Simultaneous Dose Escalation and Schedule Intensification of Carboplatin-based Chemotherapy Using Peripheral Blood Progenitor Cells and Filgrastim: A Phase I Trial

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ABSTRACT

Our purpose was to determine the maximum tolerated dose of, and the minimum interval between treatments with, multiple cycles of carboplatin (CBDCA) rescued with peripheral blood progenitors and filgrastim. Eligible patients had advanced cancers without prior chemotherapy or radiotherapy. The study design involved a sequential cross-over in which patients initially received two or three courses of cyclophosphamide (CPA) at a dose of 3.0 g/m², supported by filgrastim. Multiple leukaphere-
ses were then performed during the rebound phase of hematological recovery following each CPA-induced nadir to harvest peripheral blood progenitors, which were then reinfused as rescue following each of four courses of CBDCA. We attempted to administer the CBDCA at 14-day intervals. The CBDCA dose (mg/m²/course) was escalated as follows in successive cohorts of patients: Level I, 500; Level II, 800; Level III, 1200; Level IVa, 1000. Following determination of the maximum tolerated dose of CBDCA administered in this fashion, a subsequent cohort of patients (Level IV) were treated with two courses of high-dose CPA and four courses of the combination of CBDCA (1000 mg/m²) plus CPA (1500 mg/m²). Thirty-one patients were enrolled in the trial. Five patients were removed from study prior to completion of protocol therapy, three due to toxicity and two who developed progressive cancer while on study. The maximum tolerated dose of CBDCA was 1000 mg/m², with dose-limiting toxicity occurring at 1200 mg/m². The median inter-treatment interval for all cycles was 15 days (range, 12–30). The median intervals between CBDCA courses for each dose level were: Level I, 17 days; Level II, 17 days; Level III, 14 days; Level IVa, 15 days; Level IV, 16 days. The median dose intensity of the CPA phase was 1493 mg/m²/week. The median (and range) CBDCA dose intensities (measured from the start of CBDCA) for each dose level were: I, 185 (151–222); II, 328 (305–380); III, 567 (512–646); IVa, 465 (363–481); Level IV, 468 (333–500). Neutropenic fever complicated 35 of 113 CBDCA or CBDCA/CPA courses. Platelet transfusion was required in 51 of 113 courses. One patient had severe epistaxis. There were no treatment-related deaths. Among 27 patients with ovarian cancer who were evaluable for response, there were 5 pathologically documented complete (including 3 of 10 at Level IV) and 16 partial responses. We concluded that peripheral blood progenitors facilitate the simultaneous dose escalation and schedule intensification of carboplatin chemotherapy. The effect is sustained over four courses of treatment. The maximum tolerated dose of carboplatin administered in this fashion, either as a single agent or in combination with CPA, is 1000 mg/m², with an intertreatment interval of approximately 16 days.

INTRODUCTION

While cytotoxic chemotherapy can cure some types of disseminated cancer, in most cases it fails to do so, due to mechanisms which are collectively referred to as "drug resistance" (1). Some component of this drug resistance may be relative rather than absolute, however, inasmuch as it can be at least partially overcome by dose escalation of the drugs to which the tumor cells had become resistant. For example, patients with lymphoma (2) or germ cell cancer (3) which was refractory to prior, conventionally dosed therapy, can achieve complete remissions (some of which are durable), when treated with HDC in the range which requires autologous bone marrow infusion as rescue. HDC also produces frequent complete responses in patients with breast (4) and ovarian neoplasia (5); however, most of these remissions are temporary.

Those patients who do not respond or who have only a partial response to high-dose chemotherapy likely have tumors in which highly resistant cancer cells predominate. Conversely, the minority of patients who achieve durable complete remissions likely have tumors which consist predominantly of cells of unusual sensitivity. What, however, is the mechanism underlying the temporary complete responses which are so common after HDC? One explanation could be the survival of highly resistant subpopulations of cells in tumors composed of clones with heterogeneous patterns of drug resistance, following the chemotherapy-induced eradication of the more sensitive cells (6).

An alternative explanation, however, derives both from the study of mathematical models of tumor growth kinetics (7) and from the clinical experience with other, more curable cancers. The development of successful treatment programs for lymphoma and testicular cancer has necessitated the identification of highly active regimens and the application of a minimum number of courses of those regimens (8, 9). It is thus reasonable to hypothesize that the optimal use of these very active high-dose regimens might require the administration of multiple treatment courses. The Norton-Simon model, moreover, predicts that massive, but noneradicative cytoreduction might be followed by a phase of such accelerated regrowth of the minimal volumes of residual cancer cells that much of the advantage of multiple treatment courses might be undermined in the event of lengthy delays between these courses. In practice, the toxicity of high-dose chemotherapy has complicated attempts to administer multiple courses (10) and has necessitated substantial treatment delays where it has been attempted (11, 12).

