.9 months (*P* = .035), respectively (Figure 1 and Figure 2).[4] Both treatments were well tolerated except for vomiting and diarrhea, and patients were able to maintain good quality of life (Figure 3) and tumor control.[4] Because irinotecan has proven to significantly improve progression-free and overall survival compared to continuous-infusion 5-FU after failure of therapy with standard 5-FU, it should be considered one of the reference drugs for second-line treatment of advanced colorectal cancer.

The second trial, conducted by Cunningham et al in 279 advanced colorectal cancer patients, compared irinotecan plus best supportive care vs best supportive care alone after 5-FU failure.[5] A 90-minute infusion of irinotecan at 300 to 350 mg/m² every 3 weeks plus best supportive care was administered to 189 patients, while another 90 patients received best supportive care alone (Figure 4).[5] At a median follow-up of 13 months, overall survival was significantly better in the irinotecan arm (*P* = .0001) (Figure 5).[5] The 1-year survival reported for the irinotecan arm was 36.2%, compared to 13.8% for the best supportive care arm, thus showing a clear advantage for salvage chemotherapy with irinotecan.

A multivariate analysis adjusted to prognostic factors significantly favored irinotecan when assessed
in terms of survival ($P = .001$), survival without performance status deterioration ($P = .0001$), survival without a weight loss of more than 5% ($P = .018$), and pain-free survival ($P = .003$) (Figure 6).[5] Despite the presence of treatment-induced diarrhea, significant differences in the quality-of-life analysis were also found to favor irinotecan. This study showed that despite the side effects, patients with metastatic colorectal cancer in whom 5-FU therapy has failed have a longer survival with fewer tumor-related symptoms and better quality of life when they are treated with irinotecan, as compared to best supportive care alone.

**Four Different Schedules:** A recent randomized phase II multicenter trial compared four different schedules of irinotecan as second-line therapy in advanced colorectal cancer patients.[6] Patients were randomized to arm A (350 mg/m$^2$ every 3 weeks), arm B (125 mg/m$^2$, weekly, for 4 weeks, in 6-week cycles), arm C (250 mg/m$^2$ every 2 weeks), or arm D (10 mg/m$^2$/d by continuous infusion for 14 days every 3 weeks).

All four regimens were well tolerated and demonstrated efficacy. Arm C (every 2 weeks) and arm A (every 3 weeks) showed similar results for survival and tumor control while showing better efficacy compared to the weekly schedule (arm B). Continuous-infusion irinotecan (arm D) did not show the expected efficacy or safety (producing diarrhea, nausea, and vomiting), although it was associated with a low incidence of grade 3/4 neutropenia.[6] Therefore, the new standard schedule to be adopted for further development will consist of irinotecan administered every 2 or 3 weeks.

**Combination Regimens**

Several combination regimens containing irinotecan have been tested in Europe and the United States in recent years. The superiority of irinotecan over best supportive care and other second-line chemotherapy in colorectal cancer patients suggested that it would be of interest to combine irinotecan with other active agents such as 5-FU, oxaliplatin, or mitomycin (mitomycin-C [Mutamycin]).

**Irinotecan and 5-FU or 5-FU/Leucovorin:** A phase I trial and pharmacokinetic analysis performed between 1995 and 1997 at the Pitié-Salpêtrière Hospital in 41 patients with solid tumors (29 advanced colorectal cancer patients), demonstrated the feasibility and safety of irinotecan in combination with 5-FU (Table 3).[7,8] Irinotecan was administered on day 0 followed by 5-FU on days 1 to 5 in cycle 1 and on day 6 after 5-FU in cycle 2. The aim of the trial was to determine the relationship between the sequence of irinotecan administration and toxicity when combined with 5-FU.

