Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Policy Number: 8.01.24  Last Review: 12/2021

Blue KC has developed medical policies that serve as one of the sets of guidelines for coverage decisions. Benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies. Coverage decisions are subject to all terms and conditions of the applicable benefit plan, including specific exclusions and limitations, and to applicable state and/or federal law. Medical policy does not constitute plan authorization, nor is it an explanation of benefits.

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

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:
- Lung cancer, any histology
- Colon cancer
- Rectal cancer
- Pancreatic cancer
- Stomach cancer
- Esophageal cancer
- Gall bladder cancer
- Cancer of the bile duct
- Renal cell cancer
- Cervical cancer
- Uterine cancer
- Cancer of the fallopian tubes
- Prostate cancer
- Nasopharyngeal cancer
- Paranasal sinus cancer
- Neuroendocrine tumors
- Soft tissue sarcomas
- Thyroid tumors
- Tumors of the thymus
- Tumors of unknown primary origin
- Malignant melanoma

**Description of Procedure or Service**

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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 Hematopoietic Cell Transplantation**
For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes a RCT, a number of phase 2 single-arm studies (some of which have been summarized in a systematic review), and a retrospective registry study. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. Although a small phase 2 RCT 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 that the technology results in an improvement in the net health outcome.

For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes several RCTs, and systematic reviews of these studies. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Studies have not reported increased OS for patients with small-cell lung cancer treated with autologous HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Allogeneic Hematopoietic Cell Transplantation**
For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes small single-arm series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. 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 that the technology results in an improvement in the net health outcome.

**Background**

**Hematopoietic Cell Transplantation**
Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune 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 a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord.
blood shortly after delivery of neonates. Cord blood transplantation 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. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

**Conditioning for Hematopoietic Cell Transplantation**

**Conventional Conditioning**
The conventional (“classical”) practice of allo-HCT involves the administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

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

**Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation**
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality.
The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total 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. In this review, the term RIC will refer to all conditioning regimens intended to be nonmyeloablative.

Hematopoietic Cell Transplantation 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 nonmyeloablative 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. 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, 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 PubMed database. The most recent literature update was performed through December 1, 2020.

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 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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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.

**Autologous Hematopoietic Cell Transplantation in Solid Tumors**

**Adult Soft Tissue Sarcomas**

**Clinical Context and Therapy Purpose**
The purpose of autologous hematopoietic cell transplantation (HCT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with soft tissue sarcomas.

The question addressed in this evidence review is: Does autologous HCT improve the net health outcome for patients with soft tissue sarcomas?

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

**Populations**
The relevant population of interest is adults with soft tissue sarcomas.

**Interventions**
The therapy being considered is autologous HCT. Autologous HCT is provided by oncologists and transplant specialists in a tertiary care setting.

**Comparators**
Comparators of interest include the standard of care.

**Outcomes**
The general outcomes of interest are overall survival (OS), disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.
Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
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 16%. A variety of single-agent and combination regimens are used for treatment, with targeted therapies available for some subtypes. 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. These trials were composed of small numbers of patients (range, 2 to 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 the 5-year OS rate was 32%. One study of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease prior to HCT. In another phase 2 study, 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).

Systematic Reviews
In 2017, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas. One RCT assessing 83 patients was identified. In the RCT, OS did not differ statistically between autologous HCT following high-dose and standard-dose chemotherapy (hazard ratio, 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%. Peinemann and Labeit (2014) conducted another systematic review that included an RCT (described above) and 61 single-arm studies. The pooled TRM rate across 61 single-arm studies was 15 (5.1%) of 294.

Nonrandomized Studies
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. After 4 courses of
chemotherapy, 9 patients with at least a partial response underwent high-dose chemotherapy 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 to 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 to 34 months) and 10.8 months (range 0 to 39 months; p=0.027), respectively.

Hartmann et al (2013) reported on results from a phase 2 study of high-dose chemotherapy 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 to 120 months) in surviving patients, median PFS for all patients was 21 months (range, 1 to 94 months) and median OS was 37 months (range, 3 to 120 months), corresponding to 5-year PFS and OS rates of 39% and 48%, respectively.

A 2020 registry study retrospectively evaluated the effectiveness of autologous HCT in the treatment of soft tissue sarcoma using data from the European Society for Blood and Marrow Transplantation database between 1996 and 2016 (N=338). The PFS and OS were 8.3 and 19.8 months, respectively. The PFS and OS at 5 years were 13% and 25%, respectively. Predictors of favorable benefit with HCT were younger age, better remission status before transplantation, and melphalan-based preparative regimens. The authors concluded that autologous HCT should not be performed on patients with soft tissue sarcoma in routine clinical practice without further investigation.

**Section Summary: Adult Soft Tissue Sarcomas**

Overall, 1 RCT, several, small phase 2 studies, and a retrospective registry study 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**

**Clinical Context and Therapy Purpose**

The purpose of autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with small cell lung cancer (SCLC).

