An escalating dose finding study of liposomal doxorubicin and vinorelbine for the treatment of refractory or resistant epithelial ovarian cancer

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Background: The aim of this study was to determine the maximum tolerated dose (MTD) of liposomal doxorubicin (LD)–vinorelbine (V) in patients with refractory or resistant ovarian cancer.

Patients and methods: Thirty patients were eligible. Seven levels were studied [LD 25 V20 (three patients enrolled); LD 30–V20 (three); LD 35–V20 (three); LD 20–V25 (three); LD 25–V25 (three); LD 30–V25 (10); LD 35–25 (five)]. LD was given on day 1, while V was given on days 1 and 8 every 21 days. Cohorts of three patients were enrolled at each level, and another three patients were planned, if one dose-limiting toxicity (DLT) was registered.

Results: DLT was observed in four patients: two febrile neutropenia, one grade 4 thrombocytopenia and one grade 3 palmar-plantar erythrodysesthesia (PPE) at level 7 (LD 35 V25). Thus, liposomal doxorubicin 30 mg/m² plus vinorelbine 25 mg/m² was the MTD. The most frequent toxicity was neutropenia. Fifteen patients (50%) experienced grade 3 neutropenia and 10 (33.3%) grade 4 neutropenia. Non-hematological toxicity was mild. Mucositis and PPE were the most frequent toxicities, but in most cases were grade 1. Out of 29 assessable patients, six (20.7%; 95% confidence interval 10%–39%) experienced an objective response, with one complete response.

Conclusions: In patients with refractory or resistant ovarian cancer, the recommended doses for the combination studied are liposomal doxorubicin 30 mg/m² (day 1) plus vinorelbine 25 mg/m² (day 1 and 8). Neutropenia is the most frequent toxicity, while non-hematological toxicity is mild. Substantial activity was recorded and a phase II study is justified.

Key words: liposomal doxorubicin, ovarian cancer, phase I, vinorelbine

Introduction

The standard initial treatment of patients with advanced ovarian cancer is cytoreductive surgery, followed by combination chemotherapy with paclitaxel and a platinum compound [1, 2], although, more recently, results of the ICON3 randomized trial suggest that single-agent carboplatin is an effective alternative to combination treatment [3]. However, despite the activity of first-line chemotherapy, which gives response rates up to 70%, the majority of patients will die of their recurrent disease. Therefore, a large proportion of patients are candidates for second-line therapy.

The value of a second-line therapy and its impact on survival is modest in platinum-resistant and refractory cases [4–6]. Agents such as epirubicin, topotecan, gemcitabine and etoposide show response rates ranging from 20% to 30%, but lengthy remissions are not frequent [7]. Thus, the treatment of these patients remains a challenge in the near future and there is a need for studies on new drug combinations.

Anthracyclines are active against epithelial ovarian cancer, although their role in first-line chemotherapy is still being debated, with a meta-analysis of four randomized trials comparing cyclophosphamide–cisplatin with cyclophosphamide–cisplatin–doxorubicin, showing increased response and survival rates in patients receiving the latter [8]. Trials are ongoing to investigate the effects of the addition of an anthracycline to carboplatin–paclitaxel regimens.

Liposomal doxorubicin is a preparation of doxorubicin hydrochloride in pegylated liposomes, which confers a much longer half-life in blood and has a different toxicity profile to doxorubicin. The surface of pegylated liposome is coated with methoxypolyethylene glycol polymers, which prevent liposomal detection and destruction by the reticuloendothelial system [9]. The pegylated liposomes are small (~100 nm in diameter) and can pass through endothelial gaps or leaky membranes commonly
associated with tumors [10]. After pegylated liposomal doxorubicin administration, doxorubicin concentration is higher in neoplastic than in non-malignant tissue [11].

