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Original Paper

Oxaliplatin/cisplatin (L-OHP/CDDP) Combination in Heavily Pretreated Ovarian Cancer

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The aim of this study was to evaluate the toxicity and the activity of two non-cross-resistant platinum compounds: oxaliplatin (L-OHP) and cisplatin (CDDP) in platinum pretreated ovarian cancer patients. Chemotherapy consisted of L-OHP and CDDP given sequentially as 2 h infusions on day 1 at their standard recommended dose (130 mg/m^2 for oxaliplatin, 100 mg/m^2 for cisplatin) every 3 weeks. Dose reductions (20–35%) were planned according to baseline haematological and renal status, but the dose ratio between L-OHP and CDDP was always maintained at 1.3. Cycles were repeated until progression or treatment limiting toxicities. From September 1992 to November 1994, 25 patients with pretreated ovarian cancer entered this salvage programme. They had received a median number of three previous chemotherapy lines (1–7), one at least platinum based. Previously cisplatin had been given to 22 patients at a median total dose of 600 mg/m^2 (170–1175), while 18 had received carboplatin to a median total dose of 1135 mg/m^2 (200–2450). 9 patients had also received and were resistant to taxanes (paclitaxel, 6 patients, docetaxel, 3 patients), while the rest were considered ineligible for simultaneously ongoing single-agent taxane phase II trials. 13 and 12 patients, respectively, were considered to have platinum refractory and potentially sensitive disease, according to Markman's criteria. 77 cycles of L-OHP/CDDP were given, with a median of three cycles/patient (range 1–6) and were evaluable for toxicity. The limiting toxicity of the L-OHP/CDDP combination was a cumulative, sensory peripheral neuropathy, severe (≥grade 3 CTC) after more than three cycles, but reversible within a few months of its discontinuation. Grade 3–4 (WHO scale) neutropenia and thrombopenia were seen in 35–40% of cycles, with one neutropenic treatment-related death (septic shock). 22 patients with measurable/evaluable disease were assessable for antitumoral activity. Two complete responses (CR) (8%) (one proven histologically at laparotomy (pCR)) and 8 partial responses (PR) (32%) for an overall objective response rate (ORR) of 40% (95% CI, 21–61%) (intent to treat). The median duration of response was 4 months. Seven responses were seen among 12 potentially platinum-sensitive tumours (58%, CI 95% 28–85%), while 3/13 platinum refractory patients (23%, CI 95% 5–54%) had an objective response. These encouraging results are the basis for new first-and second-line combination treatment programmes in ovarian carcinoma. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

OVER THE past two decades, progression-free and median survival for advanced ovarian cancer have steadily improved [1]. At present, cisplatin (CDDP)-based chemotherapy is the cornerstone of management of advanced ovarian cancer [2], although carboplatin (CBDCA) has been proposed as a viable alternative [3]. Despite this true but limited survival gain, more than 80% of ovarian cancer patients still fail primary treatment and will die of their disease.

Since the definitive incorporation of platinum in the treatment of ovarian cancer, many strategies have been developed to enhance disease control and survival; the only

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effective one, proven in a GOG randomised trial (without cross-over), has been the introduction of paclitaxel replacing cyclophosphamide in first-line CDDP-based treatment [4]. However, recurrent themes in ovarian cancer chemotherapy over the last decade have been the assessment of high-dose therapy and platinum dose intensification to improve treatment results. This arose from the dose intensity (DI) analysis by Levin and Hryniuk, which suggested that cisplatin DI could be a determinant of treatment outcome [5]. Various methods of increasing the DI of platinum species have been tested (higher CDDP dose, high dose CBDCA, CDDP/CBDCA combinations). The relative 2–3-fold increase in platinum dose intensity obtained when compared to the 20–30 mg/m^2/week DI standard has failed to improve survival conclusively, despite encouraging phase II trials reported in previously untreated patients with small-volume disease [6–8]. Significant cumulative limiting toxicities (peripheral neuropathy, thrombopenia) have hampered the extensive prospective evaluation of this concept [6, 8, 9], and there is only a marginal protective effect from currently available supportive care (neuroprotectors, haematopoietic growth factors) to prevent such effects and allow the sustained high DI delivery of either agent. In the range of clinically tolerable total cisplatin dose ($\leq$600 mg/m^2), no randomised study had demonstrated the benefit of high-dose intensity independently of the total amount of administered cisplatin [10, 11].

