

Role of oxaliplatin in the treatment of colorectal cancer

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Abstract: Oxaliplatin is a third-generation platinum compound that has shown a definite role in the management of colorectal cancer (CRC). Oxaliplatin in combination with fluorouracil and leucovorin in the FOLFOX4 regimen represents a new standard of treatment in the adjuvant setting as well as for the metastatic disease. The combination of oxaliplatin with capecitabine in the XELOX regimen has been demonstrated to be not inferior to FOLFOX4 in metastatic patients, and it is under evaluation, with or without bevacizumab, in the post-surgical management of resected patients. FOLFOX4 and XELOX regimens represent a backbone on which to add new targeted drugs. Indeed, the combination of bevacizumab with either FOLFOX4 or XELOX significantly prolonged the progression-free survival and overall survival in comparison with FOLFOX4 or XELOX combined with placebo in metastatic CRC patients, while FOLFOX4 plus cetuximab produced a significantly greater activity than FOLFOX4 alone in metastatic CRC patients with *K-RAS* wild type.

Keywords: oxaliplatin, fluorouracil, leucovorin, colorectal cancer, advanced disease, adjuvant treatment, cetuximab, bevacizumab

Introduction

Colorectal cancer (CRC) is one of the most frequent causes of cancer mortality worldwide. Although the survival of patients with loco-regional disease has recently improved as a consequence of a better surgery, and of the activity of local radiotherapy and system chemotherapy, the prognosis of patients with metastatic disease remains poor. Until few years ago, the only active agent was leucovorin (LV)-modulated 5-fluorouracil (5FU). However, the recent introduction into the clinical armamentarium of new active cytotoxic drugs, such as irinotecan and oxaliplatin, and targeted agents (ie, cetuximab, panitumumab, bevacizumab) has substantially prolonged the survival.

Oxaliplatin

Oxaliplatin is a platinum compound characterized by a 1,2-diaminocyclohexane (DACH) moiety. Oxaliplatin is bounded to plasma proteins, and distributed to all body tissues. More than 50% of oxaliplatin dose is excreted through the kidneys in the urine, while only a small fraction of the drug is eliminated in feces. As a result, no alterations in oxaliplatin clearance from plasma have been observed in patients with liver dysfunction.

Cytotoxic lesions produced by oxaliplatin are the formation of intra-strand and inter-strand platinum-DNA adducts, formed by cross-linking between activated platinum species and specific base sequences, mainly two adjacent guanine residues or two adjacent guanine-adenine bases. The formation of a bulky adduct, because of the presence of the DACH moiety, prevents the mismatch repair enzyme complex from binding to the oxaliplatin adducts, and induces a greater degree of inhibition of DNA synthesis and cytotoxicity than cisplatin or carboplatin.¹

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Oxaliplatin in the management of metastatic CRC

Oxaliplatin as a single agent has demonstrated modest activity in patients with metastatic CRC, producing a response rate (RR) of 10% to 24%.²⁻⁵ Conversely, due to a synergistic activity with 5FU, the combination of oxaliplatin and 5FU has shown RRs ranging from 20% to more than 50%.^{6,7} These promising results obtained in phase II trials prompted the activation of several randomized trials in the first-line setting, either comparing a single-agent regimen of 5FU/LV versus a doublet of oxaliplatin and 5FU/LV, or directly comparing two doublets including 5FU/LV plus either oxaliplatin or irinotecan.

Oxaliplatin with 5FU/LV

Several randomized trials have assessed the combination of oxaliplatin and 5FU/LV in the first-line treatment of metastatic CRC patients (Table 1).

De Gramont et al⁸ conducted a phase III trial, in which 430 previously untreated metastatic CRC patients were randomly allocated to receive either the LV5FU2 regimen (LV 200 mg/m²/d as 2-hour infusion followed by 5FU 400 mg/m²/d bolus and 600 mg/m²/d as 22-hour infusion for 2 consecutive days, either alone or together with oxaliplatin 85 mg/m² on day 1 (FOLFOX4 regimen). Patients allocated to FOLFOX4 had significantly better RR (50.7% vs 22.3%; $p < 0.0001$), and longer progression-free survival (PFS) (median, 9.0 months vs 6.2 months, $p = 0.0003$) when compared with LV5FU2. The improvement in overall survival (OS) did not reach significance (median, 16.2 vs 14.7 months; $p = 0.12$), because almost half of the patients in the control arm received oxaliplatin in the second-line setting.

Cunningham et al⁹ conducted a randomized study in metastatic CRC patients, to compare combination treatments (oxaliplatin plus 5FU continuous iv infusion or FOLFOX4) vs single-agent treatments (5FU continuous iv infusion or LVFU2). The addition of oxaliplatin in the combination regimens significantly improved response rates (54.1% vs 29.8%; $p < 0.0001$), and progression-free survival (median, 7.9 vs 5.9 months; $p < 0.0001$). However, OS was similar, with 2-year probability of 27.3% and 24.8%, respectively.

