Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Policy Number: 8.01.24  Last Review: 12/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for hematopoietic cell transplantation for miscellaneous solid tumors in adults. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Autologous or allogeneic cell transplant is investigational for the following malignancies in adults:
- Cancer of the bile duct
- Cancer of the fallopian tubes
- Cervical cancer
- Colon cancer
- Esophageal cancer
- Gall bladder cancer
- Lung cancer, any histology
- Malignant melanoma
- Nasopharyngeal cancer
- Neuroendocrine tumors
- Pancreas cancer
- Paranasal sinus cancer
- Prostate cancer
- Rectal cancer
- Renal cell cancer
- Soft tissue sarcomas
- Stomach cancer
- Thyroid tumors
- Tumors of the thymus
- Tumors of unknown primary origin
- Uterine cancer

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Individuals: With adult soft tissue sarcomas</td>
<td>Interventions of interest are: Autologous hematopoietic cell transplantation</td>
<td>Comparators of interest are: Standard of care</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Treatment-related mortality, Treatment-related morbidity</td>
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<tr>
<td>Individuals: With small cell lung cancer</td>
<td>Interventions of interest are: Autologous hematopoietic cell transplantation</td>
<td>Comparators of interest are: Standard of care</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Treatment-related mortality, Treatment-related morbidity</td>
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<tr>
<td>Individuals: With renal cell carcinoma</td>
<td>Interventions of interest are: Allogenic hematopoietic cell transplantation</td>
<td>Comparators of interest are: Standard of care</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Treatment-related mortality, Treatment-related morbidity</td>
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<tr>
<td>Individuals: With colorectal cancer</td>
<td>Interventions of interest are: Allogenic hematopoietic cell transplantation</td>
<td>Comparators of interest are: Standard of care</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Treatment-related mortality, Treatment-related morbidity</td>
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<td>Interventions of interest are: Allogenic hematopoietic cell transplantation</td>
<td>Comparators of interest are: Standard of care</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Treatment-related mortality, Treatment-related morbidity</td>
</tr>
<tr>
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<td>Interventions of interest are: Allogenic hematopoietic cell transplantation</td>
<td>Comparators of interest are: Standard of care</td>
<td>Relevant outcomes include: Overall survival, Disease-specific survival, Treatment-related mortality, Treatment-related morbidity</td>
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Hematopoietic cell transplantation (HCT) is an established treatment for certain hematologic malignancies and has been investigated for a variety of adult solid tumors. Interest continues in exploring nonmyeloablative allogeneic HCT (allo-HCT) for a graft-versus-tumor effect of donor-derived T cells in metastatic solid tumors.
**Autologous HCT**

For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes 2 TEC Assessments, a randomized controlled trial, and a number of phase 2 single-arm studies, some of which have been summarized in a systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on autologous HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Although a small phase 2 randomized controlled trial reported longer survival for patients treated with autologous HCT than with standard chemotherapy, this trial did not show a survival benefit with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes 2 TEC Assessments, several randomized controlled trials, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on autologous HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Studies published since the TEC Assessments have not reported increased overall survival for patients with small cell lung cancer treated with autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Allo-HCT**

For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes a TEC Assessment and small single-arm series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on allo-HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of allo-HCT on patient survival. Since the publication of the TEC Assessments, the evidence for allo-HCT to treat renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

**HEMATOPOIETIC CELL TRANSPLANTATION**

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 cytotoxic drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or from umbilical cord blood 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 (GVHD). Cord blood is discussed in detail in a separate policy.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome of allo-HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

**Conditioning for HCT**

*Conventional Conditioning*
The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is a result of a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immnosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility to opportunistic infections. The immune reactivity between donor T cells and malignant cells that is responsible for the GVM effect also leads to acute and chronic GVHD.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.
**Reduced-Intensity Conditioning for Allo-HCT**

Reduced-intensity conditioning (RIC) refers to the pre-transplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

**HCT IN SOLID TUMORS IN ADULTS**

HCT is an established treatment for certain hematologic malignancies. Its use in solid tumors is less well established, although it has been investigated for a variety of solid tumors. With the advent of non-myeloablative 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.(1)

HCT as a treatment for ovarian cancer, germ cell tumors, ependymoma, or malignant glioma is addressed separately in separate policies. HCT as a treatment for breast cancer is not addressed. This evidence review collectively addresses other solid tumors of adults for which HCT has been investigated, including lung cancer, malignant melanoma, tumors of the gastrointestinal tract (affecting the colon, rectum, pancreas, stomach, esophagus, gallbladder, or bile duct), male and female genitourinary systems (eg, renal cell carcinoma, prostate cancer, cervical cancer, uterine cancer, fallopian tube cancer), tumors of the head and neck, soft tissue sarcoma, thyroid tumors, tumors of the thymus, and tumors of unknown primary origin.

