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Paclitaxel, cisplatin and lonidamine in advanced ovarian cancer. A phase II study

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Abstract

A potential way to improve the results obtained with the standard carboplatin/cisplatin (CDDP)-paclitaxel treatment regimen in advanced ovarian cancer is to incorporate a modulating agent such as lonidamine (LND). In fact, LND has been shown to revert the resistance to cisplatin and to potentiate cisplatin activity experimental models and in clinical studies. 35 consecutive patients with advanced ovarian cancer, not previously treated with chemotherapy were treated with paclitaxel at a dose of 135 mg/m^2 intravenously (i.v.) on day 1 (in a 3 h infusion) and cisplatin at a dose of 75 mg/m^2 iv on day 2 plus LND orally (p.o.) at a dose of 450 mg/die for 6 consecutive days starting two days before chemotherapy, every 3 weeks for six cycles. Complete plus partial responses were observed in 8 (80%) out of the 10 women with measurable disease. In the 25 patients with evaluable disease, only four clinical progressions were observed (16%). Median progression-free survival (PFS) and overall survival (OS) were 28.5 (95% confidence interval (CI) 22.2–34.8) and 46.5 (95% CI 32.4–60.00) months respectively. Grade 3–4 neutropenia was observed in 9 (26%) patients. Alopecia, nausea and vomiting (Grade 3) were observed in 33 (94%) and 5 (14%) patients, respectively. In conclusion, the combination of CDDP/paclitaxel plus LND is active and tolerable in the treatment of advanced ovarian cancer.

Keywords: Ovarian cancer; Cisplatin; Paclitaxel; Lonidamine; Phase II

1. Introduction

Over the last two decades, chemotherapy for ovarian cancer has undergone a definitive and positive evolution progressing from the use of alkylating agents to the current use of the paclitaxel-based combinations that usually include cisplatin (CDDP) or carboplatin [1,2]. However, the combination of CDDP and cyclophosphamide has been considered the standard treatment for years, until the publication of two large prospective randomised trials; one by the Gynecologic Oncology Group [3] and the other by European and Canadian Investigators [4] comparing cyclophosphamide and CDDP versus paclitaxel and cisplatin in more than 1000 patients with previously untreated advanced ovarian cancer. Both trials reported that overall response rates were higher for the paclitaxel-based regimen and, most importantly, that median survival was improved by 10–14 months compared with initial treatment with cyclophosphamide/cisplatin. Paclitaxel plus cisplatin, however, remained the standard of care for a short period of time. This was due to three prospective trials that compared CDDP and paclitaxel with a less toxic carboplatin/paclitaxel regimen [5–7]. All these trials demonstrated that the carboplatin/paclitaxel combination was less toxic than the CDDP/paclitaxel regimen, and consequently, this is today the most commonly used combination chemotherapy treatment in patients with ovarian cancer, even if a clear superiority over the combination of CDDP/paclitaxel in terms of results has never been demonstrated.

Although the combination of a platinum compound with paclitaxel represented an important development in the treatment of patients with ovarian cancer, improved and more active regimens are still needed, since the median time to progression of these patients is usually less than 2 years.

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Lonidamine (LND), a dichlorinated derivative of indazole-3-carboxylic acid, is a new non-conventional anticancer agent that selectively interferes with the energy metabolism of neoplastic cells by delaying their growth and inhibiting the repair processes [8]. Moreover, LND has been shown to significantly increase CDDP activity in human ovarian cancer lines either sensitive or with experimentally-induced resistance to platinum [9–11]. In previous pilot studies [12–14], we investigated the efficacy and the toxicity of LND, in combination with CDDP as a single agent, in advanced ovarian cancer patients previously treated with platinum-based chemotherapy. The good response rate (28%) in refractory or early-relapsed patients suggested that the synergism between CDDP and LND observed *in vitro* in ovarian cancer cell lines could be confirmed clinically. Moreover, in one of these studies we also demonstrated that higher serum levels of LND, determined by high-performance liquid chromatography (HPLC), were correlated with the clinical response to CDDP [14].

On account of these observations, a phase II study was designed to evaluate the efficacy and the toxicity of LND in association with the CDDP–paclitaxel combination in the treatment of patients with advanced ovarian cancer that were chemotherapy naive.