The maximum tolerated dose of irinotecan was established at 350 mg/m$^2$. For further phase II trials, the investigators recommended that irinotecan be given at 200 mg/m$^2$ in combination with 5-FU at 375 mg/m$^2$ and leucovorin at 20 mg/m$^2$ on days 1 and 5 (Mayo Clinic regimen). No difference in the clearance of irinotecan or its active metabolite SN38 was observed, but a reduction in the catabolism of 5-FU was demonstrated, suggesting a potential benefit if irinotecan is administered before 5-FU.[7,8]

In a phase I study conducted in Spain by Aranda et al, irinotecan was administered on day 1 at 150 to 250 mg/m$^2$ followed by a 14-day continuous-infusion of 5-FU at 250 mg/m$^2$/d and 1 week of rest in a variety of solid tumors. Three partial responses (gastric, colon, and rectum) and two minor responses (colon) were observed.[9,10]

Barone et al conducted a multicenter study in Italy in 33 advanced colorectal cancer patients who were treated with irinotecan at 350 mg/m$^2$, over a 90-minute infusion on day 1 every 3 weeks, plus 5-FU and leucovorin for 5 consecutive days according to the Mayo Clinic schedule as first-line treatment.[11] This combination was well tolerated despite moderate neutropenia and diarrhea and achieved an overall response rate of 31% with a median progression-free survival of 7.2 months and an overall survival of 16 months.

Rothenberg et al conducted another multicenter phase II trial in which 71 previously untreated patients received weekly irinotecan at 100 mg/m$^2$ for 4 weeks every 6 weeks and 5-FU/leucovorin over 5 days (according to the Mayo Clinic schedule) every 4 weeks.[12] The main toxicities were
diarrhea and neutropenia (without severe consequences). The overall response rate with this regimen was 32% (95% CI: 21.5%-43.3%), and the median survival was 17.8 months.[12]

Rougier et al recently published the results of a phase I/II trial in which irinotecan was administered in combination with FUFL (5-FU and leucovorin [folinic acid]) according to the de Gramont schedule in 55 advanced colorectal cancer patients who had previously been treated with 5-FU (Table 4).[13] This combination was tolerated well, with no cumulative toxicity and produced a response rate of 22%. The maximum tolerated dose of irinotecan was 300 mg/m² dose level; thus, the recommended dose for phase II trials was a 90-minute infusion of irinotecan at 180 mg/m² on day 1, and biweekly leucovorin/5-FU on days 1 and 2 every 2 weeks. A pharmacokinetic analysis performed in 21 patients showed that the maximum concentration of SN38 appeared 30 to 60 minutes after the administration of irinotecan (Table 4).[13]

These results have been confirmed at our institution in 39 patients with advanced colorectal cancer, using the recommended dose of irinotecan (180 mg/m² on day 1) and biweekly leucovorin/5-FU on days 1 and 2. Eight patients achieved an objective response (overall response rate = 20.5%), and 12 demonstrated disease stabilization or minor responses (tumor control = 49%).[14,15] Of eight patients who underwent hepatic resection, seven achieved a complete response. The median duration of response and the median survival were 14 and 11 months, respectively. Neutropenia was the most serious side effect (affecting 29% of patients in 2% of cycles), with four patients developing febrile neutropenia and grade 3 diarrhea.[14,15]

De Gramont and colleagues performed a phase II study to evaluate the FOLFIRI combination (irinotecan, 180 mg/m² on day 1, plus a simplified biweekly leucovorin/5-FU regimen, with the daily 5-FU bolus omitted) in heavily pretreated colorectal cancer patients (Figure 7).[16] The treatment was well tolerated, and the main toxicities were nausea and vomiting. Of 34 evaluable patients, 2 achieved a partial response (overall response rate: 6%), and disease stabilization was observed in 20, for a tumor control rate of 65% (Table 5).[16]

Irinotecan and Mitomycin: A phase I/II study was performed at our institution to assess the feasibility of irinotecan in combination with mitomycin, another active compound in the treatment of gastrointestinal tract tumors, including advanced colorectal cancer.[17] Between January 1996 and June 1997, the study accrued 26 heavily pretreated patients with advanced gastrointestinal cancer (22 with colorectal cancer). Mitomycin was administered as an IV bolus, and irinotecan as a 30-minute infusion. Four dose levels of irinotecan/mitomycin were evaluated: 300/8 mg/m², 325/8 mg/m², 350/8 mg/m², and 325/10 mg/m² administered on day 1 every 21 days (Table 6).[17]

