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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Stem Cell Transplant/Bone Marrow Transplant

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Stem Cell Transplantation Formerly 110.8.1 (110.23)
Local Coverage Determinations (LCD)	Non-Covered Services (L35008). And for facility-based services billed using a UB form, see Non-Covered Services (L34886)
Local Coverage Article	Stem Cell Transplantation for Multiple Myeloma, Myelofibrosis, and Sickle Cell Disease, and Mylodysplastic Syndrome (MM9620)
KPWA Medical Policy - **Stem Cell Transplant for Orthopedic Conditions**	Due to the absence of a NCD, LCD, or other coverage guidance, KPWA has chosen to use their own Clinical Review Criteria, "Stem Cell Transplant for Orthopedic Conditions," for medical necessity determinations. Use the Non-Medicare criteria below.

For Federal Members:

Please refer to the member contract for specific diagnoses and types of stem cell transplants that are covered**.**

For Other Non-Medicare Members

Type Of Transplant	Criteria
Allogenic Bone Marrow/Stem Cells	Has **ONE of the following** conditions: 1) Acute leukemia (ALL) 2) Non-refractory acute leukemia (AML and ALL) 3) Chronic myelogenous leukemia (CML) 4) Chemotherapy sensitive lymphoma 5) Myelodysplastic syndrome 6) Chemotherapy sensitive multiple myeloma 7) Aplastic anemia 8) Neuroblastoma 9) Severe combined immuno deficiency (SCID, IgM) 10) Wiscott-Aldrich syndrome 11) Metastatic neuroblastoma 12) Certain conditions where, established, published evidence of efficacy is present and based on the evidence the designated medical staff reviewer has determined coverage should be approved.
Autologous Bone Marrow/Stem	Has **ONE of the following** conditions:

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Type Of Transplant	Criteria
Cells	1) Acute mylogenous leukemia (AML) 2) Chemotherapy sensitive lymphoma 3) Resistant non-Hodgkin's lymphomas 4) Chemotherapy sensitive Hodgkin's disease (relapsed) 5) Recurrent or refractory neuroblastoma 6) Wilm's Tumor (relapsed, metastatic) 7) Germ cell tumor (relapsed, metastatic) 8) Ewings Sarcoma /Primitive neuroectodermal (PNET) 9) Chemotherapy sensitive or with Durie-Salmon stage II or III newly diagnosed multiple myeloma with age <78 and adequate cardiac, renal, pulmonary and hepatic function
Stem Cell Transplantation for Amyloidosis	Must meet **ALL of the following** criteria: 1) Less than 70 years of age 2) No significant cardiac disease: a) Ejection fractions greater than 55%; b) Intraventricular septum thickness less than 16 mm; c) Bilirubin less than 2.0.
Multiple Myeloma	Must meet **ALL of the following** criteria: 1) Member must not have significant co-morbid medical conditions. 2) Karnofsky performance score of 60% or greater, or SWOG/ECOG score of 0 - 1; and 3) Members should not have had extensive prior chemotherapy or radiation therapy (i.e., more than a year of alkylator-based chemotherapy and/or more than two prior alkylator-based chemotherapies; radiation therapy to no more than 10% of marrow producing bones). 4) Adequate liver function; bilirubin, SGOT less than 1.5x normal. 5) The member has adequate major organ function: a) Cardiac function (left ventricular ejection fraction equal or greater than 45% predicted); b) Pulmonary function [forced vital capacity (FVC) / forced expiratory volume (FEV1)/diffusion capacity of the lung for carbon monoxide (DLCO) equal to or greater than 50%]; c) Members should not have evidence of cardiac amyloid; d) Members with indolent myeloma, smoldering myeloma, and monoclonal gammopathy of uncertain significance [MGUS] are excluded. Does not have **ONE of the following**: 1) Presence of another life-limiting cancer or cancer that may become life-threatening with immunosuppression; or 2) Presence of psychiatric disease that would interfere with the member's ability to comply with the therapeutic regimen; or 3) Inadequate cardiac, renal, pulmonary, or hepatic function

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Type Of Transplant	Criteria
Multiple Myeloma - tandem transplant	Must meet **ALL of the following** criteria: 1) Member must not have significant co-morbid medical conditions. 2) Karnofsky performance score of 60% or greater, or SWOG/ECOG score of 0 - 1; and 3) Members should not have had extensive prior chemotherapy or radiation therapy (i.e., more than a year of alkylator-based chemotherapy and/or more than two prior alkylator-based chemotherapies; radiation therapy to no more than 10% of marrow producing bones). 4) Adequate liver function; bilirubin, SGOT less than 1.5x normal. 5) The member has adequate major organ function: a) Cardiac function (left ventricular ejection fraction equal or greater than 45% predicted); b) Pulmonary function [forced vital capacity (FVC) / forced expiratory volume (FEV1)/diffusion capacity of the lung for carbon monoxide (DLCO) equal to or greater than 50%]; c) Members should not have evidence of cardiac amyloid; 6) Members with indolent myeloma, smoldering myeloma, and monoclonal gammopathy of uncertain significance [MGUS] are excluded. 7) Members with Durie-Salmon stage I (one bone lesion), II or III myeloma. 8) Planned 1st and 2nd transplantation should be within a 6-month period. Does not have **ONE of the following**: 1) Presence of another life-limiting cancer or cancer that may become life-threatening with immunosuppression; or 2) Presence of psychiatric disease that would interfere with the member's ability to comply with the therapeutic regimen; or 3) Inadequate cardiac, renal, pulmonary, or hepatic function
High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis **High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer** **Scleroderma**	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)	Nonmyeloablative allogeneic stem cell transplantation (mini-allograft) may be covered in patients who would otherwise meet patient selection criteria for **High-Dose Chemotherapy and Allogeneic Stem Cell Transplantation.** Persons who are unable to tolerate a conventional allogeneic stem cell transplant may be able to tolerate a milder, non-myeloablative conditioning regimen. Non-myeloablative bone marrow/peripheral stem cell transplantation (mini-allograft) is not covered for any of the following diseases because it has not been established that allogeneic transplant (conventional ASCT or mini-allograft) is effective in treating these conditions: • **Melanoma and Renal Cell Carcinoma** • **Multiple Myeloma** There is insufficient evidence to cover tandem transplantation of high dose chemotherapy with autologous stem cell support followed by nonmyeloablative allogeneic stem cell transplantation.

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Type Of Transplant	Criteria
Allogeneic Bone Marrow Transplantation (BMT) in Low-Grade Lymphoma (LGL) and Chronic Lymphocytic Leukemia (CLL)	Because of the lack of evidence, this service will be considered on a case by case basis following a second opinion evaluation. In young patients with rapidly progressing disease requests for coverage should be reviewed via a second opinion, expert case review. The physician reviewer will use the information resulting from the second opinion to determine if coverage should be approved on an exception basis.
Stem Cell Transplant for Orthopedic Conditions	Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue or joint.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KPWA will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Evidence and Source Documents

Allogeneic Bone Marrow Transplantation (BMT) in Low-Grade Lymphoma (LGL) and Chronic Lymphocytic Leukemia (CLL)
Autologous Stem Cell Transplant (SCT)/Bone Marrow Transplant for Chronic Myeloid Leukemia (CML)
High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis
High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer
Multiple Myeloma
Nonablative SCT for Renal Cell Carcinoma and Melanoma
Scleroderma
Stem Cell Transplantation for Amyloidosis
Stem Cell Transplantation for Autoimmune Diseases

Background

A stem cell transplant is the infusion of healthy stem cells into your body. A stem cell transplant may be necessary if the bone marrow stops working and doesn't produce enough healthy stem cells. Stem cell transplantation is necessary following high dose chemotherapy/radiation for several types of cancers. Stem cells are a type of cell that divide and develop into one of the three main types of cells found in the blood; red blood cells, white blood cells, and platelets.