Goldberg et al¹⁰ conducted a three-arm (N9741) trial, in which 795 previously untreated metastatic CRC patients were randomized to receive either (1) irinotecan plus bolus 5FU/LV (IFL), or (2) FOLFOX4, or (3) a combination of irinotecan and oxaliplatin (IROX). This study showed that FOLFOX4 was superior to IFL in RR (45% vs 31%, $p = 0.002$), in PFS (median, 8.7 vs 6.9 months, $p = 0.0014$),

and in OS (median, 19.5 vs 15.0 months; $p = 0.0001$), with a more convenient safety profile.

Subsequently, the same group of investigators reported the results of a random comparison between the FOLFOX4 and an IFL regimen with a 20% dose reduction (rIFL) in 305 metastatic CRC patients.¹¹ This study confirmed that FOLFOX4 was significantly superior to rIFL regimen for RR (48% vs 32%, $p < 0.006$), PFS (median, 9.7 vs 5.5 months, $p < 0.0001$), and OS (median, 19.0 vs 16.3 months, $p < 0.026$).

Tournigand et al¹² randomized 220 untreated metastatic CRC patients to receive a 2-hour infusion of LV 400 mg/m² (or 6S-LV 200 mg/m²) followed by 5FU 400 mg/m² bolus and 2400 to 3000 mg/m² as 46-hour infusion every 2 weeks, either with irinotecan 180 mg/m² (FOLFIRI) or with oxaliplatin 100 mg/m² as a 2-hour infusion (FOLFOX6) on day 1. At progression, a cross-over was allowed. Globally, it was shown that there were no differences between FOLFIRI and FOLFOX6 in terms of RR (56% vs 54%), PFS (median, 8.5 vs 8.0 months), and OS (median, 21.5 vs 20.6 months).

Similar results were reported by Colucci et al¹³ who randomized 360 metastatic CRC patients to receive either FOLFIRI or FOLFOX4 biweekly: RR was 31% vs 34%, median PFS was 7.0 months in both arms, and median OS was 14 vs 15 months. Grade 3 to 4 toxicities were uncommon in both arms, and no statistical significant difference was observed.

Comella et al¹⁴ compared oxaliplatin vs irinotecan, both combined with 5FU/LV bolus given every 2 weeks, in 274 patients with metastatic CRC. The oxaliplatin-including regimen (OXAFUFU) was significantly more active (RR, 44% vs 31%; median PFS, 8.2 vs 7.5 months), and significantly prolonged the OS (median, 18.9 vs 15.6, $p = 0.032$) in comparison with the irinotecan-including regimen (IRIFUFU).

Kalofonos et al¹⁵ randomly compared two combination regimens of oxaliplatin or irinotecan plus bolus 5FU/LV, given weekly for 6 consecutive weeks, and 2 weeks of rest, in 295 metastatic CRC patients. There was no difference in RR (32% vs 33%), PFS (median, 7.6 vs 8.9 months), and OS (median, 17.4 vs 17.6 months) between the two arms of treatments.

In the second-line setting, it should be mentioned the three-arm study of Rothenberg et al¹⁶ who randomly treated 463 patients in progression after IFL with: (1) FOLFOX4, (2) oxaliplatin as a single agent, or (3) LV5FU2. The FOLFOX4 regimen produced an improvement in terms of RR (9.9%), and PFS (median, 4.6 months), and a better relief of tumor-related symptoms, as compared with LV5FU2.

Table 1 Randomized trials assessing oxaliplatin/fluorouracil (FU) regimens in the first-line treatment of metastatic colorectal cancer