The question addressed in this evidence review is: Does autologous HCT improve the net health outcome for patients with SCLC?

The following PICO was used to select literature to inform this review.
**Populations**
The relevant population of interest is adults with SCLC.

**Interventions**
The therapy being considered is autologous HCT. Autologous HCT is provided by oncologists and transplant specialists in a tertiary care setting.

**Comparators**
Comparators of interest include the standards of care.

**Outcomes**
The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Review of Evidence**
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 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 versus 88% in the 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 increase 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 versus 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 (hazard ratio=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**

**Review of Evidence**
Uncontrolled pilot studies of autologous HCT for patients with refractory urothelial carcinoma and recurrent or advanced nasopharyngeal carcinoma has 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 high-dose chemotherapy 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.

**Allogeneic Hematopoietic Cell Transplantation in Solid Tumors**
The evidence base for the treatment of patients with other types of solid tumors (refractory urothelial carcinoma, recurrent or advanced nasopharyngeal carcinoma, and secondary osteosarcoma) using allogeneic hematopoietic cell transplantation (allo-HCT) consists of single-case reports and small series.1,19,20

**Renal Cell Carcinoma**

**Clinical Context and Therapy Purpose**
The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with renal cell carcinoma (RCC).

The question addressed in this evidence review is: Does allo-HCT improve the net health outcome for patients with RCC?

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

**Populations**
The relevant population of interest is adults with RCC.

**Interventions**
The therapy being considered is allo-HCT. Allo-HCT is provided by oncologists and transplant specialists in a tertiary care setting.

**Comparators**
Comparators of interest include the standards of care.

**Outcomes**
The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Review of Evidence**
Metastatic RCC has an extremely poor prognosis, with a median survival of less than 1 year and 5-year survival of approximately 12%. RCC is relatively resistant to chemotherapy, but is susceptible to immune therapy. Interleukin-2 and/or interferon-α have induced responses and long-term PFS rates in 4% to 15% of patients. In addition, 9 targeted therapies are approved by the U.S. Food and Drug Administration for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, bevacizumab, cabozantinib, and lenvatinib. 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. Childs et al (2000) 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 (HLA)-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. Overall response rates 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 HLA-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 7 had progressive disease. The ORR (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (range, 12 to 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: Allogeneic Hematopoietic Cell Transplantation in Renal Cell Carcinoma
Evidence on the use of allo-HCT for RCC is based on multiple case series. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT results in improved OS among RCC patients.

Colorectal Cancer

Clinical Context and Therapy Purpose
The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with colorectal cancer (CRC).

The question addressed in this evidence review is: Does allo-HCT improve the net health outcome for patients with CRC?

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

Populations
The relevant population of interest is adults with CRC.

Interventions
The therapy being considered is allo-HCT. Allo-HCT is provided by oncologists and transplant specialists in a tertiary care setting.

Comparators
Comparators of interest include the standards of care.

**Outcomes**
The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Review of Evidence**
Aglietta et al (2009) reported on their experience with 39 patients with metastatic CRC who underwent RIC allo-HCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation centers. Patients were treated with 1 of 5 RIC regimens. Endpoints assessed were an achievement of mixed chimerism, the incidence of graft-versus-host disease (GVHD), treatment-related mortality, toxicities, OS, and time to treatment failure (in patients who responded to therapy). Patient population characteristics were heterogeneous; pretransplant disease status was a partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. Thirty-eight (97%) patients had previous treatment, some with only chemotherapy and others with surgery, chemotherapy, or both. After the 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 to 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 the 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 versus approximately 120 days for those who had no response (p<0.001). The authors concluded the allo-HCT approach should be reserved for patients with a partial response or stable disease after second-line therapy for metastatic CRC and that second-generation clinical trials in these patients would be warranted.
Section Summary: Allogeneic Hematopoietic Cell Transplantation in Colorectal Cancer
Evidence on the use of allo-HCT for CRC is based on case series. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among CRC patients.

Pancreatic Cancer

Clinical Context and Therapy Purpose
The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with pancreatic cancer.

The question addressed in this evidence review is: Does allo-HCT improve the net health outcome for patients with pancreatic cancer?

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

Populations
The relevant population of interest is adults with pancreatic cancer.

Interventions
The therapy being considered is allo-HCT. Allo-HCT is provided by oncologists and transplant specialists in a tertiary care setting.

Comparators
Comparators of interest include the standards of care.

Outcomes
The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
Review of Evidence

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 a transplant, and 10 patients received localized radiotherapy. After allo-HCT, 1 patient achieved CR, 2 had a partial response, 2 had a 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 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 relationship between longer survival and the infusion of a higher number of CD34-positive cells or the development of chronic GVHD, the authors 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 nonmyeloablative conditioning with allo-HCT. Median age was 54 years (range, 44 to 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; 1 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 to 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 HLA-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: Allogeneic Hematopoietic Cell Transplantation in Pancreatic Cancer
Evidence on the use of allo-HCT for pancreatic cancer is based on multiple case series and a small comparative study. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among pancreatic cancer patients.

