Role of Chemotherapy Dose Intensification in the Treatment of Advanced Ovarian Cancer

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Cisplatin (Platinol) has been the most active agent against ovarian cancer. The question of a relationship between platinum dose and response remains unresolved.

Introduction

Despite the advances made in the treatment of advanced ovarian cancer, the prognosis for patients with advanced disease remains disappointing, with reported 5-year survival rates of 21% [1]. Patients with ovarian cancer demonstrate high response rates and occasional cures but frequent relapses. One method of improving the curative potential of primary therapy may involve the intensification of drug dosage.

Retrospective Analyses

In their original retrospective analysis, Levin and Hryniuk explored the role of dose intensity in the treatment of advanced ovarian cancer [2]. They were able to demonstrate a statistically significant correlation between increasing the dose intensity (defined as the amount of drug delivered per unit of time [mg/m²/week]) of cisplatin and both the response rate and overall survival [2]. Analysis of the dose intensity of other drugs, such as cyclophosphamide (Cytoxan, Neosar) and doxorubicin failed to reveal a significant correlation between increasing the dose intensity and overall response. This retrospective analysis was based primarily on published trials involving mainly patients with suboptimally debulked stage III and IV disease, with nearly 90% of patients having residual disease of more than 2 cm. In this meta-analysis, the "standard" regimen employed a cisplatin dose equivalent to 15 mg/m²/week. Thus, the demonstrated dose-response relationship holds true over a range of 6 to 12 mg/m²/week. This is equivalent to a total dose of approximately 36 mg/m² over 3 weeks and thus is lower than the commonly employed "low-dose" cisplatin regimen of 50 mg/m² every 3 weeks. This analysis appears to provide support for optimal versus suboptimal dosing as opposed to high versus standard dosing of cisplatin.

A recent updated analysis of their findings has been published [3]. They analyzed data from a total of 18 platinum-containing regimens used in 9 randomized trials in addition to data from the 60 groups of patients analyzed in the previous study. This analysis confirmed that the association between outcome and dose intensity was statistically significant for both cisplatin alone and cisplatin in combination-therapy regimens. The association for cyclophosphamide as a single agent was of borderline significance ($P = 0.06$). For doxorubicin, when used in combination therapy regimens, the association was again of borderline significance; however, there were insufficient data to assess doxorubicin's effect as a single agent. Additionally, it was recognized that in all of the combination regimens evaluated, doxorubicin was used at a relative dose intensity of 10 to 15 mg/m²/week, which is lower than the 25 mg/m²/week recommended for its use as a single agent.

Randomized Trials

The debate as to the true value of dose-intensive therapy continues to be hotly contested. We now have data from a number of randomized trials addressing the issue of dose intensity (Table 1) [4-11]. However, they have served to cloud the issue further.

In a study by Kaye et al [4], at 18 months, a significant survival advantage of 73% vs 48% was noted in favor of the high-dose arm. This resulted in early discontinuance of the study. Patients on the high-dose arm of this study 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 (600 mg/m² vs 300 mg/m²) [3]. Analysis of this study is complicated further by the fact that 30% of the patients...
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Intraperitoneal Therapy--clinically significant. Despite a number of other randomized trials now reported in the literature (Table 1), an overview of these trials fails to determine the true value of dose intensity in the treatment of advanced ovarian cancer. From these studies, however, some important points can be made. Studies focusing on patients with suboptimally debulked (more than 1 cm residual) disease have consistently reported negative results in terms of statistically significant improvement in response rates and overall survival [5,11]. Furthermore, studies focusing on patients with optimally debulked disease have reported positive end points in terms of both response and overall survival. In three of the studies mentioned, the more dose-intensive treatment arm received fewer overall cycles of chemotherapy [5,9,10]. The studies that employed this design were reported to be negative, and none of the "positive" studies employed this treatment design. The studies resulting in positive outcomes focused on not only increased total dose but also increased dose intensity, indicating that both factors are of importance.