Preclinical studies have reported superiority of liposomal doxorubicin over free doxorubicin in human ovarian cancer [12], and activity against several others tumors [13, 14]. Several phase II studies demonstrated substantial and durable activity with liposomal doxorubicin in ovarian cancer refractory to platinum and paclitaxel with a safe toxicity profile [15–17]. In a phase III study, Gordon et al. [18] have recently shown that liposomal doxorubicin is at least as effective as topotecan in platinum-refractory-resistant ovarian cancer, with a statistically significant survival advantage in platinum-sensitive patients. In this study the toxicity profile of liposomal doxorubicin was significantly better compared with topotecan. As liposomal doxorubicin is well tolerated, studies using the drug combined with other antineoplastic agents are ongoing [19, 20].

Vinorelbine is a vinca alkaloid derivative that shows a better toxicity profile than vincristine and a promising activity in advanced platinum-refractory or -resistant ovarian cancer. Up to a 21% response rate has been reported in heavily pre-treated and platinum-resistant ovarian cancer patients when vinorelbine is given alone [21–24] or in combination with hexamethylmelamine [25].

Liposomal doxorubicin and vinorelbine have different toxicity profiles and mode of action. Several studies in breast and lung cancer demonstrated lack of clinical cross-resistance and a possible synergism between vinorelbine and anthracyclines [26–29].

On these grounds, we started a dose-finding study with escalated doses of liposomal doxorubicin (starting dose 20 mg/m², day 1) and vinorelbine (20 mg/m² and 25 mg/m², days 1 and 8, respectively) administered every 3 weeks for the treatment of advanced platinum-refractory or -resistant ovarian cancer.

**Patients and methods**

Eligibility criteria were: (i) a cytologically or histologically proven epithelial ovarian cancer resistant (i.e. relapsed <1 year from completion of platinum-based treatment) or refractory (i.e. progressed during platinum-based treatment or within 3 months from treatment completion) to previous platinum–paclitaxel-containing chemotherapy; (ii) age ≤70 years; (iii) Eastern Cooperative Oncology Group (ECOG) performance status ≤3; (iv) white blood count ≥4000/mm³; (v) platelet count ≥100 000/mm³; (vi) serum creatinine ≤1.5 mg/dl; (vii) AST (aspartate aminotransferase) and ALT (alanine aminotransferase) ≤1.25× upper normal value; and (viii) bilirubin ≤1.25× upper normal value. Patients previously treated with anthracyclines were not eligible.

Liposomal doxorubicin was administered intravenously, diluted in 5% glucose, as a 1-h infusion at the starting dose of 20 mg/m². The liposomal doxorubicin dose was escalated by increments of 5 mg/m² per level. Vinorelbine was given intravenously following administration of liposomal doxorubicin at the doses of 20 mg/m² (levels 1–3), and 25 mg/m² (levels 4–7). Standard antiemetic treatment was given to all patients. Both drugs were administered on day 1; vinorelbine was also given on day 8. The treatment regimen was repeated every 3 weeks, with a 1 week delay allowed, for at least four cycles. Treatment was continued for a maximum of six cycles in patients who achieved objective responses or stable disease after four cycles. Granulocyte colony-stimulating factor (G-CSF; filgrastim) was administered subcutaneously for 7 days at a dose of 5 µg/kg/day in case of grade 4 neutropenia, and prophylactic G-CSF support was given for 5 days, starting at day 9 of the following cycles.

To define dose-limiting toxicity (DLT) we analyzed toxic events recorded during cycles 1 to 4. Any of the following toxic events appearing during cycles 1 to 4 for each patient was defined as dose-limiting: grade 4 thrombocytopenia, febrile neutropenia (fever >38°C with neutrophils ≤1300/mm³ lasting >4 days), grade 3–4 non-hematological toxicity (excluding hair loss and vomiting), and any grade neutropenia or thrombocytopenia persisting at day 35. Cohorts of three patients were enrolled at each dose level and three other patients were enrolled if one DLT was recorded in the first three patients. Eligible patients observed during the evaluation of the last cohort could be enrolled at the preceding fully evaluated dose level. This rule was stated a priori and at some levels induced the inclusion of a number of patients higher than that required by the study design. Maximum tolerated dose (MTD) was defined as one dose level below that inducing two or more DLTs. This conservative definition (different from the most common definition of MTD as the level preceding the dose level inducing three or more DLTs) was chosen because of the fully palliative role of second-line chemotherapy in advanced ovarian cancer.

