Nonmyeloablative Allogeneic Transplants of Hematopoietic Stem Cells for Treatment of Malignancy

Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified. Codes associated with this policy will no longer pend for clinical review.

Policy # 00086
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider nonmyeloablative allogeneic stem cell transplantation in patients who would otherwise meet patient selection criteria for high-dose chemotherapy and allogeneic stem cell transplantation to be eligible for coverage.

Patient Selection Criteria
Patient selection criteria applicable to high-dose chemotherapy or allogeneic stem cell transplantation vary based on specific conditions or diseases being treated. See applicable medical policy related to the issue of high-dose chemotherapy and allogeneic stem cell transplantation.

Member contracts/certificate outline prior authorization requirements related to organ, tissue and bone marrow transplant benefits.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers other applications of nonmyeloablative allogeneic stem cell transplantation including its use in patients who do not meet criteria for high-dose chemotherapy and allogeneic stem cell transplantation due to either age or comorbidities, or as a treatment of other malignancies or other conditions to be investigational.*

Background/Overview
Transplantation of allogeneic hematopoietic stem cells derived from bone marrow or peripheral blood, in conjunction with myeloablative chemotherapy, is an established therapy for various malignancies, including acute and chronic leukemias, Hodgkin’s disease (HD) and non-Hodgkin lymphomas (NHLs). The treatment effect results from chemotherapeutic ablation of malignant cells, as well as an associated immune-mediated
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graft versus malignancy effect. The conventional practice of allogeneic stem cell transplantation (allo-SCT) involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at high enough doses to cause bone marrow failure in most patients. While such treatment may eradicate the malignant cells, patients are as likely to die from opportunistic infections, graft-versus-host disease (GVHD) and organ failure as from the underlying malignancy.

Recently, regimens have been developed that seek to reduce treatment-related adverse effects while retaining beneficial (i.e., graft versus malignancy) effects. So-called NMA regimens have been tentatively defined as those that do not eradicate the patient’s hematopoietic ability, allowing for relatively prompt hematopoietic recovery (e.g., 28 days or less) without a transplant. Examples of such regimens include fludarabine-cyclophosphamide and fludarabine-idarubicin-cytarabine combinations. On engraftment, patients treated with NMA regimens will demonstrate mixed chimerism initially. Most will subsequently convert to full-donor chimerism and may be supplemented with donor lymphocyte infusions to further eradicate malignant cells. Nonmyeloablative chemotherapy is now commonly referred to as reduced-intensity conditioning (RIC), with patients also receiving allo-SCT. This procedure also has been called “mini-transplant.”

Two general categories of patients have been considered candidates for NMA allotransplants: those who would otherwise be considered candidates for a conventional myeloablative allotransplant and those who would not. In the former category, NMA allotransplants could be considered as a variant of a standard chemotherapy conditioning regimen. In the latter category, NMA transplants would be considered a novel approach, either for patients whose comorbidities preclude a standard myeloablative conditioning regimen, or in those with malignancies that have not been shown to be effectively treated with conventional myeloablative allogeneic transplants.

Rationale/Source
The following discussion is based on a 2001 TEC Assessment and August 2003 review of evidence from studies published subsequent to the 2001 Assessment.

The 2001 TEC Assessment focused on NMA SCTs in patients who would not otherwise be considered candidates for conventional allo-SCT due to age or comorbidities. The Assessment further focused on those malignancies for which conventional allo-SCT has a proven treatment benefit and those malignancies for which the treatment effectiveness of conventional allo-SCT is still uncertain. The rationale for this focus was that overlap was apparent in the literature between what some consider myeloablative versus intensity-reduced versus NMA conditioning regimens. Therefore, for patients who are candidates for a conventional allogeneic transplant, the intensity of the conditioning regimen is determined primarily by physician preference. However, for those ineligible for a conventional myeloablative transplant, NMA transplants represent a unique approach.
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The 2001 TEC Assessment reported the following observations and conclusions regarding NMA SCTs:

With respect to patients with CML, AML, ALL, HD or NHL who are not eligible for conventional allo-SCT:
- The available evidence was insufficient to permit scientific conclusions. For each of the above malignancies, the sample size was inadequate even when data were pooled from all studies. In addition, the follow-up duration in all of the studies ranged from three months to slightly more than one year. This duration is short relative to either the natural history of these malignancies or the reported duration of survival after alternative therapies. No data were reported on results of conventional management of well-matched controls; thus, direct comparison of outcomes was not possible.
- The limited evidence suggested that patients with contraindications to conventional allogeneic transplant experienced a high rate of transplant-related mortality after NMA transplant.

