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Efficacy of carboplatin plus primary prophylactic filgrastim (granulocyte colony stimulating factor) in relapsed ovarian cancer: a study of the Gynecologic Oncology Group of the Comprehensive Cancer Center Limburg

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A total of 34 patients with advanced ovarian cancer, who relapsed 1–72 months after at least one first-line cisplatin-based chemotherapy protocol, were treated with carboplatin, 350 mg/m² q 4 weeks, with the adjunct of primary prophylactic granulocyte colony stimulating factor (G-CSF; filgrastim), 300 or 480 μg daily, days 5–9. Over 90% of the anticipated dose of carboplatin could be administered. Partial response, defined as a decline in CA-125 of 50% or more on two consecutive samples, occurred in 42%, while 15% of patients achieved a complete response (no clinical signs of disease with normalization of CA-125). Survival from start of carboplatin treatment was 23 months. Myelosuppression was the most important toxicity with 35% of patients experiencing grade 4 thrombocytopenia of short duration. Grade 4 leucopenia occurred in only one patient. It is concluded that single-agent carboplatin, with the adjunct of prophylactic G-CSF, can be administered with adequate dose intensity, and is an effective and acceptable palliative treatment for patients with relapse after first-line cisplatin-based chemotherapy.

Key words: Carboplatin, growth factors, ovarian cancer.

Introduction

After first-line treatment with debulking surgery and cisplatin-containing combination chemotherapy, many patients with advanced ovarian cancer remain free of disease for a considerable period of time. The median survival of patients with stage III–IV disease is now approximately 24 months, the 5 year survival 20–30% and the 10 year survival around 10%. This is in considerable contrast to the 5 year survival of below 10% in the single-agent melphalan era. There is, however, no evidence that the survival curve flattens out, so the question of whether the current treatment approach has a true curative potential remains unanswered.[1–3]

At least 80% of all patients will ultimately relapse and 30–50% of patients who achieve a pathologically documented complete response will relapse. In the case of recurrence, cure is even more unlikely, but palliation and possibly prolongation of life can still be achieved with second-line chemotherapy.

The most important drug in the treatment of advanced ovarian cancer remains cisplatin and the chance of again obtaining meaningful responses with cisplatin in second-line increases with a longer time interval between first-line treatment and relapse.[4,5] Carboplatin has similar activity compared to cisplatin, although there is still debate whether or not it will eventually replace cisplatin in the first-line treatment.[6–8] Because of the different toxicity pattern, however, this drug is particularly attractive in patients who relapse after first-line treatment with cisplatin-based chemotherapy. A steep dose–response relationship has been demonstrated retrospectively for cisplatin.[9] For carboplatin, data on dose–response relationships are scarce, but it is likely that, at least to some extent, a similar relationship may exist. It is possible, however, that beyond a certain point further dose escalation is not translated into improved activity.[10] In any case, it appears important to maintain anticipated dose intensity as well as possible.

The dose-limiting toxicity of carboplatin is myelosuppression, especially in pretreated patients, and thus the addition of hematopoietic growth factors may be of interest. So far, only limited experience is available with treatment with cytotoxic drugs and hematopoietic factors in patients with ovarian cancer. In a Dutch study, granulocyte macrophage

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colony stimulating factor (GM-CSF) was administered in a placebo-controlled trial in combination with carboplatin and cyclophosphamide. It was concluded that 3–6 μg/kg GM-CSF for 7 days significantly reduced chemotherapy-induced leucopenia.[11] We therefore proposed to assess carboplatin with primary prophylactic use of granulocyte colony stimulating factor (G-CSF) in patients who relapsed after at least one first-line cisplatin-based treatment regimen.

Patients and methods

Inclusion criteria

Eligibility criteria included histologically proven epithelial ovarian cancer, Karnofsky performance status $\geq$ 60%, age < 75 years, adequate bone marrow (WBC $\geq 4.0 \times 10^9$/l, thrombocytes $\geq 100 \times 10^9$/l), kidney (creatinine $\leq$ 130 μm/l) and hepatic (bilirubin $\leq$ 30 μmol/l) functions.

