High-dose Intensity Regimens With Epirubicin in Ovarian Cancer


Progress in the treatment of patients with advanced ovarian carcinoma is only slowly emerging, and results obtained in recent years are still far from optimal. Major steps in improving the outcome of treatment have been the introduction of upfront cytoreductive surgery and the use of cisplatin-based combination chemotherapy. Initially, cisplatin usually was given in combination with doxorubicin and cyclophosphamide (CAP) with or without hexamethylmelamine. However, when doubt was cast on the effectiveness of doxorubicin by results both from randomized phase III trials and phase II studies in patients failing first-line therapy, a number of major centers adopted cisplatin plus cyclophosphamide (CP) as standard therapy.

The addition of other drugs to the combination of cyclophosphamide and cisplatin very often leads to more toxicity and, at the same time, a greater dose intensity. This has been true in the rare case in which three of the four randomized trials mentioned above that compared CAP with CP. Although all four trials favored CAP slightly in one or more parameters studied, none of these trials showed a convincing benefit for the addition of doxorubicin. Small but real differences, however, may go unnoticed in studies with limited sample sizes. Moreover, the addition of more drugs often leads to the use of less than optimal dosages of the two drugs, which are considered to form the backbone of the combination. The question as to whether the small differences observed in the four trials were real recently has been addressed through a meta-analysis. By pooling the data of almost 1,200 patients from these trials, it was shown that a 7% difference in negative second-look operation rate and a 7% survival advantage at 6 years were statistically significant benefits of CAP compared with CP. In fact, there was a remarkably consistent benefit of CAP throughout all subsets, all studies, and all endpoints analyzed. Whatever the influence of dose intensity, it implies that in the dosages and regimens used doxorubicin made a significant contribution in these regimens. As both cyclophosphamide and cisplatin were moderately dosed (500 to 650 mg/m² every 4 weeks and 50 mg/m² every 3 to 4 weeks, respectively), with the exception of one study in which a higher dose of cyclophosphamide was used in the CP arm, dose intensities in the CP regimens were not optimal. If a dose-response effect exists for cisplatin, high-dose cisplatin might overshadow any contribution of doxorubicin. On the other hand, the dose-response question for doxorubicin has never been carefully addressed clinically. Both approaches need to be studied in the appropriate clinical trials. The meta-analysis, however, supports the idea that the role of anthracyclines perhaps needs to be reassessed in the treatment of patients with ovarian cancer.

SINGLE-AGENT ACTIVITY OF ANTHRACYCLINES IN OVARIAN CARCINOMA

The largest experience with anthracyclines in ovarian cancer has been obtained with doxorubicin. The impact of prior chemotherapy is very clear for this agent. In four trials performed with this drug in patients who had not received prior cytotoxic treatment, the response rates varied from 22% to 50%, with a cumulative response rate of 33%. In three studies using doxorubicin in 75 patients previously treated with alkylating agents, the response rate was 0% in two studies and 8% in the third, for a cumulative response rate of 4%; none of eight patients in an additional study responded after prior treatment with cisplatin. Similar negative results in

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second-line have been obtained with the two anthracycline analogues, esorubicin and idarubicin. A third analogue, epirubicin (4'-epi-doxorubicin), is clearly more promising. Used as a single agent, Trepo described 12 of 21 patients responding in first-line to a regimen in which epirubicin was given at a dose of 75 mg/m² every 3 weeks. After prior treatment with alkylating agents three of 14 patients (21%) still responded. In a pilot study of 6 of 17 patients (35%) responded to epirubicin in second-line when given at a higher dose (100 to 120 mg/m²); four of these responses were complete, as confirmed by laparoscopy, and two were partial (G. Bolis, personal communication, 1990). In this latter study, epirubicin was given to patients who either had stable disease or a partial response to first-line platinum-based chemotherapy, therefore being a selected group of patients. As in vitro data demonstrated a dose-response relationship for doxorubicin and epirubicin has a more attractive toxicity profile than doxorubicin, we initiated studies exploring the antitumor activity and toxicity of high-dose intensity regimens with epirubicin.

