Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

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I. Description

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.

II. Criteria/Guidelines

Autologous or allogeneic hematopoietic cell transplant is not covered for the following malignancies in adults as they are not known to improve health outcomes:

A. Lung cancer, any histology  
B. Colon cancer  
C. Rectal cancer  
D. Pancreatic cancer  
E. Stomach cancer  
F. Esophageal cancer  
G. Gall bladder cancer  
H. Cancer of the bile duct  
I. Renal cell cancer  
J. Cervical cancer  
K. Uterine cancer  
L. Cancer of the fallopian tubes  
M. Prostate cancer  
N. Nasopharyngeal cancer  
O. Paranasal sinus cancer  
P. Neuroendocrine tumors  
Q. Soft tissue sarcomas  
R. Thyroid tumors  
S. Tumors of the thymus  
T. Tumors of unknown primary origin  
U. Malignant melanoma

III. Limitations

n/a

IV. Administrative Guidelines

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Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

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V. Scientific Background

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 evidence review 7.01.50.

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
Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

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 events 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, immunosuppressant 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 pretransplant 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 nonrelapse mortality 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 nonrelapse mortality 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 nonmyeloablative, 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 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 (evidence reviews 8.01.23, 8.01.35, and 8.01.28, respectively). 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 (e.g., 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 MEDLINE database. The most recent literature update was performed through November 15, 2018.

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**
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**

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

The question addressed in this evidence review is: does hematopoietic cell transplantation improve health outcomes for adults with adult soft tissue sarcomas?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with adult soft tissue sarcomas.

**Interventions**
The therapy being considered is autologous hematopoietic cell transplantation.

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

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

**Timing**
Follow-up over months to years is of interest to monitor relevant outcomes.
Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults

Setting
Patients are actively managed by oncologists in an outpatient clinical setting.

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

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c. To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

d. Studies with duplicative or overlapping populations were excluded.

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%. 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, 2-55 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%. 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. 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).

In 2017, a Cochrane systematic review evaluated the use of autologous HCT following high-dose chemotherapy (HDC) for nonrhabdomyosarcoma soft tissue sarcomas. One RCT (2012) assessing 83 patients was identified. 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. 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. 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**

**Clinical Context and Therapy Purpose**
The purpose of autologous hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with small cell lung cancer.

The question addressed in this evidence review is: does hematopoietic cell transplantation improve health outcomes for patients with small cell lung cancer?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with small cell lung cancer.

**Interventions**
The therapy being considered is autologous hematopoietic cell transplantation.

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

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

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

**Setting**
Patients are actively managed by oncologists in an outpatient clinical setting.

**Study Selection Criteria**
Methodologically credible studies were selected using the principles described above.
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.14 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.15 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.16 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 carcinoma17 and recurrent or advanced nasopharyngeal carcinoma18 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.19 The 2 HCT-treated patients were alive with no evidence of disease at 33.4 and 56.4 months of follow-up.

ALLOGENIC HCT IN SOLID TUMORS
The evidence base for the treatment of patients with types of solid tumors using allo-HCT consists of single-case reports and small series.1,20,21

Renal Cell Carcinoma
Clinical Context and Therapy Purpose
The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with renal cell carcinoma.
The question addressed in this evidence review is: does allogenic hematopoietic cell transplantation improve health outcomes for patients with renal cell carcinoma?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with renal cell carcinoma.

**Interventions**
The therapy being considered is allogenic hematopoietic cell transplantation.

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

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

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

**Setting**
Patients are actively managed by oncologists in an outpatient clinical setting.

**Study Selection Criteria**
Methodologically credible studies were selected using principles described above.

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%.22 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.21 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.23 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.22 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%.20 Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC.20

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.24 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: Allogenic 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
Clinical Context and Therapy Purpose
The purpose of allogenic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with colorectal cancer.
The question addressed in this evidence review is: does hematopoietic cell transplantation improve health outcomes for patients with colorectal cancer?
The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with colorectal cancer.

Interventions
The therapy being considered is allogenic hematopoietic cell transplantation.

Comparators
Comparators of interest include standard of care.

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

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

Setting
Patients are actively managed by oncologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

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**
**Clinical Context and Therapy Purpose**
The purpose of allogenic hematopoietic cell transplantation 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 hematopoietic cell transplantation improve health outcomes for patients with pancreatic cancer?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with pancreatic cancer.

**Interventions**
The therapy being considered is allogenic hematopoietic cell transplantation.

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

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

**Timing**
Follow-up over months to years is of interest to monitor relevant outcomes.
Setting
Patients are actively managed by oncologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

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.26 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.27 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.28 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**

**Clinical Context and Therapy Purpose**
The purpose of allogenic hematopoietic cell transplantation 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 hematopoietic cell transplantation improve health outcomes for patients with nasopharyngeal cancer?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals with nasopharyngeal cancer.

**Interventions**
The therapy being considered is allogenic hematopoietic cell transplantation.

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

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

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

**Setting**
Patients are actively managed by oncologists in an outpatient clinical setting.

**Study Selection Criteria**
Methodologically credible studies were selected using principles described above.

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 (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 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.

VI. 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 (ASBMT) issued guidelines related to indications for autologous and allogeneic HCT. The tumors addressed herein for which ASBMT has provided recommendations are listed in Table 1.

<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>
<tr>
<td>Renal cancer, metastatic</td>
<td>Allogeneic HCT</td>
<td>Developmental</td>
</tr>
<tr>
<td></td>
<td>Autologous HCT</td>
<td>Not generally recommended</td>
</tr>
</tbody>
</table>

Table 1. Recommendations for Use of Autologous and Allogeneic HCT

HCT: hematopoietic cell transplantation.

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

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

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

Table 2. Summary of Key Trials

NCT: national clinical trial.
VII. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References