The dose-limiting toxicity was neutropenia, but it was of short duration and associated with rapid recovery. Cumulative thrombocytopenia occurred at the highest dose level as did one case of delayed hemolytic-uremic syndrome (both of which were due to mitomycin). Other toxicities included diarrhea and four cases of febrile neutropenia but no toxic deaths (Table 6).[17]

Objective responses were reported at all dose levels, for an overall response rate of 28% (which is higher than expected for this heavily pretreated population and suggests a possible synergism between the two drugs) (Table 6).[17] The recommended doses for further studies were 325 mg/m² of irinotecan and 8 mg/m² of mitomycin.[18]

Irinotecan and Oxaliplatin: Irinotecan in combination with oxaliplatin has also shown activity in 5-FU-refractory patients. Cvitkovic et al recently performed three phase I/II studies in which the combination was administered following two different schedules[19]:

1. Groups A and B received irinotecan, 150 to 250 mg/m², plus oxaliplatin, 85 to 110 mg/m², every 3 weeks.

2. Group C received irinotecan, 100 to 200 mg/m², plus oxaliplatin, 85 mg/m², every 2 weeks.
Of 34 patients, 15 responded (for an overall response rate of 44%), and toxicity was acceptable (Table 7). The recommended doses were irinotecan, 200 mg/m$^2$, and oxaliplatin, 85 mg/m$^2$, every 3 weeks (group A) or irinotecan, 175 mg/m$^2$, and oxaliplatin, 85 mg/m$^2$, every 2 weeks (group C).[19]

Wasserman et al published a pharmacokinetic analysis of two independent phase I studies of the combination of irinotecan and oxaliplatin in patients with gastrointestinal tumors.[20] Oxaliplatin was first administered as a 120-minute infusion followed by irinotecan as a 30-minute infusion, every 3 weeks. Pharmacokinetic analyses were performed during the first and second cycle. The maximum tolerated dose was reached at level 3, but two patients with Gilbert’s syndrome developed severe neutropenia, thrombocytopenia, and diarrhea.

Of 24 evaluable patients, 7 achieved a partial response (overall response rate: 29%), and 9 (38%) experienced disease stabilization. The pharmacokinetic parameters of the combined regimen were similar to those of the single agents.[20]

Based on previous data, a phase I/II study and pharmacokinetic analysis of four drugs in combination (irinotecan, oxaliplatin, and biweekly 5-FU/leucovorin) is ongoing at our center in patients with advanced colorectal cancer. To date, 34 patients have been enrolled to receive oxaliplatin on day 1 (in a 2- to 4-hour infusion), irinotecan on day 2 (30-minute infusion), and leucovorin/5-FU (de Gramont schedule) in a fixed dose on days 2 and 3, every 2 weeks. Pharmacokinetic samples are drawn during cycles 1 and 2. In the second cycle, irinotecan is given on day 1 and oxaliplatin on day 2 (Table 8).[21]

Five dose-levels are being evaluated: level 1 = oxaliplatin, 65 mg/m$^2$, and irinotecan, 150 mg/m$^2$; level 2 = oxaliplatin, 75 mg/m$^2$, and irinotecan, 165 mg/m$^2$; level 3 = oxaliplatin, 85 mg/m$^2$, and irinotecan, 165 mg/m$^2$; level 4 = oxaliplatin, 85 mg/m$^2$, and irinotecan, 180 mg/m$^2$. Dose level 5 is ongoing: oxaliplatin, 100 mg/m$^2$, and irinotecan, 180 mg/m$^2$. To date, the maximum tolerated dose has not been reached but preliminary results show high antitumor activity with acceptable toxicity at all dose levels (Table 8).[21]

Of 24 evaluable patients in this study, 2 achieved complete responses and 8 achieved partial responses, for an overall response rate of 41%; 6 of these patients underwent subsequent partial hepatectomy and have achieved a complete response (Table 8).[21] Preliminary pharmacokinetic results have revealed that oxaliplatin clearance is significantly lower (27.87 vs 23.24 L/h, $P = .0047$) when irinotecan is administered on day 1 before oxaliplatin, as compared to the reverse schedule.[21]