**HIGH-DOSE EPIRUBICIN IN PREVIOUSLY TREATED PATIENTS WITH OVARIAN CANCER**

Members of the European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Cooperative Group performed a phase I-II feasibility study of high-dose epirubicin in patients with advanced ovarian carcinoma previously treated with cisplatin and cyclophosphamide. Doses were escalated from 120 mg/m² to 200 mg/m². Dose steps were 120, 135, 150, 180, and 200 mg/m², with a minimum of three patients at each dose level. The interval between courses was 3 weeks. At 200 mg/m² all patients needed either dose reductions or delays, and one patient had symptoms of cardiotoxicity that did not recur after the dose was reduced to 180 mg/m². All patients receiving the 180 mg/m² dose (n = 5) were able to continue at the same dose level, although some of them needed a dose delay of 1 week at one time during therapy. Six of 19 patients treated responded (31%) for a median duration of 6 months. Four of these six patients had short intervals between the end of first-line treatment and the start of high-dose epirubicin; in fact, two of these patients had shown progression during prior cisplatin treatment. Both hematologic and nonhematologic toxicities were dose limiting at 200 mg/m².

Based on these results a straightforward phase II study was started in 1990. Eligibility criteria included histologically verified epithelial ovarian cancer, measurable or evaluable disease outside previously irradiated areas, no more than one type of prior chemotherapy, no prior use of anthracyclines or carboplatin, age between 18 and 75 years, World Health Organization performance less than 3, no active cardiac disease or history of recent myocardial infarction (<1 year), white blood cell count ≥4.0 × 10⁹/L, platelets ≥100 × 10⁹/L, bilirubin ≤25 µmol/L, serum creatinine ≤132 µmol/L and/or creatinine clearance ≥60 mL/min/1.73 m², and consent of the patient. Three groups of patients were studied: patients progressing during cisplatin treatment (group 1), patients with persistent disease after cisplatin treatment (group 2), and patients relapsing after an initial response (group 3). Epirubicin was administered by rapid intravenous injection at a dose of 150 mg/m² every 21 days. Escalation to 180 mg/m² was applied in cases in which the white blood cell count was greater than 2 × 10⁹/L and platelets were greater than 75 × 10⁹/L. Dose reduction (25%) was used in cases in which white blood cell count was less than 1.0 × 10⁹/L and/or platelets were less than 50 × 10⁹/L, when febrile neutropenia occurred, or when grade 3 or 4 nonhematologic toxicities appeared (except for nausea, vomiting, and alopecia). To date, 87 patients have been registered, of whom 54 have been reviewed. Fifty-one of these patients were considered eligible; all were evaluable for toxicity and 40 of them were evaluable for response. The main toxicities observed were myelosuppression (particularly leukopenia and neutropenia), nausea, vomiting, alopecia, and mucositis. Hematologic toxicity data on 50 evaluable patients are summarized in Table 1. In 19 of the 42 patients who received two or more treatment cycles dose escalation was applied at one point during treatment (45%). World Health Organization grade 3 nonhematologic toxicities included nausea/vomiting (29%), alopecia (74%), mucositis (23.5%), infection (4%), diarrhea (2%), renal toxicity (2%), and bone pain (2%). Overall the treatment was reasonably well tolerated. The antitumor activity observed so far is summarized in Table 2. World Health
Organization response criteria were used. High-dose epirubicin proved to be active in second-line after cisplatin-based chemotherapy, but activity appeared to be clearly related to the response to prior cisplatin. The study is continuing until 25 evaluable patients are available in each patient category.