The incorporation of new platinum analogues, especially those with an enlarged spectrum of activity and partial or non-cross-resistance with the parent compound, is therefore of current interest.

Diaminocyclohexane platinum (DACH) derivates seem to have the same mechanism of cytotoxicity as first- and second-generation platinum compounds [12], but their different *in vitro* cytotoxic profile has recently led to the proposal of classing them as a separate family of cytotoxic compounds [13]. L-OHP (oxaliplatin), recently approved in France for the treatment of 5-FU (5-fluorouracil) pretreated colorectal cancer patients, is the only DACH platinum currently in phase II–III clinical development [14]. Its non-cross-resistance with CDDP or CBDCA has been demonstrated both *in vitro* and *in vivo* in human ovarian cancer cell lines [15, 16], and its interaction with CBDCA or CDDP has been shown to be supra-additive and/or synergistic in the same models [17, 18]. Clinical data have shown that oxaliplatin lacks renal or auditive toxic effect and is marginally haematotoxic at recommended doses [14, 19, 20], its main side-effect being acute cold triggered dysesthesias and cumulative neurosensorial toxicity [21].

The activity of oxaliplatin in previously CDDP/CBDCA treated patients with relapsing/refractory ovarian cancer was suggested in both broad elegibility phase I–II trials [14] and in a study conducted by Chollet and associates [22]. In this last study, L-OHP (75–100 mg/m^2 every 3 weeks) showed an encouraging 30% response rate in 27 evaluable patients, with excellent haematological tolerance and only mild neurotoxicity (only one grade 2 neuropathy in 12 patients having previously received more than 600 mg/m^2 of oxaliplatin) in a platinum pretreated population. Amongst the 14 patients defined as refractory to platinum according to Markman's criteria [23], 3 partial responses (21%, 95% CI 5–51%) were observed: all of them had secondary refractory tumours and were previously untreated with taxanes. This information led us to consider the simultaneous utilisation of oxaliplatin and cisplatin, at their recommended dose and schedule: 100 mg/m^2 for CDDP and 130 mg/m^2 for oxaliplatin every 3 weeks. We report here the first part of our programme in which the toxicity and activity of the combination of L-OHP and CDDP was evaluated. The second part, which tested the addition of epirubicin and ifosfamide with GCSF support to the L-OHP/CDDP combination, will be reported separately.

PATIENTS AND METHODS

Eligibility criteria

All women consecutively referred to our institution with advanced histologically proven ovarian carcinoma which progressed or relapsed after at least one line of platinum-based chemotherapy (CT) and required salvage CT were considered for this trial, when unable to fit the restrictive eligibility criteria for simultaneously ongoing phase II trials (docetaxel, tallimustine), or if progressing after being included in those phase II trials.

It is noteworthy that their poor performance status (PS $\geq$ 2), altered renal function (creatinine > upper normal limit, < 180 μmol/l), high number of prior chemotherapy regimens, previous grade 1–2 (CTC) CDDP-induced peripheral neuropathy, poor bone marrow reserve secondary to multiple prior chemotherapy lines or to high-dose chemotherapy with autologous bone marrow transplantation (ABMT) including carboplatin were not exclusion criteria.

Patient population

From September 1992 to November 1994, 25 women were considered eligible. All had advanced progressive disease at the time of inclusion.

Patient characteristics are detailed in Table 1. 24 women had primary ovarian carcinoma while the other patient had a recurrent fallopian tube carcinoma. All had previously received at least one combination chemotherapy regimen including cisplatin or carboplatin, with a median number of prior chemotherapy regimens of 3 (1–7). Cisplatin–based chemotherapy had been previously administered to 22 patients with a median total dose received of 600 mg/m^2 (170–1175). Carboplatin had been previously given to 18 patients, being part of high-dose chemotherapy regimens (with autologous bone marrow rescue) in 2 of them. 3 patients had received single-agent oxaliplatin. 18 patients had received sequentially both cisplatin and carboplatin or oxaliplatin. Taxanes (paclitaxel or docetaxel) had previously been given to 9 patients. Median time from initial diagnosis was 33 (3–144) months, while the interval from the last platinum-containing chemotherapy ranged from 1 to 36 months (median, 10 months). According to Markman's criteria for clinical platinum sensitivity [23], 13 patients were classified as refractory to platinum therapy and 12 were considered potentially sensitive.

