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Epidoxorubicin and Lonidamine in Refractory or Recurrent Epithelial Ovarian Cancer

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Lonidamine (150 mg × 3 day orally, days 1–5) plus high dose epidoxorubicin (120 mg/m² intravenously, day 3) was tested in 26 patients with refractory or recurrent epithelial ovarian cancer, to assess the anti-tumour activity and the toxicity of this combination of drugs. All patients were evaluable for toxicity and 24 for tumour response. Two complete responses (8.3%) and six partial responses (25.0%) were recorded for a total response rate of 33.3%. 6 of 8 responding patients were pretreated with anthracyclines. Stable disease was obtained in 7 patients (29.2%). Toxicity was acceptable; only 1 (3.8%) patient stopped chemotherapy because of a left ventricular ejection rate reduction > 20%. The most relevant side-effect was leucopenia (grade 3–4, 34.6%). In conclusion, the association of lonidamine and high-dose epidoxorubicin has promising activity as second-line treatment in patients with refractory or recurrent epithelial ovarian cancer.

Key words: epidoxorubicin, epithelial ovarian cancer, lonidamine
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INTRODUCTION

DOXORUBICIN HAS been widely employed in the treatment of patients with advanced epithelial ovarian cancer. While doxorubicin can induce an objective response in 22–50% of patients who have not received prior cytotoxic treatment [1–4], only 0–8% of patients with refractory or recurrent disease experience tumour regression [1, 5–7]. Similar negative results in second-line treatment have been obtained with two anthracycline analogues, esorubicin and idarubicin [8, 9].

Single-agent epidoxorubicin has produced an objective response in 34% of untreated patients and in 14% of patients previously treated with chemotherapy [10, 11]. While the objective response rate to first-line treatment with epidoxorubicin is not dose-dependent, preliminary data show that higher response rates are reported with higher anthracycline dosages in second-line chemotherapy [11]. In fact, Simonsen and colleagues [11] reported that epidoxorubicin, 150 mg/m², produced a 27% response rate in patients previously treated with combination regimens including doxorubicin. Lonidamine is an indazole carboxylic acid derivative that can produce mitochondrial alterations, inhibition of oxygen consumption and aerobic glycolysis [12], and is able to exhibit anti-tumour activity in both experimental and clinical studies [13–18]. This compound can deplete cellular ATP, impede energy-dependent DNA repair, interfere with the multidrug resistance mechanisms, and can thus increase the anti-proliferative effect of anti-tumour agents. In particular, lonidamine has been found to enhance cytotoxic activity of doxorubicin in different tumour cell lines *in vitro* [19–23], as well as in murine lymhoma P-388 [22] and Reticol-sarcoma M5 *in vivo* [19].

Until now, few clinical trials of lonidamine combined with chemotherapy including anthracyclines, have been performed [24–27]. Preliminary data showed that lonidamine is devoid of any myelotoxic effect and does not potentiate chemotherapy myelotoxicity [17]. Calabresi and colleagues [24] reported a higher response rate and a longer progression-free interval for patients with metastatic breast cancer treated with combination chemotherapy including cyclophosphamide, doxorubicin and 5-fluorouracil plus lonidamine than for those who received chemotherapy alone. Tomirotti and colleagues [25] reported that 32% of 31 patients with metastatic breast cancer, refractory to doxorubicin + cyclophosphamide regimen, showed a clinical response following three cycles of lonidamine in association with doxorubicin + cyclophosphamide. In a phase II randomised trial by Ianniello and colleagues [26] on patients with advanced non-small cell lung cancer, a significant difference in terms of response rate, and a trend in terms of progression-free survival and overall survival were observed in patients receiving cisplatin, epidoxorubicin and vindesine plus lonidamine compared to patients receiving chemotherapy alone.

On the basis of these data, we decided to test high-dose epidoxorubicin in association with lonidamine in patients with platinum-refractory or recurrent epithelial ovarian cancer, to assess the anti-tumour activity and the toxicity of this combination of drugs.