Although the procedure generally is called a stem cell transplant, it's also known as a bone marrow transplant or an umbilical cord blood transplant, depending on the source of the stem cells. Stem cell transplants can use cells from your own body (autologous stem cell transplant) or they can utilize stem cells from donors (allogenic stem cell transplant).

The first step in the process of stem cell transplantation is the collection of stem cells from a patient or a donor. When a patient's own stem cells are used, they are frozen and stored until needed. Stem cells can be collected from a donor when they are needed. The patient then receives high-dose chemotherapy and the stem cells are infused into the patient's bloodstream. The stem cells travel to the bone marrow and begin to produce new blood cells, replacing the normal cells lost during high-dose chemotherapy.

Medical Technology Assessment Committee (MTAC)

Autologous Stem Cell Transplant (SCT)/Bone Marrow Transplant for Chronic Myeloid Leukemia (CML)

BACKGROUND

Chronic myelogenous leukemia (CML) also referred to as chronic myeloid leukemia, chronic myelocytic leukemia, and chronic granulocyte leukemia, is a malignant disease of the hematopoietic stem cells. Most cases occur in adults, with a median age of approximately 50 years. CML has three stages: Chronic phase, accelerated phase, and blast phase, which is always fatal. Transition from one phase to the other occurs gradually over a period of one year or more however it may take place abruptly and is called the blast crisis. The average survival of CML is 42 months, however after the development of the accelerated phase, survival is usually less than a year, and only a few months after blastic transformation.

There are many treatment options available, yet management of CML remains unsatisfactory. Currently accepted therapies for the chronic phase range from relatively non-toxic oral medications, to alpha interferon-based therapy

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or aggressive high-dose chemotherapy with allogenic stem transplantation. Conventional chemotherapy usually does not produce a lasting complete remission, nor does it prevent or delay transformation of the disease from an indolent chronic phase to an accelerated phase and blast crisis. High dose therapy, at concentrations much higher than conventional therapy, is highly toxic to the bone marrow and may be able to alter the haematopoietic environment to favor regrowth of normal stem cells. The most effective treatment of CML is high dose chemotherapy with allogenic bone marrow transplantation, which may result in long-term disease free survival in the majority of patients who receive transplants early in the chronic phase (Meloni 2001). Unfortunately, allogenic stem cell transplantation is limited by donor availability and toxicity of graft-versus-host disease (GVHD), especially in the elderly. Transplant of stem cells derived from a patient's own marrow or peripheral blood (autologous transplant) avoids the need for an HLA-matched donor, has less complications, and shorter hospital stay than allogenic transplantations. Autologous bone marrow transplantation was started at the University of Colorado in 1977, and has been successful in other haematological malignancies.

10/9/2002: MTAC REVIEW
Autologous Stem Cell Transplant (SCT)/Bone Marrow Transplant for Chronic Myeloid Leukemia (CML)
Evidence Conclusion: The studies reviewed do not provide sufficient evidence to determine the efficacy and outcome of stem cell/ bone marrow transplantation for CML patients. Results of these studies suggest that this treatment modality has a potential to lead to hematologic and cytogenic response, as well as prolonging survival of younger patients in the first chronic stage. However, the reviewed studies are limited by their design, size, length of follow-up, and lack of a control or comparison group. Their results should be interpreted cautiously. Prospective randomized clinical trials with larger patient sizes, and longer follow-up is needed to assess and compare efficacy of autologous transplantation for CML with other approaches.
The search yielded 79 articles. Articles were selected based on study type. The majority were reviews, opinion pieces, editorials, letters, and commentaries. Some used different adjunct therapies for conditioning, treatment or immunotherapy.
Articles: The literature search did not reveal any randomized controlled trials, or meta-analyses. A study that pooled data from 8 marrow transplant center, and four case series with patients who underwent an autograft after intensive chemotherapy, were identified. The studies with the larger size and/ or better methodology were selected for critical appraisal. Khouri IF, Kantarjian HM, Talpaz M, et al. Results of high dose chemotherapy and unpurged autologous stem cell transplantation in 73 patients with chronic myelogenous leukemia. The MD Anderson experience. *Bone marrow transplantation* 1996;17:1775-779. See Evidence Table McGlave PB, De Fabritis P, Deisseroth A, et al. Autologous transplants chronic myeloid leukemia: results from eight transplant groups. *Lancet* 1994;34:1486-1488. See Evidence Table Singer IO, Franklin IM, Clark RE, et al. Autologous transplantation in chronic myeloid leukemia using peripheral blood stem cells. *British Journal of Haematology* 1998;102:1359-1362. See Evidence Table

The use of autologous SCT/BMT in the treatment of CML does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis
BACKGROUND
Multiple Sclerosis (MS) is a progressive debilitating neurological disorder with a relapsing and remitting course of symptoms including tremor. MS is caused by a progressive and selective destruction of myelin that is thought to occur as a result of an autoimmune reaction. It is typically treated with anti-inflammatory and immunosuppressive agents such as high-dose steroids, cyclophosphamide and as a last resort, beta-interferon. The symptomatic improvement seen following immune suppression led investigators to propose treating MS by destroying the immune system with high dose chemotherapy and then restoring immune function by replacement of the patients own stem cells. Patient's stem cells are mobilized by administering cyclophosphamide and then harvested for later reinfusion. High doses of chemotherapeutic agents are then used to destroy the patient's immune system. The previously harvested stem cells are then re-infused and in most cases, restore normal immunologic function.

8/11/1999: MTAC REVIEW
High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis
Evidence Conclusion: Evidence identification was conducted by searching MEDLINE from 1995-1999 using terms multiple sclerosis, hematopoetic stem cell transplant, stem cells, and transplantation. The author of the largest case series was contacted to ascertain if there were any studies published which had not been previously identified.
Articles: The best, published scientific evidence consists of a case series of 15 patients with a history of progressive MS for a median of 6 yrs and severe disability. Most of the patients were observed for only a few months after treatment; only 3 of the 15 patients were followed for a year or more. Six months after treatment, 3 of

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13 patients had improved by at least 1.5 points on the Kurtzke Disability Status Scale (0=normal to 10=death from MS) and 1 patient had worsened by 1 point. The mean improvement was less than 1 point at 6 months. Using the Scripps Neurological Rating Scale (0-100) eight of 13 patients improved by 20 points or more at 6 months. The mean improvement was 22.5 points at 6 months. Transplant-related complications included sepsis and anaphylactic shock. This case series does not prove that high dose chemotherapy with stem cell rescue is an effective treatment for MS. Because some patients who carry the diagnosis of progressive MS may experience neurologic improvement without treatment, one cannot be certain that the clinical improvement documented in this study was the result of the therapeutic intervention. Fassas A, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. *Bone Marrow Transplantation* 1997;20:631-8 See Evidence Table

The use of stem cell transplantation in the treatment of multiple sclerosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer

BACKGROUND

The success of high-dose chemotherapy (HDC) for some hematologic cancers stimulated hope that high doses might also improve survival for patients with metastatic breast cancer. The usual approach for the use of high-dose chemotherapy in breast cancer treatment involves the delivery of maximally tolerable doses of a combination of chemotherapy drugs supported by autologous stem or bone marrow cells. In the last 10 years, dozens of phase I and II studies have been reported. There is agreement that HDC is highly toxic, with treatment-related mortality rates in the range of 5% to 30%. There has been serious disagreement, however, about whether existing evidence establishes that the treatment is effective in improving survival and whether the benefits, if they exist, outweigh the harms. The strongest “evidence” of the efficacy of this treatment came from the work of a South African researcher, Dr. Bezwoda. He recently admitted falsifying data in a randomized controlled trial (RCT) in which he had reported that HDC, done in conjunction with bone marrow transplantation, prolonged the lives of some women with advanced breast cancer. None of the other peer-reviewed RCTs have shown a statistically significant advantage for HDC with stem-cell support over conventional chemotherapy. The current Kaiser Permanente clinical indications include using high-dose chemotherapy for breast cancer treatment. The purpose of this review is to critically appraise the existing literature in order to evaluate the efficacy of this treatment regimen.