All patients except one had bidimensionally measurable or evaluable disease. In the exception, disease progression had been documented by laparotomy and the therapeutic response was assessed by evolution of the abnormally elevated CA 125, which had previously accurately reflected disease evolution.

Table 1. Patient characteristics

Total number of patients	25
Median age (years)	52 (30–82)
Performance status (ECOG)	0–1 = 75%
	2–4 = 25%
Prior chemotherapy regimes	
Median number/patient	3
Total number/patient	1–7 pts
	2–2 pts
	3–4 pts
	4–6 pts
	≥6 pts
Median best PFS (months)	12 (0–27)
Previous CDDP	
Number of patients	22
Median total dose (mg/m^2)	600 (170–1175)
Previous CBDCA	
Number of patients	18
Median dose (mg/m^2)	1135 (200–2450)
Previous L-OHP	
Number of patients	3
Median total dose (mg/m^2)	400 (300–800)
Previous HDCT ± ABMT	2
Previous taxanes	9
Clinical cisplatin resistance status	
Potentially sensitive	12
Secondary refractory	11
Primary refractory	2
Serum CA 125 level	
Normal (N)	2
N < CA 125 < 100	3
100 < CA 125 < 500	9
500 < CA 125 < 1000	4
CA 125>1000	7
Type of site involved	
Abdomen/pelvis	19
Liver	4
Pleural—lung	3
Median time from initial diagnosis	33 (3–144) months

Pt, cisplatin; PFS, progression-free survival; ABMT, autologous bone marrow transplantation; HDCT, high-dose chemotherapy.

The majority of patients had bulky tumour masses at the beginning of treatment, while 7 of them (28%) had visceral metastases (Table 1).

Toxicity and activity assessment

All toxicities were graded according to WHO criteria [24], except for neurotoxicity which was evaluated by the common toxicity criteria (CTC) scale [25].

Antitumoral activity was assessed every two cycles by computer tomography (CT) scan and/or echography. Responses were defined according to WHO guidelines [24] as follows: CR (complete response), disappearance of all measurable or evaluable disease; PR (partial response), ≥50% reduction in the sum of the products of all measurable disease sites with no new lesions; SD (stable disease), less than 25% change in measurable/evaluable disease in the absence of new lesions, and PD (progressive disease), ≥25% increase in any measurable disease site or the appearance of new lesions. CRs and PRs required confirmation at least 4 weeks after first assessment, whereas SD had to last for 8 weeks. Normalisation of serum CA 125 level for at least 1 month was a further requirement for assignment to the CR category.

Time to progression was measured from the first day of treatment to the date of PD assessment, while survival was calculated from treatment onset until death. Surgical re-exploration occurred when judged appropriate and feasible to confirm clinical CR status, never before four treatment cycles.

Serum CA 125 determinations were assessed before each treatment cycle, followed up only as a corroborating element of tumour evolution in all patients but one. Further measurements were also performed at regular intervals after treatment cessation to detect disease progression.

Statistical methods

Two-sided significance levels ($P < 0.05$) were calculated using χ^2 for the cross-tabulation tables.

Schedule of administration

L-OHP and CDDP were given sequentially on the same day, every 3 weeks. Patients were hospitalised for each treatment course. Before and after cisplatin, high-volume fluid hydration (≥ 4 litres/day) with normal or half normal saline supplemented with KCl and $MgSO_4$ was given intravenously; diuresis and electrolyte balance were carefully monitored for at least 36–48 h after treatment. L-OHP (oxaliplatin) was provided on a case by case compassionate use release programme basis by Debiopharm (Lausanne); it was given first, i.v. over 2 h, diluted in 500 ml of 5% dextrose. Two hours after the end of oxaliplatin administration, cisplatin was administered over 2 h, in 500 ml of NaCl 0.9%, with mannitol-induced diuresis. L-OHP and CDDP were delivered at their respective standard recommended doses of 130 and 100 mg/m^2.

