Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer

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Line(s) of Business: HMO; PPO
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Section: Transplants
Place(s) of Service: Outpatient; Inpatient

I. Description

The use of hematopoietic stem-cell transplantation (HSCT) has been investigated for treatment of patients with epithelial ovarian cancer. Hematopoietic stem cells are infused to restore bone marrow function following cytotoxic doses of chemotherapeutic agents with or without whole body radiation therapy.

Background

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Bone marrow stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in policy No. 7.01.50.

HSCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental. Initial enthusiasm for the use of autologous transplant with the use of high-dose chemotherapy and stem cells for solid tumors has waned with the realization that dose intensification often fails to improve survival, even in tumors with a linear-dose response to chemotherapy. With the advent of reduced-intensity conditioning (RIC) allogeneic transplant, interest has shifted to exploring the generation of alloreactivity to metastatic solid tumors via a graft-versus-tumor (GVT) effect of donor-derived T cells.
Epithelial Ovarian Cancer

Several different types of malignancies can arise in the ovary; epithelial carcinoma is the most common. Epithelial ovarian cancer is the fifth most common cause of cancer death in women. New cases and deaths from ovarian cancer in the United States in 2010 are estimated at 21,880 and 13,850, respectively. (1) Most ovarian cancer patients present with widespread disease, and yearly mortality is approximately 65% of the incidence rate. (1)

The current management of advanced epithelial ovarian cancer is cytoreductive surgery followed by combination chemotherapy. (2) Approximately 75% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian cancer and are treated with the combination of paclitaxel and a platinum analog being the preferred regimen for newly diagnosed advanced disease. (2,3) The use of platinum and taxanes has improved progression-free survival (PFS) and overall survival (OS) rates in advanced disease to 16–21 months and 32–57 months, respectively. (3) However, most of these women develop recurrences and die of the disease as chemotherapy drug resistance leads to uncontrolled cancer growth. (2)

High-dose chemotherapy (HDC) has been investigated as a way to overcome drug resistance. However, limited data exist on this treatment approach; the ideal patient population and best regimen remain to be established. (2) HSCT has been studied in a variety of patient groups with ovarian cancer as follows:

- to consolidate remission after initial treatment
- to treat relapse after a durable response to platinum-based chemotherapy
- to treat tumors that relapsed after less than 6 months
- to treat refractory tumors

II. Policy

Autologous or allogeneic hematopoietic stem-cell transplantation to treat epithelial ovarian cancer does not meet payment determination criteria.

Stem-cell transplantation to treat germ cell tumors of the ovary is considered separately in the Hematopoietic Stem-Cell Transplantation in the Treatment of Germ-Cell Tumors policy.

III. Scientific Background

Initially, this policy was based on a 1998 TEC Assessment, “High-dose chemotherapy with autologous stem-cell support for epithelial ovarian cancer” (4) that reached the following conclusions:

- Data were unavailable from randomized controlled trials for any of the patient groups studied (see Description). Thus, the Assessment was able to compare outcomes only indirectly, using separate studies of high-dose chemotherapy (HDC) and conventional dose regimens. (4) Although some results reported after high-dose therapy appeared encouraging, the indirect comparisons did not permit conclusions.
In previously untreated patients, reported response rates suggested that high-dose therapy increased the objective response rate compared to patients given conventional-dose chemotherapy. However, this comparison was flawed by age bias and by differences in performance status and other baseline characteristics of patients included in the two sets of studies. Response duration and survival data were unavailable for comparison. Treatment-related mortality was greater after high-dose therapy.

In previously treated patients, objective response rates after HDC also were reportedly higher than after conventional-dose regimens. Subgroup analyses showed higher response rates among platinum-sensitive, optimally debulked patients. Minimum values of the ranges reported across studies for median response duration and survival after HDC were similar to those reported after conventional-dose chemotherapy. However, the maxima for these ranges suggested improved response duration and overall survival (OS) after high-dose therapy. In contrast, data from the Autologous Blood and Marrow Transplant Registry did not show similarly high survival for comparable subgroups. Comparison with conventional-dose chemotherapy was again biased due to differences in age distributions, performance status, and other baseline characteristics of patients included in studies of high-dose or conventional therapies.

The 1998 TEC Assessment did not identify any studies reporting outcomes of allogeneic transplants for patients with ovarian cancer. A separate 1999 TEC Assessment evaluated the use of HDC with allogeneic stem-cell support (HDC/AlloSCS) as salvage therapy after a failed prior course of HDC with autologous stem-cell support (HDC/AuSCS). There were no data regarding outcomes of this strategy as therapy for epithelial ovarian cancer.