**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 (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

**Rationale**

This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 6, 2017.
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the 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.

This evidence review was initially based on a 1995 TEC Assessment that focused on adult solid tumors other than breast cancer, epithelial ovarian cancer, germ cell tumors, and glial cell–derived brain cancers. Literature on solid tumors identified in the Assessment included lung cancers, melanoma, tumors of gastrointestinal organs, genitourinary system tumors, tumors of the head and neck, soft tissue sarcomas of the extremities and torso, thyroid tumors, tumors of the thymus, undifferentiated tumors, and tumors of unknown primary. The Assessment offered the following conclusions:

- While 125 articles were identified that reported on the results of autologous hematopoietic cell transplantation (HCT) in a variety of solid tumors, only 17 included survival data from groups of patients with the same cancer. These studies reported on 4 indications: advanced small cell lung cancer (SCLC), advanced colorectal cancer, malignant melanomas, and inoperable gastric cancer.
- The evidence did not permit conclusions on the effect of autologous HCT on patient survival.

A 1999 TEC Assessment evaluated the use of allogeneic HCT (allo-HCT) as a salvage therapy after a failed autologous HCT for solid tumors. The evidence was inadequate to permit conclusions.
Autologous HCT in Solid Tumors of Adults

The evidence on the use of autologous HCT for the solid tumors of adults addressed in this evidence review consists primarily of small series.

Adult Soft Tissue Sarcomas

The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a median survival of 1 year and a 5-year survival estimate of less than 10%.\(^4\) A variety of single-agent and combination regimens are used for treatment, with targeted therapies available for some subtypes.\(^5\) Based on initial observations that patients who achieved complete remission (CR) had longer survival, several phase 1 and 2 trials using autologous HCT were conducted in the 1990s in an attempt to improve outcomes.\(^4\) These trials were composed of small numbers of patients (range, 2-55 patients), yielding overall response rates (ORRs) from 20% to 65%, with CR ranging from 10% to 43%. The longest reported 5-year progression-free survival (PFS) rate was 21%, and 5-year overall survival (OS) rate was 32%.\(^4\) One study (2007) of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease prior to HCT.\(^6\) In another phase 2 study (2006), 21 (38%) of 55 patients responded to doxorubicin-based induction chemotherapy, but estimated OS did not differ statistically between those who did (14%) and did not (3%) receive an autologous HCT (p=0.003).\(^7\)

In 2017, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy (HDC) for nonrhabdomyosarcoma soft tissue sarcomas.\(^8\) One RCT (2012) assessing 83 patients was identified.\(^9\) In the RCT, OS did not differ statistically between autologous HCT following HDC and standard-dose chemotherapy (hazard ratio [HR], 1.26; 95% confidence interval [CI], 0.70 to 2.29; p=0.44), and the point estimate for survival at 3 years was 32.7% compared with 49.4%. In 2014, Peinemann and Labeit conducted another systematic review that included an RCT (described above) and 61 single-arm studies.\(^10\) The pooled treatment-related mortality rate across 61 single-arm studies was 15 (5.1%) of 294.

A small number of studies not included in the Cochrane review have described outcomes after HCT for soft tissue sarcoma. Kasper et al (2010) reported the results of a prospective, single-institution phase 2 study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma.\(^11\) After 4 courses of chemotherapy, 9 patients with at least a partial response underwent HDC and autologous HCT. All other patients continued chemotherapy for 2 more cycles. Median PFS for patients treated with HCT was 11.6 months (range, 8-15 months) and 5.6 months for patients treated with standard chemotherapy (p=0.047); median OS for the 2 groups was 23.7 months (range, 12-34 months) and 10.8 months (range 0-39 months; p=0.027), respectively.

Hartmann et al (2013) reported on results from a phase 2 study of HDC with ifosfamide, carboplatin, and etoposide followed by peripheral blood stem cell
transplantation in patients with grade 2 or 3 histologically proven soft tissue sarcoma considered unresectable or marginally resectable. After a median follow-up of 50 months (range, 26-120 months) in surviving patients, median PFS for all patients was 21 months (range, 1-94 months) and median OS was 37 months (range, 3-120 months), corresponding to 5-year PFS and OS rates of 39% and 48%, respectively.

