Clinical Policy Bulletin:
Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

Number: 0836

Policy

Aetna considers allogeneic (ablative and non-myeloablative) hematopoietic cell transplantation medically necessary for individuals with intermediate-risk or high-risk myelodysplastic syndrome (MDS), and who have not responded to prior therapy and have an available human leukocyte antigen (HLA)-matched donor.

Aetna considers a repeat allogeneic (ablative or non-myeloablative) hematopoietic cell transplantation medically necessary for individuals with intermediate-risk or high-risk MDS due to primary graft failure or failure to engraft.

Aetna considers a repeat allogeneic (ablative or non-myeloablative) hematopoietic cell transplantation experimental and investigational for individuals with MDS who relapsed.

Aetna considers autologous hematopoietic cell transplantation experimental and investigational for individuals with MDS because the effectiveness of this approach for this indication has not been established.

See also: CPB 0634 - Non-myeloablative Hematopoietic Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant).

Background

Myelodysplastic syndromes (MDS) refer to a heterogeneous group of myeloid disorders characterized by impaired maturation of hematopoietic cells, peripheral blood cytopenias and increased risk of transformation into acute myelogenous leukemia (AML). There are 2 forms of MDS: (i) primary (e.g., idiopathic form) and (ii) secondary (as a consequence of cytotoxic therapy, ionizing radiation, or other environmental insults). Secondary MDS usually has a poorer prognosis and mainly affects adults aged 60 or older with a 2-year overall survival (OS) of less than 20 % with advanced MDS. Diagnosis of MDS is based on morphological evidence of dysplasia upon visual examination of a bone marrow aspirate and biopsy. Prognosis of patients with MDS can be
calculated using a number of scoring systems. In general, these scoring systems include analysis of peripheral cytopenias, percentage of blasts in the bone marrow and cytogenetic characteristics. The most commonly used system is the International Prognostic Scoring System (IPSS), which is likely to be replaced by a new revised score (IPSS-R) and by the incorporation of new molecular markers recently described. Treatment of patients with MDS is selected basing on risk, transfusion needs, percent of bone marrow blasts, and, more recently, cytogenetic profile. Goals of therapy are different in lower risk patients than in higher risk patients. In the former group, the goal is to decrease transfusion needs and transformation to higher risk disease or AML. In the latter group, the objective is to prolong survival. Current available treatments include growth factor support (e.g., granulocyte colony stimulating factors including Neupogen and filgrastim; granulocyte macrophage-colony stimulating factors including Leukine and sargramostim), lenalidomide, hypo-methylating agents (e.g., azacitidine and decitabine), intensive chemotherapy, and hematopoietic stem-cell transplantation (HSCT). Available data suggest that selected individuals with IPSS intermediate-2 and high-risk MDS may benefit from immediate HSCT while those with IPSS low- and intermediate-1 -risk groups may improve OS by delay of HSCT until disease progression. Currently, there are no approved interventions for patients with progressive or refractory disease especially after hypo-methylating based therapy (Alessandrino, 2002; Kindwall-Keller and Isola, 2009; NCI, 2011; Garcia-Manero, 2012).

Laport et al (2008) stated that allogeneic stem cell transplantation (ASCT) is the only curative strategy for patients with MDS and myelo-proliferative disorders (MPD). These researchers reported the results of 148 patients (median age of 59 years old) with de novo MDS (n = 40), AML after antecedent MDS/MPD (n = 49), treatment-related MDS (t-MDS) (n = 25), MPD (n = 27), and chronic myelo-monocytic leukemia (CMML) (n = 7) who underwent ASCT using a conditioning regimen of low-dose total body irradiation (TBI) alone (200 cGy) on day 0 (n = 5) or with the addition of fludarabine 30 mg/m(2)/day on days -4 to -2 (n = 143). Post-grafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. A total of 75 patients (51 %) received an allograft from a matched-related donor (MRD), and 73 patients (49 %) were recipients of unrelated donor (URD) grafts. There was no significant difference in the incidence of acute (grade II to IV) and chronic graft-versus-host disease (aGVHD, cGVHD) between the recipients of related and unrelated donor grafts. By day +28, 75 % of patients demonstrated mixed T cell chimerism. Graft rejection was seen in 15 % of patients. With a median follow-up of 47 (range of 6 to 89) months, the 3-year relapse-free survival (RFS) and OS were both 27 % for all patients, with a relapse incidence of 41 %. The 3-year RFS for the patients with de novo MDS, AML after antecedent MDS/MPD, t-MDS, MPD, and CMML were 22 %, 20 %, 29 %, 37 %, and 43 %, respectively, and the 3-year OS was 20 %, 23 %, 27 %, 43 %, and 43 %, respectively. The 3-year non-relapse mortality (NRM) was 32 %. Factors associated with a lower risk of relapse were the development of extensive cGVHD and having a low-risk or intermediate-1 risk IPSS for the de novo MDS patients. Non-myeloablative HSCT confers remissions in patients who otherwise were not eligible for conventional HSCT, but for whom relapse is the leading cause of treatment failure.