Toxicity was evaluated according to NCIC criteria [30]. Hematological toxicity was evaluated by complete blood count every week, while non-hematological toxicity was assessed before each cycle.

Staging procedures included standard physical examinations, ultrasound and computed tomography (CT) scan of the abdomen and pelvis, and two-view chest X-ray. Objective responses were evaluated at the end of the fourth and six chemotherapy cycles by repeating the staging procedures according to the response evaluation criteria in solid tumours (RECIST) [31]. CA 125 levels were evaluated at baseline and after the fourth and sixth cycles. In patients not evaluable by RECIST criteria and with increased CA 125 values, the biological response was assessed according to Rustin criteria [32].

All patients gave written informed consent.

**Results**

Thirty patients were enrolled in the study and all were assessable for toxicity. Patient characteristics are summarized in Table 1. All patients had been previously treated with platinum–paclitaxel combination chemotherapy. Five patients were refractory and 25 were resistant to previous treatment.

Seven dose levels were studied, as detailed in Table 2. Overall, 139 courses of treatment were given, with a median of four cycles per patient (range 1–6). Toxicity data were available from all patients and for all cycles. Treatment was discontinued in one patient after the first cycle for DLT, and in seven patients after four cycles for disease progression. No DLTs were recorded at levels 1, 2 or 3 with vinorelbine given at a dose of 20 mg/m².

DLT was observed in level 7 (liposomal doxorubicin 35 mg/m² and vinorelbine 25 mg/m²) in four patients. Two of them experienced febrile grade 4 neutropenia (during the first cycle of therapy in one case and the second cycle in the other); both patients also suffered grade 2 mucositis. One patient had grade 4 thrombocytopenia at the second cycle of therapy and one experienced grade 3 palmar-plantar erythrodysesthesia (PPE) at the third cycle of therapy. The MTD was therefore reached at liposomal doxorubicin 30 mg/m² and vinorelbine 25 mg/m². At this level, a 20% dose reduction was required only in two out of 10 patients.

The most frequent hematological toxicity (Table 3) was neutropenia. Fifteen patients (50%) experienced grade 3 neutropenia and 10 (33.3%) experienced grade 4 neutropenia. G-CSF support was given in all cases with grade 4 neutropenia. In these patients,
prophylactic G-CSF was given for a total of 38 cycles of treatment. Grade 3 anemia was observed in seven patients (23.3%), but no patient experienced grade 4 anemia or grade 2–3 thrombocytopenia. There were no toxic deaths.

Mucositis (stomatitis) and PPE were the most frequent non-hematological toxicities (Table 4). Grade 1 mucositis was observed in six (20%) patients while four (13.3%) experienced grade 2 mucositis. PPE was observed in nine patients (29%): seven experienced grade 1 PPE, while one grade 2 and one grade 3 episode was recorded. In two patients, grade 2 constipation (level 6) was observed. No cardiotoxic event occurred.

Response was assessed in 29 patients with measurable (n = 15) or assessable (non-measurable) (n = 14) disease. All 14 patients without measurable disease were assessable for increased CA 125 levels and ascites. Objective response was seen in six patients [20.7%; 95% confidence interval (CI) 10% to 39%], as documented by CT scans. Seven cases of stable disease (24.1%) and 16 progressions (55%) were observed.

One complete response was observed in a patient with no measurable lesions in which treatment induced the complete normalization of CA 125 levels and the disappearance of ascites. The duration of response was 11 months. Five patients obtained a partial response. Partial responses were obtained at levels 1, 5, 6 (two patients) and 7: two patients had ascites and increased CA 125, while all of the three remaining patients had hepatic lesions. One of them also had spleen lesions. The durations of such responses were 2, 4 and 5 months for patients with measurable disease, and 3 and 6 months for those with non-measurable disease, respectively. At July 2002, 11 patients were alive and all but two had disease progression.