Dose-Intensive Platinum Therapy--In none of the randomized studies reported did patients receive true high-dose chemotherapy. An important feature of dose intensity is the degree of dose intensification required to obtain a clinical effect. In the analysis by Levin and colleagues, the dose intensity achieved ranged from 0.3 to 1.1 [3]. If it is true that the benefit of dose-intensive therapy lies in its ability to overcome relative drug resistance, the in vitro models available suggest that a more than fivefold increase in dose intensity would be required to overcome this resistance [12]. Based on the initial work of Levin and associates, the focus of strategies to improve dose intensity has been consistently on platinum delivery. It is accepted that by increasing the dose of platinum delivered, responses can be obtained in tumors previously refractory to platinum therapy (Table 2) [13-17]. With the advent of carboplatin (Paraplatin), a platinum analog with a more benign toxicity profile, investigators' attention turned to attempts to increase the dose intensity of platinum using carboplatin.

Methods of Achieving Increased Dose Intensity

Among the methods of increasing dose intensity are combination platinum therapies, intraperitoneal therapy, high-dose chemotherapy with autologous bone marrow transplantation, and autologous peripheral stem cell-supported high-dose therapy.

Combination Platinum Therapies--One method of increasing the dose of platinum delivered is to combine cisplatin with other platinum analogs. This is a feasible approach because both cisplatin and carboplatin have demonstrated similar efficacy in the treatment of advanced ovarian cancer; furthermore, they have nonoverlapping toxicities, and this may allow full dosage of both platinum analogs to be administered with acceptable toxicity. A number of investigators have evaluated the role of this approach in ovarian cancer (Table 3) [18-20]. Lund et al initially reported on a phase II study combining carboplatin and cisplatin performed by the Copenhagen Ovarian Cancer Study Group [18]. Using a carboplatin dose of 300 mg/m² with cisplatin (100 mg/m² every 4 weeks), they reported an overall pathologic response rate of 62%, with a pathologic complete response rate of 22% [18]. In a subsequent study, they reported on a regimen combining cisplatin and carboplatin with ifosfamide (Ifex) in 37 previously untreated patients [19]. Carboplatin (200 mg/m²) was given on day 1, cisplatin (50 mg/m²) on days 2 and 3, and ifosfamide (1,500 mg) with mesna on days 1 to 3. More than 80% of patients in this study had residual disease equal to or greater than 2 cm. The reported pathologic complete response rate was an impressive 42%. Additionally, it was reported that of the patients with a pathologic complete response rate, 53% initially had residual disease equal to or greater than 5 cm [19]. Despite a number of combined platinum studies reported [21-25], the dose intensities in these studies did not exceed 63 mg/m²/week. Additionally, frequent dose reductions were necessary due to myelotoxicity, and, thus, the delivered platinum dose intensity was significantly lower. With the dose intensity being lower than twice that achieved with standard therapy, it is unlikely to prove to be clinically significant.

Intraperitoneal Therapy--The pharmacologic basis for intraperitoneal therapy is well described
Based on the difference between the plasma and peritoneal clearance rates of anti-neoplastic agents and the resultant differences in drug concentrations in these two compartments, intraperitoneal chemotherapy is potentially beneficial when tumor is confined to the peritoneal cavity.

Cisplatin, a drug with high plasma clearance and low peritoneal clearance, is an agent well suited to intraperitoneal administration. These pharmacokinetics result in increased drug delivery to the tumor with increased tumor exposure and decreased systemic toxicity. Additionally, it is recognized that optimal responses to intraperitoneal therapy require minimal volume disease, usually less than 1 cm. Delivered by the intraperitoneal route, cisplatin has demonstrated efficacy as salvage therapy for patients with small-volume residual ovarian disease (largest tumor mass, equal to or less than 0.5 to 1 cm in diameter), whether administered as a single agent or in several cisplatin-based combination regimens [28]. In a retrospective review of the Memorial Sloan-Kettering Cancer Center experience with salvage cisplatin-based intraperitoneal therapy in patients with ovarian cancer, 42% (15/36) of patients who had previously responded to a systemic platinum regimen and who started the second-line program with small-volume residual disease achieved a surgically defined complete response [29]. In contrast, among 14 patients with small-volume disease who had previously failed to demonstrate a response to systemic platinum, the surgically defined complete response rate was only 7% (P less than 0.025). In individuals whose largest mass was greater than 1 cm at the initiation of cisplatin-based intraperitoneal therapy, the surgical complete response rate was 10%, even if the patient previously had demonstrated an objective response to systemic platinum.

