High-Dose Therapy for Ovarian Carcinoma

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Abstract

Epithelial ovarian carcinomas are successfully treated but seldom cured with standard platinum-based chemotherapy regimens. Investigation continues on the role of high-dose chemotherapy as part of salvage, consolidation and primary induction therapy strategies. Currently, the majority of available clinical studies suggest that modest increases in the dose of platinum in primary induction therapy do not translate into increased survival and come at the cost of increased toxicity. Interest continues in the use of very high-dose chemotherapy regimens typically with peripheral blood stem cell or bone marrow transplantation. Several series have demonstrated that this approach can provide prolonged disease-free survival in a subset of carefully selected patients with low-volume chemotherapy-sensitive disease. The appropriate application of this expensive and potentially toxic treatment to women with ovarian cancer requires further clinical investigation. The Oncologist 1997;2:330-339

Introduction

Ovarian carcinoma is the fifth leading cause of cancer death among women, with an estimated 26,800 new cases in 1997 and 14,200 deaths [1]. At the time of diagnosis, the majority of women have advanced disease with tumor involving the ovaries as well as the peritoneal surfaces or retroperitoneal lymph nodes (stage III). Even more advanced metastatic disease, often to the pleura or peritoneal surfaces (stage IV), is seen in a significant proportion of women [2]. Since the late 1970s the standard treatment has been the combination of aggressive debulking surgery followed by multiagent chemotherapy [3]. Support for this two-stage approach is derived from a collection of retrospective studies, and, to a lesser extent, prospective trials that demonstrate improved survival in women whose surgery has successfully reduced their residual tumor to <0.5 cm. Indeed, median survival is 40 months in women with optimal (<0.5 cm) cytoreduction as opposed to 18 months in the women who have less complete cytoreduction and hence greater tumor burden at the conclusion of surgery (>2.0 cm) [4].

Debulking surgery is generally followed by chemotherapy. In the last 20 years, chemotherapy programs have evolved from single alkylating agents, such as melphalan, to multiagent combination chemotherapy. Most of these combinations have included cisplatin, after its demonstrated activity as both a single agent and in combination with other active chemotherapeutic drugs. Comparison of several combination chemotherapy trials reproducibly demonstrates that platinum-containing regimens lead to higher response rates and superior survival as compared to non-platinum-containing regimens [5-8]. Newer regimens have replaced cisplatin with carboplatin, a second platinum analog that demonstrates less gastrointestinal and neurologic toxicity than cisplatin. Preliminary reports from several trials have suggested essentially equivalent activity of cisplatin- and carboplatin-based chemotherapy regimens [9-11].

Taxol was introduced in the treatment of ovarian carcinoma in the late 1980s, with initial studies demonstrating a 24% response rate in women with platinum-resistant ovarian cancer [12]. Subsequent studies involving 1,000 women with recurrent ovarian cancer confirmed a response rate of 22% with very acceptable toxicity [13]. Establishment of this novel agent in the treatment of women with newly diagnosed disease came with the completion of GOG 111, a randomized Gynecologic Oncology Group (GOG) study comparing cisplatin with carboplatin to Taxol. Women receiving the combination of Taxol with cisplatin had significantly higher response rates (73% versus 60%), longer progression-free survival (18 versus 13 months), and, most importantly, overall survival (38 versus 24 months) as compared to the cyclophosphamide-cisplatin arm [14]. This regimen has been delivered with acceptable toxicity and now defines the standard treatment for advanced ovarian cancer in the United States; all new therapies will need to be compared to this regimen.

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Despite the progress in identifying more potent chemotherapy combinations, the most efficacious regimens still achieve remission in only 50% of women. Only half of these patients (25% of total group) will have a pathologic complete remission (pCR) as defined by second-look laparotomy [4]. Although patients with pCR comprise the most favorable prognostic group, they remain at risk for relapse, with only 20% of these patients achieving in excess of five years of disease-free survival [4]. Recurrent ovarian cancer is less responsive to secondary chemotherapy regimens than primary therapy. While some patients will enjoy effective palliation with salvage therapy, essentially all patients will eventually develop chemotherapy refractory disease, most within 15 months of first recurrence.