Authors	Regimens	No patients	RR (%)	Median PFS (months)	Median OS (months)
De Gramont et al ⁸	Oxaliplatin 85 mg/m ² d 1, LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	210	50.7 P = 0.0001	9.0 P = 0.0003	16.2 P = 0.12
	LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	210	22.3	6.2	14.7
Cunningham et al ⁹	Oxaliplatin 85 mg/m ² d 1 + 5FU 250 mg/m ² (CI) or Oxaliplatin 85 mg/m ² d 1, LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	362	54.1 P = 0.0001	7.9 P = 0.0001	15.9 P = 0.155
	5FU 300 mg/m ² (CI) or LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	363	29.8	5.9	15.2
Goldberg et al ¹⁰	Oxaliplatin 85 mg/m ² d 1, LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	267	45 P = 0.002	8.7 P = 0.0014	19.5 P = 0.0001
	Irinotecan 125 mg/m ² , LV 20 mg/mq + 5FU 500 mg/m ² (bolus) weekly × 4 q 6 wks	264	31 P = 0.34	6.9 P = 0.50	15.0 P = 0.04
	Oxaliplatin 85 mg/m ² + Irinotecan 200 mg/m ² q 3 wks	264	35	6.5	17.4
Goldberg et al ¹¹	Oxaliplatin 85 mg/m ² d 1, LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	154	48 P = 0.006	9.7 P = 0.0001	19.0 P = 0.026
	Irinotecan 100 mg/m ² , LV 20 mg/mq + 5FU 400 mg/m ² (bolus) weekly × 4 q 6 wks	151	32	5.5	16.4
Tournigand et al ¹²	Oxaliplatin 100 mg/mq d 1, 6S-LV 200 mg/mq d 1, 5FU 2400–3000 mg/m ² (46-h infusion) q 2 wks	109	54 P = ns	8.0 P = 0.26	20.6 P = 0.99
	Irinotecan 180 mg/mq d 1, 6S-LV 200 mg/mq d 1, 5FU 2400–3000 mg/m ² (46-h infusion) q 2 wks	111	56	8.5	21.5
Colucci et al ¹³	Oxaliplatin 85 mg/m ² d 1, 6S-LV 100 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	182	36 P = 0.60	7.0 P = 0.64	15.0 P = 0.28
	Irinotecan 180 mg/m ² d 1, 6S-LV 100 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	178	34	7.0	14.0
Comella et al ¹⁴	Oxaliplatin 85–100 mg/m ² d 1, 6S-LV 250 mg/m ² + 5FU 850–1050 mg/m ² (bolus) d 2 q 2 wks	140	44 P = 0.029	8.2 P = 0.046	18.9 P = 0.032
	Irinotecan 200 mg/m ² d 1, 6S-LV 250 mg/m ² + 5FU 850 mg/m ² (bolus) d 2 q 2 wks	136	31	7.5	15.5
Kalofonos et al ¹⁵	Oxaliplatin 45 mg/m ² , LV 200 mg/m ² + 5FU 450 mg/m ² (bolus) weekly × 6 q 8 wks	148	32	7.6 P = ns	17.4 P = ns
	Irinotecan 70 mg/m ² , LV 200 mg/m ² + 5FU 450 mg/m ² (bolus) weekly × 6 q 8 wks	147	33	8.9	17.6

Abbreviations: PFS, progression-free survival; OS, overall survival.

Oxaliplatin with oral fluoropyrimidines

Oxaliplatin and capecitabine

Capecitabine is an oral fluoropyrimidine that is converted to 5FU preferentially in tumor tissue. Capecitabine, given at the recommended dosage of 1250 mg/m² twice daily for two consecutive weeks, followed by 1 week of rest, has shown equivalent activity with the 5FU/LV monthly regimen in metastatic CRC in two randomized trials.^{17,18} In both these trials, patients treated with 5FU/LV experienced more severe stomatitis, while capecitabine led to a higher incidence of hand-foot syndrome. A pooled analysis of these two studies underlined that significantly fewer patients required hospitalization for treatment-related adverse events (11.6% vs 18.8%), and fewer physician visits were required for the treatment administration with capecitabine than with 5FU/LV (4 vs 15 visits in a 12-week period).¹⁹

Given its low toxicity profile, capecitabine is a good partner for oxaliplatin. This combination showed encouraging results in phase II trials. Cassidy et al²⁰ carried out a pivotal phase II study in 96 patients with mCRC treated every 3 weeks with oxaliplatin 130 mg/m² on day 1, followed by capecitabine 1000 mg/m² twice daily for 2 weeks (XELOX regimen). RR was 55%, median PFS and median OS were 7.7 and 19.5 months, respectively. The XELOX regimen has been proven to be safe and active also in elderly patients.^{21,22}

These observations prompted the implementation of several phase III trials (Table 2).

Porschen et al²³ randomly treated 474 metastatic CRC patients with either CAPOX (capecitabine 1000 mg/m² bid, days 1 to 14 plus oxaliplatin 70 mg/m² in days 1 and 8) repeated every 22 days, or with FUFOX (oxaliplatin 50 mg/m² followed by leucovorin 500 mg/m² plus 5FU 2000 mg/m² as a 22-hour infusion days 1, 8, 15, and 22) repeated every 36 days. Overall RRs were 48% for CAPOX (95% CI, 41%–54%) and 54% for FUFOX (95% CI, 47%–60%). Median PFS was 7.1 months in the CAPOX arm, and 8.0 months in the FUFOX arm (hazard ratio [HR], 1.17; 95% CI, 0.96–1.43; *p* = 0.117), while median OS was 16.8 months for CAPOX and 18.8 months for FUFOX (HR, 1.12; 95% CI, 0.92–1.38; *p* = 0.26).