Data on intraperitoneal therapy as "consolidation" for patients who achieve a pathologic complete response to platinum-based front-line therapy have been encouraging. However, it remains to be determined whether intraperitoneal drug administration offers any advantage over systemic drug administration. Alberts and colleagues recently have reported on the use of intraperitoneal cisplatin in the front-line management of patients with optimally debulked ovarian cancer [30]. Patients were randomized to receive either intravenous cyclophosphamide (600 mg/m²)/cisplatin (100 mg/m²) or intraperitoneal cisplatin (100 mg/m²) with intravenous cyclophosphamide (600 mg/m²). A total of 654 patients were randomized, of whom 539 were eligible. A benefit in terms of overall survival was noted in favor of the intraperitoneal arm, with a median survival of 49 months vs 41 months for the intravenous arm (P = 0.03). Use of the intraperitoneal cisplatin-containing arm resulted in a 24% reduction in the risk of death [30]. Clinical hearing loss and neutropenia were more significant in the intravenous arm.

**High-Dose chemotherapy with autologous bone marrow transplantation** has been demonstrated to be capable of achieving high rates of response in patients in whom conventional treatment regimens failed. It is an area of considerable interest in the treatment of advanced ovarian cancer for a number of reasons. First, ovarian cancer is a tumor with demonstrated chemosensitivity. Second, patients failing conventional therapy have a universally poor prognosis. Finally, dose-response relationships have been demonstrated for both platinum compounds and alkylating agents in general [31]. Doses of active agents in ovarian cancer, such as melphalan (Alkeran), cyclophosphamide, and thiotepa (Thiotepa), can be escalated substantially with the use of autologous bone marrow support [32,33].

Using high-dose melphalan in patients in whom prior cisplatin therapy failed, Dauplat et al [34] obtained a 2-year disease-free survival rate of 36%. Viens et al recently reported on the use of high-dose chemotherapy (melphalan, cyclophosphamide, carboplatin, etoposide (VePesid), and thiotepa) in patients following initial cisplatin-based therapy. Although follow-up is short, the 3-year actuarial progression-free and overall survival rates are 52.5% and 72.5%, respectively [35]. Legros and colleagues reported on a group of patients with stage III and IV ovarian cancer receiving either high-dose melphalan or carboplatin with cyclophosphamide [36]. A total of 31 patients were included, all of whom had received prior platinum-based chemotherapy. With a median follow-up of 52 months, 18 of 31 patients were alive, with 11 free of disease [36]. In a phase I setting, Shpall and associates evaluated the combination of high-dose cyclophosphamide, thiotepa, and cisplatin followed by autologous bone marrow support in patients with advanced ovarian cancer and reported an overall response rate of 75%; all patients had progressive disease on platinum-based therapy [37].

Based on the demonstrated activity of doxorubicin in advanced ovarian cancer and the limited potential for dose escalation, investigators have turned to mitoxantrone (Novantrone). Mitoxantrone, an anthrancene derivative is quite different from the drugs usually considered for dose escalation. It is cytotoxic to proliferating and nonproliferating cells in vitro [38,39]. It appears to have both an intercalative and nonintercalative effect on DNA [40,41]. Mitoxantrone has proven attractive...
due to its activity as a single agent and to the fact that it is significantly easier to dose escalate than doxorubicin [42].

Shea et al have evaluated an escalated dose of mitoxantrone (42 mg/m²) given with high-dose intraperitoneal carboplatin and intravenous thiota and etoposide, demonstrating an overall clinical response rate of 84% [43]. Mulder and associates combined either cyclophosphamide or melphalan with high-dose mitoxantrone and obtained a complete response rate of 66% [44]. The results with high-dose chemotherapy thus far have both promising and yet disappointing (Table 4). It is clear that high overall response rates can be achieved. The duration of these responses, however, remains short, and a benefit in terms of overall survival has yet to be demonstrated.

In a survey of autologous bone marrow transplantation centers in the United States, Stiff and colleagues reported on data collected from 11 centers [45]. The survey included 153 patients, of whom 95% with relapsed or refractory disease underwent transplantation. Only 5% of patients underwent transplantation during their first remission. The survey identified 20 different bone marrow transplant preparation regimens. The overall response rate was 71%, with a complete response rate of 43%. In patients with platinum-sensitive disease by conventional criteria, the overall response rate was 87%, with a clinical complete response rate of 73%. In patients with documented platinum-resistant disease, the overall response rate was 85%, with a clinical complete response rate of 34%. The median time to progression was 6 months, with 14% of patients free of disease at 1 year (Table 5).