Chemotherapy Resistance in Ovarian Carcinoma

While several mechanisms of drug resistance have been identified, a complete understanding of drug resistance in ovarian cancer has not been elucidated. Currently, mechanisms involved in acquired resistance to platinum and Taxol are the most relevant in ovarian cancer. Key mechanisms in platinum resistance may include increased expression of many genes, including the error replication repair genes [15], intranuclear topoisomerase I and II [16], and possibly increases in intracellular reducing agents [17]. Taxol is a substrate for the multidrug resistance-I (MDR-I) protein (Pgp 170), and limited studies have demonstrated the upregulation of the MDR-I gene product in some Taxol-resistant ovarian tumors [18]. Changes in tubulin isomer ratios or point mutations in specific tubulin subtypes, presumably at regions critical for either Taxol binding or tubulin polymerization, may also produce significant resistance to Taxol secondary to a shift in the tubulin monomer-polymer equilibrium, favoring depolymerization or alternatively affecting the tubulin binding site [19, 20].

Attempts to reverse or enhance chemotherapy efficacy through first-generation MDR-I inhibitors [21] has had very limited success, although newer techniques using second-generation MDR-I inhibitors are currently in progress.

Dose-Intensive Therapy for Solid Tumors

There is evidence both from bedside and the laboratory that when solid tumors recur after an initial response to chemotherapy, they have acquired resistance to chemotherapy drugs [22, 23]. Clinical trials evaluating the efficacy of high-dose chemotherapy are based on preclinical models that demonstrate that resistance to alkylating agents can be overcome in the laboratory by using a five- to tenfold higher concentration of chemotherapy drug. In the clinic, these doses can now be achieved with the assistance of hematologic stem cell support: either bone marrow (BM), or, more recently, peripheral blood stem cells (PBSC).

Typically, these high-dose chemotherapy regimens are designed with drugs that: A) each have activity against a variety of malignancies; B) have nonoverlapping mechanisms of actions and acquired resistance, and C) have myelosuppression as a common toxicity, but otherwise have nonoverlapping toxicities [23]. Typically, alkylators such as melphalan, thiopeta, cyclophosphamide, and platinum have formed the backbone of such regimens.

Recently, autologous BM has been replaced by PBSC, which both simplifies harvest and accelerates engraftment [24]. Tumors that have been successfully treated with high-dose therapy and autologous hematopoietic stem cell support include lymphoma, testicular carcinoma, and also breast cancer. In patients with metastatic breast cancer, several phase II studies have shown high complete response rates, although durable remissions have been limited to 15%-20% of chemotherapy-responsive patients [25, 26]. In the solitary small randomized study reported to date, the group of patients with metastatic breast cancer who received high-dose therapy with stem cell rescue enjoyed a higher overall response, complete response, and survival than the women receiving “standard doses” [27]. While this randomized study demonstrated a statistically significant improvement in survival, the study was somewhat small (90 total patients), and the drugs in each regimen were not identical. Several large phase III studies are currently in progress to evaluate the role of stem cell-supported therapy in the treatment of women with metastatic breast cancer.

Ovarian cancer shares several characteristics with breast cancer and other malignancies that make it a suitable tumor for treatment with high-dose therapy in the setting of a clinical trial, specifically: A) it is sensitive to chemotherapy with high response rates to induction chemotherapy, and B) there are some cures with conventional dose therapy.

Dose Intensity in Ovarian Carcinoma

In 1987, Levin and Hryniuk retrospectively analyzed dose intensity in 33 chemotherapy trials (both platinum- and non-platinum-containing) for advanced ovarian carcinoma [28]. Dose intensity was defined as the amount of drug delivered divided by the time of administration. Using the CHAP regimen (cyclophosphamide, hexamethylmelamine, doxorubicin, and cisplatin) as the standard regimen, a cisplatin dose intensity of 15 mg/m\(^2\)/week was arbitrarily defined as a dose intensity of one. Their results, as well as additional results reported in 1993, indicated that the dose intensity of cisplatin correlates with both response and overall survival over a relative dose intensity range of 0.4-0.8 (6-12 mg/m\(^2\)/week). Of interest, no dose-intensity response relationship could be established for cyclophosphamide or doxorubicin [29].
While the Hryniuk analysis supported the notion that patients receiving therapeutic platinum dosing had better outcomes than patients receiving subtherapeutic drug doses, it is less clear whether supratherapeutic doses improve survival further. Several randomized studies have evaluated the importance of platinum dose intensity in ovarian cancer (Table 1). These studies have all involved slightly different designs but have used chemotherapy doses that are easily achievable without growth factor or stem cell support. Two studies have suggested that higher cisplatin doses translate into a survival advantage.