With respect to patients with MM, CLL or myelodysplastic syndrome (MDS):
- The same limitations were noted as for the above indications.

With respect to patients with renal cell carcinoma or other tumors of solid organs:
- Only one study of patients with renal cell carcinoma met the study selection criteria. However, the study size was small (n=13) and the follow-up was short (median=13 months). No data were reported by studies that met selection criteria on outcomes of NMA transplant for other tumors of solid organs.

A 2003 systematic review by Djulbegovic et al. summarized data reported by studies included in the 2001 TEC Assessment and several subsequent studies. The review again found published data inadequate to permit conclusions with respect to patients or malignancies ineligible for conventional myeloablative allotransplants.

An August 2003 literature search identified more than 150 articles on NMA allo-SCTs not referenced in the 2001 Assessment or the review by Djulbegovic et al. The following discussion focuses on the articles identified in the literature search that:
(a) Used a NMA regimen as stated by the authors or as recognized by one working definition (see Djulbegovic et al);
(b) Included only patients who were ineligible for treatment with a myeloablative regimen by clear statement or description; and
(c) Either reported long-term outcomes (survival) for patients with the same malignancy and in the same risk category, or compared treatment-related adverse effects to controls given myeloablative conditioning regimens in populations with various malignancies.
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Twelve studies met these selection criteria: five reported disease-specific survival; four reported data on infectious or other treatment-related complications and three compared frequencies and outcomes of GVHD for NMA and myeloablative conditioning regimens.

**Disease-specific survival after nonmyeloablative allo-SCT (NMA allo-SCT)**

New data on survival after treatment with NMA allo-SCT was reported for patients with high-risk ALL (n=22), first chronic phase CML (n=24), advanced CLL (n=50) and MM (n=31). Outcome measures varied widely, reflecting the variable prognoses of these disease types: engraftment ranged from 82% to 100%, median survival ranged from 105 days to “not yet reached,” and overall survival at two years ranged from 0% to 90%. Because these studies did not include concurrent control groups, it is not possible to compare these outcomes with those of established alternatives. Furthermore, although patients in each of these clinical series were treated for a single malignancy, they were rather heterogeneous with respect to important baseline characteristics that effect outcomes of treatment (e.g., prior treatment, histotype, disease status at allo-SCT). Adverse events and complications remain a concern with one-third to one-half of the cohort in some studies dying of treatment-related causes.

**Treatment-related infections and other complications**

Two reports from a single study provided data on the incidence and outcome of bacterial, fungal and cytomegalovirus (CMV) infections in 56 consecutive patients with hematologic malignancies treated with NMA allo-SCT compared to control groups treated with conventional allo-SCT. During the 100-day period immediately following treatment, infections and infectious complications occurred significantly less frequently in the NMA allo-SCT group; this difference had disappeared by one year after transplant. A retrospective analysis of 65 consecutive patients with advanced hematologic malignancies found no difference in rate of infectious complications as a function of donor-patient HLA matching. Last, significantly fewer platelet and red cell transfusions were required in 40 patients with advanced hematologic malignancies treated with a NMA regimen compared to a concurrent control group of 60 patients treated with myeloablative regimens. The study did not present evidence on whether observed differences in post-transplant transfusion requirements affected long-term outcomes.

**Graft-Versus-Host Disease (GVHD)**

Graft-versus-host disease is a major concern with conventional, myeloablative allo-SCT and causes a large proportion of treatment-related adverse events. Two recent studies compared the incidence and outcomes of GVHD for patient groups treated with NMA versus myeloablative regimens. Results were mixed relative to acute GVHD (significantly less after NMA regimens in one study), but neither study observed a difference in chronic GVHD or survival. The use of alemtuzumab reduced the risk of GVHD in patients treated with NMA regimens, but any beneficial effect this might have had on outcome was offset by an increased risk of infection.