A 2014 case report on the use of autologous HCT for treatment of an adult histiocytic sarcoma was identified, in which the patient was alive with no evidence of disease 30 months posttreatment.

**Section Summary: Adult Soft Tissue Sarcomas**
Overall, 1 RCT and several small phase 2 studies have reported outcomes after autologous HCT in adults with soft tissue sarcoma. Although 1 small phase 2 study reported longer survival for patients treated with HCT than with standard chemotherapy, the available RCT did not show a survival benefit with autologous HCT.

**Small Cell Lung Cancer**
The interest in treating SCLC with autologous HCT stems from the extremely high chemosensitivity and poor prognosis of this tumor type. A phase 3 trial (2005) randomized 318 patients with SCLC to standard chemotherapy or to HCT. No statistically significant difference in response rates was seen between the 2 groups (response rate, 80% in standard arm group vs 88% in HCT group; difference, 8%; 95% CI, -1% to 17%; p=0.09). There was no statistically significant difference in OS between groups, with a median OS of 13.9 months in the standard arm (95% CI, 12.1 to 15.7 months) and 14.4 months in the HCT arm (95% CI, 13.1 to 15.4 months; p=0.76). One smaller, randomized study and several single-arm studies of HCT and autologous HCT for SCLC are summarized in a 2007 review article. Overall, most of the data from these studies, including the randomized study, showed no increased in OS with autologous HCT.

Jiang et al (2009) performed a meta-analysis of English-language studies through October 2008 using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC. The meta-analysis consisted of 5 RCTs (3 phase 3 trials, 2 phase 2), with a total of 641 patients. Reviewers found no significant increase in the odds ratio for response rate with autologous transplant vs control chemotherapy (odds ratio, 1.29; 95% CI, 0.87 to 1.93; p=0.206). No statistically significant increase in OS was seen among the autologous transplant patients compared with control regimens (HR=0.94; 95% CI, 0.80 to 1.10; p=0.432). Reviewers concluded that current evidence did not support the use of intensified chemotherapy and autologous HCT for treating SCLC.
**Section Summary: Small Cell Lung Cancer**
Treatment of SCLC with autologous HCT has been studied in a meta-analysis, RCTs, and small series. None of these studies showed a survival benefit with autologous HCT.

**Other Tumors**
Uncontrolled pilot studies of autologous HCT for patients with refractory urothelial carcinoma and recurrent or advanced nasopharyngeal carcinoma have not demonstrated adequate evidence of improved outcomes to alter previous conclusions. In a 2014 small series (N=8) of bilateral retinoblastoma survivors with secondary osteosarcoma, 2 patients (of 7 treated with multimodal chemotherapy) received HDC with autologous peripheral blood stem cell support. The 2 HCT-treated patients were alive with no evidence of disease at 33.4 and 56.4 months of follow-up.

**Allo-HCT in Solid Tumors of Adults**
The evidence base for the treatment of patients with types of solid tumors using allo-HCT consists of single-case reports and small series.

**Renal Cell Carcinoma**
Metastatic renal cell carcinoma (RCC) has an extremely poor prognosis, with a median survival of less than 1 year and a 5-year survival of less than 5%. RCC is relatively resistant to chemotherapy but is susceptible to immune therapy, and interleukin-2 and/or interferon-α have induced responses and long-term PFS rates of in 4% to 15% of patients. In addition, 7 targeted therapies are approved by the U.S. Food and Drug Administration for treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, and bevacizumab. Based on the susceptibility of RCC to immune therapies, the immune-based strategy of a graft-versus-tumor effect possible with an allogeneic transplant has led to an interest in its use in RCC. In 2000, Childs et al published on the first series of patients with RCC treated with nonmyeloablative allo-HCT. The investigators showed tumor regression in 10 (53%) of 19 patients with cytokine-refractory, metastatic RCC who received a human leukocyte antigen–identical sibling allo-HCT. Three patients had a CR and remained in remission 16, 25, and 27 months after transplant. Four of 7 patients with a partial response were alive without disease progression 9 to 19 months after transplantation. Other pilot trials have demonstrated the graft-versus-tumor effect of allo-HCT in metastatic RCC, but most have not shown as high a response rate as the Childs study. ORRs in these pilot trials have been approximately 25%, with CR rates of approximately 8%. Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC.

