Clinical Policy Bulletin: Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia

Number: 0674

Policy

*Aplease see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers allogeneic hematopoietic cell transplantation medically necessary for the treatment of chronic myelogenous leukemia (CML) when the member meets the transplanting institution's written eligibility criteria. In the absence of such criteria, Aetna considers allogeneic hematopoietic cell transplantation medically necessary for the treatment of members with CML who have failed to respond to, who have developed resistance to, or who are intolerant to tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib) for persons without serious organ dysfunction based on the transplanting institution's evaluation.

Aetna considers autologous hematopoietic cell transplantation (auto BM/PSCT) experimental and investigational for the treatment of CML under all circumstances because its effectiveness for this indication has not been established.

See also: CPB 0404 - Interferons, CPB 0634 - Non-myeloablative Hematopoietic Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant), CPB 0638 - Donor Lymphocyte Infusion, and CPB 0640 - Hematopoietic Cell Transplantation for Selected Leukemias.

Background

Chronic Myelogenous Leukemia:

Chronic myelogenous leukemia (CML) is a hematologic malignancy associated with a specific chromosomal abnormality in the form of the Philadelphia chromosome (Ph). This Ph abnormality represents a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, and produces the BCR–ABL fusion gene, which leads to the expression of an abnormal protein. The resulting chimeric protein is known as p210BCR–ABL, which is characterized by constitutive activation of its tyrosine kinase activity. At diagnosis, the Ph can be detected in about 95 % of patients with CML. The incidence of CML is 1 to 2 cases per 100,000 per year. Chronic myelogenous leukemia accounts for approximately 15 % of all leukemias and 7 % to 20 % of all adult leukemias. Although CML can occur at any age, it most often appears in adults with a median age of 45.

A hallmark of CML is the over-production of granulocytes. Clinically, CML is characterized by an initial chronic or stable phase lasting a median of 3 years. During this phase there is a disordered maturation and excessive proliferation of myeloid cells. Clinical manifestations that appear during the chronic
phase can usually be controlled with cytotoxic drugs or splenic irradiation, however true remissions are rare and for the most part the marrow remains predominantly populated with leukemic cells. The chronic phase typically transforms into an acute phase, known as a blast phase or crisis, which is usually terminal. In many patients the blast phase is preceded by an accelerated phase characterized by progression of symptoms and resistance to treatment. Conventional chemotherapy (e.g., busulfan, and other alkylating agents such as cyclophosphamide and anti-metabolites) used for chronic phase CML can induce multiple remissions and delay the onset of blast phase to a median of 4 to 6 years.

Until recently, treatment options for patients with CML, in addition to conventional chemotherapy, include interferon-based therapies or allogeneic bone marrow/peripheral stem cell transplantation (allo BM/PSCT). Treatment decisions are generally based on the age of the patient and the phase of the disease. Recently, several new therapies have been developed that may change the natural history of CML and patient prognosis. One of the new therapies is imatinib mesylate (ST1571, Gleevec), an oral, selective BCR-ABL kinase inhibitor that has demonstrated activity in all phases of CML. It has been reported that imatinib produces both hematologic and cytogenetic remission in CML patients. In CML patients in the chronic phase, who had previously failed interferon, imatinib induced a complete hematologic response in 88 % and a complete cytogenetic response in 30 % of patients. This agent has been rapidly adopted into treatment strategies for CML. However, the response rate generally decreases in patients with accelerated or blast phase CML.

Conventional chemotherapy during the chronic phase may improve the patient’s quality of life, however, it does not (i) influence the duration of the chronic phase, (ii) prevent blastic crisis, or (iii) prolong the overall survival time. Currently, allo BM/PSCT is considered the only potentially curative therapy for CML. Due to the indolent nature of the disease and the morbidity and mortality associated with BMTs, allo BMT was initially limited to patients with CML already in blast crisis. Although treatment with high-dose chemotherapy (HDC), followed by allo BMT (during blast phase) induced transient disappearance of the Ph, relapses were common and survivals short. The somewhat disappointing results were attributed to the advanced stage of disease and the debilitated nature of the recipients. Subsequent attempts to perform transplantation during the accelerated phase did result in prolonged disease-free survival (DFS) in a small proportion of patients. However, the incidence of relapse was high. Thus, focus was shifted to initiating HDC and allo BMT during the chronic phase of the disease. Results for this therapy during the chronic phase were very encouraging. As a result, patients are offered the option of treatment with an allo BMT as soon as possible following initial diagnosis of chronic phase CML, prior to evidence of disease progression.