Kindwall-Keller and Isola (2009) noted that HSCT is the only curative therapy for MDS; and numerous myeloablative (MA), non-myeloablative (NMA) SCT and reduced intensity conditioning (RIC) transplant studies have included MDS patients. A total of 24 MA HSCT studies published from 2000 and 2008 reported OS and disease-free survival (DFS) ranging from 25 % and 16 % at 2 years to 52 % and 50 % at 4 years. In these publications, the incidence of grades II to IV aGVHD was 18 % to 100 %, cGVHD 13 % to 88 %, relapse risk 24 % at 1 year to 54.5 % at 4 years and treatment-related mortality (TRM) 19 % at day 100 to 61 % at 5 years. From 2003 to 2008, 30 publications combining RIC and NMA HSCT reported OS and DFS from 22 % and 20 % at 2 years to 79 % and 79 % at 4 years. Incidence of grades II to IV aGVHD ranged from 9 % to 63 %, cGVHD 18 % to 80 %, relapse risk 6 % to 61 % and TRM 0 % at day 100 to 34 % at 5 years. Although no ideal
transplant conditioning has emerged, many of the MA and RIC studies used busulfan-based regimens and used a recipient age cut-off of 50 to 55 years for MA HSCT. Similarly, there is no agreement on the use of induction or hypo-methylating therapy before HSCT, but azacitidine and decitabine are gaining increasing attention as a bridge to HSCT. Until recently, the IPSS dictated the use and timing of HSCT. The World Health Organization (WHO) classification and WHO Prognostic Scoring System (WPSS) may be better suited in predicting the outcomes and should probably be incorporated in transplant algorithms. Most published MDS transplant series combine MRD and matched unrelated donors (MUD). Umbilical cord blood (UCB) grafts will likely broaden the population of MDS patients eligible for allografting, but outcome data for MDS are scant. At this time, it is reasonable to consider the availability of an MRD or MUD as separate from an UCB graft in the decision of transplantation for MDS. The development of RIC, improvements in supportive therapy and alternative donor selection will provide better OS for MDS patients undergoing transplantation. Simultaneously, better understanding and medical therapy of MDS are leading re-examination of patient selection and the timing of HSCT.