Because myeloid recovery is a common rate-limiting step in chemotherapy treatment schedules and is a principal determinant of morbidity, a possible role for hematopoietic growth factors in dose escalation and schedule intensification has been studied. While these factors have facilitated intensification of chemotherapy with cyclophosphamide, etoposide, and some other agents (13–15), attempts to increase the intensity of delivery of more profoundly myelosuppressive agents, e.g., carboplatin and thiopeta, have been limited by thrombocytopenia and cumulative myelosuppression (16, 17).

The colony-stimulating factors also mobilize hematopoietic progenitor cells into the peripheral blood, and it is possible to harvest 3 The abbreviations used are: HDC, very-high-dose chemotherapy; PBP, peripheral blood progenitors; G-CSF, granulocyte-colony-stimulating factor.
these progenitors by leukapheresis (18). The reinfection of these PBP for rescue following high-dose chemotherapy has resulted in accelerated hematological recovery compared to growth factors alone (19) and may also be associated with enhanced recovery compared to autologous marrow transplantation (20). Prengren mobilization may be even more pronounced when CSFs are administered following high-dose cyclophosphamide. Using these technologies, Gianni et al. (21) and our group (22) have designed sequential regimens, in which multiple courses of higher-dose chemotherapy in the range which does not require autologous stem cell rescue are administered with growth factor as sole support, followed by leukaphereses to harvest PBP for use as rescue following a single subsequent course of more profoundly myelosuppressive therapy. In our study, patients received these courses at approximately 2-week intervals. Other groups have studied the use of PBP as support for multiple courses of higher-dose therapy administered at standard treatment intervals (23, 24).

In order to test the hypothesis that PBP could facilitate the simultaneous dose escalation and schedule intensification of myelosuppressive chemotherapy, we devised a novel cross-over regimen in which early courses of high-dose cyclophosphamide plus filgrastim were used to mobilize PBP for use as rescue following subsequent rapidly cycled courses of high-dose carboplatin. We have previously published preliminary results of this study as correspondence (25).

**MATERIALS AND METHODS**

Eligibility criteria included: histologically documented cancer which was metastatic; no prior chemotherapy or radiotherapy; Karnofsky performance status >80%; life expectancy greater than 3 months; no evidence of bone marrow or central nervous system metastases; absence of serious comorbidity; cardiac ejection fraction >50%; absolute neutrophil count >1.5 × 10⁹/liter; platelet count >100 × 10⁹/liter; hemoglobin >9 g/dl; normal prothrombin time and normal activated partial thromboplastin time; bilirubin <1.5 × upper limit of normal; normal creatinine; signed informed consent; physiological age less than 60 years; no evidence of human immunodeficiency virus infection or chronic viral hepatitis.

The treatment plan is depicted in Fig. 1. Patients at Level I received two courses of high-dose cyclophosphamide (3.0 g/m²) followed by four courses of carboplatin (500 mg/m²), with leukapheresis carried out following both cyclophosphamide courses, and following the first two carboplatin courses. Because a considerable emphasis in this protocol was placed on achieving the minimum interval between carboplatin treatments and because the leukapheresis procedures following the first and second carboplatin treatments were delaying the next carboplatin treatments, patients who had already recovered from the toxicity of the previous cycle, the protocol was amended prior to the institution of Level II. In the amended version, patients received three cycles of cyclophosphamide, each followed by four leukaphereses. No further leukaphereses were performed following carboplatin, thus facilitating further abbreviation of the interval between carboplatin treatments. The carboplatin dose was escalated in successive cohorts of patients as follows: Level II, 800 mg/m²; Level III, 1200 mg/m²; Level IIIa, 1000 mg/m². With increasing validation of the CD34+ assay as a real time quality control test for the adequacy of PBP collections, it was subsequently possible to reduce the number of cyclophosphamide “mobility” courses. Patients at Level IV thus received two courses of cyclophosphamide at a dose of 3.0 g/m² followed by four courses of the combination of carboplatin (1000 mg/m²) plus cyclophosphamide (1.5 g/m²) (Fig. 2). All patients had a leukapheresis grade, double lumen indwelling venous catheter inserted prior to the first chemotherapy course. Patients at Dose Levels II and higher also had a bone marrow harvest performed at this time. The bone marrow (and the subsequently leukapheresed PBPs) were cryopreserved according to the method of Stiff et al. (26). The planned treatment interval between all chemotherapy courses was 14 days.