2. Patients and methods

From July 1995 to December 1998, 35 consecutive patients with histologically-proven advanced epithelial ovarian cancer not previously treated with chemotherapy entered the study. Other eligibility criteria were as follows: age <75 years; Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\leqslant 2$, life expectancy >3 months, normal blood counts (absolute neutrophil count, ANC $>1500\times10^6$/l, platelets $>130\times10^9$/l), normal renal (creatinine <123.76 μmol/l, creatinine clearance >1.2 ml/s) and liver function. Pre-treatment evaluation included physical and gynaecological examination, chest X-rays, computed tomography (CT) scan and/or ultrasound of the abdomen and pelvis. Other investigations were performed if clinically indicated to assess the extension of the disease (urography, cytoscopy, rectoscopy etc.). All patients filled in the informed consent form before starting chemotherapy. Paclitaxel was administered at the dose of 135 mg/m^2 intravenously (i.v.) on day 1 as a 3 h infusion with the classical premedication schedule, and CDDP was given at a dose of 75 mg/ m^2 i.v. on day 2; patients received LND orally (p.o.) at the fixed dose of 450 mg/die for 6 consecutive days (2 days before the start of chemotherapy, on the days of paclitaxel and cisplatin administration and for 2 more days). This regimen was repeated every 3 weeks for a maximum of six cycles, if clinical progression was not observed. A surgical second look was planned at the end of the six chemotherapy cycles. Two additional cycles were administered if microscopic residual disease was present at the second look or in case of surgically induced pathological complete response. A second-line treatment with the combination of ifosfamide plus topotecan was delivered when macroscopic residual disease was found at the second look or at any time progression occurred.

In case of impaired renal function, the dose of CDDP was fractionated over 2 days (days 2 and 3). No inter-cycle blood counts or chemistry were required, but they were done just before delivering each cycle of chemotherapy. As anti-emetics, ondansetron at a dosage of 8 mg or 3 mg of granisetron were used to prevent nausea and vomiting on the days of paclitaxel and cisplatin administration. No dose reduction was allowed. If myelosuppression occurred, the cycle was delayed until the recovery of the blood cell count. LND dosage was reduced to 50% only in cases of severe toxicity (myalgia, arthralgia, gastric pain). The characteristics of the 35 patients are reported in Table 1.

Table 1

Patients characteristics	*n* (%)
Evaluable	35 (100)
Median age (range)	59 years (45–74)
ECOG performance status	
0	16 (46)
1	16 (46)
2	3 (9)
Histology	
Serous papillary	17 (49)
Endometrioid	5 (14)
Undifferentiated	6 (17)
Mucinous	3 (9)
Positive cytology	4 (11)
Grading	
1	4 (11)
2	3 (9)
3	18 (51)
not available	10 (29)
Stage of the disease	
III	26 (74)
IV	9 (26)
Measurable disease	
2–5 cm	4 (11)
>5 cm	6 (17)
Evaluable disease	
<2 cm	13 (37)
NED	7 (20)
Microscopic disease only	5 (14)
Ascites (>100 ml)	11 (31)

ECOG, Eastern Cooperative Oncology Group. NED, No evidence of disease.

Table 2
Results in patients with measurable and evaluable disease

Measurable disease (10 pts)			Evaluable disease (25 pts)
Clinical response	*n* Patients	(%)	(%)
CR	4	(40)	No progression in 21 patients (84)
PR	4	(40)	
SD	0	(0)	
PRO	2	(20)	4 (16)

CR, complete response. PR, partial response. SD, stable disease. PRO, progression.

10 patients (29%) had clinically measurable disease (6 patients >5 cm and 4 patients 2–5 cm), whereas 25 patients (71%) had only evaluable disease (13 patients had residual disease <2 cm, 5 patients had microscopic disease only and 7 patients had no evidence of disease after surgery). Moreover, 11 patients (31%) had ascites >100 ml. In fact, all patients underwent primary debulking surgery (including total hysterectomy, bilateral salpingo-oophorectomy and omentectomy) before starting chemotherapy. All patients, receiving at least one cycle of chemotherapy, were considered evaluable for response and toxicity according to an *intention to treat* analysis.

Clinical response and toxicity were assessed according to the World Health Organization (WHO) criteria [15]. Overall survival (OS) and progression-free survival (PFS) were measured from the date of start of therapy. The duration of the survival was measured up to date of the death or up to the date of the last contact with patients. The duration of the PFS was the minimum amount of time until the onset of clinical progression, death or date of last contact [16]. Kaplan–Meier methods were used to estimate the progression-free and overall survival. Patients were followed up every 3 months with a physical examination and ultrasound and every 6 months with a CT scan, after completing the planned chemotherapy.

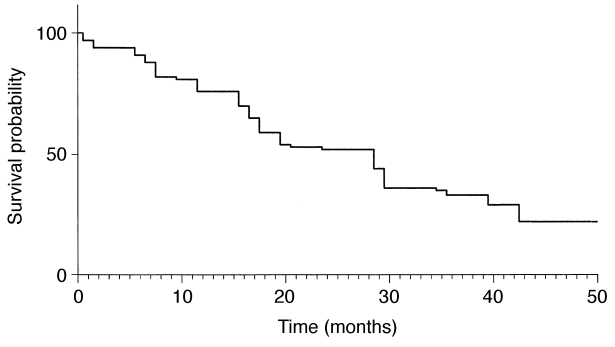

Fig. 1. Progression-free survival.