6/14/2000: MTAC REVIEW

High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer

Evidence Conclusion: A critical appraisal of the existing evidence strongly suggests that high-dose chemotherapy with stem or bone marrow cell support is not beneficial in breast cancer treatment. Studies that have shown some benefit, even in a subset of patients, have numerous threats to validity, including selection bias, small sample sizes, and confounding. Furthermore, the procedure is associated with significant morbidity and mortality, a high rate of relapse, and potentially irreversible long-term effects. The available evidence therefore does not permit conclusions about the effectiveness of this treatment. The final results of large, multi-center, randomized trials may help determine the role of HDC in the management of breast cancer.
Articles: Articles were selected based on study type. There were four randomized controlled trials (RCTs) comparing HDC with “standard treatment” as well as several prospective studies, and meta-analyses. Since the results from the randomized trials were essentially similar (except for studies by Dr. Bezwoda), evidence tables were created for one randomized controlled trial and one prospective phase II trial– 1 each with favorable and unfavorable findings (attached). Reviews, editorials, and comments were reviewed, but no evidence tables were created. *The articles (RCT) selected for critical appraisal include:* Nieto et al. Phase II trial of high-dose chemotherapy with autologous stem cell transplant for Stage IV Breast Cancer with Minimal Metastatic Disease. Clinical Cancer Research 1999 July; 5:1731-1737. See Evidence Table Staudmauer et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. NEJM 2000;342:1069-76. See Evidence Table

The use of high-dose chemotherapy followed by stem-cell transplant treatment of breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* (fails criteria 2).

Multiple Myeloma

BACKGROUND

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for almost 10% of hematologic malignancies, and about 1% of all cancer related deaths. There are approximately 50,000 patients with MM in the United States, and it is estimated that there are more than 15,000 new cases per year. The median age at onset is 66 years, and

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only 2% of patients are younger than 40 years at diagnosis. Their median survival is around 3 years, but some patients can live longer than 10 years (Hari 2006, Terpos 2005, Levy 2005, Rajkumar 2005). High dose chemotherapy (HDT) with autologous stem cell transplant (ASCT) is regarded as the standard of care for newly diagnosed myeloma in patients less than 65 years of age. This can prolong remission duration, progression free survival, and overall survival in a significant proportion of patients. However, the therapy is not curative, and survivors eventually experience relapse or progression of the disease. Only a few patients who undergo the procedure are free of the disease for more than 10 years. Recurrences are primarily due to the failure of chemotherapy to eradicate all myeloma cells. Once relapse has occurred, survival is limited despite the use of novel drugs and salvage regimens (Terpos 2005, Hari 2006, Gerull 2005, Bruno 2007). Researchers have found that allogenic hematopoietic cell transplantation, following high dose conditioning may lead to lower relapse rates and longer remissions, and possibly cure of MM. This is presumably due to the graft versus myeloma effects, in addition to the advantage of a tumor-free graft. However, only a small percentage of patients are candidates for allogenic transplants because of age, availability of an HLA-matched sibling donor, and adequate organ function. Conventional allogenic transplantation is also limited by the high transplant-related morbidity and mortality associated with myeloablative conditioning regimens, and graft versus host disease (GVHD). The risk of treatment-related mortality (TRM) could be as high as 30-60% (Bruno 2007, Gerull 2005). Reduced intensity (non-myeloablative) conditioning was thus developed to decrease toxicity and treatment related mortality while maintaining the graft versus tumor effect. However, relapses are frequent when non-myeloablative allogenic transplantation is used in patients with a relapsed or refractory disease (Harousseau 2005). In the past few years, researchers have been studying the efficacy and feasibility of performing non-myeloablative allogenic transplantation after one or two procedures of high dose therapy and ASCT. This concept combines the advantage of cytoreduction achieved with the high-dose autologous transplant with the graft versus myeloma effect of the non-myeloablative allogenic transplant in order to eradicate the minimal residual disease with a goal of long-term disease control, and hopefully cure of MM (Maloney 2003, Hari 2006).

04/10/2002: MTAC REVIEW
Multiple Myeloma
Evidence Conclusion: The case series reviewed do not provide sufficient evidence to determine the efficacy and outcome of mini stem cell transplantation, for multiple myeloma. In addition to the small sample size of the study reviewed, and the relatively short follow-up, case series provide the lowest grade of evidence; they lack a control or comparison group and are prone to selection bias, and confounding.
The search yielded 59 articles. Articles were selected based on study type. Most of the articles were reviews, opinion pieces, editorials, letters, and commentaries. The literature did not reveal any randomized controlled trials, or meta-analyses. There was only one case series on MM patients who had mini-stem transplantation.
Articles:*The following article was critically appraised:* Badros A, et al. High response rate in refractory and poor-risk multiple myeloma after transplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. *Blood* 2001;97:2574-9. See Evidence Table

The use of mini stem cell transplant in the treatment of multiple myeloma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/05/2005: MTAC REVIEW
Multiple Myeloma
Evidence Conclusion: Gerull and colleagues (2005) reported the outcomes of 52 MM patients who received non-myeloablative allogenic transplantation between September 1999 and June 2003, at the University of Heidelberg, Germany. The ages of the patients ranged from 36 to 68 years, and they were followed up for a median of 567 days, (479 days for survivors). At the time of analysis only 24 patients (46%) were alive. The results show that the estimated overall survival at 18 months was 41%, and the estimate progression free survival also at 18 month was 29.4%. 38% developed GVDH grade II-IV, and 70% developed chronic GVHD. This study only presents an analysis of a retrospective data of a heterogeneous group of patients treated at one center, followed up for a relatively short time, and the treatment was not compared to an alternative therapy or no treatment.
Articles: Compiled data in Djulbegovic's systematic review on 103 patients with MM show complete response rate of 37%, acute GVHD among 59%, and chronic GVHD among 18% of the patients.
Gerull S, Goerner M, Benner A, et al. Long-term outcome of nonmyeloablative allogenic transplantation in patients with high –risk multiple myeloma Bone Marrow Transplant 2005;doi: 10.1038/sj.bmt.1705161 See Evidence Table