Kaye et al. [30]. (Scottish study) randomized patients with stage I-III ovarian cancer to receive cyclophosphamide 750 mg/m² with either 50 mg/m² or 100 mg/m² of cisplatin every three weeks for six cycles [30]. The patients in the high-dose arm received a 67% greater total dose of cisplatin. The median survival was 69 versus 114 weeks for the low- and high-dose groups, respectively. An updated report of the same study with longer follow-up demonstrates a trend toward similar survival, 29% versus 34% for the low and high-dose arms, respectively [31]. In the Hong Kong study, patients were randomized to receive cyclophosphamide and cisplatin every three weeks for six cycles [32]. The patients in the high-dose arm received a 61.10% greater total dose of cisplatin. The median survival was 24 versus 21 weeks for the low- and high-dose arms, respectively.

Conte et al. [34]. in Italy randomized patients with stages I-III and IV recurrent ovarian carcinoma to receive cisplatin 40 mg/m² and 80 mg/m² every six cycles [34]. The patients in the high-dose arm received a 62.20% greater total dose of cisplatin. The median survival was 24 versus 21 weeks for the low- and high-dose arms, respectively [35].

Jones et al. [36]. in England randomized patients with stages I-III and IV recurrent ovarian carcinoma to receive cisplatin 50 mg/m² and 100 mg/m² every four cycles [36]. The patients in the high-dose arm received a 57.60% greater total dose of cisplatin. The median survival was 24 versus 21 weeks for the low- and high-dose arms, respectively [37].

In Table 1, we can see that the studies have shown a trend toward similar survival, but the results are not statistically significant. The studies have been criticized for either unexpectedly poor survival in the low-dose group (particularly in the Scottish trial) as well as unclear selection process in the Hong Kong study. Finally, neither study is a pure dose-intensity study since patients enrolled on the high-dose arm not only had higher platinum dose intensity but also twice as much total platinum.

In contrast, several randomized studies fail to confirm a clinically meaningful survival advantage with dose-intensive platinum-based regimens (DI = 2-2.5). The GOG recently reported a trial randomizing patients between cyclophosphamide and cisplatin with a twofold difference in dose intensity but the same total dose (i.e., a pure dose-intensity study). The low-dose group received cyclophosphamide 500 mg/m² and cisplatin 50 mg/m² for eight cycles while the high-dose group received 1,000 mg/m² and 100 mg/m², respectively, for four cycles. No statistical difference was seen in the progression-free or overall survival in this large and well-performed study [33]. Three additional studies comparing normal with double-dose cisplatin [34-36] or carboplatin [37] have reported similar survivals in both treatment arms. In summary, at the dose intensity of approximately 2, these studies do not provide convincing evidence that modest to moderate increases in platinum dose intensity produce prolonged survival for patients with ovarian cancer.

In addition to cisplatin, Taxol is a drug with substantial activity in ovarian cancer. Taxol dose intensity in recurrent ovarian carcinoma has been studied and was recently reviewed by Reed et al. [38]. Review of several phase II trials using different doses of Taxol demonstrates that dose intensity ranged from 45 mg/m²/wk to 83.3 mg/m²/wk. In most of these studies, Taxol was given as a 24-h infusion, and in some studies, G-CSF was also given. Comparison of response rates seen in these trials suggests a relationship between Taxol dose intensity and disease response (doses of 45 mg/m²/wk, 58.3 mg/m²/wk, or 83 mg/m²/wk gave objective responses of 22%, 36%, and 48%, respectively). In a study at the National Cancer Institute (NCI), 48 patients with platinum-resistant recurrent ovarian cancer were given Taxol at 250 mg/m² every 21 days with G-CSF support [39]. Of 44 evaluable patients, there were 21 responses (48%), including survival.