Díaz-Rubio et al²⁴ compared the XELOX regimen with a treatment of FUOX (5FU 2250 mg/m² infused over 48 hours on days 1, 8, 15, 22, 29, and 36 plus oxaliplatin 85 mg/m² on days 1, 15, and 29 every 6 weeks). No differences were seen between these two arms of treatment in confirmed response rate (37% vs 46%; *p* = 0.539), PFS (median, 8.9 vs 9.5 months; *p* = 0.153), and OS (median, 18.1 vs 20.8 months; *p* = 0.145).

Comella et al²⁵ have compared the OXXEL (oxaliplatin 100 mg/m² on day 1, capecitabine 1000 mg/m² twice daily from day 1 to day 11) and OXAFUFU (oxaliplatin 85 mg/m²

Table 2 Randomized trials assessing the combination of oxaliplatin and capecitabine in the first line treatment of metastatic colorectal cancer

Authors	Regimen	No. patients	RR (%)	Median PFS (months)	Median OS (months)
Porschen et al ²³	Oxaliplatin 70 mg/m ² d 1 and 8, capecitabine 1000 mg/m ² twice daily d 1–14 q 3 wks	241	48%	7.1 HR = 1.17	16.8 HR = 1.12
	Oxaliplatin 50 mg/m ² , LV 500 mg/m ² + 5FU 2000 mg/m ² (22-h infusion) weekly × 4 q 6 wks	233	54%	8.0 p = 0.117	18.8 p = 0.26
Díaz-Rubio et al ²⁴	Oxaliplatin 130 mg/m ² d 1, capecitabine 1000 mg/m ² twice daily d 1–14 q 3 wks	171	37%	8.9 HR = 1.18	18.1 HR = 1.22
	Oxaliplatin 85 mg/m ² d 1 biweekly, 5FU 2250 mg/m ² d 1 (48-h infusion) weekly	171	46%	9.5 p = 0.153	20.8 p = 0.145
Comella et al ²⁵	Oxaliplatin 100 mg/m ² d 1, capecitabine 1000 mg/m ² twice daily d 1–11, q 2 wks	158	34%	6.6 HR = 1.12	16.0 HR = 1.0
	Oxaliplatin 85 mg/m ² d 1, 6S-LV 250 mg/m ² + 5FU 850 mg/m ² (bolus) d 2, q 2 wks	164	33%	6.5 p = 0.354	17.1 p = 0.883
Cassidy et al ²⁶	Oxaliplatin 130 mg/m ² d 1, capecitabine 1000 mg/m ² twice daily d 1–14 q 3 wks ± bevacizumab	1,017	37%	8.0 HR = 1.04 (0.93–1.16)	19.8 HR = 0.99 (0.88–1.12)
	Oxaliplatin 85 mg/m ² d 1, LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks ± bevacizumab	1,017	37%	8.5	19.6

Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

on day 1, 6S-LV 250 mg/m² plus 5FU 850 mg/m² on day 2) regimens, both repeated every 2 weeks, in 322 metastatic CRC patients. RR (34% vs 33%, $p = 0.999$), PFS (median, 6.6 vs 6.5 months $p = 0.354$, and OS (median, 16.0 vs 17.1 months, $p = 0.883$) were comparable, but severe adverse events were less frequent with OXXEL.

Cassidy et al²⁶ conducted a large randomized trial, with the specific aim of demonstrating the non-inferiority of the XELOX vs FOLFOX4 regimen. They initially randomized 634 patients into these two arms; thereafter, additional 1400 patients were also randomized to receive, in combination with one of these two regimens, either bevacizumab or placebo. Therefore, a total of 2034 patients were assessed for the final analysis. Median PFS was 8.0 months in the pooled XELOX-containing arms vs 8.5 months in the FOLFOX4-containing arms (HR, 1.04; 97.5% CI, 0.93–1.16). Median OS was 19.8 months with XELOX vs 19.6 months with FOLFOX4 (HR, 0.99; 97.5% CI, 0.88–1.12). This study clearly demonstrated the non-inferiority of the XELOX vs FOLFOX4 regimen.

Recently, a pooled analysis of 6 randomized phase II or III trials, investigating the role of oxaliplatin in combination with either capecitabine or infusional 5FU in metastatic CRC, confirmed that, although the regimens including capecitabine yielded a slightly lower RR, the PFS and for OS were similar, and the 95% CI of the HRs for these two outcomes were within the range of the non-inferiority.²⁷

On the other hand, the XELOX regimen has been also evaluated in patients failing irinotecan-based treatments in a prospective randomized study. This randomized trial did not show any difference of efficacy between the XELOX and FOLFOX4 regimen in the second-line setting.²⁸

In conclusion, the XELOX regimen could be considered an effective alternative to FOLFOX4 in the first-line as well as in the second-line treatment of metastatic CRC.