In patients with altered renal function (defined as creatininaemia > upper normal limit < 180 μ ml/l and/or single functional kidney) and/or poor bone marrow reserve (defined as grade 3–4 haematological toxicity ≥1 week after the last given therapy), dose adjustments were applied for both oxaliplatin and cisplatin, while respecting the fixed L-OHP/CDDP dose ratio of 1.3, with L-OHP doses ranging from 80 to 100 mg/m^2 and CDDP from 60 to 80 mg/m^2. In patients with large ascitis, fluid overload intolerance, poor performance status and/or altered renal function, treatment administration was fractionated over 2 or 3 days.

Anti-emetic prevention consisted of anti-$5HT_3$, often complemented with steroids; metoclopramide and benzodiazepines were also added when considered necessary. Complete blood cell counts were performed at least twice a week while serum creatinine and blood electrolyte levels were obtained at least weekly.

RESULTS

Toxicity

The 25 eligible patients received 77 cycles (median 3/pt, range 1–6) of L-OHP/CDDP, all evaluated for toxicity. Dose reduction was implemented as previously defined.

No intrapatient dose escalation was allowed. Reasons for early treatment interruption (<3 cycles) were toxic death (1 case), renal toxicity (1 case), disease progression (5 cases), poor haematological tolerance (1 case), poor performance status (1 case). 14 patients received at least four cycles and the median time between their first and fourth cycles was 12 weeks (range 10–23).

Haematological. Myelosuppression was generally moderate, even though planned dose adaptation might have prevented serious toxicities in this otherwise heavily pretreated population. Grade 3–4 neutropenia and thrombopenia were seen, respectively, in 39% and 34% of cycles. Neutropenic fever occurred in 15% of cycles and was associated with toxic death in one case (this patient, with PS 3 at inclusion, died at day 8 after her first cycle due to septic shock).

Renal. With vigorous and sustained hydration, renal toxicity measured by creatininaemia variation was mild, transient and mainly grade 1 (11 patients, 30 cycles); increased serum creatinine returned to normal over a 1–2 week period. Grade 2 reversible toxicity occurred in only 4 cycles, but was the reason for treatment cessation in only one case (a 65 year old patient with large ascitis). Acute tubular dysfunction with urinary salt wasting and severe hypomagnesaemia requiring additive electrolyte replacement was frequently observed; it started usually on day 3, lasting less than 1 week. This transient renal injury was severe only in patients with residual tubular toxicity secondary to prior cisplatin treatment, as suggested by their low magnesium or potassium serum level at inclusion.

Nausea and vomiting. Acute nausea and vomiting were significantly reduced by intensive pretention with anti-HT_3, corticosteroids, metoclopramide and benzodiazepines, but delayed nausea and emesis were common, lasting a few (3–4) days after platinum delivery. This toxicity was nevertheless manageable, never resulting in treatment interruption.

Neurological. Neurotoxicity was the main limiting toxicity seen in this study. It was evaluated by physical examination before every new cycle. The specific differential clinical aspects of the oxaliplatin neuropathy, as reported in phase I–II trials, have been previously described [14, 21]. L-OHP-related acute dysesthesias were observed in the majority of patients (72% of patients and 87% of cycles); these acral symptoms (hands and perioral region) started at the end of the L-OHP infusion: they were transient, lasting a few minutes, but could reappear over the next 1 or 2 weeks, mainly triggered by cold.

The development of a progressive sensory neuropathy characterised by paresthesias, numbness, loss of tendon reflexes and decrease of proprioception was associated with the total number of L-OHP/CDDP cycles received, seen usually after two cycles. 9 patients (excluding the early TD) received no more than two cycles and were evaluable for early chronic neuropathy; their peripheral neurological status generally remained unchanged. Other patients were administered a maximum of four cycles and 3 patients had severe (grade 3) toxicity. In patients who received ≥ 5 cycles, the incidence of severe (grade 3–4) neuropathy was high (7/8 patients, 87.5%). Grade 3 toxicity was a partially disabling ataxia secondary to proprioceptive function loss which developed from 1 to 3 months after the end of therapy, and recovered progressively over the next 6 months.

As in most patients, renal function was borderline at inclusion (40–60 ml/min creatinine clearance calculated by the Cockroft formula), which could explain the severity of the toxicity observed despite reduced doses and fractionation of oxaliplatin/CDDP delivery.