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The use of non-myeloablative stem cell transplantation (mini-stem cell transplantation) in the treatment of hematologic malignancies, acute myeloid leukemia, myelodyplastic syndrome, multiple myeloma, lymphomas, renal cell carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/06/2007: MTAC REVIEW
Multiple Myeloma
Evidence Conclusion: To date, there is no high quality evidence on the safety and efficacy of mini stem cell transplantation with a preceding autologous hematopoietic cell transplantation for the treatment of multiple myeloma. There are no published randomized controlled trials that compare allografting with non-myeloablative conditioning following a cytoreductive autograft to double (tandem) autologous stem cell transplantation, or to an alternative therapy. The best published evidence to date consists of one nonrandomized controlled trial (Bruno 2007) and another study that compared two series of patients (Garban 2006). Bruno and colleagues' study (2007) recruited 245 patients < 65 years old with stage II or III multiple myeloma, from five centers in Italy. 199 of the participants had at least one sibling, and only 104 received treatment. The patients were not randomized to the treatment groups. Those with an HLA-identical sibling (n=58, 56%) received a myeloablative autograft followed by a nonmyeloablative allograft transplantation, and patients without an HLA identical sibling (n=46, 44%) received two consecutive myeloablative doses conditioning, each followed by an autologous stem cell transplant. The primary endpoints of the study were overall survival and event-free survival. After a median follow-up of 45 months, the overall survival and event free survival were significantly longer in patients who completed the autograft-allograft treatment versus those who completed the high-dose, double autograft treatment. The results of the study also show that there was no significant difference between the two groups in the treatment related deaths, but the autograft-allograft transplantation was associated with high rates ofacute and chronic GVHD (43% and 64% respectively). Thechronic GVHD was extensive among 36% of the patients in that treatment group. Garban and colleagues (2006) compared the results of two multicenter trials (IFM99-03 and IFM99-04). The studies recruited patients <65 years old with newly diagnosed MM, and with two adverse prognostic factors. After 3-4 cycles of induction regimens, the participants received their first ASCT. Then, according to the availability of an HLA-identical sibling, they either received an allograft with a nonmyeloablative conditioning (IFM99-03 trial) or a second allograft with or without anti-IL-6 monoclonal antibody (IFM99-04 trial). After a relatively short follow-up period (median 24 months) the authors compared the outcomes from both studies. The results showed no significant difference between the two strategies in terms of overall survival or event free survival. Patients were not randomized to one of the two transplantation protocols, and the study was not powered to detect any significant difference between these two treatments. The two studies have their limitations, and it is hard to compare their results because different regimens were used for conditioning, and different intensities of immune suppression drugs were used. Moreover, the participants in Garban's study had a high risk myeloma unlike those in Bruno's study who were at intermediate or good risk. Large randomized controlled trials would provide higher quality evidence the efficacy and safety of allografting with nonmyeloablative conditioning following a cytoreductive autograft, to other alternative therapies e.g. the tandem autograft used in these non- randomized studies.
Articles: The search yielded around 140 articles. Several were not related to the current review, and many others were review articles. There were two nonrandomized studies with comparison groups, and several prospective and retrospective case series. The two trials with comparison groups were selected for critical appraisal.
Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. NEJM 2007; 356:1110-1120. See Evidence Table. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-related allograft (IFM99-03 trial) with tandem autologous stem sell transplantation (IFM99-04 trial) in high risk de novo multiple myeloma. Blood 2006;107:3474-3480 See Evidence Table.

The use of mini stem cell transplant in the treatment of multiple myeloma meets the *Kaiser Permanente Medical Technology Assessment Criteria.*

Nonablative SCT for Renal Cell Carcinoma and Melanoma
BACKGROUND
Considerable morbidity and mortality are consequences of the myeloblative chemoradiotherapy utilized in conventional allogenic marrow transplantation. This has generally restricted such potentially curative treatment to patients <50-55 years with normal organ function. Recent studies indicate that purine-analogue based non-myeloblative regimens are sufficiently immunosuppressive to facilitate allogeneic donor cell engraftment. Non-ablative (non-myeloblative) bone marrow transplantation involves engrafting an HLA-matched donor's marrow into a host to obtain a graft versus tumor effect. Engraftment is done with just immunosuppressive therapy (not high dose chemotherapy) initially and then is stopped. This procedure is not FDA-approved, but Dr. Feldman states that FDA approval is not necessary.
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10/11/2000: MTAC REVIEW
Nonablative SCT for Renal Cell Carcinoma and Melanoma
Evidence Conclusion: Given the limitations of the studies presented (small sample sizes, potential selection bias, and possible toxicity associated with the procedure) there is insufficient evidence at this time to determine the efficacy of non-myeloblative allogeneic peripheral-blood stem-cell transplantation. As stated by one of the investigators "non-myeloblative allogeneic peripheral-blood stem-cell transplantation should remain an investigational approach for the treatment of metastatic renal-cell carcinoma.
Articles: Articles were selected based on study type. There was one prospective study and one case series. Evidence tables were created for these 2 studies (attached). Review articles and commentaries were reviewed, but no evidence tables were created. *The articles selected for critical appraisal include:* Childs et al. Regression of metastatic renal-cell carcinoma after non-myeloblative allogeneic peripheral-blood stem-cell transplantation. NEJM 2000; 343: 750-758. See Evidence Table Grigg et al. "Mini-allografts" for hematological malignancies: an alternative to conventional myeloblative marrow transplantation. Aust NZ J Med 1999; 29:308-314. See Evidence Table

The use of Non-ablative Stem Cell Transplantation for Melanoma and Renal Cell Carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* (fails criteria 2 for effectiveness).

12/05/2005: MTAC REVIEW
Nonablative SCT for Renal Cell Carcinoma and Melanoma
Evidence Conclusion: Peccatori and colleagues (2005), analyzed data from 70 patients who received reduced intensity stem cell transplantation for advanced renal cell carcinoma in nine European transplant centers from 1999 to 2003. The authors selected ten variables and entered them in a univariate analysis. Those significantly correlated with survival were entered in a multivariate regression analysis, which suggested three prognostic parameters according to which the authors categorized the study patients as high or low risk groups. After a median follow-up of ten months the median survival (according to Kaplan Meier estimates) was 23 months for the low-risk group, and 3.5 months for the high-risk group. The study population was a highly selected group of patients, and the therapy was not compared to an alternative strategy or to no treatment.
Articles: Peccatori J, Barkholt, Demirer, et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogenic stem cell transplantation. Cancer 2005;104:2099-2103. See Evidence Table

The use of nonmyeloablative stem cell transplantation (mini-stem cell transplantation) in the treatment of hematologic malignancies, acute myeloid leukemia, myelodyplastic syndrome, multiple myeloma, lymphomas, and renal cell carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)

BACKGROUND

Myeloablative combination of high-dose chemo-radiotherapy followed by allogenic hematopoietic stem-cell transplantation (HSCT) is an effective treatment for various hematological malignancies resistant to conventional doses of chemotherapy. Conventional allogenic HSCT involves the use of maximally tolerated myeloablative chemotherapy and/or radiotherapy conditioning regimens to eradicate the underlying disease, while the allograft serves to rescue patients from marrow aplasia induced by the treatment (Georges 2002). However, high-dose chemo/radiotherapy with allogenic HSCT is associated with significant morbidity and mortality due to toxicity of the preparative regimen, the accompanying immunodeficiency, and graft versus host disease (GVHD). The associated toxicity and mortality have limited the use of allogenic HSCT to young medically fit patients. Many patients who may potentially benefit from the treatment are not eligible for the procedure due to age, co-morbid illnesses, poor organ function, or extensive previous chemotherapy. Several hematologic malignancies e.g. acute myelogenous leukemia, chronic myelogenous leukemia, and myeloblastic syndromes peak in the seventh decade of life, which limits the options for these older patients to palliative chemotherapy (Burroughs 2004). There are indications that the main therapeutic effect of allogenic HSCT may not be solely due to the physical elimination of all tumor cells by the high doses of conditioning regimen, but also to T-cell-mediated graft-versus tumor (GVT) or graft versus leukemia (GVL) effect. Researchers also found that donor lymphocyte infusions (DLIs) can re-induce remissions in patients who have relapsed following allogenic transplantation. This has led to the exploration of non-myeloablative allogenic stem cell transplantation (NST) as a safer alternative to conventional high-dose transplant regimens, and as a means to exploit the GVD effect to cure malignancies with elimination of the need for hazardous conditioning. Conditioning regimens are referred to as non-myeloablative if they are not given at a dose that will result in permanent marrow aplasia i.e. will not completely eradicate host hematopoiesis and immunity. They have a potent immunosuppressive effect but are only mildly myelodepressive and commonly

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result in induction of mixed chimerism (Shimoni, 2002). A truly nonmyeloablative regimen is defined as a regimen that allows relatively prompt hematopoietic recovery (in less than 28 days) without a transplant and upon engraftment mixed chimerism should occur (Khouri, 2004). Clinical data indicate that NST lowers the incidence and severity of GVHD which is main cause of treatment related mortality. NST regimens were originally designed for older patients or any patient ineligible for standard conditioning due to other co-morbidities or risks. Now, they may also be considered for patients where high-dose chemo/radiotherapy is unnecessary. Reduced intensity regimens usually consist of purine analogues e.g. fludarabine combined with alkylating agents such as busulfan, or cyclophosphamide. A second approach which is nonablative, consists of 2 Gy total body irradiation either alone or combination with fludarabine. Mini stem cell transplant was reviewed by MTAC on 4/10/2002, and 6/11/2003 and did not pass MTAC criteria. They studies reviewed were all small case series with short follow-up and no control or comparison groups.

06/11/2003: MTAC REVIEW
Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)
Evidence Conclusion: There is insufficient published literature to provide evidence on the use of non-myeloablative stem cell/bone marrow transplant for cervical cancer, myeloproliferative disease, HIV patients, severe combined immunodeficiency, Wiskott-Aldrich syndrome, amyloidosis, or other metabolic disorders. There is also insufficient evidence to determine the efficacy and outcome of mini stem cell/ bone marrow transplantation in treating hematological diseases. In addition to the small sample sizes of the series reviewed, and the relatively short follow-up duration, case series provide the lowest grade of evidence; they lack a control or comparison group and are prone to selection and observation bias.
Articles: The search yielded almost 600 articles. The majority were reviews, opinion pieces, or dealt with the technical aspects of the procedure. The literature search did not reveal any randomized controlled trials, or non-randomized comparative studies. All were small case series or case reports with small sample sizes. The search did not reveal any studies or reports on non-myeloablative transplantation for cervical cancer, amyloidosis, or other metabolic disorders. There were very few case reports with 1-8 patients each on PNP deficiency, Wiskott-Aldrich syndrome, ADA severe combined immunodeficiency, DiGeorge syndrome, and HIV infection. The search also revealed a series of 50 patients with Fanconi's anemia conditioned with a non-myeloablative regimen before the transplantation, and with six years of follow-up. Most of the series published were on leukemias, lymphomas, and multiple myeloma (MM). Mini transplant for MM was reviewed by the committee in 4/10/2002, and did not pass MTAC criteria. The case series on the individual leukemias and lymphomas were too small. The two largest series that included older patients and/or patients with other co-morbid conditions, with a variety of hematological diseases were selected for critical appraisal, as well as the series on Fanconi's anemia. *The following articles were critically appraised:* McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose toxic therapy with graft-versus-tumor effects. *Blood* 2001;97:3390-3400. See Evidence Table Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and Fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood* 2001;101:1620-1629. See Evidence Table Socie G, Devergie A, Girinski T, et al. Transplantation for Fanconi's anemia: long-term follow-up of fifty patients transplanted from a sibling donor after low-dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *British Journal of Hematology* 1998;103:249-255. See Evidence Table

The use of non-myeloablative stem cell/bone marrow transplant in the treatment of cervical cancer, myeloproliferative disease, HIV patients, severe combined immunodeficiency, Wiskott-Aldrich syndrome, amyloidosis, or other metabolic disorders does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/05/2005: MTAC REVIEW
Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)
Evidence Conclusion: Hematological malignancies Djulbegovic and colleagues' systematic review included 25 case series with a total of 603 patients with a wide range of hematologic malignancies. Only 4 studies included more than 10 patients with the same malignancy. The authors compiled some extractable data from the heterogeneous studies included, but apparently they did not use standard meta-analysis techniques. The studies had different inclusion/exclusion criteria, used different conditioning, treatment, and immunosuppression regimens, and the patients had variable co-morbid conditions. The authors did not discuss any evaluation of the quality of the studies, or how they pooled the data. The results of the compiled data showed that 44% of the patients had complete response to the treatment, and that 51% developed acute GVHD, and 23% developed chronic GVHD. Some analyses were done for specific diseases. Three recent studies (Alyea 2005, Sorror 2004,
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and Diaconescu 2004) compared the outcomes of transplantations after nonablative and ablative regimens in different centers in the US. They were not randomized rather retrospective analysis of cohorts of patients selected to receive the nonablative conditioning regimens, and matched controls conditioned with myeloablative regimens. The results of these analyses showed that patients who received the nonablative conditioning had lower transplant related mortality, nonrelapse mortality rates, and experienced less or comparable grade II to IV toxicities despite the fact that they were older, had more advanced diseases, and more co-morbidities. The three studies had specific questions, defined inclusion/exclusion criteria, and comparison groups, yet they were only observational, and subject to bias and confounding. Randomization would have been ideal, but is not an option as patients conditioned with nonablative regimen are not candidates for the standard ablative conditioning. Specific hematologic diseases: AML Sayer et al's article (2003)reported on 113 patients with AML treated at ten German transplant centers between February 1998 and December 2000, using reduced intensity conditioning regimens. Their ages ranged from 16-67 years, and the survivors had a median follow-up of 12 months (range 46-937 days). The authors analyzed the outcomes of this retrospective series of patients, and did not include a control group. There were multiple baseline variations in the patient and disease characteristics, and according to the authors, inclusion criteria differed between centers, with no clear or accurate definition for who is or is not eligible for the standard conditioning regimen. The results of the analysis show that the estimated 2-year overall survival, and event free survival after the procedure were 32% and 29% respectively. The rate of acute GVHD grades II-IV was 42%, and that of chronic GVHD was 32.7%. The latter was extensive among 6.5% of the patients. The compiled data in Djulbegovic's systematic review (N=62) showed a 66% complete response rate, 36% acute GVHD, and 23% chronic GVHD. AML/MDS De Lima and colleagues (2004)compared the outcomes of 94 patients with AML or MDS treated with either a reduced intensity or a nonablative conditioning regimen. The average ages were 61 and 54 years in the two regimens respectively, and the median duration of the follow-up was 40 months. It was a retrospective analysis and there were several baseline variations in the patients' and disease characteristics among the recipients of the two regimens, as well as some variations in the source of transplant received. The analysis had the advantage of comparing two regimens but the disadvantage of non-randomization, which is a potential source of selection bias. The regimens were not compared to the conventional ablative regimen. Overall, the results of the study indicate a 3-year actuarial progressive free survival rate of 34%, and overall survival of 27% with no statistically significant difference between the two groups. The rate of acute GVHD grade II-IV was 36%, and that of chronic GVHD was 34% for all patients. Ho and colleagues (2004) presented the results of 62 patients who received a reduced intensity allogenic hematopoietic stem cell transplant for MDS, and AML with multilineage dysplasia, in one center in UK. The donors were either siblings or unrelated volunteers. The ages of the patients ranged from 5-60 years with a median of 53 years, and they were followed up for a median of 348 days (range 37-1,495 days). The overall survival was 89% at 100 days, 80% at 200 days, and 74% at one year. The corresponding disease free survival rates were 84%, 67% and 62% respectively, and the nonrelapse mortality at one year was 15%. None of the related recipients, and 9% of the unrelated recipients developed acute GVHD. Extensive chronic GVHD developed in only 3% of the population. The nonmyeloablative transplantation was not compared to any other therapeutic strategy, or to no treatment. Multiple myeloma Gerull and colleagues (2005) reported the outcomes of 52 MM patients who received nonmyeloablative allogenic transplantation between September 1999 and June 2003, at the University of Heidelberg, Germany. The ages of the patients ranged from 36 to 68 years, and they were followed up for a median of 567 days, (479 days for survivors). At the time of analysis only 24 patients (46%) were alive. The results show that the estimated overall survival at 18 months was 41%, and the estimate progression free survival also at 18 month was 29.4%. 38% developed GVDH grade II-IV, and 70% developed chronic GVHD. This study only presents an analysis of a retrospective data of a heterogeneous group of patients treated at one center, followed up for a relatively short time, and the treatment was not compared to an alternative therapy or no treatment. Compiled data in Djulbegovic's systematic review on 103 patients with MM show complete response rate of 37%, acute GVHD among 59%, and chronic GVHD among 18% of the patients. NHL Khouri and colleagues (2004) reported on the results of a prospective cohort of patients treated with nonmyeloablative stem cell transplantation for advanced recurrent NHL after a prior response to conventional treatment study, in one center in Texas. Their ages ranged from 21 –68 years with a median of 55 years. 20 (41%) patients dad follicular lymphoma, 15 (31%) had transformed or de novo diffuse large cell lymphoma, and 14 (28%) had mantle cell lymphoma. All had received a prior treatment with a range of 1-4 chemotherapy regimens (median 4), and 17% had failed a previous autologous transplant. The results of the analysis show that hematopoietic recovery occurred within 25 days (median 11 days), 22% had a persistent or progressive disease after transplantation, 20% developed acute GVHD, and 36% developed chronic extensive GVHD. 2% of the patients died within 100 days and 6% after 100 days. The study was small, with potential biases, and no comparison group. Compiled data from Djulbegovic's systematic review on patients with NHL (N=103) show complete response rate of 31%, acute GVHD among 50%, and chronic GVHD among 12% of the patients. Renal cell carcinoma: Peccatori and colleagues (2005), analyzed data from 70 patients who received reduced intensity stem cell transplantation for advanced renal cell carcinoma in nine European transplant centers from 1999 to 2003. The authors selected ten variables and entered them in a univariate analysis. Those
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significantly correlated with survival were entered in a multivariate regression analysis, which suggested three prognostic parameters according to which the authors categorized the study patients as high or low risk groups. After a median follow-up of ten months the median survival (according to Kaplan Meier estimates) was 23 months for the low-risk group, and 3.5 months for the high-risk group. The study population was a highly selected group of patients, and the therapy was not compared to an alternative strategy or to no treatment. Conclusion: The results of the published studies do not provide strong evidence on the efficacy of nonmyeloablative stem cell transplants in improving the net health outcomes of patients with hematopoietic malignancies. The studies were all observational case series with different selection criteria. Those with comparison groups were retrospective and nonrandomized. There were significant differences in patients' characteristics, disease characteristics and stages, and other co-morbid conditions. Moreover, there was no clear or accurate definition for who is, or is not eligible for the standard conditioning regimen. Multiple conditioning regimens, treatments, and GVHD prophylaxis regimens were used. Randomized controlled trials might not be an option among these patients who are not candidates for transplantation with the conventional conditioning regimens. Overall, the results of existing published studies, with their limitations, indicate good overall survival and disease free survival rates, and reduced regimen-related toxicities with the nonmyeloablative stem cell transplantations despite the older age of the patients and presence of more co-morbid conditions and/or organ dysfunctions.
The search yielded more than 600 articles. The majority were reviews, opinion pieces, or dealt with the technical aspects of the procedure. The literature did not reveal any randomized controlled trials. One systematic review of case series was identified. Other published studies were small prospective or retrospective case series or case reports, and most lacked control groups. Most studies included patients with a wide range of hematologic malignancies, and only a few included cohorts of patients with a specific disease. Hematological malignancies: The search identified several case series with population sizes ranging from six patients to just over 100. There was one systematic review with some compiling of the results of smaller studies, and several other prospective and retrospective series. The systematic review, and the studies with comparison groups were selected for critical appraisal. *Specific disease results:* Acute myeloid leukemia and myelodysplastic syndrome (AML/ MDS)
The search revealed few studies on patients with AML or MDS. The series with comparison groups, large number of patients, and published in full text were reviewed.
Articles: The literature search for articles published on MM after the last review revealed a recent case series with 52 patients (Gerull 2005), and smaller series with less than 25 patients. Gerull's study was selected for critical appraisal. Lymphoma: Hodgkin's disease (HD) and Non Hodgkin's lymphoma (NHL):
There were few small case series on either HD, and /or NHL. The largest series with 49 patients was selected for the review. Other hematopoietic diseases Studies on other hematologic conditions included small number of patients and were not critically appraised. Renal cell carcinoma (RCC): There were several reports on small case series (sizes ranging from 6-18) of patients with RCC treated with nonmyeloablative stem cell transplantation. Very recently a larger analysis of 70 patients with advanced RCC was published. The latter was critically reviewed. *The following articles were selected for critical appraisal:* Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogenic hematopoietic cell transplantation for patients older than 50 years of age. Blood 2005;105:1810-1814. See Evidence Table Diaconescu R, Flowers CR, Storer B et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. Blood 2004;104:1550-1558. See Evidence Table de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogenic hematopoietic stem cell transplantation. Blood 2004;104:865-872. See Evidence Table Djulbegovic B, Seidenfeld J, Bonnel C, Kumar A. Nonmyeloablative allogenic stem-cell transplantation for hematologic malignancies. A systematic review. Cancer Control. 2003 10:17-41. See Evidence Table Gerull S, Goerner M, Benner A, et al. Long-term outcome of nonmyeloablative allogenic transplantation in patients with high –risk multiple myeloma Bone Marrow Transplant 2005;doi: 10.1038/sj.bmt.1705161 (advance online publication) See Evidence Table Ho AYL, Pagliuca A, Kenyon M, et al. Reduced intensity allogenic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning. Blood 2004;104:1616-1623. See Evidence Table Khouri IF, and Champlin RE Nonmyeloablative stem cell transplantation for lymphoma. Seminars in Oncology 2004;31:22-26. See Evidence Table Peccatori J, Barkholt, Demirer, et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogenic stem cell transplantation. Cancer 2005;104:2099-2103. See Evidence Table Sorror ML, Maris MB, Storer B et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. Blood 2004;104:961-968. See Evidence Table Sayer HG, Kroger M, Beyer J, et al. Reduced intensity conditioning for allogenic hematopoietic stem cell transplantation in patients with acute myeloid leukemia: disease status by marrow blasts is the strongest prognostic factor. Bone marrow transplant 2003;31:1089-1095. See Evidence Table

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The use of nonmyeloablative stem cell transplantation (mini-stem cell transplantation) in the treatment of hematologic malignancies, acute myeloid leukemia, myelodyplastic syndrome, Melanoma and Renal Cell Carcinoma, Multiple Myeloma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Scleroderma

BACKGROUND

Scleroderma is a rare multi-system autoimmune disease notable for a pathologic fibrotic thickening of the skin and abnormalities of the vasculature and visceral organs. It is progressive, debilitating, and often fatal. There is no cure and treatment usually involves anti-inflammatory and immunosupressive agents such as high dose steroids. The symptomatic improvement seen following immune suppression led investigators to propose treatment of scleroderma by destroying the immune system with high-dose chemotherapy and then restoring immune function by infusing the patient's own stem cells.The patient's stem cells are mobilized by administering cyclophosphamide and then harvested for later reinfusion. High doses of chemotherapeutic agents are then used to destroy the patient's immune system. The previously harvested stem cells are then re-infused and in most cases, restore normal immunologic function.

8/11/1999: MTAC REVIEW

Scleroderma

Evidence Conclusion: Evidence identification was conducted by searching MEDLINE from 1995-1999 using terms multiple sclerosis, hematopoetic stem cell transplant, stem cells, and transplantation. The author of the largest case series was contacted to ascertain if there were any studies published which had not been previously identified.