Literature Review

This policy has been updated at regular intervals with literature searches; the most recent update was a literature search of the MEDLINE database through October 2011. Experience with hematopoietic stem-cell transplantation (HSCT) in epithelial ovarian cancer is primarily derived from registry data and Phase II trials. Over the last 20 years, more than 1,000 patients have been entered on transplant registries in Europe and in the United States. Many of the registry patients were treated following relapse and others in nonrandomized studies using HDC as first-line treatment. Case selection and retrospective review make the interpretation of the registries and nonrandomized data difficult. Survival analyses from registry data and clinical trials suggested a possible benefit treating ovarian cancer patients with HSCT.

However, as outlined here, none of the randomized trials that have been performed have provided evidence that HSCT in ovarian cancer provides any outcome benefit.

In 2007, Mobus and colleagues reported on a trial of 149 patients with untreated ovarian cancer who were randomly assigned, after debulking surgery, to standard chemotherapy or sequential HDC and peripheral blood stem-cell support. This was the first randomized trial comparing HDC
to standard chemotherapy (CT) as first-line treatment of ovarian cancer, and the investigators found no statistically significant difference in progression-free survival (PFS) or OS between the two treatment options. The median patient age was 50 years (range: 20–65) and International Federation of Gynecology and Obstetrics (FIGO) stage was Iib/Iic in 4%, III in 78%, and IV in 17%. Seventy-six percent of patients in the HDC arm received all of the scheduled chemotherapy cycles. After a median follow-up of 38 months, PFS was 20.5 months in the standard chemotherapy arm and 29.6 months in the HDC arm (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.56–1.26; \( p=0.40 \)). Median OS was 62.8 months in the standard chemotherapy arm and 54.4 months in the HDC arm (HR: 1.17; 95% CI: 0.71–1.94; \( p=0.54 \)).

In 2008, Papadimitriou and colleagues reported on the use of HDC with stem-cell support as consolidation therapy in patients with advanced epithelial ovarian cancer (FIGO stage IIC-IV). (2) Patients who achieved first clinical complete remission after conventional chemotherapy were randomly assigned to receive or not receive high-dose melphalan and autologous stem-cell transplant. A total of 80 patients were enrolled in the trial. Of the 37 patients allocated to HDC, 11 did not receive the treatment either due to refusal or failure of peripheral blood stem-cell mobilization. In an intent-to-treat analysis, there were no significant differences between the two arms in time-to-disease progression (\( p=0.059 \)) or OS (\( p=0.38 \)).

In 2004, Cure and colleagues reported on outcomes in advanced ovarian cancer patients randomly assigned after second-look surgery to receive either HDC with peripheral blood stem-cell support or conventional-dose maintenance chemotherapy. (10) These results were presented in abstract form and have yet to be published. Patients were younger than age 60 years with FIGO stage III-IV and disease sensitive to first-line chemotherapy. Enrolled were 110 patients (\( n=57 \) high-dose and \( n=53 \) conventional-dose chemotherapy). Median follow-up was 60 months. No difference was seen in disease-free or OS between the two arms. Disease-free survival in the conventional- versus the high-dose group was 12.2 months (95% CI: 7.3–17.1) versus 17.5 months (95% CI: 5.2–29.9) (\( p=0.22 \)), respectively. OS was 42.5 months (95% CI: 28.8-56.6) and 49.7 months (95% CI: 29.9–69.4), respectively (\( p=0.43 \)).

Summary

The evidence for the use of hematopoietic stem-cell transplant (HSCT) as an adjunct to high-dose chemotherapy in epithelial ovarian cancer is based on 2 published randomized trials with conflicting outcomes, and data from case series and registries. At present, the evidence is insufficient to recommend this intervention in either first-line therapy or for patients in whom epithelial ovarian cancer has relapsed following standard chemotherapy, and therefore, the use of HSCT in epithelial ovarian cancer remains investigational.

National Comprehensive Cancer Network (NCCN) Guidelines

National Comprehensive Cancer Network clinical practice guidelines for ovarian cancer indicate that HDC with peripheral blood stem-cell transplantation is considered investigational for the treatment of ovarian cancer. (11)
National Cancer Institute Clinical Trials Database (PDQ®)

No Phase III trials investigating high-dose therapy for patients with ovarian epithelial cancer were identified in the 2011 National Cancer Institute database.

Medicare National Coverage

The Centers for Medicare and Medicaid Services (CMS) currently have the following national non-coverage decision on autologous stem-cell transplantation:

“Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following condition[s]: Solid tumors (other than neuroblastoma)”. 

IV. Administrative Guidelines

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<th>CPT Code</th>
<th>Description</th>
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<td>38205</td>
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<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
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<td>38212</td>
<td>red blood cell removal</td>
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<td>38214</td>
<td>plasma (volume) depletion</td>
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V. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. References


5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem cell support for relapse following high-dose chemotherapy with autologous stem cell support for non-lymphoid solid tumors. TEC Assessments 1999; Volume 14, Tab 11.