Table 2. Antitumoral activity (WHO) according to platinum resistance status (Markman's criteria, 31)

Platinum resistance status	No. of patients	Response		
		CR	PR	RR
Potentially sensitive	12	2	5	7
Primary refractory	2	0	0	0
Secondary refractory	11	0	3	3
Total	25	2 (8%)	8 (32%)	10 (40%)

CR, complete response; PR, partial response; RR, response rate.

Activity

Twenty-two of the 25 eligible patients were assessable for response to therapy. Causes for non-evaluability were: treatment and follow-up refusal after one cycle (1 case), treatment-related death after first cycle (1 case). The other patient had recurrent disease proven by laparotomy but had no clinically measurable/evaluable tumour. Her baseline serum CA 125 (normal $\times$ 5), which had increased at the time of relapse, was used to assess tumoral evolution; she received four cycles, with CA 125 normalisation obtained before the third cycle, lasting 4 months. She has not been counted amongst the objective responses.

Twenty-two patients had bidimensional measurable disease and were assessable for treatment activity according the WHO criteria. Nevertheless, objective response rates are reported on an intent-to-treat basis; 10 had an objective response to L-OHP/CDDP, for an overall response rate of 40% (95% CI 21–61%). Two clinical CRs (8%) were assessed lasting 9 and 14 months, one of them confirmed at laparotomy. Eight PRs (32%) had a median duration of 4 months (2–15+). SD was observed in 5 cases (20%), while 7 patients (28%) discontinued treatment due to disease progression.

Eight responses observed were obtained after two treatment cycles, while the other 2 were assessed after four cycles.

Antitumoral activity was analysed according to clinical platinum resistance status (Markman criteria) [23]: there were 7 responses among 12 potentially platinum sensitive patients (58% RR, 95% CI, 28–85%) while, three of the 13 secondary platinum refractory patients had an objective response (23% RR, 95% CI, 5–54) (Table 2).

Five responses were seen in the 9 taxane refractory patients 56%). Three responders failed to respond to taxanes, while 2 progressed after an initial response.

As of February 1996, 17 patients had died, 16 from disease progression and 1 from treatment-related toxicity.

The median time to progression for the whole population was 4 months (1–15+); it was 2 months (1–5) in non-responders and 6 months (3–15+) in the responder group. Median survival for all patients was 11 months (1–20), 5 months (1–13+) for the non-responders and 14 months (8–20) for the responders.

DISCUSSION

The hope for new platinum compounds without cross-resistance with cisplatin has motivated decades-long research [26]. The DACH family, elicited as non-cross-resistant to CDDP [12], has produced two compounds reaching clinical development: tetraplatin, whose prohibitive neurotoxicity

observed in phase I stopped further trials [27], and oxaliplatin, synthesised by Kidani and associates [14]. Clinical evidence of activity in cisplatin-resistant ovarian cancer has been previously reported for oxaliplatin [14, 22]; this differs significantly from carboplatin, iproplatin, zeniplatin and lobaplatin, all of which had clinical cross-resistance with cisplatin, as a rule, in reported experiences [28–31].

We evaluated the tolerance and activity of the cisplatin/oxaliplatin combination in heavily platinum pretreated patients (mean prior regimen, 3), while assessing a 40% objective response rate. Within the context of a heterogeneous consecutive patient compassionate use programme, the activity of the L-OHP/CDDP combination is remarkable. While it is true that the activity seen in cisplatin refractory patients (3/13 objective responses) with the L-OHP/CDDP combination may be linked mainly to oxaliplatin, the high activity in potentially sensitive patients (7/12 objective responses) is higher than previously reported in such a category of patients by either single-agent or combination chemotherapy treatments [32]. The likelihood of achieving a response in patients with initially platinum-sensitive tumours increases when the interval from the last cycle of initial platinum-based treatment is longer than 12 months [36]. Median time from the last cycle of platinum containing chemotherapy in our patients responding to L-OHP/CDDP was 14 months (range 2–63).