Articles: The best, published scientific evidence consists of a case series of 15 patients with a history of progressive MS for a median of 6 yrs and severe disability. Most of the patients were observed for only a few months after treatment; only 3 of the 15 patients were followed for a year or more. Six months after treatment, 3 of 13 patients had improved by at least 1.5 points on the Kurtzke Disability Status Scale (0=normal to 10=death from MS) and 1 patient had worsened by 1 point. The mean improvement was less than 1 point at 6 months. Using the Scripps Neurological Rating Scale (0-100) eight of 13 patients improved by 20 points or more at 6 months. The mean improvement was 22.5 points at 6 months. Transplant-related complications included sepsis and anaphylactic shock. This case series does not prove that high dose chemotherapy with stem cell rescue is an effective treatment for MS. Because some patients who carry the diagnosis of progressive MS may experience neurologic improvement without treatment, one cannot be certain that the clinical improvement documented in this study was the result of the therapeutic intervention. Fassas A, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. *Bone Marrow Transplantation* 1997;20:631-8 See Evidence Table

The use of stem cell transplantation in the treatment of multiple sclerosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Stem Cell Transplantation for Amyloidosis

BACKGROUND

Amyloid is a protein that is made by plasma cells in bone marrow. There are several forms of amyloid; one form is lighter than the others. A disease called amyloidosis occurs when too much of the light form of amyloid is produced and the proteins are deposited in the body's organs and tissues. The most common form is primary (AL) amyloidosis that mainly affects the heart, lungs, skin, tongue, nerves and intestines. The accumulation of amyloid causes progressive disruption of the normal tissue structure and ultimately leads to organ failure. Signs and symptoms of amyloidosis are generally nonspecific and are seen in a small proportion of patients. Many patients have multi-system involvement at diagnosis. The natural history of amyloidosis is that it is fatal within 2 years in about 80% of patients. It is a rare condition, affecting approximately 3000 people in the United States per year (United Kingdom Myeloma Forum, 2004; Gertz & Rajkumar, 2002; Mayoclinic.com). The standard treatment for AL amyloidosis is oral melphalan. However, this has a clinical response rate of only about 20% and is not effective for rapidly progressive disease (Dispenzieri et al., 2004; Skinner et al., 2004). The use of high-dose intravenous melphalan, followed by autologous stem cell transplantation was first described in the literature in 1996. Stem cells are collected from the patient's bone marrow before high-dose chemotherapy is administered. Early case series found a substantially higher procedure-related mortality than for patients with multiple myeloma. There is also significant risk associated with stem cell mobilization in patients with AL amyloidosis. However, positive results have been reported in patients who survive the treatment. A United Kingdom guideline does not recommend high-dose chemotherapy and stem cell transplantation for patients with any of the following: over 70 years old, more than two organ systems involved, symptomatic cardiac neuropathy or autonomic neuropathy, dialysis-dependent renal failure or a history of GI bleeding due to amyloid (United Kingdom Myeloma Forum,

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2004).The amyloid patients who are eligible for high-dose chemotherapy and stem cell transplantation are a highly select group. Researchers at the Mayo Clinic reviewed their records and found that fewer than 20% of their amyloidosis patients would have theoretically been eligible for the treatment. The researchers point out that, due to the better prognosis of this group compared to other amyloidosis patients, a randomized controlled trial or study with a matched control group is needed to determine efficacy (Gertz & Rajkumar, 2002).

10/13/2004: MTAC REVIEW

Stem Cell Transplantation for Amyloidosis

Evidence Conclusion: There is evidence from a matched case-control study (Dispenzieri) that high-dose chemotherapy and autologous stem cell transplantation improves survival in patients with amyloidosis. Two-year survival in the Dispenzieri study was 70% in the cases and 40% in controls. Matching reduces, but does not eliminate the potential for selection bias. The evidence is weaker than that provided by a randomized controlled trial which can control for group differences on unmeasured characteristics. There were no appropriate randomized controlled trials or other matched studies. Experts in amyloidosis have stressed the need for randomized or matched studies because of the better prognosis of patients with amyloidosis who are eligible for high-dose chemotherapy and stem cell transplantation. The Skinner study was a descriptive analysis of one institution's experience over 8 years. It did not match patients and is therefore subject to selection bias.
The searched yielded 112 articles, many of which were reviews, opinion pieces, dealt with technical aspects of the treatment or addressed similar treatments or diseases. There was one randomized controlled trial. In the RCT, both groups received high-dose chemotherapy and stem cell transplantation, one initially and the other after two rounds of oral chemotherapy. Since there was no comparison to a different treatment, this study was not reviewed.
Articles: The best, most relevant, evidence was a matched case-control study comparing patients who did and did not receive high-dose chemotherapy and stem cell transplantation. This was critically appraised, along with the largest case series. *The two studies reviewed were:* Dispenzieri A, Kyle RA, Lacy MQ et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood* 2004; 103: 3960-3963. See Evidence Table Skinner M, Sanchorawala V, Seldin DC et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: An 8-year study. *Ann Intern Med* 2004; 140: 85-93. See Evidence Table

The use of stem cell transplantation in the treatment of amyloidosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Stem Cell Transplantation for Autoimmune Diseases

BACKGROUND

Autoimmune diseases (ADs) encompass a heterogeneous group of chronic systemic disorders with different genetic, environmental, and individual etiological factors, as well as different prognoses. They are highly prevalent, have a significant morbidity and mortality, and a considerable economic cost to the patients and the community. For most ADs the exact pathophysiology remains unclear and may vary from one disease to another. It is known however, that some immunogenic predisposition combined with environmental triggers is required to initiate most ADs (Gratwohl 2005, Tyndall 2005). Among the categories of autoimmune diseases are neurological disorders, rheumatologial disorders, vasculitis, hematological immunocytopenias, gastrointestinal and others. Multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis are the most commonly encountered ADs. Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system. It is the most frequent cause of neurologic disability in young adults in Western countries. MS is thought to be an autoimmune disease, but there are other views for its origin. The disease causes gradual demyelination and axonal degeneration in the brain and spinal cord. The clinical course of MS is widely variable ranging from isolated episodes with no clinical significance to impaired mobility, disability, and reduction of life expectancy in more severe cases (Saccardi 2005). Several therapies have been utilized, but currently immunosuppression and immunomodulation are the only recognized forms of therapy. Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that affects predominantly young women and may range from a relatively mild condition to a severe life threatening disease involving major organs such as the kidney, brain, lung, or the hematopoietic system. Renal involvement is the most common severe manifestation; it occurs in 30-50% of patients and. and has a 9-25% rate of end-stage renal failure. Lupus has no cure, but in the majority of cases it is responsive to treatment with immunosuppression and steroids. It was reported that more than half of the patients have permanent organ damage, much of which is due to, or increased by corticosteroids (Petri 2006). The disease often pursues a relapsing or refractory course that results in poor quality of life and reduced survival (Jayne 2004). Systemic sclerosis (SSc) also known as scleroderma, is a clinically heterogeneous autoimmune disease characterized by excessive collagen deposits in the skin and internal organs. It was found that rapidly progressive SSc, both in the cutaneous and diffuse forms, has a 5-year survival rate of

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20-80%, and a 10-year survival rate of 15-65% (Farge 2004). Various treatments were tried, but none has been proven effective in preventing disease progression or reversing fibrosis. Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease of undetermined etiology that affects about 1% of the population (Snowden 2004). It primarily involves the synovial membranes and articular structures of multiple joints leading to substantial pain, joint destruction, and loss of mobility. RA often affects extra-articular tissues throughout the body including the skin, blood vessels, muscles, heart, and lungs. It is a disorder for which there is no cure, and current treatment methods focus on relieving pain, reducing inflammation, slowing joint damage and improving function, and sense of well-being. Patients with severe diseases however may not be controlled by the conventional methods used. In general, immunosuppression and immunomodulation are the basic therapeutic strategies for autoimmune diseases, and are usually successful. However, certain patients do not respond to these therapies, and require more toxic drugs to achieve or maintain remissions (Gratwohl A, 2005). The ability to use immunosuppressive or cytotoxic therapy over longer periods of time is limited due to infections, bone marrow toxicity, and secondary malignancy. In the last decade, hematopoietic stem cell transplantation (HSCT) after intense immunosuppression has been proposed as a possible strategy for the treatment of severe or refractory autoimmune diseases. HSCT is a short name for a complex multi-step treatment aimed at resetting the dysregulated immune system of patients with severe autoimmune diseases. Various protocols have been tried depending on the underlying disease and experience of the transplant centers. The majority were based on autologous HSCT which is a 3-step procedure involving collection of hemopoeitic stem cells (HSCs), treating the patient with a conditioning regimen to eliminate self-reacting lymphocytes within the body, and finally re-infusion of the previously frozen autologous stem cells. The source of stem cells may be bone marrow, cord blood, or peripheral blood. Peripheral blood stem cells harvest contains more progenitor and mature lymphocytes and gives more rapid hematological and immunological reconstitution. It is also simpler to collect than bone marrow harvests, and do not require general anesthesia (Tyndall 2005). Once mobilized, the stem cells are harvested, manipulated, and may be cryopreserved. The conditioning regimens used are designed to specifically target the lymphocytes (lymphoablative regimens) or to destroy the entire hematopoietic bone marrow compartment (myeloablative regimen). However, the goal of autologous HSCT for AD is to generate new self-tolerant lymphocytes after elimination of self or autoreactive lymphocytes within the patient, rather than ablate and reconstitute the entire hematopoietic compartment (Burt 2006). A major difference between lymphoablative and myeloablative regimens is the use of total body irradiation. The latter may have deleterious effects among patients especially those with SSc as radiation can cause microvascular damage. After conditioning the patient, the graft is thawed and infused. Hematological reconstitution occurs in 10-12 days, and immunological reconstitution takes longer. HSCT for autoimmune diseases is still in its experimental stages, it has a learning curve, and some researchers are concerned that it might not be feasible, or too toxic in immunosuppressed patients with organ involvement from the underlying AD.

