Policy Number	**SUR703.034**
Policy Effective Date	**11/15/2024**

Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer

Table of Contents

Related Policies (if applicable)
SUR703.002: Hematopoietic Cell Transplantation (HCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information)
SUR703.045: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors

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Coverage

Autologous and allogeneic hematopoietic cell transplantation (HCT) **are considered experimental, investigational and/or unproven** to treat epithelial ovarian cancer.

Policy Guidelines

None.

Description

The use of hematopoietic cell transplantation (HCT) has been investigated to treat 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.

Epithelial Ovarian Cancer

Several 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 for 2021 were estimated at 21,410 and 13,770, respectively. (1) Most ovarian cancer patients present with widespread disease, and the National Cancer Institute Surveillance, Epidemiology and Results Program reported a 49.1% five-year survival for all cases between 2011 and 2017. (2)

Treatment

Current management for advanced epithelial ovarian cancer is cytoreductive surgery with chemotherapy. Approximately 75% of patients present with International Federation of Gynecology and Obstetrics stage III to IV ovarian cancer and are treated with paclitaxel plus a platinum analogue, the preferred regimen for the newly diagnosed advanced disease. (3, 4) Use of platinum and taxanes has improved progression-free survival and overall survival in advanced disease to between 16 and 21 months and 32 and 57 months, respectively. (3) However, cancer recurs in most women, and they die of the disease because chemotherapy drug resistance leads to uncontrolled cancer growth. (4)

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Bone marrow stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). 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 "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease.

HCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults is largely experimental.

Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale

This medical policy was created in April 2010 and has been updated regularly with searches of the PubMed database. The most recent update was performed through September 11, 2023.

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life,

quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Hematopoietic Cell Transplantation (HCT) for Epithelial Ovarian Cancer

Clinical Context and Therapy Purpose

The purpose of autologous or allogeneic stem cell transplantation in individuals who have epithelial ovarian cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this medical policy is: Does autologous or allogeneic stem cell transplantation used as part of the treatment of ovarian cancer improve net health outcomes?

The following PICO was used to select literature to inform this policy.

Populations

The relevant population(s) of interest are individuals with advanced epithelial ovarian cancer who have undergone debulking surgery and first-line chemotherapy.

Interventions

The therapy being considered is autologous or allogeneic stem cell transplantation. HCT has been investigated as a therapy to overcome drug resistance. HCT has been tested in various patient groups with ovarian cancer to consolidate remission after induction therapy, to treat relapse after a durable response to platinum-based chemotherapy, to treat tumors that relapse after less than six months, to treat refractory tumors.

Comparators

The following practices are currently being used to make decisions about the treatment of advanced epithelial ovarian cancer: guideline-based clinical pathways for debulking surgery and platinum-based chemotherapy.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival, change in disease status, treatment-related mortality.

Experience with HCT in epithelial ovarian cancer is primarily derived from registry data and phase 2 trials. (5-8) 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 HCT.

Randomized Controlled Trials
Mobus et al. (2007) reported on a phase 3 trial that included 149 patients with untreated ovarian cancer who were randomized, after debulking surgery, to standard chemotherapy or sequential HDC and peripheral blood stem cell support. (3) This was the first randomized trial comparing HDC with standard chemotherapy as first-line treatment of ovarian cancer, and investigators found no statistically significant differences in progression-free survival (PFS) or OS between treatments. The trial was powered such that a sample of 208 patients would be needed to detect an absolute improvement of 15% in PFS with a power of 80% and a 1-sided α of 5%. Median patient age was 50 years (range, 20-65 years) and International Federation of Gynecology and Obstetrics (FIGO) stage was IIB or IIC in 4%, stage III in 78%, and stage IV in 17%. Seventy-six percent of patients in the HDC arm received all 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 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).

Papadimitriou et al. (2008) reported on an RCT comparing 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 complete remission after conventional chemotherapy were randomized to receive or not high-dose melphalan and autologous HCT. Eighty 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 arms in time-to-disease progression (p=0.059) or OS (p=0.38).

Observational Comparative Studies
Sabatier et al. (2012) retrospectively reviewed 163 patients with advanced or metastatic (FIGO stage IIIC or IV) epithelial ovarian cancer who were treated at a single institution in France. (9) All patients received cytoreductive surgery and combination platinum plus taxane chemotherapy. Investigators compared median PFS and OS among 60 patients who received subsequent HDC with autologous HCT 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 the standard chemotherapy groups was 20.1 and 18.1 months, respectively (p 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 (81.7 months) than in women who received standard chemotherapy (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, respectively; p=0.81). Similarly, median OS was significantly longer in women younger than age 50 years who received HDC (54.6 months) than in women who received standard chemotherapy (36 months; p=0.05), but not in women older than 50 years (49.5 months versus 42 months, respectively; p not reported). The authors recommended further study of HDC with autologous HCT support in patients younger than 50 years.

Summary of Evidence

For individuals who have epithelial ovarian cancer who receive hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials and data from case series and registries. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment related mortality and morbidity. Although some observational studies have reported longer survival in subsets of women with advanced epithelial ovarian cancer than in women treated with standard chemotherapy, none of the randomized trial evidence has shown a benefit from HCT in this population. Overall, the evidence has not shown that HCT improves health outcomes in treating epithelial ovarian cancer, including survival, compared with conventional standard doses of chemotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Policy Statements

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines on ovarian cancer including fallopian tube cancer and primary peritoneal cancer (v.2.2023) do not address HCT for epithelial ovarian cancer for patients either with newly diagnosed or with relapsed or refractory disease. (10)

Accordingly, NCCN guidelines on HCT (v.1.2023) do not reference epithelial ovarian cancer as an indication for HCT. (11)

Medicare National Coverage

The Centers for Medicare & Medicaid Services currently have the following national noncoverage decision on autologous stem cell transplantation (AuSCT): “Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following condition[s]: Solid tumors (other than neuroblastoma).” (12)

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in September 2023 did not identify any ongoing or unpublished trials that would likely influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/15/2024	Reviewed. No changes.
10/15/2023	Document updated with literature review. Coverage unchanged. References updated; none added; some removed.
04/15/2022	Reviewed. No changes.
09/01/2021	Document updated with literature review. Coverage unchanged. Added reference 13.
07/15/2020	Reviewed. No changes.
06/15/2019	Document updated with literature review. Coverage unchanged. Added references 2, 3 and 13. Title changed from “Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer”.
05/15/2018	Reviewed. No changes.
06/01/2017	Document updated with literature review. Coverage unchanged.
06/01/2016	Reviewed. No changes.

06/01/2015	Document updated with literature review. Coverage unchanged. Title changed from Stem-Cell Transplant for Epithelial Ovarian Cancer.
12/01/2014	Document updated with literature review. Coverage language modified, without change to coverage position.
10/15/2013	Document updated with literature review. The following was added: 1) Donor leukocyte infusion and hematopoietic progenitor cell boost are considered experimental, investigational and 2) Any related services for the treatment of epithelial ovarian cancer, such as short tandem repeat (STR) markers are considered experimental, investigational and unproven. Otherwise, coverage unchanged. Description and Rationale significantly revised.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem Cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies. Stem cell transplant remains experimental, investigational and unproved when used to treat epithelial ovarian cancer. [NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem Cells; • Donor Leukocyte Infusion (DLI); and • Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies.