Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer

Policy Number: 8.01.23  Last Review: 1/2017
Origination: 9/2002  Next Review: 1/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for hematopoietic stem-cell transplantation for epithelial ovarian cancer. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Autologous or allogeneic hematopoietic stem-cell support is considered investigational to treat epithelial ovarian cancer.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With advanced-stage epithelial ovarian cancer</td>
<td>• Hematopoietic stem cell transplantation</td>
<td>• Standard chemotherapy regimen</td>
<td>• Overall survival</td>
</tr>
</tbody>
</table>

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 after cytotoxic doses of chemotherapeutic agents with or without whole body radiotherapy.

Evidence for the use of HSCT as an adjunct to high-dose chemotherapy (HDC) in epithelial ovarian cancer is based on 3 published randomized trials and data from
case series and registries. Currently, evidence is insufficient to recommend this intervention either as first-line therapy or for patients in whom epithelial ovarian cancer has relapsed after standard chemotherapy. Therefore, use of HSCT in epithelial ovarian cancer remains investigational.

**Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (SCT) 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 SCT) or from a donor (allogeneic SCT). 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. Cord blood is discussed in greater detail in a separate policy.

SCT 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 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 2015 are estimated at 21,290 and 14,180, respectively. (1) Most ovarian cancer patients present with widespread disease, and yearly mortality is approximately 65% of the incidence rate.

The current management of advanced epithelial ovarian cancer is cytoreductive surgery in addition to combination chemotherapy. (2) Approximately 75% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian cancer, with the combination of paclitaxel and a platinum analog being the preferred regimen for newly diagnosed advanced disease. (3,4) 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 their disease as chemotherapy drug resistance leads to uncontrolled cancer growth. (4)

High-dose chemotherapy has been investigated as a way to overcome drug resistance. However, limited data exist on this treatment approach, and the ideal
patient population and best regimen remain to be established. (4) Hematopoietic stem-cell transplantation 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

**Rationale**

This evidence review was originally created in 1999 and has been updated at regular intervals with literature searches of the MEDLINE database. The most recent update covered the period through December 18, 2015.

This policy was originally based on a 1998 TEC Assessment, “High-dose chemotherapy with autologous stem-cell support for epithelial ovarian cancer” 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. Although some results reported after HDC appeared encouraging, indirect comparisons did not permit conclusions.
- In previously untreated patients, reported response rates suggested that HDC increased objective response rates compared with 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 2 sets of studies. Response duration and survival data were unavailable for comparison. Treatment-related mortality was greater after HDC.
- 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 HDC. 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 chemotherapies.

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).(6) There were no data regarding outcomes of this strategy as therapy for epithelial ovarian cancer.

Experience with hematopoietic stem cell transplantation (HSCT) in epithelial ovarian cancer is primarily derived from registry data and phase 2 trials.(7-10) Many registry patients were treated after relapse and others in nonrandomized trials using HDC as first-line treatment. Case selection and retrospective review make interpretation of registry and nonrandomized data difficult.(3) Survival analyses from registry data and clinical trials have suggested a possible benefit in treating ovarian cancer patients with HSCT. However, as outlined here, no randomized trial has provided evidence that HSCT in ovarian cancer provides any outcome benefit.

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In 2012, Sabatier et al reported on a retrospective review of 163 patients with advanced or metastatic (Federation of Gynecology and Obstetrics [FIGO] stage 3c/4) epithelial ovarian cancer who were treated at a single institution in France.(11) All patients received cytoreductive surgery and combination platinum/taxane chemotherapy. Investigators compared median progression-free survival (PFS) and OS between 60 patients who received subsequent HDC with autologous HSCT support and 103 patients who did not. HDC regimens varied, but all contained alkylating agents. At a median follow-up of 47.5 months, PFS in the high-dose and standard chemotherapy groups was 20.1 and 18.1 months, respectively (p value not reported). OS was 47.3 and 41.3 months, respectively (p=0.29). In prespecified subgroup analyses, median PFS was significantly longer in women younger than age 50 years who received HDC compared with women who received standard chemotherapy (81.7 months vs 11 months; p=0.02); in women older than 50 years, median PFS did not differ statistically between groups (17.9 months vs 18.3 months; p=0.81). Similarly, median OS was significantly longer in women younger than age 50 years who received HDC compared with women who received standard chemotherapy (54.6 months vs 36 months; p=0.05) but not in women older than 50 years (49.5 months vs 42 months; p value not reported). The authors recommended further study of HDC with autologous HSCT support in patients younger than 50 years.