04/2/2007: MTAC REVIEW
Stem Cell Transplantation for Autoimmune Diseases
Evidence Conclusion: The use of hematopoietic stem cell transplantation in the treatment of severe refractory autoimmune diseases is still in the experimental phase. All published studies were case reports or small case series that assessed the feasibility, tolerance, and efficacy of the transplant for patients with ADs. None included a control or comparison group. These cases were registered in databases, the largest of which is The European Bone Marrow transplant/European league against Rheumatism (EBMT/EULAR) registry. Gratwohl, and colleagues (2005), analyzed the data recorded in the EBMT registry up to 2003. It included records for 473 patients treated in 110 transplant centers in 21 countries in Europe and Australia. This has the advantage of studying the efficacy and safety of the procedure in a larger series of patients, but has several limitations including the variations between these centers in the eligibility criteria, patient characteristics, autoimmune disorders and stage of the disease, protocol and techniques of the transplant, and experience in performing the procedure as well as others. Moreover the analysis did not include a control or comparison group that received an alternative or no treatment. The results of the analysis show that the overall treatment mortality was 7% and with large differences between the ADs (20% for immune thrombocytopenia, 14% for SLE, and 2% for rheumatoid arthritis). The results also show that the more aggressive conditioning regimen was statistically associated with slowing down of the disease progression, but was also associated with a significantly higher treatment related mortality. In conclusion the published studies to date do not provide sufficient evidence to determine the efficacy and safety and long term net health outcome of stem cell transplantation in the treatment of autoimmune diseases.
All studies on HSCT published to date are phase I-II clinical trials (only case series with no controls). Phase III RCTs are underway in US and Europe, and none has been completed and reported to date. The published reports are mostly on one or two individual cases or small case series that either included patients with a specific autoimmune disease, or grouped patients with different ADs who underwent an autologous HSCT. The inclusion/exclusion criteria, patient characteristics, protocol, and technique of the procedure, as well as the population size and duration of follow-up varied between the trials. The population sizes of the case series ranged
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from as low as 8 patients with miscellaneous ADs in one study with 12 months of follow-up, to 50 patients with systemic lupus erythematosus who were followed up for a mean of 29 months. The majority of the published reports collected their data from databases, and had overlapping population. The largest database is The European Bone Marrow transplant/European League Against Rheumatism (EBMT/EULAR) International Stem Cell Project database. Other databases for stem transplantation include the International Bone Marrow Transplantation (IBMTR) registry, and the Autologous Blood and Marrow Transplant Registry (ABMTR) in the US, the Sylvia Lawry Center, Munich, Germany database, and the International Autoimmune Diseases stem cell Database in Basel, Switzerland.

Articles: There is insufficient literature on reduced intensity conditioning and allogenic HSCT. The article (Gratwohl 2005) that analyzed data on the efficacy and toxicity of HSCT recorded in the EBMT database was critically appraised. Gratwohl A, Bocelli-Tyndall C, Fassa A, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases. Bone Marrow Transplantation 2005; 35:869-879. See Evidence Table

The use of stem cell transplantation in the treatment of autoimmune disorders does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Allogeneic Bone Marrow Transplantation (BMT) in Low-Grade Lymphoma (LGL) and Chronic Lymphocytic Leukemia (CLL)

BACKGROUND

Low grade lymphomas (LGL) are indolent malignancies with a high rate of initial response to treatment and median survival duration of 7-10 years. Radiation therapy or the combination of radiation and chemotherapy can produce durable remissions in some patients with stage I, II, or III disease. Patients with an advanced, recurrent or refractory disease have a poor prognosis. The use of myeloablative therapy and autologous BMT showed positive results among patients with recurrent disease, but not among those with an extensive bone marrow involvement or refractory disease. Allogenic BMT is viewed as an attractive option to treat younger patients with refractory or recurrent disease, with the idea that donor lymphoid cells can potentially mediate a graft versus lymphoma (GVL) effect, and achieve a long term disease control. Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Europe and North America. Although it is generally considered a disease of the elderly, it is increasingly recognized in younger patients. CLL is characterized by the heterogeneity in clinical behavior and life expectancy for those affected by it. Treatment options for CLL are the use of steroids, alkylating agents, or observation. Bone marrow transplantation is not a standard therapy but autologous and allogeneic transplants are increasingly being used. BMT which induces high remission rates, yet a small percentage of durable remissions, is an appealing treatment strategy for younger patients. The use of tumor free grafts constitutes an obvious advantage of allogeneic over autologous bone transplantation. The allogeneic transplantation however, has considerable treatment-related complications and mortality, particularly graft-versus-host disease (GVHD) and infections. Other reasons for the infrequent use of allogeneic BMT are the frequent lack of a matched sibling donor and the higher cost of care. Many questions regarding patient selection, efficacy and outcome are still unresolved. Description: Before BMT, patients are conditioned with total body irradiation (TBI) containing regimens, which may also include cyclophosphamide. After the infusion of the bone marrow, immune suppression is generally used for GVHD. The bone marrow source is human leukocyte antigen (HLA) matched sibling, syngeneic donor, or HLA matched unrelated donor.

12/12/2001: MTAC REVIEW

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Evidence Conclusion: The case series reviewed do not provide sufficient evidence to determine the efficacy and outcome of allogenic bone marrow transplantation, for low-grade lymphoma, and chronic lymphocytic leukemia. Case series provide the least grade of evidence; they lack a control or comparison group and are prone to selection bias, and confounding. The search yielded 161 articles. Articles were selected based on study type. Most of the articles were reviews, opinion pieces, editorials, letters, and commentaries.

Articles: The literature did not reveal any randomized controlled trials, or meta-analyses, only clinical reports and case series. Evidence tables were created for the following articles: van Besien, K ; et al. Allogeneic bone marrow transplantation for low-grade lymphoma. Blood 1998; 92: 1832-6 See Evidence Table Toze CL, Shepherd JD, et al. Allogeneic bone marrow transplantation for low-grade lymphoma and chronic lymphocytic leukemia. Bone Marrow Transplantation 2000; 25: 605-612. See Evidence Table

The use of allogenic bone marrow transplantation in the treatment of low-grade lymphoma, and chronic lymphocytic leukemia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Date Created	Date Reviewed	Date Last Revised
5/1996	05/04/2010 MDCRPC, 03/01/2011 MDCRPC, 01/03/2012MDCRPC, 11/06/2012MDCRPC ,09/03/2013MPC,07/01/2014MPC, 05/05/2015MPC, 03/01/2016MPC, 01/03/2017MPC, 11/07/2017MPC , 10/02/2018MPC	02/06/2018

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
02/06/2018	MPC approved criteria for Mesenchymal Stem Cell Therapy for orthopedic conditions
05/29/2018	Added coverage language for Medicare members to use KPWA criteria for stem cell use for orthopedic conditions

Codes

CPT: 38205, 30206, 30207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, S2150

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