Hehlmann and colleagues (2007) noted that early allo-PSCT has been proposed as primary treatment modality for patients with CML. This concept has been challenged by transplantation mortality and improved drug therapy. In a randomized study, primary allo-PSCT and best available drug treatment (interferon-based) were compared in newly diagnosed chronic phase CML patients. Assignment to treatment strategy was by genetic randomization according to availability of a matched related donor. Evaluation followed the intention-to-treat principle. A total of 621 patients with chronic phase CML were stratified for eligibility for allo-PSCT. Three hundred and fifty four patients (62 % male; median age of 40 years; range of 11 to 59 years) were eligible and randomized. A total of 135 patients (38 %) had a matched-related donor, of whom 123 (91 %) received a transplant within a median of 10 months (range of 2 to 106 months) from diagnosis; 219 patients (62 %) had no related donor and received best available drug treatment. With an observation time up to 11.2 years (median of 8.9 years), survival was superior for patients with drug treatment (p = 0.049), superiority being most pronounced in low-risk patients (p = 0.032). The authors stated that the general recommendation of allo-PSCT as first-line treatment option in chronic phase CML can no longer be maintained. It should be replaced by a trial with modern drug treatment first.

**Allogeneic BM/PSCT:**

High-dose chemotherapy followed by allo BM/PSCT is currently considered the only potentially curative therapy for CML. Studies have confirmed that patients who receive allo BM/PSCT during the
chronic phase have significantly better survival rates than those who receive transplants during the accelerated or blast phase.

Fyles et al (1991) reported on long-term results of allo BMT for patients with CML (n = 70). Patients were stratified according to risk (good risk subgroup was defined as first chronic phase CML; poor risk subgroup was defined as other than first chronic phase CML), as well as diagnosis. The median follow-up was 67 months with a range of 33 to 120 months. According to the authors, the most important factor that determined the outcome in this patient population was disease status at the time of BMT. The effect of risk status was evaluated separately for each diagnosis. Good risk patients with CML had a 5-year event-free survival (EFS) of 43 %, as compared to the poor risk patients who had only a 15 % chance of DFS over the same time interval. Patients with CML in first chronic phase showed a significantly better long-term EFS than patients transplanted with more advanced disease. The effect of risk status was also evaluated for each diagnostic subgroup. Patients with CML in the good risk category relapsed significantly less frequently at 5 years than poor risk patients: 13 % versus 58 %. Sixteen patients with CML relapsed. A hematologic relapse was noted in 14 of these 16 recipients. All 14 were in the poor risk category and eleven of the 14 poor risk recipients have died from their disease. The remaining 2 patients (categorized as good risk) relapsed cytogenetically only. Both of these patients were treated with interferon and have subsequently become Ph negative. The authors concluded that in order to achieve the best results, patients should be transplanted early in their disease.

Wagner et al (1992) described results of a retrospective study evaluating the efficacy of HDC and total body irradiation followed by allo BMT in patients with chronic phase CML (n = 75). Patients were classified into groups according to age and graft-versus-host disease (GVHD) prophylaxis. Groups were defined as follows: Group 1 -- patients less than 30 years of age receiving immunosuppressive therapy and unmanipulated bone marrow; Group 2 -- patients 30 years of age or over receiving immunosuppressive therapy and unmanipulated bone marrow; Group 3 -- patients 30 years of age or over receiving lymphocyte-depleted bone marrow plus immunosuppressive therapy. Survival rate at 4.5 years was 52 %. When classified by age and GVHD prophylaxis, the actuarial survival was 65 % in Group 1, 33 % in Group 2, and 38 % in Group 3. In uni-variate analysis, patients age 30 years and over, and the use of lymphocyte-depleted bone marrow negatively influenced EFS. Thirty-seven of the 79 patients died following BMT. The principal causes of treatment failure were acute and chronic GVHD and disease relapse. According to the authors, results of the study confirm previous reports that allo BMT for CML in chronic phase improves survival in over 50 % of the patients. In addition, the authors recommended that for patients aged 55 or younger with CML in the chronic phase, allo BMT should be considered early after disease presentation.