Patients should have a relapse after at least one first-line cisplatin-based treatment with any disease-free interval. Relapse was defined as clinical relapse, or significant increase of CA-125, i.e. $\geq$ 50% increase in lowest pretreatment level or $\geq$ 25 U/l in case the value had returned to normal after first-line treatment. Increase had to be documented in two consecutive samples, at least 4 weeks apart.

Treatment

Carboplatin was administered in a fixed dose of 350 mg/m^2, dissolved in 500 ml glucose 5%, every 28 days. Calculation of the dose in order to reach a certain area under the curve was not performed. Filgrastim was administered in doses of 300 or 480 μg s.c., days 5–9 after carboplatin administration. Treatment was continued until progression or severe toxicity and to a minimum number of six courses.

Antiemetics, preferably 5-HT$_3$-receptor antagonists plus corticosteroids, were used liberally according to the institution's schedule, in almost all cases a combination of 5-HT$_3$ antagonists with corticosteroids.

Dose modification

Hematologic dose modifications for carboplatin were accomplished as follows: if on the day of therapy the WBC was $< 4 \times 10^9$/l or platelets $< 100 \times 10^9$/l, treatment was to be delayed for a maximum of two additional weeks with weekly blood counts. If the counts did not return to normal values the following dose modification scheme was employed: WBC or platelets WHO grade 3, 75% dose; WHO grade 2, 50% dose; WHO grade 3, off study. In case of a WHO grade 4 nadir, the dose of carboplatin was reduced by 25% in the next cycles.

In case of WHO grade 3–4 toxicities other than alopecia the dose was reduced by 25%.

The dose of G-CSF always remained the same. Paracetamol was administered in the case of bone pains.

Definition and assessment of response

In cases of measurable disease the usual WHO criteria were applied. In case an increase in CA-125 was the first sign of progression, extensive clinical investigations (CT scans) were not necessary and the patient was considered non-measurable. For practical reasons, in these cases a complete remission was defined as normalization of CA-125 for at least 2 months and a partial remission as a decrease of $\geq$ 50% in CA-125 level in two consecutive samples for at least 2 months. Progressive disease was defined as continued increase in CA-125 after at least two cycles.

Follow-up

Follow-up studies were kept to a minimum. CT scanning or ultrasound for the evaluation of clinical response after six cycles were optional. Determination of CA-125 during treatment and follow-up was mandatory.

Results

The study was performed between January 1992 and October 1995. Thirty-four patients were included and all were evaluable. Patient characteristics are listed in Table 1. Twenty-seven patients were treated in second-line, six patients in third-line and one in fifth-line. The median disease-free interval (DFI) for all patients was 13 months (range 1–84 months). Ten patients had a DFI of 1–6 months. One patient received irradiation between first- and second-line chemotherapy. The median number of cycles was 6 (range 1–10). CA-125 dropped from a median pretreatment level of 188 (range 25–11 000) to a

Table 1. Patient characteristics

Characteristic	Number
Median age (range)	60 (49 73)
Median performance status	1 (0–2)
First-line treatment	
EP	11
EP + i.p. cisplatin	2
CEP	6
CEP + i.p. cisplatin	4
other	4
Second-line treatment	
same regimen	3
i.p. cisplatin	2
i.p. carboplatin	1
other	1
Measurable/non-measurable	18/16
Median DFI (range)	13 (1–84) months
Median pretreatment CA-125 (range)	188 (25–11 000)

EP, epirubicin + cisplatin; CEP, cyclophosphamide + epirubicin + cisplatin.

median post-treatment level of < 20 (range < 5–278). Treatment was well tolerated, 12 patients experienced grade 4 thrombocytopenia as the main toxic event. The duration of thrombocytopenia was short (median 2 days; range 1–5 days) and platelet suspensions were administered in only one patient. One patient, who was previously irradiated, had a grade 4 leucopenia. Other toxicities were virtually absent. Overall dose intensity was well maintained and the median dose of carboplatin actually received was > 90% (range 75–100%) of the anticipated dose. In 18 patients treatment was initiated on the basis of clinical progression and 16 received carboplatin because of an increase of CA-125. A total of 19 patients responded (five CR and 14 PR) while seven patients achieved stable disease. Seven patients had progression, including two patients who received treatment in third or even more advanced line. In one patient response was unknown. Median survival was 23 months (range 1–62+ months).