### Table 1. Randomized trials of cisplatin dose intensity

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Patients</th>
<th>Response</th>
<th>Median survival (months)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaye [30]</td>
<td>1992</td>
<td>Scottish</td>
<td>159</td>
<td>61%</td>
<td>29</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34%</td>
<td>17</td>
<td>27%</td>
</tr>
<tr>
<td>Ngan [32]</td>
<td>1989</td>
<td>Hong Kong</td>
<td>50</td>
<td>55%</td>
<td>NA</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30%</td>
<td>NA</td>
<td>30%</td>
</tr>
<tr>
<td>McGuire [33]</td>
<td>1995</td>
<td>GOG</td>
<td>458</td>
<td>59%</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65%</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td>Conte [34]</td>
<td>1996</td>
<td>Italy</td>
<td>145</td>
<td>57.50%</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61.10%</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>Jones [37]</td>
<td>1992</td>
<td>England</td>
<td>72</td>
<td>69%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Colombo [36]</td>
<td>1993</td>
<td>Italy</td>
<td>296</td>
<td>61%</td>
<td>33</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>66%</td>
<td>36</td>
<td>NA</td>
</tr>
<tr>
<td>Ackerman [35]</td>
<td>1997</td>
<td>Germany</td>
<td>125</td>
<td>72%</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60%</td>
<td>12</td>
<td>25</td>
</tr>
</tbody>
</table>

AUC = area under the curve; Carbo = carboplatin; Cis = cisplatin; GOG = Gynecologic Oncology Group; OS = overall survival; NA = not available.
six patients with a complete clinical response. Despite the correlation with dose and response, there is no evidence that Taxol dose intensity affects survival.

Additional evidence for the possible role of Taxol dose intensity comes from another study from the NCI in which a higher dose of Taxol (250 mg/m²) was used in combination with cisplatin (75 mg/m²) and cyclophosphamide (750 mg/m²) with G-CSF support in a group of women with advanced-stage, suboptimally debulked disease. The pathologic response rate was 36%, with an additional 25% having minimal microscopic disease, and the overall response rate was 89%. The median progression-free and overall survival had not been reached at a median follow-up of 22 months [40]. These results support the incorporation of higher doses of Taxol in the initial treatment of ovarian carcinoma and suggest that it may be useful in very high-dose regimens that would require stem cell support. Confirmatory trials using this three-drug regimen are currently in progress.

**ST-cell-Supported Phase I Trials Including Ovarian Cancer Patients**

Several phase I studies evaluating high-dose multiagent chemotherapy included patients with refractory ovarian carcinoma [39-50]. Conclusions from these studies are limited by the small study sizes, heterogenous patient populations, and the wide variety of regimens used. Nevertheless, there were occasional pathologic complete responses seen in these studies, supporting the concept that high doses of chemotherapy can overcome platinum resistance in some tumors [41-52]. In 1984, Vriesendorp and colleagues reported on two patients with persistent ovarian cancer after conventional chemotherapy which contained cisplatin. The high-dose regimen consisted of high-dose cyclophosphamide and etoposide with autologous bone marrow rescue. At 10 months after the high-dose therapy, one patient was in clinical remission and the other in pathologic complete remission [44]. Stiff et al. reported on their experience with the combination of mitoxantrone/cyclophosphamide/carboplatin [51]. The maximum tolerated doses in this phase I study were 75 mg/m² for mitoxantrone, 120 mg/kg for cyclophosphamide and 1,500 mg/m² for carboplatin. There were seven patients with ovarian cancer, all refractory to platinum; six assessable patients responded (CR in five and partial remission [PR] in one). At the time of transplant, four patients had residual disease more than 3 cm. The median progression-free survival was eight months, and the median survival was 15 months. Included in the study was one woman who was free of disease 30 months post-transplant.

In summary, these studies demonstrate very high response rates (50%-70%) in patients with platinum refractory disease, although the duration of responses in all studies has been disappointingly short, measured in a few months (5-10), with only occasional long-term survivors (>30 months).