Our regimen produced activity which compares favourably with results obtained after high-dose cisplatinum or high-dose carboplatinum in patient populations with recurrent ovarian cancer. High-dose (HD) cisplatin (40 mg/m^2 daily for 5 days) was first explored by Ozols and associates [37]; it produced significant antitumoral activity in 6/19 patients with ovarian cancer refractory to standard-dose cisplatin regimen (32% RR); in their report, the number of patients with truly refractory disease who responded to HD cisplatin was not clearly defined. The median duration of response (5 months) and the median duration of survival (12 months) in their patient population did not seem better than those reported from recent phase II trials in similar populations with paclitaxel, docetaxel, ifosfamide or hexamethylmelamine [32–35]. Kehoe and associates [38] also explored the same schedule in 13 platinum pretreated patients (none had progressed on primary therapy); again they found a significant association between response and remission duration ≥ 1 year from first-line therapy.

When HD carboplatin (800 mg/m^2) was given to cisplatin or carboplatin refractory ovarian cancer patients, the objective response rate was comparable to HD cisplatin (27%). Marked cross-resistance between carboplatin and cisplatin was confirmed, since no responses were observed in patients whose disease progressed during prior cisplatin-based regimens. Several reports with cisplatin/carboplatin combinations have been limited to first-line patients, and although promising, they cannot be compared to our series [8].

Distal neurotoxicity remains a limiting toxicity of cisplatin-based treatment intensification [39, 40], while cumulative myelosuppression has imposed progressive dose reduction and caused treatment delay with HD carboplatin [41]. In our programme, maximal treatment duration with LOHP/CDDP was not planned initially but prospectively assessed; severe progressive neuropathy onset was the main reason for treatment cessation. The highest incidence of severe toxicity was seen in heavily pretreated patients (median total dose of prior cisplatin, 600 mg/m^2, compared to a 438 mg/m^2 median total dose in Ozol's series) who started L-OHP/CDDP therapy both with residual neurological toxicity secondary to prior platinum treatment (60% Grade 1–2) and altered renal function, which predicts decreased free and total platinum clearance for the two drugs [42, 43]. Of note is the reversible nature of this toxicity within a relative short time after treatment discontinuation (6 months). This differs significantly from those described with HD cisplatin alone [37] and encouraged us to continue the therapeutic exploration of L-OHP/CDDP in patients with a lighter previous therapeutic history. Haematological toxicity was generally mild, with a median cycle interval of 3–4 weeks in patients without major bone marrow reserve impairment, allowing the addition of other active agents (epirubicin, ifosfamide) in a series of ovarian cancer patients which will be reported separately [44]. Our results show that the combination activity is offset by the acute morbidity and cumulative neurotoxicities seen, but the border line renal function and heavy platinum-based pretreatment characteristics of our population are far worse than those seen in phase I–II trials in ovarian cancer.

We feel that the eventual therapeutic interest of an incrementalist approach with non-cross-resistant platinum compounds is justified in previously untreated or less pretreated patients. The head-to-head confrontation of oxaliplatin and cisplatin both in terms of efficacy and tolerance in first-line disease has been addressed in a multicentric phase III trial, chaired by J.L. Misset comparing both drugs combined with cyclophosphamide (1 g/m^2/cycle) [45].

The issue of oxaliplatin single-agent activity in platinum refractory ovarian cancer is being further clarified by two ongoing studies: the first, a French phase II study, has the same strict defined eligibility criteria of resistance to previous platinum, and a randomised phase II study between paclitaxel and oxaliplatin conducted by the EORTC Gynaecology Group.

The eventual value of the addition of non-cross-resistant platinum compounds (L-OHP + CDDP or carboplatin) in ovarian cancer patients should also be addressed through its addition to the new reference drug in this disease, paclitaxel. Three possibilities come to mind: (a) a phase II study of paclitaxel/L-OHP/CDDP in favourable prognosis recurrent disease, defined by a long disease-free interval (>24 months) to assess both its long-term activity and tolerance, (b) a controlled comparison of paclitaxel/cisplatin versus paclitaxel/L-OHP/CDDP in suboptimally debulked previously untreated patients, (c) a controlled comparison in cisplatin refractory patients of paclitaxel versus the combination of paclitaxel and oxaliplatin. The first concept has been already implemented in 6 patients, with excellent antitumour activity. Neurotoxicity and neutropenia (with associated morbidity) are the limiting toxicities of the three-drug combination at full recommended dose [46]. Further phase I–II exploration in previously untreated patients is planned to define the three-drug combination dose intensity and treatment duration while assessing its eventual enhanced antitumoral activity.

All these currently ongoing or planned studies will contribute to establishing the real value of oxaliplatin in the management of ovarian cancer.

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