Overview: Stem cells are defined by their ability to self-renew and their ability to produce cells that differentiate. Stem cells can be obtained from human embryos or somatic tissues in the adult. Hematopoietic stem cell transplantation has become a standard means of treating individuals with hematologic malignancies as well as clinical and acquired bone marrow failure, including radiation injury.

Policy and Coverage Criteria:

NOTE: Prior Authorization is NOT required

Harvard Pilgrim covers non-experimental stem cell transplantation and related procedures that are reasonable and medically necessary for individuals with specific conditions. Covered conditions include:

- Autologous stem cell transplantation:
  - Hodgkin lymphoma
  - Multiple myeloma
  - Non-Hodgkin lymphoma
  - Primary (AL) amyloidosis
  - Testicular germ cell tumor
  - Acute promyelocytic leukemia (in second remission) (AML M3)
  - Pediatric cancers

- Allogeneic stem cell transplantation:
  - Acute lymphocytic leukemia (ALL)
  - Acute myeloid leukemia (AML)
  - Aplastic anemia
  - Chronic lymphocytic leukemia (CLL)
  - Chronic myelogenous leukemia (CML)
  - Hodgkin lymphoma
  - Myelodysplastic syndrome
  - Non-Hodgkin lymphoma
  - Advanced myeloproliferative neoplasms/disorders (MPD/MPN) including:
    - Primary myelofibrosis
    - Secondary myelofibrosis (spent phase of P. Vera, ET)
    - Chronic Myelomonocytic leukemia (CMML)

Harvard Pilgrim covers repeat allogeneic stem cell transplantation due to primary graft failure, failure to engraft or rejection.

Harvard Pilgrim covers Hematopoietic stem cell harvesting.

Exclusions: Stem cell transplants for conditions not listed above.

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1 Hematopoietic stem cell harvesting does not include the transplant procedure if cells are harvested for treatment of non-covered conditions.
Supporting Information:

1. Technology Assessment: There are two main types of stem cell transplants: allogeneic and autologous. An allogeneic transplant involves receiving stem cells from a donor who may or may not be related to the recipient. An autologous transplant involves receiving the patient’s own blood stem cells which are collected and stored at a prior time point.

2. Literature Review:

Multiple myeloma:
Kumar et al (2012) did an analysis of early versus delayed autologous transplantation after immunomodulatory agents-based induction therapy in patients with newly diagnosed multiple myeloma. A total of 290 patients with untreated multiple myeloma who received immunomodulatory drugs as an initial therapy were studied. Additionally, 123 patients who received thalidomide-dexamethasone and 167 patients who received lenalidomide-dexamethasone induction prior to stem cell transplantation were studied. The results indicated that transplantation-eligible patients who received immunomodulatory drugs as initial therapy followed by stem cell mobilization, delayed stem cell transplant results in similar overall survival compared with early stem cell transplantation.

Attal et al (1996) conducted a randomized study comparing conventional chemotherapy with high-dose therapy supported by autologous bone marrow transplantation. The study included 200 patients previously untreated patients under the age of 65 who had myeloma. The patients were randomly assigned to either conventional therapy or to high-dose therapy and autologous bone marrow transplantation. The response rate among patients receiving high-dose therapy was 81% compared to 57% in the patients treated with conventional chemotherapy. The probability of event-free survival for 5 years was 28% in the high-dose patients compared to 10% in the conventional patients. The overall estimated rate of survival for 5 years was 52% in the high-dose patients compared to 12% in the conventionally treated patients.

Non-Hodgkin and Hodgkin lymphoma:
Van Kampen et al (2011) analyzed the outcome of patients with diffuse large B-cell non-Hodgkins lymphoma who relapsed after an autologous stem-cell transplantation and treated with an allogeneic stem-cell transplantation. A total of 101 patients were included and followed for a median of 36 months. Myeloablative conditioning regimen was used in 37 patients and RIC was used in 64 patients. Three-year NRM was 28.2%, relapse rate was 30.1%, PFS was 41.7%, and OS was 53.8%. Non-relapse mortality was significantly increased in patients greater than or equal to 45 years and in those with an early relapse (less than 12 months) after ASCT. Relapse rate was significantly higher in refractory patients. A time interval to relapse after ASCT of less than 12 months was associated with lower PFS. The use of RIC regimens was followed by a trend to a lower NRM and a trend to a higher relapse rate, with no differences in PFS and OS. No differences were seen between HLA-identical siblings and matched unrelated donors. The authors concluded that allo-SCT in relapsed DLBCL after ASCT is a promising therapeutic modality. Patients with a long remission after ASCT and with sensitive disease at allo-SCT are the best candidates for this approach.