Oxaliplatin and UFT/LV

UFT is an orally administered mixed compound, composed of a fixed combination of tegafur and uracil in a 1:4 molar ratio. Tegafur is a prodrug of 5FU, while uracil reversibly inhibits the dihydropyrimidine-dehydrogenase (primary catabolic enzyme for 5FU). Both tegafur and uracil are well absorbed after oral administration. Phase I/II studies using varying regimens of UFT and LV showed that this combination resulted in impressive objective RRs with an acceptable safety profile.^{29–32}

Two large randomized phase III trials compared a regimen of UFT (300 mg/m²/d) and LV (90 mg/d), administered for

28 days every 35 days, with the 5FU/LV monthly regimen in metastatic CRC patients, showing similar activity and better toxicity profile.^{33,34} On this background, the combination of UFT/LV plus oxaliplatin has been investigated in some phase II trials as first-line treatment of metastatic CRC.

A phase II study showed that UFT 300 mg/m²/d and LV 90 mg/d from day 1 to day 14 may be combined with oxaliplatin 130 mg/m² given on day 1, recycling every 3 weeks (TEGAFOX regimen).³⁵ Among 58 treated patients, 1 complete response and 20 partial responses were observed, yielding a response rate of 34% (95% CI, 22–47). The median PFS and OS were 5.88 months (95% CI, 4.34–8.21) and 18.2 months (95% CI, 10–20.7), respectively.

Feliu et al³⁶ tested the combination of oxaliplatin, 85 mg/m² on days 1 and 15; 6S-LV 250 mg/m² given iv on day 1, followed by oral UFT 390 mg/m²/d, and oral 6S-LV 15 mg/d on days 2–14. Cycles were repeated every 28 days. There was one complete response (1%) and 28 partial responses (34%) among 82 patients, for an overall response rate of 35% (95% CI, 24%–46%). The median PFS was 7.3 months, and the OS was 16.8 months. However, it should be noted that, due to excessive toxicity on the first 16 treated patients, UFT dosage was reduced to 300 mg/m²/d in the following patients.

Bajetta et al³⁷ conducted a phase II randomized trial, assessing either the TEGAFOX (UFT 250 mg/m²/d plus LV 90 mg/d on days 1–14, and oxaliplatin 120 mg/m² on day 1), or the TEGAFIRI (UFT 250 mg/m²/d plus LV 90 mg/d on days 1–14, and irinotecan 240 mg/m² on day 1) every 3 weeks. RR was 41.7% for TEGAFIRI, and 38.9% for TEGAFOX. Median OS was 20 and 19 months, respectively, while median PFS was 8 months for both groups. In summary, the TEGAFOX regimen has shown an activity similar to the FOLFOX4 regimen. However, because no phase III trial directly compared the FOLFOX4 and TEGAFOX combinations, this latter should not be considered as a standard of care for metastatic CRC patients.

Oxaliplatin in triplet combinations

The combination of oxaliplatin with both irinotecan and 5FU (triplet regimen) has been investigated in a pivotal phase I–II trial in metastatic CRC patients.³⁸ The high RR obtained with this triplet prompted the activation of some phase III trials.

The Italian GONO (Gruppo Oncologico Nord Ovest) group compared the FOLFOXIRI regimen (irinotecan 165 mg/m² day 1, oxaliplatin 85 mg/m² day 1, LV 200 mg/m² day 1, 5FU 3200 mg/m² as 48-hour continuous infusion starting on day 1) with the standard FOLFIRI regimen every 2 weeks in 244 metastatic CRC patients aged up to

75 years (an excellent performance status was required for patients aged 71–75 years). Confirmed RR was significantly higher for FOLFOXIRI (60%, vs 34%, $p < 0.0001$). The R0 secondary resection rate was 36% vs 12% ($p = 0.017$) among patients with liver metastases only. Median PFS (9.8 vs 6.9 months, $p = 0.0006$), and median OS (22.6 vs 16.7 months, $p = 0.032$) were also significantly in favor of the triplet regimen.³⁹

The HORG (Hellenic Oncology Research Group) conducted a phase III trial in 283 metastatic CRC patients. They randomly compared a 3-day regimen of irinotecan 150 mg/m² on day 1, LV 200 mg/m² followed by 5FU 400 mg/m² as iv bolus, and 600 mg/m² as a 22-h continuous iv infusion, on days 2 and 3, plus oxaliplatin 65 mg/m² on day 2, versus the FOLFIRI regimen. Although superior results were reported for FOLFOXIRI in terms of RR (43% vs 33.6%, $p = 0.168$), PFS median, (8.4 vs 6.9 months, $p = 0.17$), and OS (median, 21.5 vs 19.5 months, $p = 0.337$), these differences were not significant.⁴⁰

Preliminary data were reported from phase I-II trials assessing the combination of oxaliplatin and irinotecan with oral capecitabine.

