Minireview

Dose Intensity in Advanced Ovarian Cancer: Have We Answered the Question?

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Introduction

For advanced ovarian cancer, the prognosis remains poor in spite of real advances in treatment. Reported 5-year survival rates range between 15 and 20% (1). Analysis of ovarian cancer mortality rates over the past 10 years reveal an increase from approximately 16/100,000 in 1981 to at present a rate of 22/100,000 cases (2). Ovarian cancer is a tumor that has demonstrated chemosensitivity, with overall response rates of 60–80% reported, but in spite of this encouraging response rate, treatment is complicated by frequent relapses from therapy. The cellular mechanisms by which ovarian and other cancers escape eradication by chemotherapy are collectively termed drug resistance.

One can consider drug resistance as being expressed in two principal forms: absolute or irreversible resistance, or relative resistance. While absolute resistance cannot be overcome by any dose level of drug, relative resistance refers to resistance which may be overcome by manipulations of dose or schedule of drug administration. Manipulations of dose and, to some extent schedule, have long been demonstrated to be of value in the treatment of hematological cancers. Recently, the value of induction and late intensification have been demonstrated in the treatment of some forms of acute leukemia (3).

In advanced ovarian cancer, efforts to overcome this emerging drug resistance have largely focused on dose escalation. A seminal article by Levin and Hryniuk (74) analyzed retrospectively the role of dose intensity in the treatment of this disease. They defined dose intensity as the amount of drug delivered divided by the time of administration. A total of 33 trials of combination chemotherapy in advanced ovarian cancer were analyzed, both cisplatin and non-cis-platinum based. Based on drug doses received, relative dose intensity achieved, they were able to demonstrate a statistically significantly correlation between increasing dose intensity of cisplatin and both response rate and overall survival. Analysis of the dose intensity of other drugs such as cyclophosphamide and Adriamycin failed to reveal a significant correlation between increasing dose intensity and overall response. The majority of patients in this analysis were suboptimally debulked stage III and IV patients, with over 90% of them having bulky residual disease on initiation of chemotherapy.

The results of this analysis have largely been responsible for the impetus behind clinical trials involving dose intensity in advanced ovarian cancer. However, there are a number of features which must be considered when analyzing this study. First, as pointed out by McGuire (4), outcome and average dose intensity are not highly correlated ($r^2 = 0.17$–0.23). Second, an important feature is the amount of dose escalation required to obtain a clinical effect. In the meta-analysis published by Levin and Hryniuk, the dose-response relationship holds over a range of 0.4–0.8. In this analysis, the “standard” regimen used a cisplatin dose equivalent of 15 mg/m$^2$/week. The demonstrated dose-response relationship thus holds true over a range of 6–12 mg/m$^2$/week. This is equivalent to a total dose of approximately 36 mg/m$^2$ over 3 weeks, and thus is lower than the commonly used “low-dose” cisplatin regimen of 50 mg/m$^2$ every 3 weeks. This analysis would thus appear to provide support for optimal versus suboptimal dosing as opposed to high versus standard dosing of cisplatin. In the initial meta-analysis, the dose intensity achieved ranged from 30 to 110% of a standard. This is a relative range of only 3–4-fold. If it is true that the benefit of dose-intensive therapy lies in its ability to overcome relative drug resistance, then the in vitro models available would suggest that a greater than 5-fold increase would be desirable (5). These factors may explain why no clear-cut dose-response relationship is universally acknowledged.

Randomized Trials of Dose Intensity

Many randomized trials of platinum dose intensity are now mature, and the data are available for analysis (Refs. 6–13; Table 1). At present the published data from the randomized trials of dose intensity in ovarian cancer have failed to confirm a benefit in favor of the dose-intense approach.

Kaye et al. (6) reported on a randomized study of two doses of cisplatin given with cyclophosphamide. Patients were randomized to receive six doses of cyclophosphamide every 3 weeks with either 50 mg/m$^2$ or 100 mg/m$^2$ cisplatin. In this study patients on the high-dose arm received 1.3 times the dose intensity of the low-dose arm. Additionally, the high-dose arm delivered a 66% greater total dose of cisplatin than the low-dose arm. This study was stopped early due to the emergence of a significant survival advantage at 18 months of 73% for the high-dose arm versus 48% for the low-dose arm (4). Analysis of this study is further complicated by the fact that a significant number of patients treated had early stage ovarian cancer and were treated in an adjuvant setting.