Bregni et al (2009) assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received reduced-intensity conditioning (RIC) with allo-HCT from a sibling who was human leukocyte antigen–identical. All patients received the same conditioning regimens.
Response to allograft was available in 24 patients, with a CR in 1 patient and partial response in 4 patients. Twelve patients had a minor response or stable disease, and seven had progressive disease. ORR (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (range, 12-2332+ days). The 1-year OS rate was 48% (95% CI, 28% to 68%) and the 5-year OS rate was 20% (95% CI, 4% to 36%). The authors concluded that allografting can induce long-term disease control in a small fraction of cytokine-resistant patients with RCC but that with the availability of novel targeted therapies for RCC, future treatment strategies should consider incorporating these therapies into the transplant regimen.

Section Summary: Allo-HCT in Renal Cell Carcinoma
Evidence on use of allo-HCT for RCC is based on a TEC Assessment and multiple case series. TEC Assessments found that HCTs did not meet the criteria for treatment of RCC or other solid tumors. In absence of RCTs, current evidence is insufficient to conclude whether allo-HCT results in improved OS among RCC patients.

Colorectal Cancer
Aglietta et al (2009) reported on their experience with 39 patients with metastatic colorectal cancer who underwent RIC allo-HCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation centers. 25 Patients were treated with 1 of 5 RIC regimens. End points assessed were achievement of mixed chimerism, incidence of graft-versus-host disease, treatment-related mortality, and toxicities, OS, and time to treatment failure (in patients who responded to the therapy). Patient population characteristics were heterogeneous; pretransplant disease status was partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. Thirty-eight (97%) patients had had previous treatment, some with only chemotherapy and others with surgery, chemotherapy, or both. After transplant, tumor responses were complete and partial in 2% and 18% of patients, respectively, and 26% of patients had stable disease, for overall disease control in 46% of patients. Transplant-related mortality was 10%. Median overall follow-up was 202 days (range, 6-1020 days), after which time 33 patients had died and 6 were still alive. Tumor progression was the cause of death in 74% of patients. An assessment of OS of patients was performed after stratifying by potential prognostic factors. Achievement of response after transplantation was associated with a difference in OS, with the 18 patients who had a response having a median OS of approximately 400 days vs approximately 120 days for those who had no response (p<0.001). The authors concluded that the allo-HCT approach should be reserved for patients with a partial response or stable disease after second-line therapy for metastatic colorectal cancer and that second-generation clinical trials in these patients would be warranted.
**Section Summary: Allo-HCT in Colorectal Cancer**

Evidence on use of allo-HCT for colorectal cancer is based on a TEC Assessment and a case series. The TEC Assessment concluded that allo-HCT did not meet the criteria for treatment of solid tumors. In absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among colorectal carcinoma patients.

**Pancreatic Cancer**

Kanda et al (2008) reported on the efficacy of RIC allo-HCT for advanced pancreatic cancer in 22 patients from 3 transplantation centers in Japan. RIC regimens differed across centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 having locally advanced disease. All but 1 patient received chemotherapy of various combinations before transplant, and 10 patients received localized radiotherapy. After allo-HCT, 1 patient achieved CR, 2 had partial response, 2 had minor response, and 8 had stable disease, with an ORR of 23%. Median survival was 139 days, and the major cause of death was tumor progression (median duration of survival in advanced pancreatic cancer in the nontransplant setting is less than 6 months, even in patients treated with gemcitabine). Only 1 patient survived longer than 1 year after transplantation. The authors concluded that a tumor response was observed in 25% of patients with advanced pancreatic cancer who underwent allo-HCT and that the response was not durable. However, based on their observation of a relation between longer survival and the infusion of a higher number of CD34-positive cells or the development of chronic graft-versus-host disease, they recommended additional study to evaluate the immunologic effect on pancreatic cancer.

Abe et al (2009) reported on outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative conditioning with allo-HCT. Median age was 54 years (range, 44-62 years). All patients had advanced disease, either with metastases or peritonitis, and had received at least 1 course of chemotherapy including gemcitabine. After allo-HCT, tumor response was only observed in 2 patients—one had complete disappearance of the primary tumor and the other had a 20% reduction in tumor size; the remaining patients had progressive disease (n=2) or stable disease (n=1). Four patients died of progressive disease (median, 96 days; range, 28-209 days posttransplant). One patient died at day 57 secondary to rupture of the common bile duct from rapid tumor regression. The authors concluded that findings showed a graft-versus-tumor effect, but, to obtain durable responses, an improved conditioning regimen and new strategies to control tumor growth after nonmyeloablative allo-HCT would be needed.