Bajetta et al⁴¹ conducted a dose-finding study on this combination, and defined the recommended dosages as follows: irinotecan 180 mg/m² on day 1, oxaliplatin 85 mg/m² on day 2, and capecitabine 1000 mg/m² twice daily from day 2 to 6, recycling every 2 weeks. They reported a partial response in 17 of 27 patients (RR = 63%) treated at these recommended doses.

The GONO group⁴² also performed a dose finding study, and their recommended dosages were: irinotecan 165 mg/m² on day 1, oxaliplatin 85 mg/m² on day 1, and capecitabine 1000 mg/m² twice daily from day 1 to 7, recycling every 2 weeks. They achieved a partial response in 18 of 26 patients (RR, 69%) treated at these recommended dosages.

Oxaliplatin-based regimens with anti-EGFR agents

Recently, two monoclonal antibodies directed against the EGFR, ie, cetuximab and panitumumab, have shown activity in heavily pretreated metastatic CRC patients.

Some phase II trials have assessed the combination of cetuximab with oxaliplatin-based regimens in the management of metastatic CRC patients. The ACROBAT study⁴³ evaluated the FOLFOX4 plus cetuximab (starting dose of 400 mg/m² on week 1, followed by 250 mg/m² weekly thereafter) in 43 previously untreated EGFR-expressing mCRC patients. The overall confirmed RR was 72%, with an acceptable toxicity.

Souglakos et al⁴⁴ conducted a phase II trial to evaluate the safety and efficacy of cetuximab combined with capecitabine and oxaliplatin (CAPOX) in the treatment of 44 patients with metastatic CRC progressing under oxaliplatin-based chemotherapy. Cetuximab (loading dose 400 mg/m² and then 250 mg/m² iv weekly) was combined with CAPOX (oxaliplatin 85 mg/m² on day 1, and capecitabine 2000 mg/m²/d on days 1–7, every 2 weeks). One complete and 7 partial responses were achieved (RR, 20%). The median PFS was 3.0 months, and the median OS was 10.7 months.

The Swiss Group of Clinical Cancer Research (SAKK) delivered the XELOX, either alone or in combination with cetuximab, in 74 patients with metastatic CRC. The RR was 33% and 53% for XELOX and XELOX plus cetuximab, respectively.⁴⁵

The addition of cetuximab to the FOLFOX4 regimen has been randomly investigated in comparison with FOLFOX4 alone in the OPUS trial.⁴⁶ The combination regimen increased both the complete (1.2% vs 0.6%) and partial RR (44.4% vs 35.1%), but the difference was of borderline significance ($p = 0.064$). However, FOLFOX4 plus cetuximab produced a significantly greater RR than FOLFOX4 alone in patients with ECOG performance status 0 or 1 (49.0% vs 36.8%, $p = 0.032$). A retrospective analysis of this study on 233 out of 337 patients, for whom the *K-RAS* status was known, demonstrated that the combination regimen obtained a significantly greater RR (61% vs 37%) and a significantly longer PFS (median, 8.6 vs 5.5 months) in patients with *K-RAS* wild type, while it had no benefit in patients with mutated *K-RAS*.⁴⁷

Oxaliplatin-based regimens with anti-VEGF agents

Bevacizumab, the monoclonal antibody binding and inhibiting the circulating VEGF, has also been evaluated in combination with oxaliplatin-based cytotoxic regimens in patients with metastatic CRC.

Saltz et al⁴⁸ reported the results of a 2 × 2 factorial phase III trial, where 1401 previously untreated patients were randomized to one of these four arms: (1) XELOX plus placebo, (2) XELOX plus bevacizumab, (3) FOLFOX4 plus placebo or (4) FOLFOX4 plus bevacizumab. The superiority of bevacizumab over placebo when added to oxaliplatin-based treatments was seen in the prolongation of PFS (median, 8.0 months vs 9.4 months, $p = 0.0023$), and OS (median, 21.3 months vs 19.9 months, $p = 0.077$). However, the independently reviewed RR obtained with XELOX/FOLFOX4 was exactly the same (38%), with or without the addition of bevacizumab.

By contrast, the TREE study⁴⁹ showed that the addition of bevacizumab to 3 different oxaliplatin-based regimens: (1) FOLFOX6, (2) bFOL (oxaliplatin/LV/5FU bolus), or (3) CAPOX, in 223 patients with metastatic CRC (TREE-2 study) produced a greater RR, and a longer PFS and OS, in comparison with those reported in 150 patients treated in the previous (TREE-1) study with the same regimens without bevacizumab. However, it should be noted that capecitabine dosage in combination with oxaliplatin was reduced from 2000 mg/m²/d of the TREE-1 study to 1700 mg/m² in the TREE-2 study. Moreover, these results should be interpreted with caution, due to the limited number of treated patients, and to the cross-comparison of findings from two consecutive series of patients.