In 2008, Papadimitriou et al reported on the use of HDC with stem-cell support as consolidation therapy in patients with advanced epithelial ovarian cancer (FIGO stage IIC-IV).(4) 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 37 patients allocated to HDC, 11 (30%) did not receive the treatment either due to refusal or failure of peripheral blood stem-cell mobilization. In an intention-to-treat analysis, there were no significant differences between the 2 arms in time-to-disease progression (p=0.059) or OS (p=0.38).
In 2007, Mobus et al 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 with standard chemotherapy as first-line treatment of ovarian cancer, and investigators found no statistically significant difference in PFS or OS between the 2 treatments. Median patient age was 50 years (range, 20-65) and FIGO stage was 2b/2c in 4%, stage 3 in 78%, and stage 4 in 17%. Seventy-six percent of patients in the HDC arm received all scheduled chemotherapy cycles. After a median follow-up of 38 months, progression-free survival (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 to 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 to 1.94; p=0.54).

**Ongoing and Unpublished Clinical Trials**
A search of online site ClinicalTrials.gov found no trials of HSCT for epithelial ovarian cancer.

**Summary of Evidence**
The evidence for HSCT in patients who have advanced stage epithelial ovarian cancer includes 3 randomized trials and data from case series and registries. Relevant outcomes are overall survival, disease-specific survival, change in disease status and treatment related morbidity and mortality. The evidence has not shown an improvement in health outcomes, including survival, with the use of HSCT versus conventional standard doses of chemotherapy.

**National Comprehensive Cancer Network Guidelines**
The current NCCN guidelines (v.2.2015) do not address Hematopoietic Stem Cell Transplant for ovarian cancer for either newly diagnosed patients, nor for patients with relapsed/refractory disease.

**U.S. Preventive Services Task Force Recommendations**
Stem-cell transplantation is not a preventive service.

References:
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose chemotherapy with autologous stem-cell support for epithelial ovarian cancer. *TEC Assessments*. 1998;Volume 13, Tab 6. PMID
6. 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. PMID

**Billing Coding/Physician Documentation Information**

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
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<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</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>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
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<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
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<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
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<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
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<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
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<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
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<td>38230</td>
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<td>38241</td>
<td>Bone marrow transplantation; autologous</td>
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38242  Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte Infusions
Q0083  Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit
Q0084  Chemotherapy administration by infusion technique only, per visit
Q0085  Chemotherapy administration by both infusion technique and other technique(s) (e.g., subcutaneous, intramuscular, push), per visit
S2140  Cord blood harvesting for transplantation, allogeneic
S2142  Cord blood-derived stem cell transplantation, allogeneic
S2150  Bone marrow or blood-derived peripheral stem cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and 28 days of post-transplant care (including drugs; hospitalization; medical surgical, diagnosis and emergency services)

ICD10 Codes:
Investigational for all relevant diagnoses
C56.0–C56.9  Malignant neoplasm of ovary code range

Policy Implementation/Update Information
9/1/02  New policy added to the Surgery and Transplant sections.
9/1/03  No policy statement changes.
9/1/04  No policy statement changes.
9/1/05  No policy statement changes.
9/1/06  No policy statement changes.
9/1/07  No policy statement changes.
9/1/08  No policy statement changes.
9/1/09  No policy statement changes. “High-dose chemotherapy” removed from policy title.
9/1/10  No policy statement changes.
9/1/11  No policy statement changes.
9/1/12  No policy statement changes.
9/1/13  No policy statement changes.
1/1/15  No policy statement changes.
1/1/16  No policy statement changes.
3/1/16  No policy statement changes.
1/1/17  No policy statement changes.

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