**Irinotecan and Raltitrexed:** In a recent phase II study conducted by Nobile et al, the combination of irinotecan and raltitrexed was evaluated in 14 patients with advanced colorectal cancer.[22] Irinotecan was given at 300 to 350 mg/m$^2$ on day 1, and raltitrexed at 3 mg/m$^2$ on day 2, with the cycle repeated every 3 weeks. The main toxicities were grade 3/4 diarrhea in 14% of patients, grade 3/4 nausea/vomiting in 42% of patients, and asthenia in 35.7% of patients; the incidence of febrile neutropenia was rare (7%). Of 10 evaluable patients, 3 achieved a partial response, 1 a minor response, and 4 disease stabilization (overall response rate: 30%). This represents an encouraging level of tumor control for this combination (Table 9).[22]

**Phase III Trials of Irinotecan/FUFOL Combinations:** Two important randomized trials of irinotecan and FUFOL in combination have been conducted in the United States and Europe. The first trial, performed by Saltz et al, compared weekly irinotecan plus FUFOL to FUFOL (Mayo Clinic regimen) or weekly irinotecan alone in patients with previously untreated metastatic colorectal cancer.[23] This trial demonstrated that the combination achieves better results than either single-agent therapy. The overall response rates were 49%, 27%, and 29% for the combination, irinotecan, and FUFOL, respectively. Although more grade 3/4 diarrhea and vomiting were observed with the combination, more grade 4 neutropenia and mucositis were seen with 5-FU/leucovorin alone.[23]

The second randomized phase III trial, conducted by Douillard et al, compared FUFOL (at high doses, either according to the AIO [Arbeitsgruppe Internistische Onkologie, of the German Cancer Society] or de Gramont regimen) with or without irinotecan.[24] Included in the trial were 385 previously
untreated metastatic colorectal cancer patients: 145 received irinotecan plus biweekly
leucovorin/5-FU and 143 received FUFOL alone, while 54 and 43 patients received FUFOL according
to the AIO regimen, in combination with irinotecan or FUFOL/AIO alone, respectively.

More toxicity was observed with the combination than with FUFOL alone, resulting in higher rates of
grade 3/4 neutropenia (42% vs 11% of patients) and febrile neutropenia (5% vs 1% of patients), as
shown in Table 10.[24] In terms of nonhematologic grade 3/4 toxicities, patients who received the
combination experienced more diarrhea than those who received FUFOL alone (22% vs 10% of
patients). Of 169 patients evaluable for response in both arms, 4% achieved a complete response,
and 37% a partial response, for an overall response rate of 41% for irinotecan plus 5-FU/leucovorin
and a 23% overall response rate for the 5-FU/leucovorin combination (P < .001).

A substantial number of patients experienced disease stabilization in both groups (38% and 50%,
respectively) (Table 10)[24]; however, the disease-free survival and median overall survival (Figure 8
) was also significantly superior (16.8 vs 14 months, P = .031) in favor of the irinotecan/FUFOL
combination, with good quality-of-life results (Figure 9).[24]

A pooled analysis of these two phase III randomized trials, comparing irinotecan plus FUFOL vs
FUFOL alone in advanced colorectal cancer patients who received no prior chemotherapy showed
that the time to progression and overall survival were significantly higher for the irinotecan plus
FUFOL combination in both studies, as well as in the combined analysis (time to progression: P < .001; overall survival: P < .009). In conclusion, the combination of irinotecan and FUFOL as first-line
treatment significantly improved tumor control and overall survival compared to FUFOL alone. This
combination may, therefore, be considered the new standard for first-line treatment of advanced
colorectal cancer.[25]

**Oxaliplatin**

Oxaliplatin is a new-generation platinum compound, the first DACH platinum that has demonstrated
a spectrum of activity in vitro in human colorectal cancer cell lines, together with low
cross-resistance with cisplatin (Platinol) and paraplatin (Carboplatin).[26,27] It has also
demonstrated synergistic activity with fluorouracil in vitro and in vivo models, without renal
toxicity.[26,27]

In phase I trials in a variety of tumors—breast, head and neck, ovary, cervix, non-small-cell lung
cancer, hepatocarcinoma, biliary tract, prostate, small intestine, and schwannoma—the dose-limiting
toxicity of oxaliplatin was cumulative and dose dependent, with reversible sensory peripheral
neuropathy.[28] However, there was no auditory or renal toxicity at the recommended doses.