Gratwohl and co-workers (1993) conducted a retrospective analysis on data collected by the European Bone Marrow Transplantation Group since 1979. A total of 1,480 BMTs for CML were done between 1979 and 1990. Of these, 1,082 patients were transplanted in first chronic phase, 88 in a subsequent chronic phase, 251 in accelerated phase and 59 in blast crisis. For these 4 disease stages leukemia-free survival at 5 years was 39 %, 22 %, 22 % and 0 %, respectively. A more detailed analysis was done on 947 patients who received transplants in the first chronic phase from an human leukocyte antigen (HLA)-identical sibling. There were 526 patients alive 2 to 10 years after transplant, 409 have died and 12 were lost to follow-up. The great majority who died, 350 patients, had a transplant-related death, while 59 patients died with or due to relapsed disease. Of the 526 patients alive, 428 were alive without any signs of relapse, 98 were alive with relapse. This meant a total of 157 patients relapsed. The probability of staying alive without relapse at 8 years was 34 %. Since not all patients with relapse have died, actual survival is better and the probability of being alive for the whole group was 47 % at 8 years. This long-term analysis allowed a few conclusions: (i) patients with CML in blastic transformation should not be considered routine candidates for BMT; (ii) BMT should be carried out as soon after diagnosis as possible if an HLA-identical sibling is available; and (iii) age, donor/recipient sex combination, time span from diagnosis to transplant and initial disease status influence outcome.

The National Comprehensive Cancer Network’s practice guidelines on CML (2003) states that 3
effective modalities are currently available for the primary management of CML: (i) allo-BMT, (ii) interferon alpha with or without cytarabine, and (iii) imatinib mesylate. Moreover, in a recent review on therapeutic strategies for the treatment of CML, Garcia-Manero et al (2003) stated that allo-PSCT is curative in selected patients, and is most effective when carried out during the chronic phase of disease. For patients with a high-predicted risk of disease recurrence (e.g., transplantation in accelerated-blastic phase) after allo-PSCT, preventive post-allo-PSCT maintenance measures such as interferon alpha or imatinib may be beneficial.

Guidelines from the British Society of Haematology on CML (Goldman, 2007) state that allogeneic stem cell transplantation may be considered for patients with suitable donors as an alternative to a second generation tyrosine kinase inhibitor or if they fail such treatment.

Guidelines from Cancer Care Ontario (Imrie et al, 2009) state that allogeneic stem cell transplantation is an option for patients with CML for whom medical therapy has failed, as well as those in accelerated phase or blast crisis.

Chalandon et al (2014) noted that patients with CML relapsing after allogeneic stem cell transplantation may be treated by tyrosine kinase inhibitors and/or by donor lymphocyte infusions. Best strategies and timing of administration of lymphocytes are unclear. These investigators analyzed 155 patients who relapsed after allogeneic stem cell transplantation for CML with disease detectable only by molecular methods and who subsequently received lymphocytes. Transplants were performed in first chronic phase (n = 125) or in advanced disease (n = 29) from identical siblings (n = 84) or unrelated donors (n = 71) between 1986 and 2003. They received lymphocytes either during molecular relapse (n = 85) or upon progression to more advanced disease between 1993 and 2004. The median interval from relapse to lymphocytes infusion was 210 (0 to 1,673) days. The median follow-up after it was 46 (3 to 135) months. Overall survival was 76 ± 4 % at 5 years after lymphocyte infusions (89 ± 8 % with sibling donors and 63 ± 13 % with unrelated donors (p = 0.003)). Survival was 69 ± 14 % if lymphocytes were given within 6 months of the detection of molecular relapse and 81 ± 10 % (p = 0.061) if given later; 81 ± 11 % if given at molecular relapse versus 71 ± 12 % (p = 0.26) with more advanced disease. In multivariate analysis survival was worse if the donor was unrelated (HR 2.54 (95 % confidence interval [CI]: 1.15 to 5.53), p = 0.021) and better with lymphocyte infusion beyond 6 months from molecular relapse (HR 0.4 (95 % CI: 0.19 to 0.84), p = 0.0018). These data confirmed the remarkable effectiveness of lymphocyte infusion for this disease. The authors concluded that there appears to be no advantage of administering it early upon detection of molecular relapse in patients who received allogeneic stem cell transplantation for CML.

**Autologous BM/PSCT:**

Available scientific evidence has not established autologous bone marrow/peripheral stem cell transplantation (auto-BM/PSCT) as an effective treatment for CML. Patient populations varied across these studies. Some focused on newly diagnosed patients or those in the first year since diagnosis. Others focused on patients who did not respond to or relapsed after initial treatment using interferon alpha. Finally, some focused on patients transplanted in late chronic phase or after transformation to accelerated phase or blast crisis. Although some patients achieved complete or partial molecular remissions and long-term DFS, these studies do not permit conclusions free from the influence of patient selection bias. Moreover, all autotransplanted patients included in these reports were treated before Gleevec became available. Since this drug has been shown to induce major hematologic and, less often, cytogenetic remissions even among patients in accelerated phase and blast crisis, future studies of autotransplants for CML, may focus on patients who fail or become resistant to imatinib mesylate. Alternatively, it may be incorporated into combination regimens used for high dose therapy.