Lazarus et al (2010) compared the outcomes of 916 patients with diffuse large B-cell lymphoma who were undergoing their first autologous (n=837) or myeloablative allogeneic hematopoietic cell transplant (n=79). Median follow-up for the allogeneic group was 81 months and 60 months for the autologous group. Allogeneic HCT recipients were more likely to have high-risk disease features including higher stage, more prior chemotherapy regimens, and resistant disease. Allogeneic HCT was associated with a higher 1 year treatment-related mortality, treatment failure, and overall mortality. Risk of disease progression was similar between the 2 groups. No significant differences were observed for TRM, progression, progression-free or overall survival for 1-year survivors. Increased risks of TRM and mortality were associated with older age, lower performance score, chemoresistance, and earlier year of transplant.

Mink and Armitage (2001) in their review found that autologous stem cell transplantation has proven to be beneficial in selected patients with Hodgkin’s disease and non-Hodgkin’s lymphoma. Transplantation appears to increase event-free survival in Hodgkin’s disease patients who fail to enter complete remission with initial therapy. For patients with diffuse large-cell non-Hodgkin’s lymphoma, transplantation can be considered standard therapy for relapsed patients if they have chemotherapy-sensitive disease.
Guidelines from Cancer Care Ontario (2009) recommend autologous stem cell transplantation as a treatment option for eligible chemosensitive patients with Hodgkin's lymphoma who are refractory to or who have relapsed after primary chemotherapy. Allogeneic stem cell transplantation is an option for chemosensitive patients with refractory or relapsed Hodgkin's lymphoma who are not candidates for autologous stem cell transplantation or who have a syngeneic donor. The guidelines do not recommend stem cell transplantation as part of primary therapy for Hodgkin's lymphoma.

Laurence and Goldstone (1999) stated that there is an increasing tendency to consider allogeneic transplantation in Hodgkin's disease. Limited graft-versus-Hodgkin's lymphoma effect has been noted, however, this is outweighed by the greatly increased treatment toxicity associated with the allogeneic procedure. Modern low-intensity conditioning regimens may increase the use of allogeneic transplantation for poor-prognosis Hodgkin's lymphoma patients in the future.

Primary (AL) amyloidosis:
Comenzo and Gertz (2002) note that high-dose melphalan with autologous SCT can reverse the disease process in some patients with AL. Due to the poor prognosis that AL patients carry, SCT should be considered for treatment. They reported that STC for AL is applicable to a minority of patients, such as those with limited organ disease and no significant cardiac involvement. Response rates with SCT appear to be higher than those seen in patients treated with traditional melphalan and prednisone.

Sanchorawala et al (2001) developed treatment protocols using high-dose melphalan with autologous SCT to treat AL. Over 200 patients were treated with this regimen and results showed that patients with AL, despite multisystem involvement and compromised organ function can tolerate this aggressive form of treatment. Additionally, this treatment resulted in durable hematologic responses associated with clinical improvement, decreased amyloid-related organ dysfunction, and prolonged survival. They recommend HDM/SCT as the treatment of choice for patients with AL who have good performance status and limited cardiac involvement at the time of diagnosis.

Testicular germ cell tumors:
Einhorn et al. (2007) conducted a retrospective review of 184 patients with metastatic testicular cancer that had progressed after receiving cisplatin-containing combination chemotherapy. 173 patients were given two consecutive courses of high-dose chemotherapy followed by an infusion of autologous peripheral-blood hematopoietic stem cells. The other 11 patients received a single course of the same treatment. Complete remission without relapse was seen in 116 patients at a median follow-up of 48 months. Of the 135 patients who received the treatment as second-line therapy, 94 were disease-free during follow-up; 22 of 49 patients who received treatment as third-line or later therapy were disease free. Among the 184 patients, there were three drug-related deaths during therapy. Acute leukemia developed in three additional patients after therapy. The authors concluded that testicular tumors are potentially curable by means of high-dose chemotherapy plus hematopoietic stem-cell rescue.

Acute promyelocytic leukemia (APL):
de Botton et al. (2005) conducted a retrospective analysis to determine the outcome of 73 relapsing APL patients who underwent autologous or allogeneic SCT during second complete remission. Second complete remission was generally achieved after a salvage regimen of all-trans-retinoic acid (ATRA) combined with chemotherapy. Seven-year relapse-free survival, event-free survival, and overall survival in the autologous SCT group were 79.4%, 60.6%, and 59.8%, with a transplant related mortality of 6%. In the allogeneic SCT group, 7-year RFS, EFS, and OS were 92.3%, 52.2%, and 51.8%, with 39% TRM. OS was significantly better in the autologous SCT group than in the allogeneic SCT group, whereas there was no difference in RFS and EFS. In patients not receiving transplantation, 7-year RFS, EFS, and OS were 38%, 30.4%, and 39.5%, respectively. The authors conclude that the autologous SCT is very effective in APL relapsing after treatment with ATRA if performed in molecular remission. Allogeneic SCT yields few relapses, but is associated with high TRM when performed after salvage with intensive chemotherapy.