Discussion

In patients with ovarian cancer who relapse after a certain disease-free interval, good responses can be obtained with retreatment with cisplatin. The toxicity of cisplatin upon retreatment, however, is significant and therefore carboplatin may offer a reasonable alternative. The main toxicity of carboplatin is myelosuppression, which is increased in patients who had already developed significant myelosuppression on first-line cisplatin treatment.

It has not been demonstrated so far that any cytokine can effectively prevent carboplatin-induced thrombocytopenia, but neutropenia can be prevented. Our data suggest that this can be accomplished with prophylactic filgrastim during 5 days, i.e. half of the usually recommended duration of treatment. Because of the absence of a control arm, however, we cannot make firm statements whether or not the administration of G-CSF contributed definitely to the prevention of leucopenia and to the maintainance of an adequate dose intensity.

Although it is controversial whether retreatment of patients with an increase in CA-125, without clinical progression, has an impact on survival, withholding intended treatment until clinical progression is more difficult to accept and will probably not result in an enhanced treatment outcome. Furthermore, many oncologists will agree that response to chemotherapy will be higher when the tumor load is small.

Our data suggest that carboplatin, dosed in the traditional way per square meter, supported by G-CSF, can be administered safely without significant neutropenia and with acceptable thrombocytopenia, such that adequate dose intensity can be maintained. Results in terms of response and survival in this open phase II trial must be regarded cautiously but appear satisfactory from the clinical point of view.

References

1. Wils JA. Long-term follow-up of patients with advanced ovarian carcinoma treated with debulking surgery and chemotherapy consisting of cisplatin, doxorubicin, and cyclophosphamide. *Oncology* 1990; **47**: 115–20.
2. Neijt JP, ten Bokkel Huinink WW, van der Burg MEL, *et al.* Long-term survival in ovarian cancer. Mature data from the Netherlands Joint Study Group for Ovarian Cancer. *Eur J Cancer* 1991; **27**: 1367–72.
3. Vermorken JB, Hoekman K. Chemotherapy for gynecologic malignancies. *Curr Opin Oncol* 1995; **7**: 457–65.
4. Gersherson DM, Kavanagh JJ, Copeland LJ, *et al.* Retreatment of patients with recurrent epithelial ovarian cancer with cisplatin-based chemotherapy. *Obstet Gynecol* 1989; **73**: 798–802.
5. Markman M, Rothman R, Hakes T, *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991; **9**: 389–93.
6. McGuire WP, Abeloff MD. Carboplatin substitution for cisplatin in the treatment of ovarian carcinoma—a world of caution (editorial). *J Natl Cancer Inst* 1989; **81**: 1438–9.
7. Neijt JP. Ovarian cancer: rethinking prognostic factors and chemo-therapy. *ASCO Educational Book* 1994: 214–20.

8. Alberts DS, Canetta R, Mason-Liddil N. Carboplatin in the first-line chemotherapy of ovarian cancer. *Semin Oncol* 1990; **17** (suppl 2): 54–60.
9. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. *J Clin Oncol* 1987; **5**: 756–67.
10. Ozols RF, Thigpen JT, Dauplat J, *et al.* Dose intensity. *Ann Oncol* 1993; **4** (suppl 4): 49–56.
11. De Vries EGE, Biesma B, Willemse PHB, *et al.* A double-blind placebo-controlled study with GM-CSF during chemotherapy for ovarian carcinoma. *Cancer Res* 1991; **51**: 116–22.

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