All cyclophosphamide courses were administered on an inpatient basis during a 2-day admission period. Patients received overnight hydration prior to cyclophosphamide. The cyclophosphamide dose was administered over a 1-h period as an i.v. infusion, and inpatient hydration was continued until the following day. Patients commenced daily s.c. injections of G-CSF at a dose of 5 μg/kg/day, on the third day of each cyclophosphamide cycle. Patients had complete blood counts with differential leukocyte counts performed three times/week during this phase of therapy. Four leukapheresis procedures were performed during the hematological recovery following each cyclophosphamide course. Leukapheresis was commenced when the leukocyte count was at least 1.0 × 10⁹/liter. Patients with neutropenic fever during the nadir period had to have negative blood cultures at the time of leukapheresis. A total of four leukapheresis procedures were performed. A Fenwall CS 3000 (Baxter, Chicago, IL) cell separator was used. Ten liters were processed per procedure, using continuous flow centrifugation at a flow rate of 70 ml/min. Subsequent cycles of chemotherapy were scheduled for administration 14 days following the previous cycle, provided the patients had achieved a neutrophil count of 1.0 × 10⁹/liter, a platelet count of 50 × 10⁹/liter and were off antibiotics. G-CSF was administered as per the initial cycle.

Flow cytometric analysis was performed on the PBP collections of the last 21 patients on study using a Coulter EPICS Profile 2 (Coulter, Hialeah, FL). Cells were studied for the expression of the CD34+ antigen using the HPCA-1 antibody (Becton-Dickinson, San Jose, CA) and for the CD33+ antigen using the MY9 antibody (Coulter).

Carboplatin was administered either on an inpatient basis or in our ambulatory facility. For patients at Level II or higher, the carboplatin dose was divided over 2 days. Patients at Level IV received the cyclophosphamide component on Day 1 of each carboplatin/cyclophosphamide course, with the carboplatin administered in divided doses on Days 1 and 2. PBP were rein infused i.v. 72 h following each carboplatin course. G-CSF was recommended on the following day.

Cyclophosphamide dose intensity was calculated by dividing the total dose of cyclophosphamide by the interval in weeks from the first day of cyclophosphamide administration to the first day of the first cycle of carboplatin. Carboplatin dose intensity was calculated in two ways. In both cases the numerator was the total delivered dose of carboplatin. In the first calculation, which reflects the rate of carboplatin delivery throughout the whole program, this was divided by the interval in weeks between the first chemotherapy cycle.
DOSE ESCALATIONS/SCHEDULE INTENSIFICATION AND CARBOPLATIN

RESULTS

Thirty-one patients (all female) were enrolled on the study between July 1991 and December 1992 (Table 1). The median age was 47 years (range, 28–66). Among 29 patients with ovarian carcinoma, there was 1 with Stage II, 19 with International Federation of Gynecologists and Obstetricians Stage III (6 optimally debulked), and 9 with Stage IV. One patient had an undifferentiated retroperitoneal tumor, and one had a nonulmonary small cell carcinoma. Three patients were withdrawn from the study due to toxicity (see below). Two patients were removed from study due to disease progression. All other patients (26 patients) received all scheduled courses of treatment.

The leukapheresis collections of 17 patients were analyzed for the presence of cells expressing the CD34+ antigen. A median number of 2.5 x 10^6/kg (range, 0.05 x 10^6-14 x 10^6) CD34+ cells were collected per leukapheresis, and the median number reinfused per cycle was 4.6 x 10^6/kg (range, 1.32 x 10^6-13.9 x 10^6).

Toxicity. Hematological toxicity is depicted in Table 2. The frequency of grade III/IV neutropenia may in fact have been higher, because patients did not have daily blood counts carried out. Neutropenic fevers necessitated admission following 23 of 76 cyclophosphamide courses, and after 35 of 113 courses of carboplatin or carboplatin/cyclophosphamide. Neutropenic fever occurred following 17 of the first 31 courses of cyclophosphamide, with positive blood cultures in 4. Subsequently, a dilute vancomycin-heparin solution was used for all catheter flushes, and the occurrence of neutropenic fever following cyclophosphamide declined to 6 of 45, with 1 episode of bacteremia. Overall, there were ten episodes of bacteremia throughout the study. One patient at Level IIIa developed Gram-negative septicemia with hypotension following carboplatin Cycle 2 and required transfer to the intensive care unit. She made a complete recovery.