**Phase II High-Dose Chemotherapy Studies in Women with Ovarian Cancer**

Based on the results from phase I studies, various regimens have been studied for activity in phase II studies. There have only been about one dozen published phase II studies in ovarian cancer. These studies are limited by their small size and the frequent inclusion of heterogeneous populations.

**High-Dose Therapy in Refractory Disease**

Ovarian carcinoma which progresses during platinum therapy (absolutely platinum-refractory) or relapses within six months of completion of platinum (relatively or potentially platinum-refractory) carries a poor prognosis and a low response rate to chemotherapy. For instance, treatment with Taxol produces an overall response rate of 24%-30% in most trials, with complete response of up to 18% [53]. Progression-free survival (PFS) is relatively short (four to six months).

There have been at least six phase II studies that included patients with chemotherapy-refractory disease [49, 52-57]. The number of evaluable patients is quite small (no study had more than 20 refractory patients), but there were complete responses (12%-75%), most of which were not documented surgically. The median PFS in most studies is four to six months, although there have been occasional long term survivors at 30+ months.

Stiff and colleagues recently reported on their experience with high-dose therapy followed by autologous transplantation [55]. Treatment of 66 patients with platinum-refractory disease demonstrated a response rate in this group of 81% (50% CR and 31% PR). The median overall survival was 9.6 months (16 days to 49+ months), although the median PFS was only five months.

Viens and Maraninchi reported the Marseilles experience treating 27 patients with high-dose therapy as “salvage” treatment [56]. Of these 27 patients, 17 had primary refractory disease, while 10 patients had relapsed disease (six refractory and four sensitive relapses). Different conditioning regimens were used, with most patients receiving a melphalan-containing regimen. All the patients relapsed in a median of four months, and their median survival was 10 months.

Other investigators evaluated the efficacy of intraperitoneal therapy in conjunction with high-dose therapy. Shpall reported on the use of cyclophosphamide and thiotepa given intravenously, combined with intraperitoneal administration of cisplatin (120 mg/m²) [57]. Twelve patients with platinum-resistant disease were enrolled. Therapy was toxic, with three treatment deaths. Six of the eight evaluable patients had pathological partial responses. Only two of the eight patients were
alive at a median of 3.5 months; the others died of progressive disease at a median of nine months after the transplant.

These and other studies suggest that current high-dose chemotherapy with associated marrow support do not overcome clinically apparent drug resistance.

**High-Dose Therapy in Chemotherapy-Sensitive and Relapsed Ovarian Cancer**

The experience from breast cancer and lymphoma suggests that high-dose therapy and transplantation is more effective in patients who have chemotherapy-sensitive disease at the time of transplant [60, 61]. There have been only a few studies that have included patients who are in sensitive relapse of ovarian cancer (Table 2).

In the study by Stiff et al. [55], 34 patients with platinum-sensitive relapse were treated with high-doses of carboplatin, mitoxantrone, and Cytoxan, or, alternatively, thiotepa/mitoxantrone or carboplatin/thiotepa/cyclophosphamide followed by transplant. In this study, 94% of patients responded, with 88% of patients achieving a clinical CR. The median PFS was 10.1 months, and the median overall survival was 23.1 months. These results compare very favorably with the GOG study evaluating Taxol for relapsed disease [53]. In that study, among the subset of patients with platinum-sensitive disease, there was a 44% response rate, but the median PFS was only 4.9 months.

Multivariate analysis by Stiff and colleagues suggested that young patients in a surgically or chemotherapy-induced near remission with platinum sensitivity enjoyed the most favorable outcome, with a median survival of 30 months.

There is a need for more studies of patients with chemotherapy-sensitive recurrent disease with special attention to defining sensitive disease, the extent and prior response to platinum therapy, and the evaluation of response with objective criteria.

**High-Dose Therapy for Positive Second-Look Laparotomy**

High-dose chemotherapy has also been tried in patients who are found to have residual tumor during second-look laparotomy [57, 62, 63]. Survival after a positive second-look laparotomy is influenced by the extent of the disease after the laparotomy. Patients with microscopic disease enjoy significantly better survival than those with macroscopic disease (55% versus 19% four-year survival) [62, 63].