**Toxicity**

Oxaliplatin has a favorable tolerability profile and, as a single agent, has a low potential for
myelosuppression and gastrointestinal adverse events. Oxaliplatin in combination with
5-FU/leucovorin is associated with low hematologic and gastrointestinal toxicity, depending on the
5-FU regimen employed, with no increase in the risk of neurotoxicity induced by the addition of
oxaliplatin. Moreover, oxaliplatin does not increase the incidence of alopecia related to treatment
with 5-FU.

**Neurotoxicity:** Two types of neurotoxicity occur with oxaliplatin. Patients may experience a sensory
peripheral neuropathy, which is mild and cold-related with acute symptoms. This reaction is very
common (occurring in 80% to 85% of patients) and short-lived (occurring within hours of infusion).
The second type involves dysesthesia and paresthesia of the distal extremities, occurring over a few
hours or days at the beginning of treatment. Both types are easily prevented by prolonging the
infusion of oxaliplatin over 6 hours. Chelation affects oxaliplatin and its metabolites so it must be
diluted in water and infused only in glucose solutions.[28]

Cumulative neurotoxicity occurred in 10% to 15% of patients after a total cumulative dose of 780 to
850 mg/m². Dysesthesia and paresthesia persisting between cycles with secondary difficulties in
activities that require fine sensory motor coordination resulted in discontinuation of treatment.[29] Gabapentin (Neurontin) therapy seems to be effective in reducing oxaliplatin-related symptoms but further data are needed to confirm the duration of response and the optimal dose range.[29]

Single-Agent Trials

**Phase I/II Studies:** Six phase I studies of oxaliplatin have been performed in a total of 125 patients according to three schedules: (1) bolus, (2) 30-minute to 12-hour infusion, and (3) 5-day continuous infusion (chronomodulated). The doses ranged from 0.45 to 200 mg/m², and the cycles were repeated every 3 weeks. Oxaliplatin was diluted in water or 5% glucose solution without electrolytes. The recommended dose for phase II trials is either 130 mg/m² administered as a 2- to 6-hour infusion every 3 weeks or 85 mg/m² every 2 weeks.[30,31]

Clinical phase II trials of oxaliplatin as a single agent were conducted in Spain and France and demonstrated the efficacy of oxaliplatin in advanced colorectal cancer in first- and second-line settings.[30,31] Two different schedules were used: 150 mg/m² over 5 days or 130 mg/m² on day 1, every 3 weeks. Among the 62 previously untreated patients enrolled in two phase II studies, the response rate was 18%; the median duration of response, median progression-free survival, and median overall survival were 6.7 months, 4 months, and 13 to 14 months, respectively (Table 11).

In the second-line setting, after 5-FU failure, pooled data from three phase II investigations involving a total of 135 patients showed overall response rates of 10%, with disease stabilization in 24% to 42%. Progression-free survival ranged from 4.6 to 4.8 months, and median overall survival ranged from 8.2 to 10 months (Table 11).[32,33]

Combination Regimens

Oxaliplatin has also proven to be effective in combination with 5-FU and leucovorin in patients who are refractory or progressing under 5-FU therapy. Between 1995 and 1998, de Gramont et al conducted three phase II trials of the combination of oxaliplatin and FUFOL as second-line therapy in advanced colorectal cancer using two different doses of oxaliplatin (100 mg/m² and 85 mg/m² every 2 weeks) plus fixed doses of FUFOL (biweekly leucovorin/5-FU regimen). The response rate for 203 patients ranged between 21% and 46%, and the patient population included 22 patients who had progressed while receiving the same 5-FU regimen and 39 patients refractory to 5-FU.[34]

Levi et al in 1992 and Garufi[35,36] in 1995 conducted phase II trials of oxaliplatin and FUFOL in combination as second-line treatment of advanced colorectal cancer patients using a chronomodulated approach. Chronotherapy is a special method of drug administration that relates to biological rhythms, and allows significant reductions in toxicity and increased dose intensity of drugs like 5-FU, oxaliplatin, floxuridine (FUDR), or interferon-alpha.