**Nasopharyngeal Cancer**

**Clinical Context and Therapy Purpose**
The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with nasopharyngeal cancer.

The question addressed in this evidence review is: Does allo-HCT improve the net health outcome for patients with nasopharyngeal cancer?

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

*Populations*
The relevant population of interest is adults with nasopharyngeal cancer.

*Interventions*
The therapy being considered is allo-HCT. Allo-HCT is provided by oncologists and transplant specialists in a tertiary care setting.

*Comparators*
Comparators of interest include the standards of care.

*Outcomes*
The general outcomes of interest are OS, disease-specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest to monitor relevant outcomes.

*Study Selection Criteria*
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.
Review of Evidence
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 to 57 years), and patients had received a median of 2 previous chemotherapy regimens (range, 1 to 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 to 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: Allogeneic Hematopoietic Cell Transplantation in Nasopharyngeal Cancer
Evidence on the use of allo-HCT for nasopharyngeal cancer is based on a phase 2 trial. In the absence of RCTs, current evidence is insufficient to conclude whether allo-HCT improves OS among nasopharyngeal cancer patients.

Mixed Tumor Types

Review of Evidence
Omazic et al (2016) 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 Hematopoietic Cell Transplantation
For individuals who have adult soft tissue sarcomas who receive autologous HCT, the evidence includes a RCT, a number of phase 2 single-arm studies (some of which have been summarized in a systematic review), and a retrospective registry study. Relevant outcomes are overall survival (OS), disease-specific survival, and treatment-related mortality and morbidity. Although a small phase 2 RCT 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 that the technology results in an improvement in the net health outcome.

For individuals who have small cell lung cancer who receive autologous HCT, the evidence includes several RCTs, and systematic reviews of these studies. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. Studies have not reported increased OS for patients with small-cell lung cancer treated with autologous HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Allogeneic Hematopoietic Cell Transplantation
For individuals who have renal cell carcinoma, colorectal cancer, pancreatic cancer, or nasopharyngeal cancer who receive allo-HCT, the evidence includes small single-arm series. Relevant outcomes are OS, disease-specific survival, and treatment-related mortality and morbidity. 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (2020) on the tumors addressed in this evidence review do not discuss hematopoietic cell transplantation (HCT) as a treatment option.  

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) issued guidelines related to indications for autologous and allogeneic HCT. 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 Hematopoietic Cell Transplantation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment Option</th>
<th>Recommendation</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>
Renal cancer, metastatic  | Allogeneic HCT  | Developmental  |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous HCT</td>
<td></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).”\(^{32}\).

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing and 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><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04530487</td>
<td>Donor Stem Cell Transplant After Chemotherapy for the Treatment of Recurrent or Refractory High-Risk Solid Tumors in Pediatric and Adolescent-Young Adults</td>
<td>40</td>
<td>May 2025</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**REFERENCES**
peripheral blood stem cell rescue in chemo-sensitive patients with metastatic soft tissue sarcomas. Oncology. 2006; 71(1-2): 32-9. PMID 17344669


**Billing Coding/Physician Documentation Information**

<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>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</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>
</tbody>
</table>
Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer

Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

Hematopoietic progenitor cell (HPC); autologous transplantation

Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit

Chemotherapy administration by infusion technique only, per visit

Chemotherapy administration by both infusion technique and other technique(s) (e.g., subcutaneous, intramuscular, push), per visit

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

**ICD10 Codes:**

**C11.0-C11.9** Malignant neoplasm of nasopharynx code range

**C15.3-C15.9** Malignant neoplasm of esophagus code range

**C16.0-C16.9** Malignant neoplasm of stomach code range

**C18.0-C18.9** Malignant neoplasm of colon code range

**C20** Malignant neoplasm of rectum

**C23** Malignant neoplasm of gallbladder

**C24.0-C24.9** Malignant neoplasm of other and unspecified parts of biliary tract code range

**C25.0-C25.9** Malignant neoplasm of pancreas code range

**C31.0-C31.9** Malignant neoplasm of accessory sinuses code range

**C34.00-C34.92** Malignant neoplasm of bronchus and lung code range

**C37** Malignant neoplasm of thymus

**C43.0-C43.9** Malignant melanoma of skin code range

**C46.1** Kaposi's sarcoma of soft tissue

**C53.0-C53.9** Malignant neoplasm of cervix uteri code range

**C54.0-C54.9** Malignant neoplasm of corpus uteri code range

**C55** Malignant neoplasm of uterus, part unspecified

**C57.00-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
C65.0- Malignant neoplasm of renal pelvis code range
C65.9
C73 Malignant neoplasm of thyroid gland
C7a.00- Malignant neuroendocrine tumors code range
C7b.8
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.
12/1/19 No policy statement changes.
12/1/20 No policy statement changes.
12/1/21 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 healthcare providers are independent contractors and are neither employees nor agents Blue KC and are...