Hematopoietic Stem-Cell Transplantation for Miscellaneous Solid Tumors in Adults

I. Description

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to 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 radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). 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 “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on 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).

Conventional Preparative Conditioning for HSCT

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-
body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is a result of a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT 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 prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic HSCT

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 traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT 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.

HSCT in Solid Tumors in Adults

HSCT is an established treatment for certain hematologic malignancies; however, its use in solid tumors in adults continues to be largely experimental. Initial enthusiasm for the use of autologous HSCT for solid tumors has waned with the realization that dose intensification often fails to improve survival, even in tumors with a linear-dose response to chemotherapy. (1) 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. (2)
MISCELLANEOUS SOLID TUMORS IN ADULTS

Hematopoietic SCT as a treatment either of breast, ovarian, or testicular cancer, ependymoma, or malignant glioma is addressed in separate policies, No. 8.01.27, 8.01.23, 8.01.15, 8.01.28, or 8.01.31, respectively. This policy collectively addresses other solid tumors of adults for which SCT has been investigated, including lung cancer; malignant melanoma; tumors of the gastrointestinal tract (include colon, rectum, pancreas, stomach, esophagus, gallbladder, and bile duct); male and female genitourinary systems (e.g., renal cell carcinoma, cervical carcinoma, cancer of the uterus, fallopian tubes, and prostate gland); tumors of the head and neck; soft tissue sarcoma; thyroid tumors; tumors of the thymus; and tumors of unknown primary origin.

II. Policy

A. Autologous or allogeneic hematopoietic stem-cell transplant is not covered for the following malignancies in adults as they are not known to improve health outcomes:
   1. Lung cancer, any histology
   2. Colon cancer
   3. Rectal cancer
   4. Pancreas cancer
   5. Stomach cancer
   6. Esophageal cancer
   7. Gall bladder cancer
   8. Cancer of the bile duct
   9. Renal cell cancer
   10. Cervical cancer
   11. Uterine cancer
   12. Cancer of the fallopian tubes
   13. Prostate cancer
   14. Nasopharyngeal cancer
   15. Paranasal sinus cancer
   16. Neuroendocrine tumors
   17. Soft tissue sarcomas
   18. Thyroid tumors
   19. Tumors of the thymus
   20. Tumors of unknown primary origin
   21. Malignant melanoma

III. Administrative Guidelines

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<td>; autologous</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of</td>
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<td>Chemotherapy drugs code range</td>
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ICD-10 codes are provided for your information. These will not become effective until 10/01/2014.

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IV. Scientific Background

This policy has been updated annually, with the most recent MEDLINE literature search performed through September 26, 2013.

This policy was initially based on a 1995 TEC Assessment that focused on the malignancies listed in the Policy section. (3) The Assessment offered the following conclusions:

• While 125 articles were identified that reported on the results of HSCT 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, advanced colorectal cancer, malignant melanomas, and inoperable gastric cancer.

• The evidence did not permit conclusions as to the effect of HSCT on patient survival.

A 1999 TEC Assessment evaluated the use of allogeneic hematopoietic stem-cell transplantation (HSCT) as a salvage therapy after a failed prior autologous HSCT for solid tumors. (4) Data were inadequate to permit conclusions.

Autologous HSCT in Solid Tumors of Adults

Data on the use of autologous HSCT for the solid tumors of adults addressed in this policy consist mainly of anecdotal reports and small series, and the number of randomized trials is limited.

Adult soft tissue sarcomas

The prognosis of patients with unresectable or metastatic soft tissue sarcomas is poor, with a median survival of approximately 1 year and less than a 10% 5-year survival. (5) In general, dose-intensive doxorubicin and ifosfamide-based regimens have yielded higher response rates and prolonged disease-free survival but not overall survival (OS). (5) However, as it was shown that patients who achieved complete remission (CR) had longer survival; several Phase I and II trials using autologous HSCT were conducted in the 1990s in an attempt to improve outcomes. (5) These trials were composed of small numbers of patients (ranging from 2–55), yielding overall response rates from 20–65%, with CR from 10–43%. The longest reported 5-year progression-free survival
(PFS) rate was 21%, and 5-year OS was 32%. (5) One study of 21 patients with soft tissue sarcoma showed a PFS and OS benefit only in patients with no evidence of disease before undergoing HSCT. (6) The data from these small trials are insufficient to support the use of autologous HSCT in adult patients with soft tissue sarcoma. In 1 additional Phase II study, 21 of 55 (38%) patients responded to doxorubicin-based induction chemotherapy (14% vs. 3%; p=0.003), but estimated OS was not statistically different between those who received an autologous SCT and those who did not. The authors felt that their results warranted a Phase III trial examining the role of HSCT as consolidation therapy in these patients. (7) No Phase III trials involving HSCT for first-line therapy of advanced or metastatic adult soft tissue sarcoma compared to conventional standard-dose chemotherapy were found in a systematic review. (8)