A literature review performed through March 2007 did not identify any studies that would prompt reconsideration of the coverage statement. Work continues to explore the role of NMA allo-SCT in patients...
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with MM, CLL, renal cell cancer and other malignancies and conditions that would not routinely be considered for conventional myeloablative stem cell allotransplant. One review article examines means to optimize allogeneic transplant conditioning, primarily focusing on older patients and those who for other reasons would not be eligible for conventional myeloablative conditioning regimens. Issues of importance include patient characteristics, the disease under treatment, pretransplantation induction chemotherapy, stem cell source, and post-transplant management. The authors conclude that while important insights have been gained over the past decade regarding differences between high-dose and NMA conditioning regimens, more disease-specific trials, dose-optimization studies and well-designed prospective trials are needed to determine the relative role of specific conditioning approaches. A second review summarizes clinical results from 39 published studies of NMA allo-SCT for hematologic malignancies. The median age at transplant ranged from 31 to 59 years, but is over 50 years in most protocols. Inclusion of younger patients in some studies implies they had other comorbidities, often including prior ASCT, which dictated this type of therapy. However, outcomes often were not reported separately for patients with significant comorbidities or age older than 50.

Taken together, the available evidence suggests that NMA allo-SCT may achieve favorable outcomes in some patients who would not normally be considered for SCT. However, these regimens suffer from many of the same limitations as standard-intensity transplants—relapse, GVHD (particularly chronic GVHD), and mortality from treatment-related causes other than myelotoxicity. However, the underlying premise of this policy is that NMA SCT is one of many types of conditioning regimens that can be used for malignancies for which the evidence supports that allo-SCT improves health outcomes. The role of NMA transplant in other settings is uncertain and requires direct comparative trials with adequate follow-up to analyze its safety and effectiveness. No such controlled trials were identified. It also seems unlikely that properly designed and powered trials will be conducted to compare standard SCT with NMA transplantation in populations clearly eligible for transplant, largely because the two methods are applied to different patient populations.

A literature search performed in March 2008 did not identify any comparative trials of NMA allo-SCT versus either myeloablative allogeneic transplant or cytotoxic chemotherapy alone in similar patients. Several review articles compiled results from numerous single-arm series or retrospective studies of NMA or RIC regimens with allogeneic stem-cell support for a number of hematologic and solid malignancies. Taken together, the available data suggest that RIC regimens with allogeneic stem cell support are associated with lower rates of treatment-related morbidity and mortality, but at the expense of a greater risk for disease relapse.

Reduced-intensity conditioning regimens with allogeneic stem cell support are increasingly being used in many centers, and it is clear that they will continue to evolve and will likely supplant myeloablative conditioning regimens for select patients. However, the scientific evidence available to date does not provide direct comparison of health outcomes with sufficiently long follow-up in similar patient groups to draw sound conclusions about the net health benefit of this therapeutic approach.

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Based on the discussion above, the current coverage statements are unchanged.

References

2. Blue Cross and Blue Shield Association, TEC Assessments 2001; Tab 3.
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Policy History
Original Effective Date: 01/27/2003
01/27/2003 Managed Care Advisory Council approval
12/16/2003 Medical Policy Committee review
01/26/2004 Managed Care Advisory Council approval
01/04/2005 Medical Director review
01/18/2005 Medical Policy Committee review. Format revision. No substance change to policy.
01/31/2005 Managed Care Advisory Council approval
02/01/2006 Medical Director review
02/15/2006 Medical Policy Committee review. Format Revisions.
04/02/2008 Medical Director review

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04/16/2008 Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009 Medical Director review
04/15/2009 Medical Policy Committee approval. Changed title from “Nonmyeloablative Allogeneic Stem Cell Support for the Treatment of Malignancies” to “Nonmyeloablative Allogeneic Transplants of Hematopoietic Stem Cells for Treatment of Malignancy”. No change to coverage eligibility.
04/08/2010 Medical Policy Committee approval
04/21/2010 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2011 Medical Policy Committee review
04/12/2012 Medical Policy Committee review. Recommend archiving.
04/25/2012 Medical Policy Implementation Committee approval. Archived.
Next Scheduled Review Date: Archived medical policy.

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

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A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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