Prophylactic platelet transfusions were necessary in 4 of 76 cyclophosphamide courses, and following 51 of 113 carboplatin or carboplatin/cyclophosphamide courses. Two patients developed clinical evidence of bleeding, one with epistaxis and subconjunctival hemorrhage who made a complete recovery. One patient with pre-existing diabetes and a history of diabetic retinopathy and hemorrhages developed a further episode of retinal bleeding while thrombocytopenic.

The number of days to the recovery of the platelet count to >20 x 10^9/liter and to recovery of the absolute neutrophil count to greater than 0.5 x 10^9/liter following PBP infusion are depicted in Table 3. Severe thrombocytopenia requiring platelet transfusion was more common following the last cycle of carboplatin or carboplatin plus cyclophosphamide (18), compared to the first course (eight). Similarly, admissions for febrile neutropenia (11 of 26) were more common following the fourth course of carboplatin or carboplatin/cyclophosphamide than following the first (9 of 30).

There were no treatment-related deaths. One patient with a history of palpitations was found to have atrial fibrillation following cyclophosphamide Cycle 1 and was removed from study. Ototoxicity was dose limiting at 1200 mg/m². At this level, two of four patients developed severe tinnitus and moderate hearing loss following two treatment cycles and were removed from the study. The third patient developed this toxicity after three treatments and received a fourth carboplatin course at half-dosage. A fourth patient who was profoundly deaf from birth received two courses at 1200 mg/m², but due to concerns on the investigators' part that other manifestations of neurotoxicity might occur unheralded in this already deaf patient, the remaining two courses were administered at 800 mg/m².

Two patients developed dermatomal herpes zoster infection following carboplatin treatments at Level II. Both patients made a complete recovery.

Toxocities associated with PBP infusion included nausea and vomiting, facial flushing, and hemoglobinuria. One patient had a syncopal episode at the time of infusion, which resolved with conservative management. One patient developed subclavian vein thrombosis related to the leukapheresis catheter. One patient at Level IV had only seven PBP collections available due to persistent pyrexia on a scheduled day of leukapheresis and also had three rather than two bags of PBP infused following the third course of carboplatin/cyclophosphamide. As a result no PBP were available to rescue the fourth course of high dose chemotherapy, and the previously stored autologous marrow was used as support. This patient achieved platelet and neutrophil recovery at 15 and at 10 days, respectively, following marrow reinfusion.

Overall, patients on study spent a median of 36 days (range, 21–55 days) as hospital inpatients. Of this, 18 days were scheduled inpatient days for protocol therapy, and 18 days were for therapy of complications.

There is increasing evidence that pharmacokinetic-based dosing of carboplatin might be more appropriate than dosing based on body

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total patients</th>
<th>Median age (range)</th>
<th>Epithelial ovarian cancer</th>
<th>FIGO Stage II</th>
<th>FIGO Stage III</th>
<th>Optimally debulked</th>
<th>FIGO Stage IV</th>
<th>Adenocarcinoma</th>
<th>Papillary-serous</th>
<th>Endometrioid</th>
<th>Small cell</th>
<th>Clear cell</th>
<th>Undifferentiated</th>
<th>Other tumor types</th>
<th>Median creatinine clearance</th>
</tr>
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<tr>
<td>Total patients</td>
<td>31</td>
<td>47 (28–66)</td>
<td>29</td>
<td>1</td>
<td>19</td>
<td>6</td>
<td>9</td>
<td>18</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td></td>
<td>93 ml/min (range, 58–148)</td>
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</table>

* FIGO, International Federation of Gynecologists and Obstetricians.