The Gynecological Oncology Group similarly performed a prospective randomized study concentrating on a population with suboptimally debulked disease (≥1 cm residual disease following laparotomy; Ref. 7). In this large study, which evaluated 460 patients, although a trend toward both progression-free and overall survival was seen, this did not reach statistical significance. The GOG study was stopped early when a significant sample of patients in the low-dose arm developed late relapses. It is apparent that the lack of side effects noted in the previously described studies does not translate into an increased benefit for patients receiving low-dose chemotherapy.

It has become clear that drug resistance can be overcome by dose escalation. In the treatment of ovarian cancer, the ability to achieve higher dose intensities may help overcome drug resistance. However, it is unknown whether dose escalation by itself is a sufficient therapeutic approach for patients with advanced ovarian cancer. Determination of dose intensity lies in the ability to overcome relative drug resistance, then the in vitro models available would suggest that a greater than 5-fold increase would be desirable.
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Table 1 Platinum dose intensity and total doses of platinum received in randomized studies published in ovarian cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Cisplatin treatment</th>
<th>Response (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaye et al.6</td>
<td>100 mg every 3 wk</td>
<td>61</td>
<td>114 wk</td>
</tr>
<tr>
<td></td>
<td>50 mg every 3 wk</td>
<td>34</td>
<td>69 wk</td>
</tr>
<tr>
<td>Bella et al.9</td>
<td>100 mg ×3, ×2</td>
<td>69 pCR = 19</td>
<td>(P = 0.0008)</td>
</tr>
<tr>
<td></td>
<td>100 mg ×6</td>
<td>65 pCR = 9</td>
<td>31% (4 yr)</td>
</tr>
<tr>
<td>Jones et al.8</td>
<td>CBDDCA AUC 12</td>
<td>58 CCR</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>CBDDCA AUC 6</td>
<td>36 CCR</td>
<td>NS</td>
</tr>
<tr>
<td>Ngan et al.10</td>
<td>120 mg every 3–4 wk</td>
<td>55</td>
<td>60% (3 yr)</td>
</tr>
<tr>
<td></td>
<td>60 mg every 3–4 wk</td>
<td>30</td>
<td>30% (3 yr)</td>
</tr>
<tr>
<td>McGuire et al.7</td>
<td>100 mg every 3 wk ×4</td>
<td>59 RR</td>
<td>24 mo</td>
</tr>
<tr>
<td></td>
<td>50 mg every 3 wk ×8</td>
<td>65 RR</td>
<td>21 mo</td>
</tr>
<tr>
<td>Ehrlich et al.11</td>
<td>100 mg every 4 wk ×3</td>
<td>80 RR</td>
<td>27.5 mo</td>
</tr>
<tr>
<td></td>
<td>50 mg every 3 wk ×6</td>
<td>75 RR</td>
<td>23.5 mo</td>
</tr>
<tr>
<td>Colombo et al.12</td>
<td>75 mg q 3 wk ×6</td>
<td>61 RR</td>
<td>33 mo</td>
</tr>
<tr>
<td></td>
<td>50 mg q wk ×9</td>
<td>66 RR</td>
<td>36 mo</td>
</tr>
<tr>
<td>Conte et al.13</td>
<td>100 mg every 4 wk ×6</td>
<td>43.6</td>
<td>19 mo</td>
</tr>
</tbody>
</table>

*pCR, pathological complete response; CCR, clinical complete response; NS, not stated, RR, response rate; pfs, progression-free survival.

significance. In this study the high-dose arm received a 2-fold increase in dose intensity, with identical total doses of drug being delivered.