PATIENTS AND METHODS

The present study included patients with histologically-proven epithelial ovarian cancer who had progressed during

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(refractory patients) or recurred within 6 months of first-line cisplatin- or carboplatin-based chemotherapy, or who had progressed during or recurred after second-line chemotherapy (secondary recurrent patients). Eligibility criteria also included measurable disease, age ≤75 years, ECOG performance status ≤2, life expectancy >6 months, normal renal function (creatinine clearance >60 ml/min), hepatic function (bilirubin <1.5 mg/ml) and bone marrow function (leucocytes >3500/ml, platelets > 100 000/ml), normal left ventricular ejection rate (>55%) assessed by cardiac ultrasonography or miocardioscintigraphy and no more than two types of previous chemotherapy. Exclusion criteria were previous chemotherapy including doxorubicin at a cumulative dose >270 mg/m^2 or epidoxorubicin at a cumulative dose >360 mg/m^2; serious concomitant chronic disease, previous or concomitant malignancy, except basal cell carcinoma of the skin or cervical intraepithelial neoplasia, signs or symptoms of brain or leptomeningeal metastases, previous heart stroke or other cardiopathy. Patients currently requiring anti-hypertensive drugs were eligible, but patients requiring anti-arrhythmic or anti-anginal drugs were excluded from the study. All patients gave informed consent.

The treatment protocol was lonidamine 150 mg × 3/day orally, days 1–5, epidoxorubicin 120 mg/m^2 intravenously (i.v.), day 3. Treatment was repeated as 3-week intervals as tolerated.

At entry into study, disease extent was documented by physical examination, chest X-ray, abdominal-pelvic ultrasound or computed tomography (CT) scan. Cardiac function was evaluated with clinical examination, ECG, cardiac ultrasound or miocardioscintigraphy. Before each course of chemotherapy, patients underwent a complete blood cell count, platelet cell count, renal and liver function tests and CA 125 assay.

After the third course of chemotherapy, non-invasive evaluation of tumour response was carried out by physical examination, chest X-ray, abdominal-pelvic ultrasound or CT scan, and heart function was reassessed by heart ultrasound or miocardioscintigraphy.

Patients previously untreated with anthracyclines responding to treatment received a maximum of six courses of chemotherapy; conversely, in patients pretreated with anthracyclines, the length of chemotherapy was stated on the basis of heart function. Treatment was stopped if the left ventricular ejection fraction, calculated by heart ultrasound or miocardioscintigraphy, was reduced by 20% of basal values or was less than 45%.

Tumour response and toxicity were categorised according to WHO criteria [27]. Toxicity was recorded as the worst grade for each patient.

RESULTS

To date, 26 patients have entered this study. All patients were evaluable for toxicity and 24 for tumour response. Characteristics of patients are summarised in Table 1. Previous chemotherapy included doxorubicin in 4 patients (270 mg/m^2 for each patient), and epidoxorubicin in 14 patients (median dose 360 mg/m^2, range 240–360 mg/m^2).

The patients received a median number of three courses of chemotherapy (range 1–7) and a total of 85 courses were administered. The median dose of epidoxorubicin was 360 mg/m^2 (range 120–840 mg/m^2).

In the 24 patients evaluable for response, two complete responses (8.3%) and six partial responses (25.0%) were recorded for a total response rate of 33.3% (Table 2). Of the 2 patients who achieved a complete response, 1 had recurrent disease in the para-aortic lymph nodes after six courses of combination chemotherapy including cisplatin, doxorubicin and cyclophosphamide and six courses of single-agent carboplatin. The other had persistant pelvic disease after four courses of combination chemotherapy with carboplatin plus cyclophosphamide and five courses of cisplatin, doxorubicin and cyclophosphamide.