Dauplat reported on 14 patients who had a positive second-look laparotomy, most of whom initially presented with stage III disease [64]. Twelve patients went to high-dose therapy with minimal residual disease and two with a tumor nodule present in the pelvis. The high-dose regimen consisted of melphalan followed by bone marrow rescue. The mean follow-up after the second-look operation (SLO) was 43 months; five patients (35.7%) were still disease-free at 30 to 60 months after SLO without any further chemotherapy. Actuarial three-year survival was 64% and three-year disease-free survival was 33%.

In another study, Mulder and colleagues treated 11 patients with persistent disease at second-look laparotomy after induction therapy with cisplatin and cyclophosphamide [65]. Three patients had microscopic disease only, five had minimal disease (<2 cm), and three had bulky disease (two with masses over 7 cm not amenable to surgical debulking). The high-dose therapy consisted of cyclophosphamide and etoposide. Re-evaluating laparotomy/laparoscopy was performed in ten patients. Six out of 11 patients achieved CR (five having a pathologic CR, one a clinical CR). The median duration of CR was 15 months, with two patients having sustained CR at 43 and 75 months. All of the CRs were attained in patients with microscopic or minimal disease; those with macroscopic disease did not respond. This study, despite the small number of patients with minimal residual disease at second-look laparotomy, shows that a subset of patients may enjoy long disease-free intervals.

The French group has recently reviewed their experience with high-dose therapy in a group of 22 patients with macroscopically positive second-look procedures in which eighteen patients could be debulked to microscopic disease. This group received either high-dose melphalan or carboplatin

### Table 2. High-dose therapy in patients with sensitive disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Regimen</th>
<th>Patients</th>
<th>Evaluable for response</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotz [59]</td>
<td>1996</td>
<td>Ifosfamide Carboplatin VM-26 (tandem)</td>
<td>7</td>
<td>2</td>
<td>PR 2/2</td>
<td>NA</td>
</tr>
<tr>
<td>Stiff [55]*</td>
<td>1997</td>
<td>3 different regimens</td>
<td>34</td>
<td>NA</td>
<td>CR 88% PR 6%</td>
<td>PFS 12.2 mo. OS 23.1 mo.</td>
</tr>
</tbody>
</table>

*Also [51, 54].
with cyclophosphamide. This group had a median survival of 39 months with a five-year survival and disease-free survival of 34% and 19%, respectively.

These results demonstrate that a subset of patients with minimal disease (microscopic) can obtain long-term control with high-dose therapy. These results compare favorably with but are not clearly superior to conventional, second-line regimens such as Taxol, hexamethylmelamine, abdominal radiation, or intraperitoneal therapy. Finally, it is disappointing that two-thirds of patients with minimal disease at second-look surgery relapsed.

Upfront Transplant for Advanced Ovarian Carcinoma

The poor five-year survival for women with advanced-stage ovarian carcinoma has led to the use of high-dose therapy with hematologic stem cell support at initial diagnosis rather than on relapse (Table 3). There are several theoretical benefits to this approach as compared with the use of high-dose therapy at the time of recurrent disease [66-70]. These include less residual tumor, greater chemotherapy sensitivity, and better end organ function.

In the largest study, Benedetti and coworkers reported on 20 patients with stage III-IV ovarian carcinoma treated with up-front high-dose therapy [67]. All patients had >0.5 cm residual disease after initial debulking surgery, with 80% having 0.5-2 cm. The treatment consisted of induction chemotherapy with 40 mg/m² cisplatin from days 1 to 4 and 1,500 mg/m² cyclophosphamide on day 4. Interval surgery was performed in four patients. High-dose therapy consisted of 100 mg/m² cisplatin on day 1, 1,650 mg/m² etoposide on day 2, and 1,800 mg/m² carboplatin as a continuous infusion on day 3. Peripheral stem cells or bone marrow were infused on day 5. One toxic death was attributed to fungemia. The median delivered dose intensity for platinum was 48.3 mg/m²/week (compared with 33.3 mg/m²/wk in the Glasgow and GOG dose-intensity studies). All patients had second-look laparotomy; pathologic CR was found in 7 of 19 patients (37%). Nine patients had partial response, while three had no change. With a follow-up time of 60 months from diagnosis and 52 months from second-look laparotomy, median survival has not been reached and exceeds 47 months (range 9-64+). The five-year overall survival was 60%, and PFS was 51% with nine patients still disease-free. This study does not show improved pathologic CR rate as compared with conventional therapy; nevertheless, the durability of response in this small study is encouraging.