In a third study, Jones et al. (8) randomly assigned patients to receive either standard-dose or high-dose carboplatin, based on a pharmacokinetically defined dose model. Frequencies of response were 58% versus 36% in favor of the high-dose arm, a statistically significant result. Bella et al. (9) randomly assigned patients to receive 600 mg/m² over either a 9-week or a 20-week period. Median survival was not significantly different, but 4-year survival was 31% for the higher dose-density arm versus 13% for the standard-dose arm. Subsequent analysis has demonstrated persistence of this survival advantage at 8 years of follow-up (14).

Conte et al. (13) reported on the use of high doses versus standard doses of cisplatin used in combination with cyclophosphamide and epirubicin in patients with bulky residual disease following laparotomy. Patients were randomized to receive cisplatin (50 mg/m²), epirubicin (60 mg/m²), and cyclophosphamide (600 mg/m²), all on day 1 of each 28-day cycle (called PEC 50) versus a regimen consisting of epirubicin and cyclophosphamide as above with cisplatin (50 mg/m²) given on days 1 and 2 (PEC 100). All patients had residual disease ≥2 cm following laparotomy. Overall response rates reported were 55.7% for PEC 50 versus 43.6% for PEC 100. Median survival has not been reached. These investigators published a recent follow-up analyzing received dose intensity. They identified three different dose levels on the basis of dose intensity received: ≤12.5 mg/m²/week, >12.5 < 25 mg/m²/week, and ≥25 mg/m²/week. Median survival for the three dose levels respectively was 37.1, 28.4, and 28.7 months (15); however, it is unlikely at the dose intensities achieved that a clinically significant difference could be detected.

Ehrlich et al. (11) randomized patients to cisplatin (100 mg/m² every 4 weeks for three cycles), with Adriamycin and cyclophosphamide versus cisplatin (50 mg/m² every 3 weeks for six cycles) with Adriamycin and cyclophosphamide. The pathological complete response rate for the high-dose arm was 20% versus 47% for the standard-dose arm, with an overall response rate of 88% for the high-dose arm versus 75% for the standard arm. Although not reaching statistical significance there is a trend toward improved survival of 27.5 versus 23.5 months in favor of the high-dose arm. Of note is that over 30% of patients had ≥3 cm of residual disease following surgery.

Colombo et al. (12) reported on a randomized study of cisplatin (75 mg/m² every 3 weeks for six cycles), versus a dose-intensive regimen of cisplatin (50 mg/m²/week for nine cycles). Patients by virtue of the trial design were to receive the same total dose of cisplatin with patients in the dose-intense arm receiving twice the dose intensity achieved in the standard arm. Overall response rates were 66% for the dose-intense arm versus 61% for the standard arm. Again, a trend toward improved progression-free (21 months versus 18 months) and overall survival (36 months versus 33 months) was noted. Further follow-up will again be required to further evaluate this trend.

An overview of all of these trials fails to answer the question of the true value of increased dose intensity (largely by increasing dose level) in the treatment of advanced ovarian cancer. However, some important points are clear. First, those studies that focused on patients with suboptimally debulked disease consistently reported negative results regarding statistically significant improvements in response rates and overall survival. Studies focusing on patients with optimally debulked disease have reported positive end points both in terms of response rate and overall survival; however, the number of patients available for analysis is small. Second, in three of the studies cited the more dose-intensive treatment arm delivered fewer overall cycles of chemotherapy. Studies using fewer treatment cycles have usually produced negative results, while none of the positive studies incorporated this treatment design. Positive trials demonstrated improvement in the pathological complete response rate as opposed to the overall response rate (partial plus complete remission), and improvement in long-term survival as distinguished from median survival.

More important however, if the in vitro models are correct, a dose intensity of approximately 5-fold will be required to
overcome the emergence of platinum resistance. The published studies have thus far failed to analyze what might be considered clinically significant dose intensity.

Combination Platinum Strategies

Another method of increasing the dose of platinum delivered is to combine cis-platinum with other platinum analogues. Due to comparable efficacy and nonoverlapping toxicities, this has proved to be a feasible approach. A number of investigators have evaluated the role of this approach in ovarian cancer.