In Levi’s study, oxaliplatin was given at 25 mg/m²/d over 5 days in combination with leucovorin, 300 mg/m²/d over 5 days, and 5-FU, 800 mg/m²/d over 5 days every 3 weeks. All three drugs were administered by chronomodulation.[36] The study enrolled 42 patients, and the overall response rate was 55%. In another study conducted by Garufi, oxaliplatin was given at 20 to 25 mg/m²/d over 4 days in combination with 5-FU/leucovorin. Cycles were repeated every 2 weeks, and the overall response rate was 29% for the 25 patients treated. However, this approach still needs to be confirmed in more extensive studies.[37]

Phase III Studies of Oxaliplatin

Two multicenter randomized phase III studies of first-line treatment of advanced colorectal cancer with oxaliplatin and FUFOL in combination have been conducted in France by Giacchetti et al (study 2961) and de Gramont et al (study 2962).[37,38]

Study 2691 enrolled a total of 200 advanced colorectal cancer patients, with 100 patients randomly allocated to FUFOL alone and 100 patients to FUFOL plus oxaliplatin as front-line treatment of metastatic disease. Fluorouracil, 700 mg/m²/d, and leucovorin, 300 mg/m²/d, were administered as 12-hour infusions on a chronomodulated schedule (sinusoidal curve)[37] with the peak delivery rate
at 4 am for 5 consecutive days. Oxaliplatin, 125 mg/m$^2$/d, was administered at a constant rate (during the day) over 2- to 6-hour infusions on day 1. Cycles were repeated every 3 weeks.

Objective responses were reported in 53% of patients in the FUFOL plus oxaliplatin arm vs 16% in patients receiving FUFOL alone ($P < .001$). Maintained responses at 9 weeks were also significantly better in patients receiving oxaliplatin (34% vs 12%, $P < .001$). The median progression-free survival for the oxaliplatin arm was 6.1 months, compared with 8.7 months for the control arm ($P = .048$), but no differences in overall survival were observed (median overall survival: 19.9 vs 19.4 months), probably because 57% of patients in the control arm received oxaliplatin as second-line treatment.

Study 2962, conducted by de Gramont, compared the biweekly leucovorin/5-FU regimen (Figure 10) with biweekly leucovorin/5-FU plus oxaliplatin. Patients received leucovorin at 200 mg/m$^2$ on day 1 followed by a 5-FU bolus at 400 mg/m$^2$ and then continuous-infusion 5-FU over 22 hours at 600 mg/m$^2$ on day 1, either alone or with oxaliplatin, 85 mg/m$^2$ as a 2-hour infusion on day 1. Fluorouracil and leucovorin were repeated on day 2, and cycles were repeated every 2 weeks until disease progression or excessive toxicity.[38]

For the trial, 210 patients were randomized to receive biweekly leucovorin/5-FU alone, and 210 patients received oxaliplatin plus leucovorin/5-FU. More than half the patients in the study (71%) had metastatic colon carcinoma, and 29% had advanced rectal cancer. In each arm, 20% of patients had received prior adjuvant chemotherapy. An objective response was observed in 50.7% (over 207 evaluable patients) of patients in the oxaliplatin/leucovorin/5-FU arm vs 22.3% (over 206 evaluable patients) in the leucovorin/5-FU arm ($P = .0001$). The median time to response was 2.8 months in the control arm vs 2.1 months in the oxaliplatin arm, and median duration of response was 10.5 months in both arms.

With a median follow-up of 27.7 months, the progression-free survival significantly favored the regimen that included oxaliplatin (Figure 11), but no differences were found in overall survival (Figure 12).[38] The probability of survival without a deterioration in quality of life was significantly higher in patients treated with the oxaliplatin/FUFOL combination, compared to those treated with biweekly leucovorin/5-FU alone.