Table 2. Hematological toxicity of carboplatin

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of courses</th>
<th>Grade III/IV neutropenia</th>
<th>Fever</th>
<th>Sepsis</th>
<th>Grade III/IV platelet</th>
<th>Platelet toxicity</th>
<th>Days to</th>
<th>PLAtelets &gt;50</th>
<th>ANC &gt;0.5</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>14 (13–18)</td>
<td>6</td>
<td>1</td>
<td>12 (13–30)</td>
<td>12 (9–16)</td>
<td>9</td>
<td>10 (6–15)</td>
<td>10 (6–15)</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>15 (13–20)</td>
<td>1</td>
<td>1</td>
<td>12 (13–25)</td>
<td>12 (9–16)</td>
<td>9</td>
<td>10 (6–15)</td>
<td>10 (6–15)</td>
</tr>
<tr>
<td>Median</td>
<td>16 (13–25)</td>
<td>10 (9–12)</td>
<td>10</td>
<td>1</td>
<td>10 (7–11)</td>
<td>10 (7–11)</td>
<td></td>
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</tr>
</tbody>
</table>

* ANC, absolute neutrophil count.
Table 4 Dose intensity (mg/m²/week)

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Cyclophosphamide</th>
<th>Median</th>
<th>Range</th>
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<tr>
<td>I</td>
<td>1493</td>
<td>1511-1551</td>
<td></td>
</tr>
<tr>
<td>CBDOCA</td>
<td>1185 (133)⁴</td>
<td>135-154</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>326 (206)</td>
<td>305-380</td>
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<tr>
<td>III</td>
<td>567 (240)</td>
<td>512-646</td>
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<tr>
<td>IIIa</td>
<td>465 (263)</td>
<td>363-481</td>
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<tr>
<td>IV</td>
<td>468 (307)</td>
<td>333-500</td>
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</table>

* Numbers in parentheses, carboplatin dose intensity calculated from the day of administration of the first cyclophosphamide course.

surface area. We retrospectively calculated the area under the concentration-versus-time curve (for 28 patients in whom creatinine clearance had been measured) at Dose Levels I, II, III and IIIa (27). The median and range AUCs at these dose levels were (in mg/ml/min) 8.7 (8-15.9), 13.4 (3.1-16.9), 17.3 (7.9-32), and 13.9 (12.8-15.4), respectively. Interestingly, the two patients who developed severe otoxicity received areas under the concentration-versus-time curve of 23.7 and 32 respectively.

Treatment Intervals and Dose Intensity. Treatment intervals are depicted in Table 3. The median interval between all treatments was 15 days (range, 12-30 days). The median interval postcyclophosphamide was 14 days (range, 12-26 days), and that between carboplatin or carboplatin/cyclophosphamide courses was 16 days (range, 13-30 days). For Levels III and IV, the median intervals between the first and second carboplatin courses were 15 days (range, 13-18) and 15 days (range, 13-21), respectively. The corresponding intervals between the third and fourth courses were 16 days (range, 14-18) and 17 days (range, 13-25), respectively.

Dose intensity (calculated using both denominators, as outlined in "Materials and Methods") is depicted in Table 4. The achieved dose intensity as a percentage of planned did not decrease with increasing carboplatin dose levels; and in fact at the maximum tolerated dose, the mean percentage of planned dose intensity that was achieved (93%) was higher than at the the initial dose levels.

Response to Treatment. Among 29 patients with ovarian cancer, 2 were not evaluable for response, 1 due to removal from study for possible toxicity following the initial cyclophosphamide course, and 1 for failure to attend for follow-up. Among the 27 evaluable patients described in Table 5, there were 5 complete responses (1 patient with parenchymal liver metastases, 2 optimally debulked Stage III, 1 suboptimally debulked Stage III, 1 Stage Ic) documented at second look surgery. These five patients remain in complete remission at 15+, 15+, 16+, 26+, and 25+ months post-completion of therapy. One of the patients in complete remission was subsequently enrolled on a protocol of consolidative i.p. chemotherapy. Sixteen patients achieved partial response. All of these patients were placed on "salvage" chemotherapy protocols, complicating the assessment of their response duration. Five patients developed evidence of progressive cancer while receiving therapy or soon afterwards. Overall, 22 patients remain alive at from 13.7 to 30.3 months of follow-up (median, 20.8).

One patient with nonpulmonary small cell carcinoma and metastases to skin and bone had a complete resolution of her skin lesions, with persistent abnormalities on bone scan. She developed progressive cancer 3 months following completion of protocol therapy. One patient with undifferentiated cancer was treated. She did not have clinically measurable disease but developed progressive cancer at 9 months.

DISCUSSION

While PBP have been used both to decrease the toxicity of HDC (28) and to facilitate the administration of multiple courses of higher dose therapy (23), this study is the first exploration of their use to facilitate the simultaneous dose escalation and acceleration of chemotherapy.