The Copenhagen Ovarian Cancer Study Group reported on a Phase II study combining carboplatin and cisplatin. They reported an overall pathological response rate of 62% using a dose of 300 mg/m², with 100 mg/m² cisplatin given every 4 weeks. Pathological complete response rate in this study was 22% (16). A subsequent study combined cisplatin and carboplatin with ifosfamide in 37 previously untreated patients, with a pathological complete response rate of 42% reported (17). A number of combined platinum studies have now been reported in the literature (19–23). The planned platinum dose intensity for these trials varies between 37.5 and 63 mg/m²/week. It is clear that due to myelotoxicity frequent dose reductions were necessary, and thus the delivered platinum dose intensity was significantly lower.

Analysis of these and other studies demonstrate that in spite of this treatment schema, the dose intensity achieved is less than twice that achieved with standard therapy. Based on our knowledge of the relationship between dose intensity and response and the relative drug resistance that emerges, this increase is unlikely to be clinically significant.

On the basis of Levin's initial work (74), strategies to improve dose intensity have consistently focused on platinum delivery. It is accepted that by increasing the dose of platinum delivered, responses can be obtained in relative platinum-refractory disease (24–26). With the advent of carboplatin, a platinum analogue with a more benign toxicity profile, the attention of investigators turned to attempts to increase platinum dose intensity using carboplatin. Jodrell and colleagues (75) analyzed in a retrospective fashion the relationship between total carboplatin exposure (AUC²; in mg/ml/min) and ultimate outcome. They calculated the exposure to platinum on the basis of creatinine clearance at the time of the first cycle of chemotherapy resulting in an AUC value. They were able to demonstrate that the peak response was seen at an AUC of 6 mg/ml/min, and that increasing the dose of platinum resulted in increased toxicity without improvement in response rates. In their analysis, the first cycle AUCs only were used to predict ultimate outcome. It is possible that treatment delays and dose reductions in subsequent cycles resulted in some of the disparity between dose and response in this analysis. This factor serves to emphasize the importance of manipulations to allow not only increased doses of cytotoxic therapy but also timely retreatment.

Multicycle Regimens

The inability of high-dose chemotherapy to eradicate clones of highly resistant cancer cells, in spite of massive degrees of tumor volume regression, might account for the frequency with which relapse from complete remission is observed following this modality. However, an analysis of curative chemotherapy for other neoplastic diseases suggests another possibility. Successful treatment programs for chemotherapy-curable cancers have two features in common. The first feature is the availability of a regimen which produces frequent complete responses. The second feature is the feasibility of delivering a minimum number of courses of that regimen in full doses. These two requirements are logical extrapolations from animal studies (27). Laboratory experiments have shown that multiple administrations of chemotherapy are usually more effective than a solitary treatment that delivers the same cumulative dosage (9). While there are no randomized clinical trials of single versus multiple courses of the same "effective" chemotherapy in patients with curable cancers, the contention that a minimum number of treatment courses are necessary to cure is defensible.

For Hodgkin's disease, nitrogen mustard-vincristine-procarbazine-prednisone chemotherapy is curative in approximately 50% of patients with advanced disease. The median time to the attainment of a complete remission is 3 months, which is equivalent to three cycles of therapy. Thus, few if any patients would have been cured had treatment for them consisted of only one course of this combination. Four courses of cisplatin and etoposide will be curative in the majority of patients with testicular carcinoma (28). However, three courses of this two-drug regimen produced results (in the context of a prospective randomized comparison against a three-drug regimen), which appeared to be inferior to those achieved historically with four courses of the doublet (29). There is also anecdotal evidence that patients who default following one course of cisplatin-based therapy have poor outcomes (30–32). Even patients with gestational trophoblastic disease, known to be highly responsive to chemotherapy, properly receive repeated courses of therapy until their serum chorionic gonadotrophin level has become normal (33).

