Autologous Stem-Cell Transplantation in Ovarian Cancer: Is More Better?

Although advanced-stage epithelial ovarian cancer is highly responsive to initial therapy, most patients ultimately succumb to the disease. According to a series of studies conducted by multi-institution cooperative groups, such as the Gynecologic Oncology Group, surgery to accomplish maximal cytoreduction followed by six cycles of carboplatin and paclitaxel, or cisplatin and paclitaxel, is the current standard of care (1–4). Better treatment is urgently needed to improve long-term disease-free survival for patients with ovarian cancer.

On the basis of extrapolation of data (1–4), it can be expected that approximately 80% of patients with ovarian cancer will at some point achieve complete clinical remission. However, disease will recur in approximately 40% of patients within 2 years and in another 20% within the next 2 to 5 years. Only approximately 20% of patients with ovarian cancer will have long-term disease-free survival.

Several general approaches have been developed in an attempt to increase the percentage of patients in whom disease can be permanently eradicated. Among these approaches are consolidation intraperitoneal chemotherapy (4, 5), consolidation systemic chemotherapy (4, 6), and autologous stem-cell transplantation, which is discussed by Stiff and colleagues (7) in this issue. Other factors that should be considered but are usually not reported are careful analysis of treatment costs, comparative toxicities, toxicity costs, and quality-of-life issues (8).

Stiff and colleagues report data from the Autologous Blood and Marrow Transplant Registry (ABMTR) on all patients with ovarian cancer treated in participating ABMTR centers between 1 January 1989 and 31 December 1996. Their study involved 57 North American transplantation centers and 513 eligible registered patients but focused on 421 women for whom comprehensive data were available.

Autologous stem-cell transplantation has been shown to be a reasonable treatment approach for several malignant diseases. It is usually most effective when tumor burden is low, and it can have a favorable impact in subsets of patients with acute myelogenous leukemia or myelodysplasia (9–11), Hodgkin disease (12), and non-Hodgkin lymphoma (13). To determine the role of autologous stem-cell transplantation in ovarian cancer, one should compare available data with data from other treatment strategies in similar patients. We compare “best-case scenario” data on several approaches.

Stiff and colleagues report that the best progression-free and overall survival (35% [95% CI, 17% to 53%] and 60% [CI, 39% to 76%]) were seen in the 34 patients (8% of the entire group) who received transplants while in first complete remission. The best-case scenario for intraperitoneal chemotherapy performed in a similar setting was seen in a study by Howell and coworkers (5), which reported a 2-year progression-free survival of 69% in 25 patients with minimal residual disease who received intraperitoneal cisplatin and antimetabolites. The best-case scenario for systemic chemotherapy was seen in a study by Kohn and colleagues (6), in which 36 patients received a three-drug combination of paclitaxel, cisplatin, and cyclophosphamide for six cycles; second-look surgery; and two to four cycles of paclitaxel and cyclophosphamide. Two-year progression-free survival in this study was 71%.

Stiff and colleagues found that within the first 100 days of therapy, 14 patients died of infection, 13 died of organ failure, and 4 died of hemorrhage. Therefore, 7.4% of patients (31 of 421) died of potential treatment-related complications. No treatment-related deaths were noted in the 25 patients studied by Howell and coworkers (5) or the 36 patients studied by Kohn and colleagues (6). The number of deaths related to autologous stem-cell transplantation seems to be substantially higher than the number of deaths following other treatment approaches for advanced disease (4). Physicians and patients should decide whether the toxicity of autologous stem-cell transplantation is acceptable.

In addition to concerns about toxicity, there are other questions to consider. What subset of patients should be studied with dose-intensity approaches in the future? What is the optimal dose-intensity approach for ovarian cancer? What level of cost is acceptable for a given level of efficacy? What are the tradeoffs in terms of quality of life? Stiff and colleagues suggest that phase III clinical trials of autologous stem-cell transplantation are necessary. Should other treatment arms of such trials be structured along the lines of the work of Howell and coworkers (5), Kohn and colleagues (6), or both? What about newer “graft-versus-tumor” types?
of autologous stem-cell transplantation, antiangiogenesis agents, vaccines, other biological agents, or agents directed against specific molecular targets? Although the future may lie with one or more of these newer treatment options, they are not yet sufficiently developed to be seriously considered for phase III testing in human ovarian cancer.

Current "standard" chemotherapy at "standard" doses holds limited promise for major improvement in advanced epithelial ovarian cancer. We believe that four general approaches to chemotherapy could be considered for phase III studies in this disease: a standard dosing approach of novel combinations, standard dosing followed by consolidation of autologous stem-cell transplantation, standard dosing followed by cisplatin-based combination intraperitoneal therapy, and standard or intermediate dosing followed by paclitaxel-based systemic consolidation. The timing of the first surgical procedure (14) and the concept of interval debulking (15) are matters that also should be considered in the overall development of new treatment strategies. Autologous stem-cell transplantation is a reasonable experimental approach to explore, but other potentially useful strategies have not been fully studied in phase III trials. Because autologous stem-cell transplantation seems to be somewhat toxic and offers limited improvement in efficacy, less toxic approaches should also be considered in patients with ovarian cancer.

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References