Acute lymphocytic leukemia (ALL):
Goldstone et al. (2008) evaluated the role of allogeneic transplantation in adults with ALL compared with autologous transplantation with standard chemotherapy. Patients were randomized to allogeneic transplantation, if they had a compatible sibling donor, or to chemotherapy for 2.5 years versus an autologous transplantation.
Philadelphia chromosome-negative patients with a donor had a 5-year improved overall survival, 53% versus 45%, and the relapse rate was significantly lower. The chemotherapy patients had a higher 5-year overall survival than the autologous transplantation patients (46% and 37%). The authors concluded that sibling donor allogeneic transplantation is the treatment of choice for adult standard-risk ALL in remission. Autologous transplantation has a less favorable outcome than consolidation/maintenance chemotherapy for those without a donor.

Sebban et al (1994) compared allogeneic bone marrow transplantation with other postremission therapies using the result of the HLA typing as a random allocation. Participants were between the age of 15 and 40, had at least one potential sibling donor, and complete response to induction or salvage therapy. Patients with an HLA-identical sibling were assigned to the bone marrow transplantation group and patients without a sibling donor were placed in a control group. The BMT group received allogeneic transplantation and the control group received either chemotherapy or autologous transplantation. The 5-year survival rates were not statistically significantly different between the two groups. When only patients with high-risk ALL were considered, overall survival and disease-free survival were better for the BMT group compared with the control group (5-year overall survival rates, 44% v 20%; 5-year disease-free survival rates, 39% v 14%).

Acute myeloid leukemia (AML):
Vyas et al. (2015) published a review with an overview of important recent data defining molecular factors associated with treatment failure in AML and identifies the emerging importance of leukemia stem cell biology in determining myeloablative and reduced-intensity conditioning regimens. The authors note that the advent of novel conditioning regimens and biological agents with the potential to manipulate the alloreactive response after transplantation present opportunities to reduce transplantation toxicity and disease relapse.

Craddock (2008) notes that allogeneic stem cell transplant represents the most active form of anti-leukemia therapy for AML. Improved outcomes in patients allografted using a myeloblative conditioning regimen are seen due to advances in transplant technology and supportive care. The increased availability of alternative stem cell sources has established allogeneic transplantation as a key therapeutic treatment for patients with AML.

IQWiG (2007) reported that indications of a superiority of stem cell transplantation over chemotherapy can only be inferred for non-myeloablative therapy with a related donor in patients with AML. Additionally, the use of allogeneic stem cell transplantation with dose-reduced conditioning may show an advantage in patients with refractory ALL or AML. It could not be inferred from the data whether the type of donor is important in this context. Non-myeloblatative allogeneic stem cell transplantation with a related donor in patients with AML showed indications of a reduction in mortality compared with conventional chemotherapy. Furthermore, in patients with refractory AML or ALL, indirect indications were available for a prolonged overall survival after dose-reduced stem cell transplantation.

Aplastic anemia:
Li et al (2013) conducted a study investigating the effects of high-dose cyclophosphamide/ATG combined with cord blood infusion as first-line therapy for patients with severe aplastic anemia. A total of 16 treatment-naïve patients were treated with cord blood infusion after high-dose cyclophosphamide and rabbit antithymocyte globulin therapy. Of the 16 patients, 14 had rapid autologous hematopoietic recovery. Of 15 patients who showed a response, all of them achieved treatment-free remission and 9 patients met the criteria for a complete remission. Partial remission was seen in 6 patients.

UpToDate (2014) states in Aplastic anemia: Prognosis and treatment that treatment should include a combination of withdrawal of potentially offending agents, supportive care, and a form of definitive therapy (eg, hematopoietic cell transplantation [HCT]) for patients with severe aplastic anemia or very severe aplastic anemia. For severe and very severe aplastic anemia, HCT is the most effective therapy, but its usefulness declines with age. HCT could be the first choice up to age 40 to 50 if the patient is in otherwise excellent health and has a fully HLA-matched sibling donor.