In the treatment of ovarian carcinoma, the use of high-dose chemotherapy with autologous bone marrow support has been demonstrated to be capable of achieving high rates of response in patients failing conventional treatment regimens. This is an area of considerable interest for a number of reasons. First, ovarian cancer is a tumor with demonstrated chemosensitivity, although clearly less sensitivity than the hematological cancers. Second, patients failing conventional therapy have a universally poor prognosis. Additionally, as described above, there is a rising dose-response relationship for both the platinum compounds and the alkylating agents in general (34, 35). Agents such as melphalan, cyclophosphamide, and thiopeta are active in ovarian cancer, and can be substantially dose escalated with the use of autologous bone marrow support (36, 37). Using high-dose melphalan in patients who had failed prior cisplatin therapy, Dauplat et al. (38) obtained a 36% two-year disease-free survival rate. Preclinical studies by Lidor et al. (39) have demonstrated synergy between cisplatin and cyclophosphamide and cisplatin plus thiopeta. Shpall et al. (40) evaluated in a Phase I setting the combination of high-dose cyclophosphamide, thiopepa, and cisplatin followed by autologous bone marrow supporting patients with advanced ovarian cancer. Cisplatin was delivered by the i.p. route in an escalating dose schedule commencing at 90 mg/m² divided over 3 days. They reported an
Dose Intensity in Advanced Ovarian Cancer

Based on the demonstrated activity of doxorubicin in advanced ovarian cancer and the limited potential of this agent for dose escalation (because of dose-limiting mucositis and cardiotoxicity), investigators have turned to mitoxantrone for incorporation into dose-escalated approaches (41). Mitoxantrone is an anthracycene derivative, with an intercalative and nonintercalative effect on DNA (42, 43), which is cytotoxic to proliferating and nonproliferating cells in vitro (44, 45). Clinical congestive heart failure occurs in less than 3% of patients with conventional dosing of mitoxantrone, up to cumulative doses of 100 mg/m² in patients previously treated with anthracyclines, and up to 160 mg/m² in previously untreated patients (46). In experimental systems, mitoxantrone showed some lack of cross-resistance to anthracyclines (47). In the human tumor colony-forming assay, mitoxantrone has been demonstrated to be highly cytotoxic to ovarian cancer cells (48). It has also demonstrated activity against ovarian cancer, when delivered by either the i.v. (49) or i.p. routes (50). Mitoxantrone is an unusual drug to dose escalate because it is not an alkylating agent. Yet a number of investigators have evaluated mitoxantrone in the setting of autologous marrow reinfusion. Shea et al. (51) have evaluated escalated-dose mitoxantrone in addition to high-dose i.p. carboplatin and i.v. thiotepa and etoposide. The dose of mitoxantrone used was 42 mg/m². The Southwest Oncology Group is currently evaluating mitoxantrone at a dose of 75 mg/m² in a Phase II study of high-dose chemotherapy with marrow support for patients with advanced ovarian cancer. Mulder et al. (52) combined either cyclophosphamide or melphalan with high-dose mitoxantrone and obtained a 66% clinical complete response rate.

Many other single-course dose-escalated combinations have been tested against advanced ovarian carcinoma. Legros et al. (53) evaluated the long-term results achieved with high-dose chemotherapy and autologous bone marrow transplants in 31 patients. All patients had received induction therapy with a cisplatin-containing regimen followed by debulking surgery and consolidation with high-dose chemotherapy with autologous bone marrow support. Patients received either high-dose melphalan (140 mg/m²) or a combination of carboplatin (1000–1500 mg/m²) with cyclophosphamide (6 g/m²). With a median follow-up of 52 months, 18 of 31 patients were alive; 11 were free of disease. Overall disease-free survival at 3 years was 35%. Stiff et al. (54) published a survey of 11 autologous bone marrow transplant centers in the United States. The overall response rate was 71%, with a 43% clinical complete response rate. Thus far however, there remains little evidence that these high-response rates translate into superior survival or improved quality of life in patients with this disease. An ongoing randomized study by the South-West Oncology Group is evaluating two different high-dose chemotherapy regimens with autologous bone marrow support in patients with either progressive disease, responding but persistent disease (residual disease at second-look of >5 mm in diameter), or disease recurrent after platinum-based therapy. Patients are treated with either high-dose cyclophosphamide, mitoxantrone, and carboplatin or high-dose thiotepa, cyclophosphamide, and cisplatin. In both cases hematological support is being provided by autologous bone marrow reinfusion.