In second-line, the E3200 phase III trial⁵⁰ showed a significant prolongation of OS with the combination of FOLFOX4 and bevacizumab compared to FOLFOX4 in irinotecan-refractory metastatic CRC patients (median, 10.7 vs 12.5 months, $p = 0.0024$).

Oxaliplatin in the adjuvant setting

The results of the oxaliplatin plus 5FU/LV regimens in the treatment of metastatic CRC strongly supported the investigation of the role of oxaliplatin-based combinations in the adjuvant setting (Table 3).

The Multicenter International Study of FOLFOX4 in the Adjuvant Treatment of Colon Cancer (MOSAIC) was conducted in 2246 patients with stage II or III resected colon cancer to randomly compare 6 months of adjuvant treatment with either LV5FU2 or FOLFOX4. A significant improvement of the 3-year disease free-survival (DFS)

was seen for the whole group of patients treated with FOLFOX4 (78.2% vs 72.9%; HR, 0.77, $p = 0.002$).⁵¹ The 5-year follow-up confirmed a benefit in DFS (73.3% vs 67.4%, HR 0.80, $p = 0.003$) for patients treated with the FOLFOX4 arm. In addition, at a longer follow-up, there was a trend for a benefit in OS for the whole population, that was significant for stage III (72.9% vs 68.3%; HR 0.80, $p = 0.029$).⁵² On the contrary, there was no statistically significant benefit in DFS for patients with stage II, but an improved DFS was observed for stage II at high-risk (T4 tumor, bowel obstruction, tumor perforation, poorly differentiated histology, venous invasion, or less than 10 examined lymph nodes).

The NSABP C-07 was a similar study, in which 2407 patients with stage II or III colon cancer were randomized to receive adjuvant therapy with either LV (500 mg/m² iv infusion) and 5FU (500 mg/m² iv bolus) weekly for 6 consecutive weeks, followed by a 2-week rest period, or the FLOX regimen (5FU and LV as described, plus oxaliplatin 85 mg/m² administered as a 2-hour infusion on days 1, 15, and 29 of the treatment cycle) for a total of 6 months. A significant benefit in 4-year DFS rate for FLOX-treated patients was reported. DFS rate increase from 67% to 73.2% (HR, 0.80; $p < 0.004$) in favor of FLOX.⁵³

The XELOXA trial randomized 1864 patients with stage III colon cancer to receive adjuvant treatment with either XELOX for a total of 8 cycles or intravenous bolus 5FU/LV (monthly or weekly regimen). Preliminary safety data showed that patients receiving XELOX showed less diarrhea, alopecia, febrile neutropenia, but presented more neurosensory toxicity, vomiting and hand-foot syndrome compared with patients receiving 5FU/LV.⁵⁴

Table 3 Randomized trials assessing the combination of oxaliplatin and 5FU/LV in the adjuvant setting

Authors	Regimen	No. patients	DFS	OS
André et al ⁵¹	Oxaliplatin 85 mg/m ² d 1, LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	Stage II–III = 1123	5-year 73.3%	6-year 78.6%
De Gramont et al ⁵²	LV 200 mg/m ² + 5FU 400 mg/m ² (bolus) and 600 mg/m ² (22-h infusion) d 1 and 2 q 2 wks	Stage II = 451 Stage II I = 672	83.7% 66.4%	86.9% 73.0%
			$p = 0.005$	$p = 0.057$
		Stage II–III = 1123	5-year 67.4%	6-year 76.0%
		Stage II = 448	79.9%	86.8%
		Stage III = 675	58.9%	68.6%
Kuebler et al ⁵³	Oxaliplatin 85 mg/m ² q 2 wks, LV 500 mg/m ² + 5FU 500 mg/m ² (bolus) weekly × 6 q 8 wks	Stage II–III = 1247	4-year 73.2%	
		Stage II = 28.9%	84.2%	
		Stage III = 70.9%	68.9%	
			$p = 0.0034$	
	LV 500 mg/m ² + 5FU 500 mg/m ² (bolus) weekly × 6 q 8 wks	Stage II–III = 1245	4-year 67.0%	
		Stage II = 28.8%	81.0%	
		Stage III = 70.5%	61.1%	

Abbreviations: DFS, disease-free survival; OS, overall survival.

Some ongoing trials are assessing the addition of targeted agents to oxaliplatin-based adjuvant treatment.

In the AVANT study, patients with resected stage II or III colon cancer were randomized to one of three arms: (1) FOLFOX4 for 24 weeks followed by observation, (2) FOLFOX4 plus bevacizumab for 24 weeks followed by bevacizumab monotherapy for 24 weeks, and (3) XELOX plus bevacizumab followed by bevacizumab monotherapy for 24 weeks. Accrual was accomplished, but results are still pending.