**High-Dose Chemotherapy with Autologous Peripheral Stem Cell Support**—Much of the currently available data on tumor growth kinetics are derived from work in the area of breast cancer. The application of these mathematical tumor kinetics models to ovarian cancer favors the administration of multiple cycles of high-dose chemotherapy with short, intertreatment intervals; the accelerated regrowth that would be predicted to follow a massive, but nonradicative, cell-kill would undermine much of the advantage of this retreatment if the interval between courses was delayed due to toxicity [46]. It has become clear that the chemotherapy dose level and dose intensity are critical factors in response and response duration in patients with ovarian cancer. The effect of high-dose levels in achieving higher response rates may be based on the observation that much drug resistance is relative, rather than absolute. Relative drug resistance depends upon the dose level employed. In the preponderance of animal experiments, log-kill is greater when the dose level is greater. It is possible, therefore, that clinical results could be improved by increasing the dose intensity of chemotherapy while shortening the time of administration.

**Multiple High-Dose Courses at Short Intervals**—Joddrell and colleagues analyzed in a retrospective fashion the relationship between total carboplatin exposure (AUC [area under the curve] mg/mL/minute) and ultimate outcome [47]. 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 value of 6 mg/mL/minute and that increasing the dose of platinum resulted in increased toxicity without improvement in response rates. In their analysis, only the first cycle AUCs were used to predict ultimate outcome. It is likely 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.

**Use of Peripheral Blood Progenitor Cells**—Based on the previous hypotheses, our group at Memorial Sloan-Kettering Cancer Center have studied peripheral blood progenitor (PBP) cell-supported, multicycle, high-dose chemotherapy, administered at abbreviated intertreatment intervals. Our initial studies addressed patients with advanced ovarian and other cancers. An induction-mobilization regimen of 2 to 3 courses of cyclophosphamide (3.0 gm/m²) plus granulocyte colony-stimulating factor (G-CSF) was used. Patients then underwent multiple peripheral blood leukapheresis. They subsequently were treated with a sequence of 4 courses of high-dose carboplatin (500 to 1,200 mg/m², with no intrapatient dose escalation) rescued with PBPs. The planned intertreatment interval was 14 days. A maximum tolerated dose of carboplatin (1,000 mg/m²) was defined [48], with ototoxicity being dose-limiting at a carboplatin dose of 1,200 mg/m². The median interval between carboplatin treatments was 15 (range 12 to 30) days. The median dose intensity of carboplatin achieved at the final dose level was 468 mg/m²/week, which compared with a dose intensity of 75 mg/m²/week on a standard regimen. Among 27 patients with ovarian cancer evaluable for response, the overall response rate was 77% (21/27), with 5 patients achieving a pathologic complete response. At the final dose level of carboplatin (1,000 mg/m²) with cyclophosphamide (1.5 gm/m²), a total of 10 patients were entered. The overall response rate was
70% (7/10), with 3 patients achieving a pathologic complete response (Table 6).

With the recognition of the activity of paclitaxel (Taxol) in advanced ovarian cancer, we initiated a phase-I evaluation of an escalating dose of paclitaxel (150 to 300 mg/m²) as a 24-hour continuous infusion with high-dose cyclophosphamide (3 gm/m²) followed by 4 cycles of carboplatin (1,000 mg/m²) plus cyclophosphamide (1.5 gm/m²; Table 7). We demonstrated that cyclophosphamide (3 gm/m²) could be given with paclitaxel(300 mg/m²) with an intertreatment interval of 14 days. The incorporation of paclitaxel into an induction chemotherapy regimen did not compromise the PBP cell yield. A total of 16 patients were enrolled in this study, with 62.5% of patients having suboptimally debulked disease. A total of 13 patients were evaluable for response, and the overall response rate was 100% (13/13), with 5 patients achieving a pathologic complete response [49].

At Memorial Sloan-Kettering Cancer Center, we have now rescued more than 100 courses of high-dose chemotherapy with PBPs without autologous bone marrow support. In only two instances has reinfusion of backup marrow been necessary, and in both cases, the CD34 count was less than 0.4 x 106 cells/kg.

A number of other investigators have explored the role of PBP cells in the delivery of repetitive cycles of high-dose chemotherapy. In prior studies, the substantial toxicity of high-dose chemotherapy has complicated attempts at timely retreatment. However, through the use of PBP cells, this has now proven to be an attainable goal.