However, the inability of single courses of high-dose chemotherapy to cure most patients with advanced "solid" tumors should not be regarded as evidence against the potential value of dose escalation. Given the value of multiple cycle regimens, we are left with the important question of how to design such treatments. Is dose escalation the key feature of multicycle therapies, even if we must compromise the rapidity with which such chemotherapy can be recycled? That is, if it takes many weeks for a patient to recover from a high-dose exposure, is this still preferable to lower doses given more frequently? If we have more agents than can be delivered concurrently, how should we combine their combinations to achieve optimal cancer cell kill?

Dose-Escalation (with Hematopoietic Support)

One of the most important developments in modern medical oncology has been in the technology of hematopoietic support. G-CSF and GM-CSF accelerate leukocyte recovery following chemotherapy, resulting in the amelioration of associated morbidity (55, 56). These observations have prompted extensive investigations of these agents as facilitators of dose escalation (57). A general result has been a substantial reduction in the need for attenuations of dose in conventional combination regimens. However, major dose escalations of single courses have proven to be more difficult to achieve.

For many other chemotherapy agents, hematopoietic cytokines have provided even less protection from myelosuppression. A reason is that both G-CSF and GM-CSF are active primarily in leukocyte pathways. While some accelerated platelet recovery has been reported, this has not been a consistent finding (58). For example, an attempt to escalate the dose of thiotepa by the administration of GM-CSF was not successful because of thrombocytopenia (59). Thrombocytopenia and cumulative myelosuppression have also limited dose-escalation strategies for carboplatin.

High-dose chemotherapy to a degree requiring autologous bone marrow reinfusion has been able to produce a very high rate of overall and complete response in patients with a variety of tumors such as lymphoma, breast cancer, and germ-cell cancers. The use of marrow-supported high-dose chemotherapy has produced long-term disease-free survivals, which for practical purposes may be tantamount to cure, for patients with lymphomas (60) and germ-cell cancers (61) who have had diseases refractory to standard-dose therapy. Some regimens have used high doses of the single agents melphalan, cyclophosphamide, and thiotepa (62–64). Because of its limited nonhematological toxicity, thiotepa has particular potential for dose escalation. A Phase I study published in 1992 recommended that 75 mg/m² be considered the Phase II dose, but the dose of 30 mg/m² had been in use for decades (59). High-dose thiotepa with autologous marrow rescue has produced response and survival data similar to those reported for combination regimens (65). Above a dose of approximately 700 mg/m² mucosal toxicity becomes prominent (66), and doses above 1200 mg/m² produce neurological toxicity in approximately 10% of patients.

Exploiting the idea of multicycle regimens, some investigators have used induction chemotherapy at conventional dose levels followed by a single course of high-dose combination chemotherapy with autologous bone marrow rescue. Others
have tried to use repeated cycles of high-dose chemotherapy. At the M.D. Anderson Hospital interesting results were achieved with double applications of such high-dose chemotherapy (37). However, toxicity necessitated substantial intertreatment delays averaging 6–8 weeks.

**Dose Escalation (Progenitor Cell Supported)**

A more recent application of the CSFs is in the mobilization of hematopoietic progenitor cells, which may then be collected from the peripheral blood. The use of progenitor cell infusions could potentially allow for abbreviated intertreatment intervals due to more rapid hematological recovery. Investigators at the Dana-Farber Cancer Institute reported that the administration of GM-CSF to cancer patients enriched the pool of PBPC (67). An increase in peripheral progenitors was also noted during the recovery phase from myelosuppressive chemotherapy. Administration of hematopoietic growth factor during the recovery phase markedly augmented the effect. Gianni et al. (68), Peters et al. (69), and others subsequently found that these PBPC, when reinfused simultaneously with autologous marrow, accelerated hematological, especially platelet, recovery from high-dose chemotherapy. This resulted in decreased morbidity and mortality. The combination of cyclophosphamide and CSF increases the peripheral blood colony-forming unit count by up to a 1000-fold (65). Similarly, the addition of escalated doses of paclitaxel to cyclophosphamide has been shown not to compromise, and perhaps augment, the progenitor cell yield (70). Gianni et al. (68) have also reported that a sequence of high-dose single agents could be delivered, with PBPC plus CSF after the last high-dose course, and that this therapy seems promising in the treatment of lymphoma (69) and in breast cancer (63).