**HIGH-DOSE INTENSITY REGIMEN OF WEEKLY CISPLATIN AND EPIRUCIBIN (WITH GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR)**

In retrospective studies the intensity with which the chemotherapy was given proved to be an important determinant in predicting outcome in patients with advanced ovarian cancer. In particular, the dose intensity of cisplatin in that respect seemed to play an important role. Very recently and for the first time, survival benefit has been observed in a prospective trial comparing 50 mg/m² with 100 mg/m² of cisplatin given in combination with cyclophosphamide (750 mg/m²) every 3 weeks for six courses. Unfortunately, the preliminary results of two other prospective trials studying the relationship between intensity of drug administration and outcome were disappointing. An explanation for these differences in outcome is difficult to provide, but influences of total dose, dose intensity of chemotherapy, and patient and tumor characteristics (tumor volume after surgery) might have played a role. Therefore, it remains to be seen whether a clinically relevant dose-response relationship exists and whether any further improvement with the existing drugs is possible. Several experimental approaches are being investigated to abrogate dose-limiting toxicity and to increase the intensity of chemotherapy, eg, high-dose carboplatin with hematopoietic growth factors, high-dose cisplatin with Ethyl (WR-2721) or glutathione, the combination of carboplatin and cisplatin, and high-dose regimens with autologous bone marrow transplantation (or peripheral stem cell transfusion). Another attractive approach that has been used is the more frequent administration of cisplatin with or without other antineoplastic agents. From a theoretical point of view, frequent and adequate dosing is an attractive approach as it may diminish repair of sublethal damaged DNA. Moreover, short intensive chemotherapy is overall a more attractive approach as it may avoid longlasting exposure to

## Table 1. EORTC 55892: Hematologic Toxicity in 50 Evaluable Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients With Nadir Values in WHO Grades</th>
<th>Percentage of Patients With Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6 - 5 - 25 - 14 - 78</td>
<td></td>
</tr>
<tr>
<td>Neutrophils*</td>
<td>10 - 1 - 7 - 23 - 73</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>27 - 4 - 8 - 7 - 42</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin†</td>
<td>5 - 11 - 11 - 1 - 20</td>
<td></td>
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</tbody>
</table>

Abbreviations: WHO, World Health Organization; WBC, white blood cell count.
* n = 41.
† n = 30 (all with normal values at the start).

## Table 2. EORTC 55892: Response Rate by Patient Category

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>WHO Response Criteria</th>
<th>Overall Response Rate</th>
<th>Evaluable Patients (%)</th>
<th>Eligible Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 13)</td>
<td>CR 2 PR 3 NC 6 PD 1</td>
<td>18.2</td>
<td>15.4</td>
<td></td>
</tr>
<tr>
<td>II (n = 15)</td>
<td>CR 2 PR 4 NC 5 PD 2 (2)* 2</td>
<td>15.4</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>III (n = 23)</td>
<td>CR 1 PR 6 NC 4 PD 5†</td>
<td>43.7</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td>All patients (n = 51)</td>
<td>CR 1 PR 10 NC 11 PD 16 ED 5 NE 8</td>
<td>27.3</td>
<td>21.5</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: The duration of CR and PR was 28 weeks and 27 weeks (range, 19 to 49 weeks, respectively).
Abbreviations: WHO, World Health Organization; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; ED, early death; NE, not evaluable.
* Due to progressive disease.
† One patient with >50% tumor reduction but no second measurement.
toxic drugs and its attendant interference with daily life and reduction of quality of life.

At the Free University Hospital in Amsterdam, a dose-finding study has been performed using a weekly regimen. The treatment plan included nine cycles of weekly cisplatin and epirubicin in which the dose of cisplatin was fixed at 50 mg/m²/wk and the doses of epirubicin were escalated, with a minimum of three patients at each dose level. The starting dose of epirubicin was 30 mg/m²/wk. No dose escalation was allowed in individual patients. For bone marrow protection, granulocyte-macrophage colony-stimulating factor (GM-CSF) (Behringwerke AG, Marburg, Germany) was given subcutaneously at a dose of 250 μg/m²/d from days 2 to 6 of each cycle. Eleven patients have been treated, of whom four had recurrent disease (median chemotherapy-free interval, 14 months) and seven had not had any prior chemotherapy. The maximum tolerated dose of this weekly cisplatin/epirubicin regimen with GM-CSF was 50 mg/m² of cisplatin in combination with 40 mg/m² of epirubicin. Dose-limiting toxicities were both hematologic (leukopenia, neutropenia, and thrombocytopenia; Table 3) and nonhematologic; in particular, there was ototoxicity and subclinical evidence of cardiac injury (decrease in left ventricular ejection fraction > 10%). Nonhematologic toxicities are summarized in Table 4. At a dose of 50 mg/m² cisplatin and 50 mg/m² epirubicin, three of the four patients discontinued treatment after three cycles because of intolerance, general malaise, and decrease in performance status; two of these patients showed important decreases in left ventricular ejection fraction. As significant decreases in left ventricular ejection fraction already occurred at low cumulative doses of epirubicin (90 to 150 mg/m²) and were mostly reversible after discontinuation of treatment, a relationship with the use of GM-CSF is under consideration. However, an influence of timing of the left ventricular ejection fraction cannot be ruled out. The dose intensity actually reached was 33.3 mg/m²/wk (range, 33.3 to 36.3 mg/m²/wk) for cisplatin and 26.7 mg/m²/wk (range, 25.8 to 29.0 mg/m²/wk) for epirubicin at maximum tolerated doses. The median length of survival of the eight patients who did not discontinue treatment for toxicity was 26+ months (range, 9 to 33+ months).