Bhatia et al (1997) stated that the role of autologous transplantation in the early therapy of CML is not yet understood. Analysis of a first generation of autologous transplants performed largely in previously treated, older patients unsuitable for allogeneic transplantation or not responding to interferon alpha therapy suggests that this approach has anti-leukemia activity associated with prolongation of survival.
and acceptable peri-transplantation mortality. However, because these trials were uncontrolled and patient selection could have contributed to the longer than expected survival, controlled studies are needed to confirm the encouraging findings of these early reports and determine if autologous transplantation prolongs survival.

Podesta et al (2000) examined changes that occur in the percentage of Ph-negative- and Ph-positive-committed progenitor cells and ascertained the relationship between changes and clinical outcome in 15 patients with CML who were autografted soon after diagnosis with 85% to 100% Ph-negative peripheral blood progenitor cells (PBPC). The authors reported that a prolonged period of complete or almost complete Ph-negative hemopoiesis was achieved in patients with CML who underwent autografting with Ph-negative progenitors. These researchers stated that longer follow-up studies are needed to evaluate whether these changes are associated with improved survival.

Michallet et al (2000) reported data on 28 CML patients autotransplanted in chronic phase with PBPC mobilized with G-CSF (5 ug/kg/day for 5 days) given subcutaneously while continuing interferon alpha therapy. The authors concluded that the results of this strategy were encouraging in poor interferon alpha responders, however, other prospective studies that try to maintain the cytogenetic responses obtained immediately after transplantation are needed.

Meloni and associates (2001) stated that the potential role of auto-SCT as an alternative therapeutic strategy in CML has been widely explored in pilot studies, but the clinical results in terms of survival have so far been evaluated only retrospectively and in heterogeneous groups of patients. These investigators evaluated the feasibility and long-term efficacy of unmanipulated auto-SCT followed by low dose interferon alpha in a homogeneous group of patients affected by CML in a very early phase of disease (n = 26). The authors concluded that high dose therapy followed by unmanipulated peripheral blood stem cell transplantation and low-dose interferon alpha is a feasible approach, which results in long-term survival in newly diagnosed CML patients. However, these findings need to be confirmed in controlled trials comparing auto-SCT with other therapeutic approaches, such as the use of interferon alpha alone or in combination with other agents.

Koziner et al (2002) evaluated the role of auto-SCT in prolonging DFS and overall survival (OS) in patients with CML who received autografts of Ph-positive or Ph-negative cell harvests (n = 53). The authors found that auto-SCT with Ph-negative cell harvests after myeloablative chemotherapy resulted in prolonged periods of hematologic and cytogenetic remission or stable disease after cytogenetic/molecular recurrence in some patients with CML. A superior DFS was observed without any benefit observed for OS. These investigators concluded that auto-SCT with Ph-negative cells is a promising procedure because it can improve the DFS probability of patients who are unsuitable for allo-SCT from a histo-identical sibling.

The National Comprehensive Cancer Network’s practice guidelines on CML (2009) as well as a recent review on therapeutic strategies for the treatment of CML did not discuss the use of autologous transplantation as a treatment option (Garcia-Manero et al, 2003). Schiffer and colleagues (2003) stated that auto-SCT following intense chemoradiotherapy may prolong survival and reduce complications and mortality during peri-transplantation in patients with CML, however, this procedure is not curative. The collection of stem cells when the patient is in complete cytogenetic response for use in case of relapse is considered an investigative procedure.

A meta-analysis of 6 randomized studies (CML Autograft Trials Collaboration, 2007) reported that the results do not suggest a role for auto-SCT in initial treatment for CML, but it may still merit investigation in patients resistant to tyrosine kinase inhibitors.

Guidelines from Cancer Care Ontario (Imrie, et al., 2009) state that autologous stem cell transplantation is not recommended for patients with CML.

Appendix
The Hematopoietic Cell Transplantion-Specific Comorbidity Score Calculator is available at the following website: [http://www.qxmd.com/calculate-online/hematology/hct-ci](http://www.qxmd.com/calculate-online/hematology/hct-ci).

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The above policy is based on the following references:

**Allogeneic Bone Marrow Transplantation:**


**Autologous Bone Marrow Transplantation:**


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0674 Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia

There are no amendments for Medicaid.