At Memorial Sloan-Kettering Cancer Center, we have pursued an aggressive approach to the management of newly diagnosed ovarian cancer. In this regard, we have assessed the feasibility of administering rapidly sequenced high-dose chemotherapy regimens availing of cytokine and peripheral blood progenitor cell support (Fig. 1). We conducted an initial trial in which patients with advanced ovarian cancers received two to three cycles of cyclophosphamide (3000 mg/m²) plus G-CSF for mobilization of PBPC followed by a course of escalating doses of carboplatin (500–1200 mg/m²) with PBPC plus G-CSF for hematological rescue. The median intertreatment interval for cyclophosphamide courses was 14 days, between carboplatin treatments 15 days. This trial established the feasibility of rapidly sequenced high-dose chemotherapy and the efficacy of chemotherapy plus cytokine mobilization of PBPC, and enabled us to develop a reliable threshold number of CD34+ PBPC to support cycles of high-dose chemotherapy. We reached a maximum tolerated dose of 1000 mg/m², with ototoxicity being dose limiting at a carboplatin dose of 1200 mg/m². We have recently completed a Phase I dose-escalation study of taxol administered with high-dose cyclophosphamide. Patients received two cycles of high-dose cyclophosphamide (3 g/m²) with escalating doses of paclitaxel from 150 to 200, 250, and eventually 300 mg/m² as a 24-h continuous infusion. This was followed by four cycles of a combination of carboplatin (1000 mg/m²) plus cyclophosphamide (1.5 g/m²). We demonstrated the feasibility of administering taxol (300 mg/m²) with high-dose cyclophosphamide as induction therapy. Additionally, we identified taxol as an agent which did not compromise the progenitor cell yield following high-dose cyclophosphamide (71). We are currently addressing in a Phase I study high-dose cyclophosphamide (3 g/m²), paclitaxel (300 mg/m²), followed by four cycles of carboplatin (1000 mg/m²) plus an escalating dose of paclitaxel from 150 to 200, 250, and 300 mg/m².

This approach is not unique, and Shea et al. (72) have also demonstrated the feasibility of a strategy of sequential leukapheresis and reinfusion of peripheral blood progenitors to support patients through three courses of carboplatin at a dose of 1200 mg/m². Similarly, investigators at the Dana-Farber Cancer Institute treated patients with a single course of high-dose cyclophosphamide (4.0 g/m²) plus G-CSF and multiple leukapheresis, followed by four courses of cyclophosphamide (600 mg/m², a standard dose) plus carboplatin (600 mg/m², approximately 50% higher than standard dose), supported by the previously collected PBPC (73). These investigators have shown that PBPC plus GM-CSF leads to faster hematological recovery than GM-CSF alone (73).

**Discussion**

We can at this early stage of clinical development draw a few conclusions from the available published data. The inability of chemotherapy to eradicate tumors is in general related to the emergence of drug resistance. This drug resistance appears to be relative, in that by increasing the dose of drug delivered, more cancer cells are often killed. Single courses of high-dose chemotherapy, such as those rescued with autologous bone marrow reinfusions, have achieved high rates of response in patients whose cancers grew in spite of conventional chemotherapy. These responses however are frequently of short duration. However, the use of hematopoietic progenitor cells plus G-CSF has enabled us to deliver repeated cycles of high-dose chemotherapy at short intertreatment intervals. On the basis of our experience with curative standard chemotherapy for Hodgkin’s and other diseases, we might expect that repeated application of regimens capable of producing such high response rates will improve long-term survival. It is clear that the approach of delivering repeated cycles of high-dose chemotherapy utilizing cytokine...
and peripheral blood progenitor cell support is practicable and safe.

With regard to the published data available addressing the issue of “dose intensity,” much of this data addresses dose intensities which, on the basis of in vitro studies, would appear to be clinically insignificant. It remains to be determined whether the application of repeated high-dose regimens, by achieving the required dose intensity as predicted by in vitro models, will result in improvement in overall response rates and ultimately improved survival for this group of patients with poor prognosis ovarian cancer.

References


Dose intensity in advanced ovarian cancer: have we answered the question?

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