Shea and colleagues demonstrated the feasibility of a strategy of sequential leukapheresis and reinfusion of PBP cells to support patients through 3 courses of carboplatin, at a dose of 1,200 mg/m² [50]. More recently, these same investigators have reported on a phase I study of carboplatin and paclitaxel rescued with PBP cells. The carboplatin dose was based on the calculated AUC value, and a phase-II dose of paclitaxel (250 mg/m²) with carboplatin (AUC 18 mg/mL/minute) every 21 days was established. Major responses were seen in 58% of patients, including 6 of 7 patients with non-small-cell lung cancer [51].

Investigators at the Dana Farber Cancer Institute treated patients with a single course of high-dose cyclophosphamide (4.0 gm/m²) plus GCSF and multiple leukapheresis; this regimen was followed by 4 courses of cyclophosphamide (600 mg/m², a standard dose) plus carboplatin (600 mg/m², approximately 50% higher than a standard dose) and was supported by the previously pheresed PBP cells. The first carboplatin/cyclophosphamide course was rescued with granulocyte-macrophage colony-stimulating factor (GM-CSF), and the subsequent courses were rescued with PBP cells and GM-CSF. Recovery was significantly faster for patients who underwent PBP-rescued courses [52].

Treatment Implications

It is clear that dose intensity has an important role to play in the treatment of advanced ovarian cancer. However, the current generation of randomized trials has focused on dose intensities ranging from 1.3- to 2-fold standard dose intensity. If, as stated previously, it is true that the benefit of dose-intensive therapy lies in its ability to overcome relative drug resistance, the in-vitro models available suggest that a more than fivefold increase in dose intensity would be required to overcome this resistance [4]. The dose intensities evaluated thus far in the setting of randomized trials are unlikely to be of clinical significance, a fact that is borne out by analysis of the published results. We can, however, draw a number of conclusions from the available published data. The inability of chemotherapy to eradicate tumor in general appears to be related to the emergence of drug resistance. This drug resistance seems to be relative resistance, because it has been demonstrated that by increasing the dose of drug delivered, this resistance can be overcome.

Single-course, high-dose chemotherapy rescued with autologous bone marrow has been demonstrated to be capable of achieving high rates of response in patients in whom conventional chemotherapy failed. These responses, however, are frequently of short duration.

Curative chemotherapy requires the application of repeated doses of a chemotherapy regimen capable of achieving high rates of response. For Hodgkin’s disease, MOPP (mechlorethamine, Oncovin, vincristine, procarbazine, and prednisone) chemotherapy is curative in approximately 50% of patients with advanced disease. The median time to the attainment of complete remission is three months, which is equivalent to the time to complete remission with three cycles of therapy. Thus, few, if any, patients would have been cured had treatment consisted of only one course of this combination.

For patients with testicular cancer, four courses of cisplatin and etoposide have been curative in the majority of patients [53], although it also has been demonstrated that three courses of this two drug regimen produced inferior results when compared with historic controls [54]. Furthermore, poor
results have been documented for patients receiving a single cycle of cisplatin-based therapy [55-57].

The use of PBP cell technology has enabled us to deliver repeated cycles of high-dose chemotherapy at short, intertreatment intervals. The single application of these high-dose chemotherapy treatments has resulted in impressive response rates. Based on the knowledge developed with regard to standard chemotherapy, it would follow that repeated application of these regimens will be required to improve long-term survival, the ultimate goal of chemotherapy.

The critical issue that remains is to identify the patient population who will derive maximal benefit from this approach. To define the true efficacy of this approach in patients with ovarian cancer, it will be necessary to apply it as first-line therapy in newly diagnosed patients.

The bulk of residual disease appears to be a significant predictive factor with respect to the effect of dose intensity. It has been demonstrated that increased dose intensity correlates with both increased response rates and improved survival in a patient population with minimal residual disease. It is likely that the bulk of disease influences the outcome with regard to dose-intensive therapy as much as it does with conventional chemotherapy. These factors may help us to identify a patient population who will derive the maximal benefit from this aggressive approach.

**Conclusions**

Based on the tumor kinetic models available and our knowledge of conventional chemotherapy, further studies must address the role and comparative efficacy of single vs repetitive applications of high-dose chemotherapy. Additionally, we must identify the patient population who will derive the maximal benefit from this promising, but still investigational, approach.

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