Myelodysplastic syndrome:
UpToDate states that allogeneic HCT is a primary treatment for high risk myelodysplastic syndrome. Allogeneic HCT is the only treatment for myelodysplastic syndrome with the potential for cure. Allogeneic HCT is recommended for patients with high or very high IPSS-R risk scores and have an available matched donor. The National Comprehensive Cancer Network’s clinical practice guideline on “Myelodysplastic Syndromes” (NCCN, version 2.2013) stated that “allogeneic HSCT from an HLA-matched sibling donor is a preferred approach for
treating a selected group of patients with MDS, particularly those with high-risk disease. Matched non-myeloablative transplant regimens and matched unrelated donor stem-cell transplants are becoming options at some centers to treat these patients. In certain investigative settings, autologous bone marrow or peripheral blood stem cell transplantation is being considered. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been established. Comparative clinical trials are needed to determine these points”.

Chronic lymphocytic leukemia (CLL):
According to UpToDate, “patients with CLL are generally elderly and, due to the relatively benign course of the disease in the majority of patients, only a selected subset is considered for aggressive treatments such as HCT. The determination of transplant eligibility should be made based on a risk-benefit assessment, and the needs and wishes of the patient….In most centers in the United States, patients are considered eligible for nonmyeloablative allogeneic HCT if they are less than 75 years of age, with normal cardiac, liver, and renal function, and have a good performance status (ECOG performance status 0 or 1)”. Moreno et al (2005) investigated whether allogeneic STC may overcome the negative impact of VH genes in the outcome of patients whit CLL. A total of 34 patients with unmutated VH genes were treated with either allogeneic SCT (14) or autologous SCT (20). A total of 16 patients with mutated VH genes were also treated with either allogeneic SCT (9) or autologous SCT (7). The risk of relapse was significantly higher after autologous SCT than after allogeneic SCT. In the unmutated group, 13 of 20 autologous SCT and two of 14 allogeneic SCT patients experienced disease progression, with a risk of relapse at 5 years of 66% (v 17% respectively. The results showed that allogeneic SCT may overcome the unfavorable effect of unmutated VH genes in patient with CLL.

Chronic myelogenous leukemia (CML):
UpToDate states that allogeneic hematopoietic cell transplantation (HCT) is a curative treatment option that comes at the cost of increased potential toxicity and early mortality. This option may be considered in younger patients who have a suitable donor. HCT is also a key component of the treatment of accelerated phase and blast crisis. Allogeneic HCT can achieve excellent long-term control of CML, particularly in patients under the age of 50 who are transplanted in chronic phase within one year of diagnosis. However, as with all allogeneic transplants, there is considerable up-front risk due to toxicity, infection, and GVHD. Mortality risk in the first 100 days following transplantation is in the range of 10 to 20 percent for ideal transplant candidates with fully HLA-matched sibling donors; comorbid conditions increase this risk. Kerbauy et al. (2005) evaluated the outcome of allogeneic HCT in 43 patients with CML. Twenty-one patients received transplants from related donors and 22 from unrelated donors. The results suggested that patients with few or no comorbidities and those who undergo transplantation earlier in the disease course have the highest probability of successful outcome after allogeneic HCT. The European Society for Medical Oncology (ESMO) recommends that the first line of treatment for CML is tyrosine kinase inhibitors (TKI). If TKI treatment fails or is contraindicated, allogeneic hematopoietic stem cell transplantation is the standard second-line treatment.

Myelofibrosis:
Kroger et al. (2015) analyzed the outcomes in 438 patients under the age of 65 years at primary myelofibrosis diagnosis who received ASCT or conventional therapy. Among patients with low risk, the relative risk of dying after receiving ASCT versus those treated with conventional therapies was 5.6. The relative risk for intermediate-1 was 1.6, for intermediate-2 was 0.55, and for high risk was 0.37. The authors concluded that patients with intermediate-2 or high risk primary myelofibrosis benefit from ASCT. Ballen (2012) states in his review that although allogeneic stem cell transplantation is the only known cure for myelofibrosis, other treatment options should be considered in patients with lower risk disease. Patients whose survival is likely to be less than 5 years with conventional therapy and patients with monosomal karyotype are typically considered for transplantation. Kroger and Mesa (2008) state in their review of primary myelofibrosis (PMF) that a curative therapy is only possible with allogeneic hematopoietic stem cell transplantation.

3. Professional Governmental Organizations:

CMS: The following uses of allogeneic HSCT are covered under Medicare:
Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary.

Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.

Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
- Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
- Recurrent or refractory neuroblastoma; or
- Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
- Adequate cardiac, renal, pulmonary, and hepatic function.

Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%.

Nationally Non-Covered Indications

Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non primary AL amyloidosis; and,
- Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §1862(a)(1)(A) of the Act and is not covered under Medicare.


Codes:

38205 - Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206 - Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207 - Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208 - Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209 - Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210 - Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211 - Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212 - Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213 - Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214 - Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215 - Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38240 - Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241 - Hematopoietic progenitor cell (HPC); autologous transplantation
38242 - Allogeneic lymphocyte infusions
38243 - Hematopoietic progenitor cell (HPC); HPC boost

References:


Summary of Changes

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