3. Results

All patients were assessable for toxicity and response. Clinical response (complete plus partial) to chemotherapy were observed in 8 (80%) out of the 10 women with measurable disease (Table 2). In the 25 patients with evaluable disease only four clinical progressions were observed (16%). The second look laparotomy was carried out in five women with measurable disease (4 complete plus 1 partial) and in 8 with evaluable disease: pathological response was observed in 3 (60%) and in 8 (100%) patients, respectively. Among the patients with evaluable disease, only 8 out of 21 candidates for second look were submitted to surgical re-evaluation because 13 patients refused the second look threatment.

Figs. 1 and 2 show the PFS and OS curves. Median PFS and median OS were 28.5 (95% confidence interval (CI) 22.2–34.8) and 46.5 (95% CI: 32.4–60.0) months, respectively. The median follow-up duration of women alive at the last contact was 28 months (range 4–48). The total number of administered chemotherapy courses was 189 (the mean for each patient 5.4). Six women did not complete six cycles of therapy, either because of LND-related toxicity (1 patient) or because of disease progression or death (5 patients). Only 12 cycles (6%) were delayed and in 18 cycles (10%) dose was reduced because of myelosuppression. So far, the actual dose intensity of CDDP, paclitaxel and LND was 94, 90 and 74% respectively. The toxicity observed in each cycle of chemotherapy, graded according to WHO criteria, is reported in Table 3. Neutropenia (Grades 3 and 4) was observed in 9 (26%) patients. Of these patients, only one had fever and was treated with antibiotic therapy. No patients needed haematopoietic growth factors. Alopecia (G3) and nausea and vomiting (G3) were observed in 33 (94%) and 5 (14%) patients, respectively. The most frequent LND-related side-effects were: G3

Table 3
Toxicity observed in 189 cycles

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	16	12	4	5
Thrombocytopenia	1	3	3	–
Anaemia	11	6	2	–
Nausea and vomiting	7	15	6	–
Fever	–	3	–	–
Gastric pain	3	7	–	
Myalgia + arthralgia	3	2	6	–
Neuropathy	2	6	2	–
Altered renal function	11	7	1	–
Altered liver function	–	3	–	–
Asthenia	5	–	–	–
Arrhythmia	–	2	–	–
Mucositis	–	2	–	–
Diarrhoea	1	2	–	–

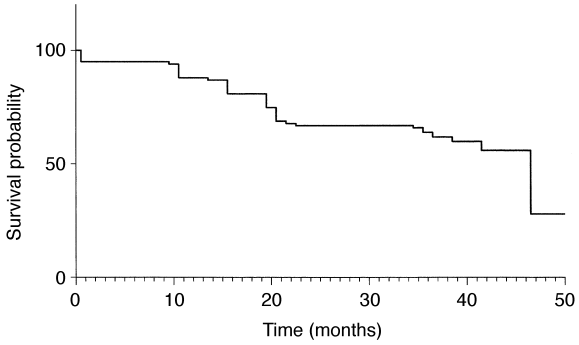

Fig. 2. Overall survival.

myalgia in 3 patients (9%), G2 gastric pain in 2 patients (6%) and G2 vomiting in 2 (6%) patients, respectively.

4. Discussion

New experimental studies on LND have been recently published. De Cesare and co-workers [17], using human tumour xenografts, suggested that the therapeutic synergism between LND and CDDP may be attributed to the ability of LND to induce apoptosis. Orlandi and co-workers [18] showed that LND is also able to modulate the paclitaxel anti-tumour activity in human ovarian cancer cell lines. Ravagnan and co-workers [19] demonstrated that LND triggers apoptosis via a direct, Bcl-2 inhibited effect on the mitochondrial permeability transitional pore. Biroccio and co-workers observed LND was able to induce apoptosis in doxorubicin resistant MCF-7 cells [20]. All these results strongly support the use of the combination of CDDP/paclitaxel and LND in the treatment of ovarian cancer.

In fact, the 80% overall response (40% complete), observed in our study compares well with the percentage of objective responses observed by McGuire [3] and Stuart [4] (73 and 77%, respectively), although the small number of patients with measurable disease in our series does not allow any real comparison in terms of response rate. Nevertheless, the unexpected long median time to progression of our series (28.5 months; 95% CI: 22.2–34.8) compared with that usually reported in the literature (less than 2 years) suggests that LND may have had a role in prolonging the time to progression. Moreover, the median survival of our patients (46.5 months; 95% CI: 32.4–60.0) was also longer than previously reported. This may be attributed to the good prognostic features of our series (i.e. a high percentage of the patients had only evaluable disease after surgical debulking): however, LND may also have played a part.

In conclusion, the combination of LND, paclitaxed and CDDP showed a good activity and tolerability in the treatment of advanced ovarian cancer, suggesting that the addition of LND may play a role in prolonging the patients' time to progression and consequently the overall survival. However, only a phase III trial comparing the combination of CDDP/paclitaxel with or without LND will assess the real value of LND as a modulating agent of the cytotoxic activity of cisplatin and paclitaxel in advanced ovarian cancer.

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