Kasper and colleagues reported the results of a prospective, single institution Phase 2 study that enrolled 34 patients with advanced and/or metastatic soft tissue sarcoma. (9) After 4 courses of chemotherapy, patients with at least a partial response underwent high-dose chemotherapy and autologous HSCT (n=9). All other patients continued chemotherapy for 2 more cycles. The median PFS for patients treated with HSCT was 11.6 months (range 8-15 months) versus 5.6 months for patients treated with standard chemotherapy (p=0.047) and median OS for the 2 groups was 23.7 months (range 12-34 months) versus 10.8 months (range 0-39 months) (p=0.027), respectively. The improved PFS and OS observed in the HSCT group probably reflected chemoresponse; however, this would need to be addressed in a randomized study.

Small-cell lung carcinoma

The interest in treating small-cell lung carcinoma (SCLC) with HSCT stems from the extremely high chemosensitivity and poor prognosis of this tumor type. A Phase III trial of 318 patients with SCLC randomly assigned patients to standard chemotherapy or HSCT. (10) No statistically significant difference in response rates was seen between the 2 groups (80% response rate in the standard arm vs. 88% in the HSCT group [difference: 8%, 95% confidence interval (CI): -1% to 17%; p=0.09]). There was no statistically significant difference in OS between the 2 groups, with a median OS of 13.9 months in the standard arm (95% CI: 12.1 to 15.7 months) versus 14.4 months in the HSCT arm (95% CI: 13.1 to 15.4); p=0.76. One smaller, randomized study and several single-arm studies of HSCT and autologous HSCT for SCLC are summarized in a review article. (11) Overall, the majority of the data from these studies, including the randomized study, showed no increased OS with autologous HSCT.

Jiang and colleagues performed a meta-analysis of the medical literature through October 2008 of English language studies using intensified chemotherapy with autologous hematopoietic progenitors to treat SCLC. (12) The meta-analysis consisted of 5 randomized, controlled trials (RCTs; 3 were Phase III trials and 2 were Phase II), for a total of 641 patients. They found no significant increase in the odds ratio for response rate with autologous transplant versus control chemotherapy (odds ratio [OR]: 1.29; 95% CI: 0.87–1.93; p=0.206). No statistically significant increase in OS was seen among the autologous transplant patients compared to control regimens (hazard ratio [HR]: 0.94; 95% CI: 0.80–1.10; p=0.432). The authors concluded that current evidence does not support the use of intensified chemotherapy and autologous HSCT for treating SCLC.
**Miscellaneous**  
Uncontrolled pilot studies of HSCT for patients with refractory urothelial carcinoma (13) and recurrent or advanced nasopharyngeal carcinoma (14) failed to provide adequate evidence of improved outcomes to alter previous conclusions.

A review article summarizes the data from studies of autologous HSCT for solid tumors in adults. (15)

**Allogeneic HSCT in Solid Tumors of Adults**  
Single-case reports and small series of patients with various types of solid tumors have been treated with allogeneic HSCT, including some of the tumor types addressed in this policy. (1, 2, 16)

**Renal cell carcinoma**  
Metastatic renal cell carcinoma (RCC) has an extremely poor prognosis, with a median survival of less than 1 year and a 5-year survival of less than 5%. (17) RCC is relatively resistant to chemotherapy but is susceptible to immune therapy, and interleukin-2 (IL-2) and/or interferon alpha have induced responses and long-term PFS in 4–15% of patients. (16) Therefore, 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 and coworkers published the first series of patients with RCC treated with nonmyeloablative allogeneic HSCT. (17) The investigators showed regression of the tumor in 10 of 19 (53%) patients with cytokine-refractory, metastatic RCC who received an HLA-identical sibling allogeneic HSCT. 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 allogeneic transplant in metastatic RCC, but most have not shown as high a response rate as the Childs’ et al. study. Overall response rates in these pilot trials have been approximately 25%, with CR rates of approximately 8%. (1) Prospective, randomized trials are needed to assess the net impact of this technique on the survival of patients with cytokine-refractory RCC. (1)