Table 3. High-dose therapy as upfront treatment for ovarian carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Regimen</th>
<th>Patients</th>
<th>Initial debulking</th>
<th>Evaluable for response</th>
<th>Response</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menichella</td>
<td>1991</td>
<td>Cisplatin + Carboplatin + Etoposide</td>
<td>13</td>
<td>13 (&gt;0.5 cm)</td>
<td>12</td>
<td>pCR 4/12 (33%) cCR 3/12 (25%) pPR 5/12 (41%)</td>
<td>No data</td>
</tr>
<tr>
<td>Benedetti</td>
<td>1995</td>
<td>Cisplatin + Carboplatin + Etoposide</td>
<td>20</td>
<td>16 (0.5-2 cm) + 3 (&gt;5 cm)</td>
<td>19</td>
<td>pCR 7/19 (37%) pPR 4/19 (21%) micro 5/19 (26%)</td>
<td>Median FU 52 mo. from 2nd look Median OS &gt;47 mo. (9-64+ mo.) Median PFS &gt;24 mo. (9-64+ mo.) 5 yr OS 60% 5 yr PFS 51%</td>
</tr>
<tr>
<td>Fennelly</td>
<td>1995</td>
<td>Cytoxan + Carboplatin + Rapidly sequenced</td>
<td>16</td>
<td>10 (&gt;1 cm) + 6 (&lt;1 cm)</td>
<td>13</td>
<td>pCR 5/13 (38%) pPR 2/13 (15%) micro 6/13 (46%)</td>
<td>No data</td>
</tr>
<tr>
<td>Vieni</td>
<td>1995</td>
<td>Melphalan + Cytoxan or Melphalan + Carboplatin + Etoposide</td>
<td>28</td>
<td>6 (&lt;2 cm) + 22 (&gt;2 cm)</td>
<td>NA</td>
<td>NA</td>
<td>PFS (5 yrs) 20% OS (5 yrs) 50%</td>
</tr>
<tr>
<td>Legros</td>
<td>1997</td>
<td>Melphalan or Cytoxan + Carboplatin</td>
<td>53</td>
<td>11 complete + 5 no debulking</td>
<td>NA</td>
<td>NA</td>
<td>OS (5 yrs): 59.9% Median OS: 65.8 mo. DFS (5 yrs): 23.6% Median PFS: 30.4 mo. Median survival of 78.8 mo. for pts. with negative 2nd look laparotomy</td>
</tr>
<tr>
<td>GOG 111</td>
<td>1996</td>
<td>Cisplatin + Taxol + no transplant</td>
<td>184</td>
<td>All &gt;1 cm</td>
<td>160</td>
<td>pCR 42/160 (26%) micro RD 23/160 (14%) macro RD 95/160 (59%)</td>
<td>Median PFS 18 mo. Median OS &gt;38 mo. Median OS &gt;38 mo. Median OS &gt;38 mo.</td>
</tr>
</tbody>
</table>
Alternatively, high-dose therapy has been used to intensify therapy in women with a pathologic, negative, second-look laparotomy. This approach is justified in that most of these "good prognosis" patients will still die of ovarian cancer. In a recently reported study from France, 19 patients with a negative second-look laparotomy after six cycles of conventional-dose cyclophosphamide, Adriamycin, and platinum received high-dose melphalan or carboplatin/cyclophosphamide with stem cell rescue. This group enjoyed a median survival of 79 months with a five-year survival of 74.2%.

These studies, as well as the other studies reported in Table 3, are limited by their use of cisplatin in their dose-intensive regimens. The dose-limiting toxicity of cisplatin is not myelotoxicity, and, hence, the achievable dose intensity is limited. The correlation of dose-intensive alkylators such as cyclophosphamide or melphalan with response or survival is unclear. Newer drugs such as Taxol and topotecan are just now entering high-dose chemotherapy trials with stem cell support.

