Commentary (Homesley/Muss): Role of Chemotherapy Dose Intensification in the Treatment of Advanced Ovarian Cancer

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We agree with Drs. Fennelly and Schneider that data from prior clinical trials performed in patients with suboptimally debulked ovarian cancer indicate that increasing the dose intensity of cisplatin (Platinol) does not translate into meaningfully higher response rates, longer response durations, or improved survival. The Gynecologic Oncology Group study is most persuasive in showing that doubling the standard dose of cisplatin and cyclophosphamide (Cytoxan, Neosar) while delivering the same total dose does not improve outcome [1].

The authors reinforce the belief that suboptimally debulked ovarian cancer patients derive little to no benefit from moderate increases in dose intensity of currently available standard treatments, but that optimally debulked (less than 1 cm) patients may have improved response to higher dose-intensity therapy. This suggests that both tumor volume and dose intensity are critical factors. Admittedly, if the more dose-intensive regimen cannot be delivered on schedule, the high-dose regimen may, in reality, not be substantially more dose intensive than standard treatment. The combination of cisplatin (100 mg/m²) and carboplatin (Paraplatin, 300 mg/m²), with their nonoverlapping toxicities, facilitates the administration of somewhat higher doses of platinum chemotherapy, with reported higher response rates. However, dose-limiting myelotoxicity and thrombocytopenia do not allow for consistent full dosing, and overall results are not convincingly better than standard regimens containing either cisplatin or carboplatin.

In the survey by Stiff et al of autologous bone marrow transplant centers in the United States, overall response and complete clinical response rates in platinum-sensitive patients (87% and 73%, respectively) was somewhat better than corresponding rates in platinum-resistant patients (overall response, 85%; clinical complete response, 43%). Unfortunately only 14% of all patients were disease free at 1 year [2]. The Southwest Oncology Group, in a randomized phase II trial, is attempting to determine response rates in both platinum-sensitive and platinum-resistant patients who receive high-dose cyclophosphamide, mitoxantrone (Novan-trone), and carboplatin, or high-dose thiotepa (Thiotepa), cyclophosphamide, and cisplatin, both regimens followed by autologous bone marrow rescue. To date, high response rates of short duration have been observed; survival benefit has yet to be determined. The use of high-dose mitoxantrone in these regimens is intriguing, since major dose escalation of this drug is possible (fivefold or more).

More Frequent Dose Intervals
Relative drug resistance may be overcome not only by increasing the dose of a chemotherapeutic agent but also by decreasing the time between dose administration. Thus, the Memorial Sloan-Kettering Cancer Center group is employing peripheral blood progenitor cells to support multiple courses of very-high-dose chemotherapy administered at frequent intervals. Using this technique, 300 mg/m² of paclitaxel (Taxol) and 3 g/m² of cyclophosphamide can be given at 14-day intervals. However, even these doses do not meet the authors' criteria of the fivefold increase in dose intensity that appears to be necessary for overcoming relative drug resistance in vitro. A major pitfall in using a single course of high-dose chemotherapy with autologous bone marrow rescue (which approaches a four- to fivefold increase in drug dose compared to standard treatment) is the strong possibility that, in most patients, not enough log kills of tumor cells can be obtained to result in a "cure." Moreover, using such treatment as second- and third-line therapy increases the likelihood that relative drug resistance may be even higher.
It appears clear that drug resistance increases as tumor volume increases, and that increasing the dose intensity of chemotherapy can overcome such resistance. The major toxicity of dose-intensive regimens is myelosuppression, and the use of autologous bone marrow and/or peripheral blood progenitor cells (stem cells) allows for increases in dose intensity of threefold or more for several agents, including alkylators, carboplatin, and mitoxantrone.

Published trials of high-dose therapy in ovarian cancer are small, have used different regimens, and have included highly selected patients. Since mortality for patients with optimally debulked ovarian cancer given standard therapy approaches 80%, we believe that high-dose therapy should be studied in this group, as well as in patients with more extensive disease. Such treatment should be compared, in a randomized trial, to the best standard therapy currently available (paclitaxel and cisplatin, for example). The major cooperative groups should consider developing such a trial in order to determine whether currently available high-dose regimens employing stem cell and/or autologous marrow rescue are superior to less toxic and less expensive standard regimens.

References:


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