The relative contributions of total dose, peak dose, and the interval between treatments to the putative benefit of dose intensification remain undetermined (29). Several groups have used PBP to facilitate an increase in the dose intensity of chemotherapy by altering one or other of these variables. Shea et al. demonstrated that PBP could facilitate the delivery of three cycles of high-dose carboplatin, resulting in increases in both the dose per course and the total dose of this agent. The treatment intervals, however, were slightly longer than those achieved using standard doses of carboplatin (23). Investigators at the Dana-Farber Cancer Institute used PBP which had been mobilized by a single course of cyclophosphamide to support four courses of the combination of standard dose cyclophosphamide, plus a dose of carboplatin which was approximately 50% higher than standard, and achieved a 4-week retreatment schedule (24).

It is possible that alterations in each of these components of dose intensity might be independent determinants of the curative potential of a regimen. This position is supported by the Norton-Simon model, which predicts that the dose of the individual courses would influence the cell kill per course, and that the interval between treatments would determine the amount of regrowth prior to the subsequent cycle. In addition, an insufficient number of courses of a partially active regimen might not eradicate a relatively sensitive cancer, whereas a greater number (with an increased total dose) might be curative. The data from several prospective random assignment trials in patients with ovarian cancer support this interpretation. McGuire et al. (30) found that a smaller number of higher dosed courses of therapy did not increase tumor response or patient survival compared to a larger number of lower dose courses delivering the same total dose, despite a 2-fold difference in dose-intensity. In two British studies, advantages in response (31) and/or survival (32) were described for treatment arms which delivered higher peak and total doses of carboplatin or cisplatin compared to the same number of equivalently spaced lower dose courses. Investigators in Italy randomly assigned patients to receive a higher or a lower intensity schedule of cisplatin chemotherapy. Patients in both arms received the same number of identically dosed courses of cisplatin, with the treatment interval isolated as the sole variable. Patients receiving the more intensive schedule achieved prolonged disease-free survival approximately twice as frequently as patients receiving the same doses in a more attenuated schedule (33).

Our data demonstrate that all of these variables (peak dose, total dose and the treatment interval) can be favorably and simultaneously altered using the newer hematopoietic support technologies. Compared to a standard regimen of carboplatin and cyclophosphamide (400 and 600 mg/m², respectively, every 4 weeks) which would deliver (if administered without treatment delay or attenuation) total doses of these drugs of 2400 and 3600 mg/m², respectively, over a
24-week period (34), patients treated at the maximum tolerated dose of our regimen receive total doses of carboplatin and cyclophosphamide of 4000 and 12000 mg/m², respectively, over 13 weeks. Patients treated at this level achieved dose intensities of cyclophosphamide and carboplatin which were 10-fold higher and 3–4-fold higher, respectively, than patients receiving the standard regimen. It is possible, however, that some of these comparisons are somewhat undermined by the lack of prospective pharmacokinetic dosing in our study and in the others which we have quoted.

While only 19% of patients with ovarian cancer achieved a pathologically documented complete response in this study, the relatively small numbers per dose level prevent meaningful conclusions regarding the antitumor efficacy of this regimen. In addition, the antitumor activity of the carboplatin might have been compromised by the relatively lengthy cyclophosphamide treatment, which was included principally because of its ability to mobilize PBPs. In this regard, the results of Perren et al. (35), who found the patients who were randomized to receive sequential ifosfamide followed by carboplatin had an inferior complete response rate compared to patients who were randomized to receive six courses of carboplatin, may be relevant. Hence, the optimization of this approach might require the development of a more active treatment than single agent cyclophosphamide in the mobilization phase. We are thus currently studying a successor regimen in which the combination of taxol plus cyclophosphamide is used both as therapy and to mobilize PBPs, which are then used to support four courses of high-dose carboplatin plus cyclophosphamide (36).

This treatment strategy could also be adapted for other neoplasias. For example, multiple courses of high-dose etoposide (37) or doxorubicin (38) have been administered with G-CSF, and both have been demonstrated (either singly or in combination with cyclophosphamide) to mobilize hematopoietic progenitors into the peripheral blood. Thiotepa and melphalan are broadly active agents which can be administered in very high doses with hematopoietic cellular support. Preliminary data from our institution suggest that sequences of these drugs can be administered at approximately 16-day intervals, when PBPs are used as rescue (39, 40). Thus regimens could be devised which would deliver high doses of agents known to be highly active in breast, lung, and hematological cancers.

Prospective random assignment trials will be required to determine the precise role of dose intensification in cancer chemotherapy. Our results suggest that regimens consisting of multiple, rapidly cycled courses of HDC can now be studied in this fashion.

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REFERENCES


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