The introduction of hematopoietic growth factors and the use of peripheral blood stem cells instead of bone marrow has created new potentials for high-dose therapy. Multiple cycles of high-dose therapy can be delivered, each with peripheral stem cell rescue, increasing the dose intensity of chemotherapy. At Memorial Sloan-Kettering, a study was conducted evaluating cyclophosphamide (3 gm/m²) plus escalating doses of Taxol (150-300 mg/m² by 24-h infusion), plus G-CSF and leukapheresis to harvest peripheral stem cells [66]. This was followed by four cycles of high-dose cyclophosphamide (1,500 mg/m²) and carboplatin (1,000 mg/m²) and rescue with stem cells after each cycle. Sixteen patients with advanced ovarian cancer were enrolled. Thirteen patients completed the treatment and were assessable for response; 5 of 13 had pathologic complete response (38.5%), and 6 of 13 (46%) had microscopic disease. Further chemotherapy escalation may be possible with this regimen either by increasing the doses of cyclophosphamide or carboplatin or by using other drugs that can be dose-escalated, such as thiotepa or melphalan.

### Table 4. Summary of high-dose therapy for ovarian cancer

<table>
<thead>
<tr>
<th>Disease status</th>
<th>CR</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>50%</td>
<td>36 mo.</td>
<td>60 mo.</td>
</tr>
<tr>
<td>Positive second look</td>
<td>40%</td>
<td>18 mo.</td>
<td>30 mo.</td>
</tr>
<tr>
<td>Chemosensitive relapse</td>
<td>80%</td>
<td>12 mo.</td>
<td>24 mo.</td>
</tr>
<tr>
<td>Chemoresistant relapse</td>
<td>25%</td>
<td>6 mo.</td>
<td>6-10 mo.</td>
</tr>
</tbody>
</table>

**Conclusions and New Directions**

At the current time, several phase I/II studies have been completed looking at the role of high-dose alkylates, often in combination with additional agents for the treatment of women with high-risk ovarian carcinoma. The heterogeneity of the treated patient population, variability in treatment regimens, and lack of careful patient follow-up in many of these studies make it difficult to draw definitive conclusions. Nevertheless, review of these studies, as well as the recently published bone marrow transplant registry data [71], allows investigators to draw some cautious conclusions (Table 4). First, treatment of women with advanced ovarian carcinoma with very high-dose chemotherapy and peripheral stem cell support clearly leads to a very high clinical response rate, including clinical complete response. These responses are, in general, dramatically higher than those seen with conventional single-agent salvage chemotherapy. Second, the duration of responses is disappointingly brief, typically measured in the 4- to 12-month period. Third, several studies clearly demonstrate that patients with bulky chemotherapy refractory disease experience significant toxicity with this approach and seldom enjoy prolonged disease-free intervals. Finally, patients with minimal residual disease and continued chemotherapy sensitivity demonstrate high response rates, some of which are quite durable. While these patients appear to enjoy better survival than those treated with a standard therapy, it is important to remember that these represent carefully selected, young, and typically otherwise-healthy women. Both the National Cancer Institute and the Groupe Investigation Nationale Etude Cancer Ovaïe (GINECO) are currently evaluating the role of high-dose intensification with stem cell transplantation as compared with prolonged standard therapy in a group of women with high-risk ovarian carcinoma. These protocols are still in the early enrollment stage, and answers from these trials are still many years off.

Completion of these randomized trials is important. In addition, several institutions are participating in the development of new-generation phase I/II trials incorporating agents such as Taxol, etoposide, and topotecan into current high-dose regimens in an attempt to define chemotherapy combinations that may be more efficacious for the treatment of women with advanced ovarian carcinoma. Finally, it is likely that high-dose therapy will provide effective but incomplete cytoreduction in many patients. This population of women is a candidate for the evaluation of novel consolidation strategies using agents which work through novel mechanisms of action, including inhibitions of cell invasion, cell growth, and angiogenesis, as well as heightened immune surveillance.
REFERENCES