Omazic et al (2017) reported on outcomes for 2 patients who received allo-HCT from human leukocyte antigen–identical sibling donors following resection of pancreatic ductal adenocarcinoma. These patients were compared with 6 controls who underwent radical surgery for pancreatic ductal adenocarcinoma but did not receive HCT. Both patients receiving HCT were tumor free after 9 years
following diagnosis, whereas all the patients in the control group died within 4 years of diagnosis.

**Section Summary: Allo-HCT in Pancreatic Cancer**
Evidence on use of allo-HCT for pancreatic cancer is based on a TEC Assessment, multiple case series, and a small comparative study. The TEC Assessment concluded that allo-HCT did not meet the criteria for treatment of solid tumors. In absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among pancreatic cancer patients.

**Nasopharyngeal Cancer**
Toh et al (2011) reported on outcomes of a phase 2 trial of 21 patients with pretreated metastatic nasopharyngeal cancer. Median patient age was 48 years (range, 34-57 years), and patients had received a median of 2 previous chemotherapy regimens (range, 1-8 regimens). All patients had extensive metastases. Patients underwent a nonmyeloablative allo-HCT with sibling allografts. Seven (33%) patients showed a partial response and 3 (14%) achieved stable disease. Four patients were alive at 2 years, and 3 showed prolonged disease control of 344, 525, and 550 days. After a median follow-up of 209 days (range, 4-1147 days), the median PFS was 100 days (95% CI, 66 to 128 days) and the median OS was 209 days (95% CI, 128 to 236 days). One- and 2-year OS rates were 29% and 19%, respectively, comparable to the median 7- to 14-month OS rates reported in the literature for metastatic nasopharyngeal patients treated with salvage chemotherapy without HCT.

**Section Summary: Allo-HCT in Nasopharyngeal Cancer**
Evidence on use of allo-HCT for nasopharyngeal cancer is based on a TEC Assessment and a phase 2 trial. The TEC Assessment concluded that allo-HCT did not meet the criteria for treatment of solid tumors. In absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among nasopharyngeal cancer patients.

**Mixed Tumor Types**
In 2016, Omazic et al reported on long-term follow-up for 61 patients with a variety of solid tumor types considered incurable with conventional therapies who were treated with allo-HCT from 1999 to 2012. Tumors included metastatic renal carcinoma (n=22), cholangiocarcinoma (n=17), colon cancer (n=15), prostate cancer (n=3), pancreatic adenocarcinoma (n=3), and breast cancer (n=1). Most patients (n=59) had undergone surgical debulking of the primary tumor, and 31 patients had previously undergone additional therapy with cytotoxic chemotherapy, radiotherapy, or immunotherapy. Conditioning was myeloablative in 23 patients, reduced-intensity in 36 patients, and nonmyeloablative in 2 patients. Over a median follow-up of 8 years, OS rates at 5 and 10 years were 15% and 9%, respectively.
Summary of Evidence

Autologous HCT
For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes 2 TEC Assessments, a randomized controlled trial, and a number of phase 2 single-arm studies, some of which have been summarized in a systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on autologous HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Although a small phase 2 randomized controlled trial reported longer survival for patients treated with autologous HCT than with standard chemotherapy, this trial did not show a survival benefit with HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes 2 TEC Assessments, several randomized controlled trials, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on autologous HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of HCT on patient survival. Studies published since the TEC Assessments have not reported increased overall survival for patients with small cell lung cancer treated with autologous HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

Allo-HCT
For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes a TEC Assessment and small single-arm series. Relevant outcomes are overall survival, disease-specific survival, and treatment-related morbidity and mortality. The 1995 and 1999 TEC Assessments, focusing on allo-HCT as primary and salvage therapy for a variety of solid tumors, found that the available evidence did not permit conclusions about the effect of allo-HCT on patient survival. Since the publication of the TEC Assessments, the evidence for allo-HCT to treat renal cell carcinoma, colorectal cancer, pancreatic cancer, and nasopharyngeal cancer has been limited to small case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (2017-2018) on the tumors addressed in this evidence review do not discuss hematopoietic cell transplantation as a treatment option.  

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation issued guidelines related to indications for autologous and allogeneic hematopoietic cell transplantation. The tumors addressed herein for which the Society has provided recommendations are listed in Table 1.