Table 1. Patients' characteristics

	No. of patients
Total no. of patients	26
Age (years)	
Median	59
Range	44–75
ECOG performance status	
Median	1
Range	(0–1)
Histology	
Serous ovarian carcinoma	12
Undifferentiated ovarian carcinoma	7
Mucinous ovarian carcinoma	5
Endometrioid ovarian carcinoma	1
Undifferentiated tubal carcinoma	1
Tumour stage at diagnosis	
I	1
III	11
IV	14
Previous platinum-based chemotherapy	26
Including antracyclines	18
Not including antracyclines	8
Response to previous platinum-based chemotherapy	
Refractory	5
Recurrent within 6 months	14
Secondary recurrent	7

Of the 6 patients who achieved a partial response, 4 had been previously treated with regimens including cisplatin or carboplatin and anthracyclines, and 2 had previously received combination chemotherapy with cisplatin and cyclophosphamide. Therefore, 6 of 8 responding patients were pretreated with anthracyclines (Table 3). Stable disease was obtained in 7 patients (29.2%).

Neoplastic progression during treatment occurred in 9 (37.5%) patients. One was the patient with Fallopian tube carcinoma.

An objective response was achieved in 1 of 5 refractory patients, 4 (30.8%) of 13 who recurred within 6 months after first-line chemotherapy and 3 (50%) of 6 secondary recurrent patients (Table 3).

In the 26 patients evaluable for toxicity, grade 3–4 leucopenia was reported in 34.6% of patients (Table 4).

Table 2. Clinical response rates

	No. of Patients	Duration of response (months)
Complete response	2 (8.3%)	24+, 6
Partial response	6 (25.0%)	17+, 3+, 3+, 3, 3, 2
Stable disease	7 (29.2)	7, 4, 4, 4, 3, 2, 2
Progression	9 (37.5%)	
Total	24 (100.0%)	

Table 3. Clinical response according to previous chemotherapy

	CR	PR	SD	P	Total
(A) Type of previous chemotherapy					
Platinum-based chemotherapy including anthracyclines	2	4	6	5	17
Platinum-based chemotherapy not including anthracyclines		2	1	4	7
(B) Response to previous chemotherapy					
Platinum refractory		1	2	2	5
Recurrent within 6 months after platinum	1	3	3	6	13
Recurrent after second-line chemotherapy	1	2	2	1	6
Total	2	6	7	9	24
	8.3%	25.0%	29.2%	37.5%	100%

CR, complete response; PR, partial response; SD, stable disease;, P, progression.

Grade III thrombocytopenia, anaemia and mucositis occurred in 3.8, 15.4 and 7.7% of patients, respectively, while mild to moderate (grade 1–2) myalgia, asthenia and gastralgia were reported in 26.9, 30.8 and 26.9 of patients, respectively. Grade I–II nausea and vomiting was observed in 61.6% of patients.

Only 1 (3.8%) patient had a decrease of left ventricular ejection rate greater than 20%. All patients experienced alopecia. No significant hepatic toxicity, nephrotoxicity or neurotoxicity was found.

The administration of lonidamine was stopped in 2 patients because of gastralgia in 1 case and tremors in 1 case, and the dose was reduced to 300 mg/day in 4 patients because of myalgia in 2 cases and asthenia in 2 cases.

The administration of epidoxorubicin was stopped in 1 patient because of cardiotoxicity and the dose was reduced to 75% in 7 patients because of leucopenia (5 cases) and mucositis (2 cases).

