Fennelly and Schneider review a controversial area in ovarian cancer management in a comprehensive, objective, and thoughtful manner. This review is particularly timely in light of the ever-increasing number of ovarian cancer patients in whom high-dose chemotherapy, with either bone marrow transplantation or peripheral stem-cell transfusion, is being proposed as a treatment option. The authors support the contention that the majority of such patients are being offered a treatment that has little likelihood of providing a meaningful benefit. The take home message from this review is that outside of an appropriately designed clinical trial, there is no established role for high-dose chemotherapy with hematologic support in any subset of patients with advanced ovarian cancer. At the conclusion of this commentary, I will return to the issue of what constitutes an appropriate clinical trial design to evaluate the efficacy of high-dose chemotherapy in ovarian cancer.

Randomized Trials of High-Dose Therapy
The clinical trials summarized by the authors in Table 1 provide little evidence that high-dose chemotherapy with cisplatin (Platinol) offers any advantage over more standard doses. The study by Kaye et al [1] is frequently cited in support of high-dose cisplatin in ovarian cancer patients. However, this study may have been prematurely closed after an interim analysis suggested increased benefit for patients receiving cisplatin at a dose of 100 mg/m² compared with those receiving 50 mg/m². Furthermore, the trial included a heterogeneous group of patients, which makes analysis difficult.

Until long-term survival data from this trial are published, it should not be accepted as providing unqualified "proof" of the importance of dose intensity of cisplatin. This is particularly the case when compared with well-designed large trials, such as that done by the Gynecology Oncology Group (GOG) [2], which failed to demonstrate any beneficial effect of high-dose therapy in patients with advanced suboptimally debulked disease.

The important caveat emerging from these trials is that dose intensity cannot overcome bulk disease. Most of these trials were conducted in patients with suboptimally debulked ovarian cancer, a group of patients who are not likely to substantially benefit from a doubling or tripling of cisplatin dose.

High-Dose Platinum in Previously Treated Patients
The studies listed in the authors' Table 2 were phase II trials using high-dose therapy in patients who had undergone prior treatment with platinum compounds. One cannot support the routine use of such high doses in previously treated patients with ovarian cancer, since their toxicity is prohibitive, and the overall response rates do not justify the substantial toxicity. The primary reason for high-dose therapy in phase II trials is to determine whether such therapy can be safely used in previously untreated patients.

High-Dose Chemotherapy/ABMT Programs
It is in this regard that the authors have made their greatest contribution. It now appears that hundreds of previously treated advanced ovarian cancer patients in the United States have been given high-dose chemotherapy regimens that have required autologous bone marrow transplant or peripheral stem-cell infusions. Although many of these patients have responded to treatment, the remissions have been of a relatively short duration. Thus, outside of a clinical trial, there is no justification for such an approach in patients with drug-resistant bulky recurrent ovarian cancer.

**Role of Paclitaxel-Based Chemotherapy**

Paclitaxel (Taxol) has emerged as perhaps the most active agent in the treatment of patients with ovarian cancer. A GOG trial of cisplatin plus cyclophosphamide (Cytoxan, Neosar) vs paclitaxel plus cisplatin has provided convincing evidence for the superiority of the paclitaxel combination. In this trial, over 400 patients with suboptimal stage III and IV disease were randomized to standard therapy or the paclitaxel combination. Patients receiving the paclitaxel combination had a higher overall response rate than those given standard therapy (77% vs 62%), a higher clinical complete remission rate (54% vs 33%), a higher negative second look or microscopic positive second look (41% vs 25%), a longer time to median survival (13 vs 18 months), and, most importantly, a marked prolongation of median survival time (23 vs 36 months).

Based on these findings, all previously untreated ovarian cancer patients entering GOG protocols now receive paclitaxel together with a platinum compound. Numerous issues remain regarding how paclitaxel should be administered, however, including the impact of paclitaxel dose intensity. The GOG has performed a prospective randomized trial, the results of which are currently unavailable, in which previously treated patients were randomized to one of three paclitaxel doses. Some previous phase II trials have suggested that patients receiving high-dose paclitaxel (250 mg/m²) have a substantially higher response rate than those receiving more standard doses (135 to 175 mg/m²). Until the prospective randomized trials are analyzed, the lower doses remain the standard of care.

**Peripheral Stem-Cell Transfusions**

An important point made by the authors is the necessity for multiple cycles of high-dose therapy to produce a meaningful increase in dose intensity. In contrast to autologous bone marrow transplantation, peripheral stem-cell transfusions permit multiple cycles of a high-dose regimen to be administered. The investigators at Memorial Sloan-Kettering Cancer Center, the University of North Carolina, and the Fox Chase Cancer Center, under the auspices of the GOG, are joining together to perform a pilot study of such an approach in previously untreated patients with ovarian cancer.

**Clinical Trials of Peripheral Stem-Cell Transfusions**

What, then, is the optimal clinical trial design to evaluate the place of high-dose chemotherapy in ovarian cancer patients? Two obvious clinical situations need to be explored. The first is those patients who have had an excellent response to induction chemotherapy with standard doses but are left with small-volume disease. The second group that needs to be studied is previously untreated patients with small-volume disease. These patients remain the group in which a definitive answer regarding the role of high-dose chemotherapy can best be determined. Once the pilot study discussed above demonstrates the efficacy and feasibility of repeated cycles of high-dose therapy in previously untreated patients with small-volume disease, a prospective randomized trial will be necessary to determine the impact of this approach upon survival in patients who have residual small-volume disease after induction therapy-a group in whom there already is a significant baseline for long-term survival. Until the completion of such a trial, high-dose chemotherapy with hematologic support should not be considered a routine approach in patients with advanced ovarian cancer.

**References:**