### Table 1. Recommendations for Use of Autologous and Allogeneic HCT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Option</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Ewing sarcoma, high risk</td>
<td>Allogeneic HCT</td>
<td>Not generally recommended</td>
</tr>
<tr>
<td></td>
<td>Autologous HCT</td>
<td>Standard of care, clinical evidence available</td>
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<tr>
<td>Renal cancer, metastatic</td>
<td>Allogeneic HCT</td>
<td>Developmental</td>
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<tr>
<td></td>
<td>Autologous HCT</td>
<td>Not generally recommended</td>
</tr>
</tbody>
</table>

HCT: hematopoietic cell transplantation.

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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

### Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03236883</td>
<td>Phase I Study of Nonmyeloablative Allogeneic Hematopoietic Stem Cell Transplantation in the Treatment of Pancreatic Cancer</td>
<td>30</td>
<td>Apr 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults 8.01.24

References


<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic progenitor cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Bone marrow; biopsy, needle or trocar</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
<tr>
<td>Q0083</td>
<td>Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit</td>
</tr>
<tr>
<td>Q0084</td>
<td>Chemotherapy administration by infusion technique only, per visit</td>
</tr>
<tr>
<td>Q0085</td>
<td>Chemotherapy administration by both infusion technique and other technique(s) (e.g., subcutaneous, intramuscular, push), per visit</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>

**ICD10 Codes:**

- **C11.0-** Malignant neoplasm of nasopharynx code range
C11.9  Malignant neoplasm of esophagus code range
C15.3-  Malignant neoplasm of stomach code range
C15.9  Malignant neoplasm of colon code range
C16.0-  Malignant neoplasm of stomach code range
C16.9  Malignant neoplasm of pancreas code range
C18.0-  Malignant neoplasm of colon code range
C18.9  Malignant neoplasm of other and unspecified parts of biliary tract code range
C20  Malignant neoplasm of rectum
C23  Malignant neoplasm of gallbladder
C24.0-  Malignant neoplasm of thymus
C24.9  Malignant neoplasm of gallbladder
C25.0-  Malignant neoplasm of accessory sinuses code range
C25.9  Malignant neoplasm of accessory sinuses code range
C31.0-  Malignant neoplasm of bronchus and lung code range
C31.9  Malignant neoplasm of accessory sinuses code range
C34.00-  Malignant melanoma of skin code range
C34.92  Malignant melanoma of skin code range
C37  Malignant neoplasm of thymus
C43.0-  Malignant melanoma of skin code range
C43.9  Malignant melanoma of skin code range
C46.1  Kaposi's sarcoma of soft tissue
C53.0-  Malignant neoplasm of cervix uteri code range
C53.9  Malignant neoplasm of corpus uteri code range
C54.0-  Malignant neoplasm of corpus uteri code range
C54.9  Malignant neoplasm of corpus uteri code range
C55  Malignant neoplasm of uterus, part unspecified
C57.00-  Malignant neoplasm of fallopian tube code range
C57.02  Malignant neoplasm of fallopian tube code range
C61  Malignant neoplasm of prostate
C64.0-  Malignant neoplasm of kidney, except renal pelvis code range
C64.9  Malignant neoplasm of kidney, except renal pelvis code range
C65.0-  Malignant neoplasm of renal pelvis code range
C65.9  Malignant neoplasm of renal pelvis code range
C73  Malignant neoplasm of kidney, except renal pelvis code range
C7a.00-  Malignant neuroendocrine tumors code range
C7b.8  Malignant neuroendocrine tumors code range
C80.1  Malignant (primary) neoplasm, unspecified

**Additional Policy Key Words**
N/A

**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  Policy statement revised to include malignant melanoma to the list of investigational indications.
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  Policy statement revised to add allogeneic stem-cell transplant as investigational. High-dose chemotherapy” removed from title and policy statement.
9/1/10  No policy statement changes.
9/1/11  No policy statement changes.
9/1/12  No policy statement changes.
11/1/12 No policy statement changes.
12/1/13 No policy statement changes.
12/1/14 Updated CPT definitions. No policy statement changes.
12/1/15 No policy statement changes.
1/1/16  No policy statement changes.
3/1/16  No policy statement changes.
12/1/16 No policy statement changes.
12/1/17 Changed “hematopoietic stem cell transplantation” to “hematopoietic cell transplantation” per NCCN terminology change.
12/1/18 No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.