Bregni and colleagues assessed the long-term benefit of allografting in 25 patients with cytokine-refractory metastatic RCC who received an RIC allograft from a sibling who is human leukocyte antigen (HLA) identical. (18) 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 minor response or stable disease, and 7 reported progressive disease. Overall response rate (complete plus partial) was 20%. Six patients died because of transplant-related mortality. Median survival was 336 days (12–2,332+). One-year OS was 48% (95% CI: 28–68), and 5-year OS was 20% (95% CI: 4–36). The authors concluded that allografting is able to 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 the incorporation of these therapies into the transplant regimen.
Colorectal carcinoma
Aglietta and colleagues reported their experience with 39 patients with metastatic colorectal cancer who underwent reduced-intensity conditioning (RIC) allogeneic HSCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation (EBMT) centers. (19) Patients were treated with 1 of 5 different RIC regimens. Endpoints that were assessed were achievement of mixed chimerism, incidence of graft-versus-host disease (GVH), 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 patients (97%) had been previously treated, some with only chemotherapy and others with surgery and/or chemotherapy. After transplant, tumor responses were complete in 2% of patients, partial in 18%, 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: 6–1,020 days), after which time 33 patients had died and 6 were still alive. Tumor progression was the cause of death in 74% of patients. A comparison of OS of patients was performed after stratifying by some 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=0.00018). The authors concluded that the HSCT approach should probably 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 are warranted.

Pancreatic cancer
Kanda and colleagues reported on the efficacy of RIC allogeneic HSCT against advanced pancreatic cancer in 22 patients from 3 transplantation centers in Japan. (20) The RIC regimens differed among the centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 locally advanced disease. All but 1 patient received chemotherapy of various combinations before transplant, and 10 patients received local radiation. After HSCT, 1 patient achieved complete response, 2 patients had partial response, 2 had minor response, and 8 had stable disease, with an overall response rate 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 one fourth of patients with advanced pancreatic cancer who underwent HSCT and that the response was not durable. However, they felt that their observation of a relationship between longer survival and the infusion of a higher number of CD34-positive cells or the development of chronic graft-versus-host disease (GVHD) warrant future studies to enhance the immunologic effect against pancreatic cancer.

Abe and colleagues reported the outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a nonmyeloablative allogeneic peripheral blood HSCT. (21) The conditioning regimen consisted of fludarabine and low-dose total-body irradiation. The median patient 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 HSCT, tumor response was only observed in 2 patients—one had complete disappearance of the primary tumor and 1 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, ranging from post-transplant day 28 to day 209 (median: 96 days). One patient died at day 57 secondary to rupture of the common bile duct from rapid tumor regression. The authors concluded that their study showed a graft-versus-tumor effect but that in order to obtain durable responses, an improved conditioning regimen and new strategies to control tumor growth after nonmyeloablative allogeneic HSCT are needed.

**Nasopharyngeal carcinoma**

Toh and colleagues reported the outcomes of a Phase 2 trial of 21 patients with pretreated metastatic nasopharyngeal carcinoma. (22) Median patient age was 48 years (range: 34-57 years), and patients had received a median of 2 previous chemotherapy regimens (range: 1-8). All patients had extensive metastases. Patients underwent a nonmyeloablative allogeneic HSCT with sibling allografts. Seven patients (33%) 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: 4-1,147 days), the median PFS was 100 days (95% CI: 66-128 days), and median OS was 209 days (95% CI: 128-236 days). One- and 2-year OS rates were 29% and 19%, respectively, comparable to the median 7-14 months OS for metastatic nasopharyngeal patients in the literature treated with salvage chemotherapy without HSCT.

**Clinical Trials**

A September 2013 search of the online site Clinicaltrials.gov showed a Phase III trial of sequential, high-dose chemotherapy followed by peripheral stem-cell or bone marrow transplant compared with chemotherapy alone in treating patients with SCLC (NCT00011921); the recruitment status is unknown. No additional ongoing Phase III clinical trials of chemotherapy followed by HSCT in treating adults with miscellaneous solid tumors listed in this policy were identified.

**Summary**

Hematopoietic stem-cell transplantation (HSCT) is an established treatment for certain hematologic malignancies. The use of autologous HSCT in solid tumors in adults continues to be largely experimental, as most studies have failed to show an improvement in health outcomes. Interest continues in exploring non-myeloablative allogeneic HSCT for a graft-versus-tumor effect of donor-derived T cells in metastatic solid tumors.

In summary, as of September 2013, no trials have been published that would alter the current policy statement; this is considered investigational.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network (NCCN) Guidelines**

As of September 2013, National Comprehensive Cancer Network (NCCN) guidelines on the tumors addressed in this policy do not indicate HSCT as a treatment option. (23)
V. 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.

VI. References

4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage HDC/AlloSCS for relapse following HDC/AuSCS for non-lymphoid solid tumors. TEC Assessments 1999; Volume 14, Tab 11.