The safety profile showed mild toxicities in both arms, and only a slightly higher incidence of grade 4 neutropenia without febrile neutropenia (12% vs 1%), grade 3/4 diarrhea (11.9% vs 5.2%), and grade 3/4 mucositis (5.8% vs 1.4%) in patients treated with oxaliplatin and 5-FU/leucovorin.

Although all patients initially had unresectable metastatic disease, 57% and 28% of those with liver metastases underwent a successful partial hepatectomy in studies 2961 and 2962, respectively. Giaccchetti et al analyzed the impact on survival after oxaliplatin/5-FU chemotherapy and surgery in 151 patients with initially unresectable liver metastasis. Surgery was possible in 77 patients (50%) and resulted in macroscopically complete resection in 58 patients. Of these 58 patients, 50% are alive at 7 years follow-up vs 30% for the other patients who underwent surgery (Figure 13).[39,40]

De Gramont’s study demonstrated that oxaliplatin-induced sensory neuropathy causing functional impairment is experienced by 16% of patients who receive the drug. The onset of this phenomenon occurs at a median total dose of 850 mg/m$^2$ (10 cycles) and is responsible for treatment discontinuation in only 5% of patients; the median time to recovery is about 13 weeks.

**Conclusions**

After a long period during which the only therapeutic approach to colorectal cancer was a fluoropyrimidine or optimization of fluoropyrimidine-based therapy, new therapeutic possibilities have arisen with the introduction of irinotecan and oxaliplatin, effectively changing the natural history of the disease. New combinations with these compounds have consistently increased the response rate (by 35% to 55%) even in 5-FU-refractory patients and produced increases in time to progression and survival.

Chemotherapy has demonstrated its superiority vs best supportive care without impairing quality of
life. Both drugs are effective in combination with 5-FU and leucovorin as first- and second-line therapy. Moreover, they have demonstrated a synergism of action in combination with 5-FU, and they show efficacy when combined with 5-FU after failure of the same 5-FU treatment regimen.

Colorectal cancer patients are most likely to develop metastases to the liver, the lung, or both. Hepatic metastases develop most frequently, and the proportion of these patients with resectable disease is small. Oxaliplatin- and irinotecan-based therapies have significantly increased the resectability of inoperable patients. The fact that a substantial number of patients can be downstaged after treatment with oxaliplatin or irinotecan, administered as part of first- or second-line combinations, offers the hope of cure for some. New combinations with other drugs are under investigation. Agents such as raltitrexed, capecitabine (Xeloda), UFT (uracil and tegafur), eniluracil, and mitomycin are being evaluated in order to increase response and survival rates. Oxaliplatin and irinotecan in combination with FUFOLO can now be considered standard therapy for the first-line treatment of advanced colorectal cancer patients.

The adjuvant setting is the obvious next step to be considered, for both Dukes’ C and high-risk Dukes’ B patients. The role of adjuvant chemotherapy is now established in Dukes’ C patients after curative resection; treatment reduces the risk of recurrence by 19% to 40%, and of death, by 16% to 33%. The benefit of adjuvant chemotherapy for patients with Dukes’ B colon cancer is less clear. A number of clinicopathologic features are known to be associated with poor prognosis, including perforated or obstructed tumors, stage T4 tumors, poorly differentiated tumors, extramural vascular invasion, and mucinous differentiation. In addition, certain molecular prognostic markers are now emerging, such as loss of the DCC tumor-suppressor gene and the immunohistologic demonstration of carcinoembryonic antigen mRNA in the lymph nodes.

Overexpression of thymidylate synthase correlates with poor prognosis in patients with colorectal cancer (when measured by immunohistochemistry on tumor sample or in serum) and is an independent prognostic factor for response to treatment, survival, and relapse-free survival in these patients. High levels of thymidylate synthase correlate with a markedly decreased response to 5-FU but not to other agents such as oxaliplatin or irinotecan. Based on these observations, the tailoring of chemotherapy treatments to thymidylate synthase expression should be considered.

References:


38. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil, with or without oxaliplatin,


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