8.01.23	Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer		
Original Policy Date:	June 28, 2007	**Effective Date:**	April 1, 2024
Section:	11.0 Transplant	**Page:**	Page 1 of 10

Policy Statement

I. Autologous and allogeneic hematopoietic cell transplantation are considered **investigational** to treat advanced stage epithelial ovarian cancer.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Stem cell transplantation to treat germ cell tumors of the ovary is considered separately in evidence review Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors.

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. Stem cell transplantation to treat germ cell tumors of the ovary is considered separately in evidence review Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors.

Related Policies

- Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Rationale

Background

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 2023 were estimated at 19,710 and 13,270, respectively.[1,] Most ovarian cancer patients present with widespread disease, and the National Cancer Institute Surveillance, Epidemiology and Results Program reported a 50.8% 5-year survival for all cases between 2013 and 2019.[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 (e.g. cisplatin), 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.

Literature Review

Evidence reviews 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 function¾including 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Hematopoietic Cell Transplantation 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 following PICO was used to select literature to inform this review.

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 6 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.[5,6,7,8,] 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.

Review of Evidence

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 $\alpha$of 5%.Median patient age was 50 years (range, 20-65 years) and International Federation of Gynecology and Obstetrics 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, 0.84; 95% confidence interval, 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 (hazard ratio, 1.17; 95% confidence interval, 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 (International Federation of Gynecology and Obstetrics 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 (International Federation of Gynecology and Obstetrics 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 months and 18.1 months, respectively (p not reported). OS was 47.3 months 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 vs 42 months, respectively; p not reported). The authors recommended further study of HDC with autologous HCT support in patients younger than 50 years.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines on epithelial ovarian cancer including fallopian tube cancer and primary peritoneal cancer (v.2.2023) do not address hematopoietic cell transplantation (HCT) for epithelial ovarian cancer for patients either with newly diagnosed or with relapsed or refractory disease.[10,]However, use of high-dose chemotherapy with HCT received a category 2B recommendation for individuals with certain malignant germ cell tumors demonstrating abnormal tumor markers and definitive recurrent disease and a category 2A recommendation in those with persistently elevated markers and definitive residual disease. NCCN notes that "patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy."

Accordingly, NCCN guidelines on HCT (v.3.2023) only reference ovarian germ cell tumors as an indication for HCT.[11,]

Use of HCT for germ cell tumors is addressed separately in evidence review Blue Shield of California Medical Policy: Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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 December 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. American Cancer Society. Cancer Facts & Figures 2023. Atlanta, GA: American Cancer Society; 2023; https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf.Accessed December 29, 2023.
2. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Ovarian Cancer. n.d.; https://seer.cancer.gov/statfacts/html/ovary.html. Accessed December 29, 2023.
3. Möbus V, Wandt H, Frickhofen N, et al. Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: intergroup trial of the AGO-Ovar/AIO and EBMT. J Clin Oncol. Sep 20 2007; 25(27): 4187-93. PMID 17698804
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5. Donato ML, Aleman A, Champlin RE, et al. Analysis of 96 patients with advanced ovarian carcinoma treated with high-dose chemotherapy and autologous stem cell transplantation. Bone Marrow Transplant. Jun 2004; 33(12): 1219-24. PMID 15122311
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8. Stiff PJ, Veum-Stone J, Lazarus HM, et al. High-dose chemotherapy, and autologous stem-cell transplantation for ovarian cancer: an autologous blood and marrow transplant registry report. Ann Intern Med. Oct 03 2000; 133(7): 504-15. PMID 11015163
9. Sabatier R, Gonçalves A, Bertucci F, et al. Are there candidates for high-dose chemotherapy in ovarian carcinoma?. J Exp Clin Cancer Res. Oct 16 2012; 31(1): 87. PMID 23072336
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 2.2023. https://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf. Accessed December 29, 2023.
11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Cell Transplantation (HCT). Version 3.2023.

https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed December 28, 2023.
12. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (110.23, formerly 110.8.1). 2016: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366. Accessed December 29, 2023.

Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- Referring provider history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring provider (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of individual's ability to be an adequate candidate for transplant
- Radiology reports including:
  - Chest x-ray (CXR)
  - PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
  - EKG
  - Echocardiogram
  - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
  - Bone marrow biopsy
  - Lymph node biopsy (as appropriate)
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
	38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
	38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
	38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
	38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
	38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
	38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	38230	Bone marrow harvesting for transplantation; allogeneic
	38232	Bone marrow harvesting for transplantation; autologous
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	S2140	Cord blood harvesting for transplantation, allogeneic
	S2142	Cord blood-derived stem-cell transplantation, allogeneic
	S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
06/28/2007	BCBSA Medical Policy adoption
07/02/2010	Policy Revision with title change from High-Dose Chemotherapy and Hematopoietic Stem-Cell Support for Epithelial Ovarian Cancer
12/08/2010	Policy revision without position change
07/31/2015	Coding update

Effective Date	Action
09/30/2015	Policy revision without position change
03/01/2016	Policy revision without position change
03/01/2017	Policy title change from Hematopoietic Stem Cell Transplantation for Epithelial Ovarian Cancer Policy revision without position change
01/01/2018	Coding update
03/01/2018	Policy revision without position change
03/01/2019	Policy revision without position change
11/01/2019	Policy revision without position change
04/01/2024	Policy reactivated. Previously archived from 05/01/2020 to 03/31/2024.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer 8.01.23** **Policy Statement:** I. Autologous and allogeneic hematopoietic cell transplantation are considered **investigational** to treat advanced stage epithelial ovarian cancer.