**Discussion**

In this study we investigated the feasibility of combination chemotherapy with liposomal doxorubicin–vinorelbine in patients with refractory/resistant ovarian cancer. We found that liposomal doxorubicin 30 mg/m² and vinorelbine 25 mg/m² represent the MTD as second-line treatment in platinum–paclitaxel pre-treated patients. This combination showed significant activity with manageable toxic effects.

Ovarian cancer patients who respond to induction chemotherapy and subsequently experience early tumor re-growth or who are primarily resistant to platinum-containing therapy have a poor prognosis [33]. Second-line chemotherapy remains a major problem for these patients, with low remission and short survival periods. Strategies to improve the outcome of systemic therapy in

### Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
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</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Median</td>
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</tr>
<tr>
<td>Range</td>
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<tr>
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<td>Serous</td>
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<tr>
<td>Endometrioid</td>
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</tr>
<tr>
<td>Others</td>
<td>5</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
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<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Evident disease</td>
<td></td>
</tr>
<tr>
<td>Measurable</td>
<td>15</td>
</tr>
<tr>
<td>Non-measurable*</td>
<td>15</td>
</tr>
<tr>
<td>Response to previous cisplatin</td>
<td></td>
</tr>
<tr>
<td>Refractory</td>
<td>5</td>
</tr>
<tr>
<td>Resistant</td>
<td>25</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
*Increased CA 125 levels, ascites.

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### Table 2. Studied dose levels

<table>
<thead>
<tr>
<th>Level</th>
<th>Drug doses (mg/m²)</th>
<th>Patients</th>
<th>No. of cycles (range/patient)</th>
<th>DLT*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Vinorelbine</td>
<td>Liposomal doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>25</td>
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<td>18 (6–6)</td>
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<td>16 (4–6)</td>
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<tr>
<td>5</td>
<td>25</td>
<td>25</td>
<td>3</td>
<td>10 (3–4)</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>30</td>
<td>10</td>
<td>47 (2–6)</td>
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<tr>
<td>7</td>
<td>25</td>
<td>35</td>
<td>5</td>
<td>22 (1–6)</td>
</tr>
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</table>

*Dose-limiting toxicity.
*Two cases of febrile neutropenia grade 4, one case of thrombocytopenia grade 4, one case of PPE grade 3.
this setting have included the combination of non-cross-resistant drugs. However, because of the overlapping toxicities, there have been challenges in combining some of these agents. On the other hand, no randomized study has demonstrated the superiority of polychemotherapy over monochemotherapy, either in platinum-resistant [34, 35] or sensible disease [36], while all these studies showed an excessive toxicity in the arms of polychemotherapy. Thus, the combination of new drugs with a favorable toxicity profile is the only approach to develop schemes of polychemotherapy for patients with ovarian cancer refractory/resistant to platinum–paclitaxel. In fact, since cure is not the goal for these patients, palliation and improved quality of life become the most important aims and excessive toxicity should be avoided.

Vinorelbine and liposomal doxorubicin are very well tolerated when given as single agents. The toxicity profiles of the two drugs differ and overall their combination is appealing. Vinorelbine has shown clinically meaningful activity in patients with ovarian cancer primarily resistant to cisplatin [22–24]. Responses were seen in both refractory and resistant disease, and a favorable side-effect profile was observed in heavily pre-treated patients [24].

Since the anthracyclines doxorubicin and epirubicin are rarely included in standard first-line chemotherapy of ovarian cancer, they are often used as second-line treatment, particularly for those patients who are not eligible for platinum re-treatment [33–37]. The new liposomal formulation of doxorubicin has renewed interest in anthracyclines for use in ovarian cancer. Liposome defends the drug from detection and phagocytosis by the reticuloendothelial system, resulting in prolonged circulation [38]. Pegylated liposomal doxorubicin allows retained, encapsulated active drug to reach the tumor site at higher concentrations, along with significantly lower systemic toxicity [11]. Several phase II studies have shown substantial activity of the drug in the second-line setting [15–17]. More recently, a phase III study has demonstrated the equivalence of liposomal doxorubicin and topotecan in terms of response rate, time-to-failure and survival, and a more favorable safety profile for liposomal doxorubicin mainly due to the lower hematological toxicity [18].

Several clinical studies have been performed in lung and breast cancer, with anthracyclines and vinorelbine showing significant activity [26–29]. High response rates have been described with vinorelbine in breast cancer patients pre-treated with anthracyclines, suggesting a lack of cross-resistance between the two drugs [39, 40].

The combination of vinorelbine–liposomal doxorubicin has only been studied in metastatic breast cancer [28]. Burstein found that liposomal doxorubicin 40 mg/m² (day 1), can be given safely along with up to 30 mg/m² of vinorelbine (days 1 and 15) every 28 days [28]. Severe neutropenia was recorded with vinorelbine given on days 1 and 8, every 21 days. In this study, 63% of patients had received prior anthracycline-based chemotherapy and most were heavily pre-treated.

We looked for the MTD of liposomal doxorubicin–vinorelbine in patients with ovarian cancer pre-treated with carboplatin and paclitaxel. Two doses (20 mg/m² and 25 mg/m²) of vinorelbine, given on days 1 and 8, were studied with increasing doses of liposomal doxorubicin. DLT was recorded at level 7 (liposomal

<table>
<thead>
<tr>
<th>Level</th>
<th>Patients</th>
<th>Cycles</th>
<th>Leukopenia</th>
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</tr>
<tr>
<td>Total</td>
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<td>47</td>
<td>3</td>
<td>10</td>
<td>1</td>
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</table>

Table 3. Worst-grade of hematological toxicity per patient and per cycle.
doxorubicin 35 mg/m² and vinorelbine 25 mg/m², days 1 and 8) and, thus, MTD was found at level 6 with liposomal doxorubicin 30 mg/m² (day 1) and vinorelbine 25 mg/m² (days 1 and 8), every 21 days. Compared with the results of Burstein [28], our study demonstrated the same dose intensity of liposomal doxorubicin and a higher dose intensity of vinorelbine. In particular, the dose intensity of liposomal doxorubicin at MTD (10 mg/m²/week) was 20% lower than that used when the drug was given as a single agent (12.5 mg/m²/week).

In our study, this schedule of administration yielded moderate hematological toxicity. Neutropenia grade 4 was observed in 33% of patients, with fever requiring patient hospitalization in two cases only. Grade 3 anemia was present in 23% of the patients, while thrombocytopenia was rare.

Non-hematological toxicity was mild. The most frequent toxicities were mucositis (stomatitis) and PPE. Grade 2 mucositis affected 13.3% of patients, while no grade 3 episodes were recorded. PPE occurred in 29% of patients (grade 1 in most cases). These toxicities were dose related: both grade 2 mucositis and grade 2–3 PPE were recorded at dose level 7.

At the doses used in this study, liposomal doxorubicin induced lower incidence and toxicity grades of both PPE and mucositis compared with the data reported by Gordon [18] in a phase III study with the drug given as a single agent. This finding is in accordance with data reported by Burnstein, suggesting a lower severity of PPE when liposomal doxorubicin is given in combination with other agents [28].

Although the number of patients with measurable disease assessable for response is too small to draw any definitive conclusions, responses were seen at all levels studied, so all the dose levels could theoretically be considered effective. Nevertheless, based on our data it is not possible to conclude whether or not there is an additive effect of the two drugs in combination. A phase II trial should be performed to formally test the activity of this regimen for second-line treatment of platinum–paclitaxel-refractory/-resistant ovarian cancer.

In conclusion, the combination of liposomal doxorubicin and vinorelbine is feasible as second-line treatment in platinum–paclitaxel pre-treated ovarian cancer patients. This combination shows a tolerable profile of toxicity, with a very low rate of severe non-hematological toxicities. Substantial activity was recorded and a phase II study is justified.

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References