The NSABP C-08 trial is currently evaluating the combination of FOLFOX6, with or without bevacizumab, in 2710 patients with resected stage II or III colon cancer. Preliminary safety data have shown no unexpected toxicity in the combination arm.⁵⁵

Two ongoing phase III trials, the PETACC-8 and the NCCTG-N0147, are assessing the role of cetuximab in combination with FOLFOX4 vs FOLFOX4 alone in the adjuvant treatment for patients with stage III resected colon cancer.

Neurotoxicity of oxaliplatin

Oxaliplatin can produce an acute neuropathy (ie, muscle spasms, breathing or swallowing difficulties), and a chronic, cumulative peripheral sensory neurotoxicity (PSN), consisting of paraesthesias and/or dysesthesias of the hand, feet, and mouth. This chronic neurotoxicity is correlated with the cumulative dose of oxaliplatin, usually developing after a dose >600 to 800 mg/m². While PSN is considered reversible, it may persist for a long time also after oxaliplatin discontinuation.

Different attempts have been made for preventing or reducing the oxaliplatin neurotoxicity, but no treatment has been accepted as standard. The intravenous administration of calcium and magnesium (Ca&Mg) salts before and after the administration of oxaliplatin, that was reported effective in a retrospective study,⁵⁶ has been evaluated in prospective trials. In the adjuvant setting, a phase III double-blind placebo-controlled trial was planned by the North Central Cancer Treatment Group, to assess addition of Ca&Mg for preventing grade 2+ PSN. Although prematurely closed to patients accrual, this study (conducted in only 102 patients) showed that Ca&Mg significantly delayed the occurrence of grade 2+ PSN. Moreover, in treated patients, the cumulative occurrence of PSN was significantly reduced (22% vs 41% according to the NCI-CTC scale, or 28% vs 51% according to an oxaliplatin-specific scale).⁵⁷ In the metastatic setting, it should be mentioned the CONcept trial, that (with a two-by-two factorial design) simultaneously investigated

two strategies for preventing PSN: the intermittent delivery of oxaliplatin, and the concurrent administration of Ca&Mg. Indeed, patients were randomly allocated to 4 arms of treatment: (1) mFOLFOX7 regimen (oxaliplatin 85 mg/m² on day 1, LV 200 mg/m² on day 1, 5FU 2400 mg/m² as 46-hour infusion) plus bevacizumab 5 mg/kg every 2 weeks until treatment failure; (2) mFOLFOX7 + bevacizumab for 4 months, then oxaliplatin was discontinued, and reintroduced after 4 months (or earlier in the case of tumor progression); (3) and (4): the same treatment as in (1) and (2), with or without the addition of Ca&Mg before and after oxaliplatin infusion. This study was prematurely closed after an unplanned interim analysis suggested a lower activity in patients receiving Ca&Mg. However, a subsequent independent review found no evidence of any detrimental effect of Ca&Mg on response rate. Although conducted on a limited number of patients, the intermittent strategy significantly prolonged the time to treatment failure, and the progression-free survival. Moreover, the intermittent strategy significantly reduced the occurrence of grade 3+ PSN (10% vs 24%), while Ca&Mg showed no effect on PSN.⁵⁸

At the 2006 ASCO Meeting, Cassidy et al presented the final results of the XENOX trial, assessing the efficacy of xaliproden in reducing the cumulative PSN induced by FOLFOX4 in metastatic CRC patients. Xaliproden is a neuroprotective agent that increases the expressions of neurotrophins, and it was shown to minimize the experimentally induced neuronal lesions (including the oxaliplatin-induced lesions). In the XENOX trial, 649 metastatic CRC patients were treated with FOLFOX4 until progression, while randomly receiving oral xaliproden or placebo daily during chemotherapy. In the xaliproden-arm, occurrence of grade 3+ PSN was significantly lower (but grade 2 higher) as compared to placebo-arm, namely in patients receiving a high cumulative oxaliplatin dosage. No beneficial effect was seen on the occurrence of acute neurotoxicity. In addition, this large trial demonstrated that the addition of xaliproden to FOLFOX4 did not affect the RR (44.9% vs 42.6%), nor the overall survival (median, 20.1 vs 18.9 months) of patients.⁵⁹ A further study has been planned to confirm the results of the XENOX trial, and to assess the effect of continuing xaliproden, after oxaliplatin discontinuation, on recovery from PSN.

Conclusion

The combination of oxaliplatin plus 5FU/LV represents a new standard of care for both resected stage III (and high risk stage II) CRC, and for metastatic patients. The ongoing trials assessing the addition of new targeted agents (such as

cetuximab, bevacizumab, and panitumumab) to this cytotoxic combination could demonstrate whether the prognosis of resected as well as of metastatic patients could be further improved.

Disclosures

The authors declare no conflicts of interest.

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