A similar study has been performed in the past without the use of hematopoietic growth factors.

| Table 3. Hematologic Toxicity During Weekly Cisplatin and Epirubicin Treatment (With Granulocyte-Macrophage Colony-Stimulating Factor) |
|---|---|---|---|---|
| Patient No. | Cisplatin/Epirubicin | GM-CSF | No. | WHO Toxicity Grading |
| | Dose Regimen (mg/m²) | | of Cycles | WBC | ANC | PLT | HB |
| Recurrent disease patients | | | | | | | |
| 1 | 50/30 | −/+/− | 9 | 3 | 3 | 1 | 2* |
| 2 | 50/30 | − | 9 | 2 | 3 | 3 | 2* |
| 3 | 50/30 | + | 4 | 0 | 0 | 3 | 8† |
| 4 | 50/40 | + | 9 | 3 | 4 | 3 | 2* |
| Untreated patients | | | | | | | |
| 5 | 50/40 | + | 8 | 3 | 4 | 41 | 3* |
| 6 | 50/40 | + | 9 | 3 | 4 | 3 | 2* |
| 7 | 50/40 | + | 9 | 3 | 4 | 3 | 2* |
| 8 | 50/50 | + | 3 | 3 | 4 | 0 | 1 |
| 9 | 50/50 | + | 9 | 3 | 4 | 2 | 3* |
| 10 | 50/50 | + | 3 | 4 | 4 | 3 | 1 |
| 11 | 50/50 | + | 3 | 3 | 3 | 0 | 1 |

Abbreviations: WHO, World Health Organization; WBC, white blood cell count; ANC, absolute neutrophil count; PLT, platelet count; HB, hemoglobin.

* Red blood cell transfusion.
† Pre-existing toxicity.
‡ Platelet transfusion.
and using doxorubicin instead of epirubicin. However, contrary to the present study, the doxorubicin dose was fixed at 20 mg/m² intravenously weekly and the cisplatin doses were escalated by 2 mg/m² each week (after starting with a dose of 22 mg/m² weekly) until the dose of 30 mg/m² was reached, and treatment continued until the total dose of cisplatin given was 460 mg/m². Severe toxicities also were encountered in that study, and two patients died from treatment-related causes. Severe toxicity was responsible for four other patients discontinuing treatment prematurely. While the planned weekly doses of doxorubicin and cisplatin were 20 mg/m²/wk and 28.75 mg/m²/wk, respectively, the actual median doses of doxorubicin and cisplatin received were 13.2 mg/m²/wk and 22.6 mg/m²/wk, respectively. Median length of survival for the patients was 18 months.

Both our regimen with cisplatin and epirubicin (with GM-CSF) and the above-mentioned weekly regimen reported by O'Connell et al were unacceptable toxic. The results of both studies also indicate that in anthracyclines in particular, very little increase in dose intensity can be reached in comparison to standard regimens. Nevertheless, further studies with high-dose cisplatin and epirubicin using different schedules, but with hematopoietic growth factor support, are needed. However, these studies should carefully monitor cardiac function.

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