DISCUSSION

The clinical outcome of patients with advanced epithelial ovarian cancer refractory to or relapsing after cisplatin-based chemotherapy is unfavourable. While, in patients who experience a disease-free interval greater than 6 months, the use of carboplatin or the retreatment with cisplatin can induce a 30% response rate, no effective second-line chemotherapy is available for patients who progressed during cisplatin treatment or relapsed within 6 months [28–30]. Paclitaxel is considered to be a promising anti-proliferative drug for patients previously treated with cisplatin-based regimens. By administering paclitaxel, McGuire and colleagues [31, 32] reported a response rate of 24% among 25 patients refractory to cisplatin (with progressive disease during cisplatin or within 6 months after the end of cisplatin therapy), and of 40% among 15 patients not clearly refractory to cisplatin. Recently, ten Bokkel Huinink and colleages [33] reported the preliminary data of a multicentric randomised European Canadian trial comparing low- (135 mg/m^2) versus high- (175 mg/m^2) dose, and short (3-h) versus long (24-h) infusion of paclitaxel in patients with CDDP-pretreated ovarian carcinoma. In their study, the overall response rate was only 18.5% among the 113 evaluable patients.

Patients with refractory or early recurrent epithelial ovarian cancer should be encouraged to enter clinical trials.

A phase I study of the EORTC Gynaecological Cancer Cooperative Group (GCCG) showed that patients with advanced epithelial ovarian cancer failing platinum-based regimens could safely receive epidoxorubicin at a dose of 150 mg/m^2 every 3 weeks and that such second-line chemotherapy was able to induce a partial response in 31% of 19 patients [34]. A phase II study conducted by the same cooperative group showed that epidoxorubicin, at a dose escalating from 150 to 180 mg/m^2 according to bone marrow toxicity obtained an objective response in 31.4% of 35 evaluable patients whose disease was progressive during first-line chemotherapy, or relapsing after an

Table 4. Toxicity according to WHO criteria

	G1 No. (%)	G2 No. (%)	G3 No. (%)	G4 No. (%)
Leucopenia	9 (34.6)	3 (11.5)	5 (19.2)	4 (15.4)
Anaemia	9 (34.6)	3 (11.5)	4 (15.4)	—
Thrombocytopenia	3 (11.5)	1 (3.8)	1 (3.8)	—
Mucositis	7 (26.9)	3 (11.5)	2 (7.7)	—
Diarrhoea	2 (7.7)	2 (7.7)	1 (3.8)	—
Nausea/vomiting	10 (38.5)	6 (23.1)	—	—
Myalgia	4 (15.4)	3 (11.5)	—	—
Asthenia	6 (23.1)	2 (7.7)	—	—
Gastralgia	3 (11.5)	4 (15.4)	—	—
Alopecia	—	—	26 (100)	—

Left ventricular ejection rate reduction >20% occurred in 1 patient (3.8%).

initial response to first-line chemotherapy, including cisplatin or cisplatin and cyclophosphamide [35, 36]. The median duration of response was 27 weeks (range 13–48 weeks). It is worth noting that 20% of patients developing tumour progression during first-line chemotherapy were responsive to high-dose epidoxorubicin. WHO grade III–IV leucopenia, thrombocytopenia and mucositis occurred in 80, 17 and 22.5% of cases, resepectively. Grade I cardiac toxicity was detected in only 3 patients.

In the present series, the combination of lonidamine (450 mg days 1–5 orally) and epidoxorubicin (120 mg/m^2 day 3) achieved a 33.3% response rate in patients with heavily pretreated, prognostically unfavourable epithelial ovarian cancer; 6 of 8 responding patients had previously received anthracycline-containing regimens. The toxicity of treatment was acceptable. In particular, only 1 (3.8%) patient stopped chemotherapy because of a left ventricular ejection rate reduction > 20%. The most relevant toxicity was leucopenia (grade 3–4 34.6%), but utilisation of granulocyte colony-stimulating factor could reduce this side-effect.

In conclusion, these preliminary data show that the association of lonidamine and high-dose epidoxorubicin has promising activity as second-line treatment in patients with platinum-refractory or recurrent epithelial ovarian cancer. Of course, it is impossible to draw definitive conclusions about the contribution of lonidamine to the activity of epidoxorubicin in this subset of patients. Further investigation is needed to establish the ability of lonidamine to reverse anthracycline chemoresistance.

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