Warlick et al (2009) stated that ASCT is the only known curative therapy for MDS. These investigators presented the transplant outcomes for 84 adult MDS patients undergoing ASCT (median age of 50; range of 18 to 69 years). By WHO criteria, 35 (42 %) had refractory anemia with excess blasts (RAEB-1 or 2), 23 (27 %) had refractory cytopenia with multi-lineage dysplasia (RCMD) or RCMD and ringed sideroblasts (RCMD-RS), and the remaining 26 (31 %) had refractory anemia (RA), MDS-unclassifiable (MDS-U), CMML, MDS/MPD, or MDS-not otherwise specified (MDS-NOS). Graft source was related in 47 (56 %), URD marrow in 11 (13 %), and UCB in 26 (31 %). The conditioning regimen included TBI in 94 % of transplantations; 52 (62 %) MA conditioning; and 32 (38 %) NMA conditioning. Cumulative incidence of neutrophil engraftment by day +42, aGVHD by day +100, and cGVHD by 1 year were 88 % (80 % to 96 %, 95 % confidence interval [CI]), 43 % (36 % to 50 %, 95 % CI), and 15 % (10 % to 20 %, 95 % CI), respectively. One-year TRM, relapse, DFS, and OS were 39 % (28 % to 50 %, 95 % CI), 23 % (12 % to 32 %, 95 % CI), 38 % (28 % to 48 %, 95 % CI), and 48 % (38 % to 58 %, 95 % CI) respectively. Cumulative incidence of relapse at 1 year in patients with pre-ASCT complete remission (CR) or less than 5 % blasts was improved at 18 % (8 % to 28 %, 95 % CI) compared to 35 % (16 % to 54 %, 95 % CI) in patients with 5 % to 20 % blasts (p = 0.07). Additionally, with MA conditioning, the incidence of relapse at 1 year trended lower at 16 % (6 % to 26 %, 95 % CI) versus 35 % (18 % to 52 %, 95 % CI) in NMA (p = 0.06), and a statistically significant decrease in relapse was noted in patients entering ASCT with CR or less than 5 % blasts with an incidence of 9 % (0 % to 18 %, 95 % CI) (MA) versus 31 % (11 % to 51 %, 95 % CI) (NMA) (p = 0.04). For those patients with greater than or equal to 5 % blasts, MA conditioning did not significantly decrease relapse rates. One-year TRM was similar between MA and NMA conditioning. For patients entering transplant in CR or with less than 5 % blasts, prior treatment to reach this level did not impact rates of relapse or TRM when all patients were analyzed; however, when broken down by conditioning intensity, there was a trend toward improved DFS in those NMA patients who were pre-treated. Finally, 1-year DFS was similar using related donor peripheral blood stem cell (PBSC)/marrow, URD marrow, or UCB grafts. The authors concluded that these data suggested that (i) blast percentage of less than 5 % at ASCT is the major predictor of improved DFS and relapse and prior treatment to reach this disease status may have value in leading to improved DFS; (ii) MA conditioning is associated with lower relapse risk, particularly in patients with CR or less than 5 % blasts, but is not able to overcome increased disease burden; (iii) NMA conditioning yields equivalent TRM, DFS, and OS, and is reasonable in patients unsuited for MA conditioning; and (iv) the donor sources tested (PBSC, bone marrow [BM], or UCB) yielded similar outcomes.

De Witte et al (2010) noted that ASCT is usually considered the only curative therapeutic option for patients with advanced or transformed MDS in CR, but post-remission chemotherapy and
autologous SCT are potential alternatives, especially in patients over 45 years old. These researchers evaluated, after intensive anti-leukemic RIC, the impact of the availability of a human leukocyte antigen (HLA)-identical sibling donor on an intention-to-treat basis. Additionally, all patients without a sibling donor in CR after the first consolidation course were randomized to either autologous peripheral blood SCT or a second consolidation course consisting of high-dose cytarabine. The 4-year survival of the 341 evaluable patients was 28%. After achieving CR, the 4-year survival rates of patients under 55 years old with or without a donor were 54% and 41%, respectively, with an adjusted hazard ratio (HR) of 0.81 (95% CI: 0.49 to 1.35) for survival and of 0.67 (95% CI: 0.42 to 1.06) for DFS. In patients with intermediate-risk/high-risk cytogenetic abnormalities, the HR in multi-variate analysis was 0.58 (99% CI: 0.22 to 1.50) (p = 0.14) for survival and 0.46 (99% CI: 0.22 to 1.50) for DFS (p = 0.03). In contrast, in patients with low-risk cytogenetic characteristics the HR for survival was 1.17 (99% CI: 0.40 to 3.42) and that for DFS was 1.02 (99% CI: 0.40 to 2.56). The 4-year survival of the 65 patients randomized to autologous peripheral blood SCT or a second consolidation course of high-dose cytarabine was 37% and 27%, respectively. The HR in multi-variate analysis was 1.22 (95% CI: 0.65 to 2.27) for survival and 1.02 (95% CI: 0.56 to 1.85) for DFS. The authors concluded that patients with a donor and candidates for ASCT in first CR may have a better DFS than those without a donor in case of MDS with intermediate-risk/high-risk cytogenetics. They stated that autologous peripheral blood SCT does not provide longer survival than intensive chemotherapy.

The American Society for Blood and Marrow Transplantation’s clinical guideline on “The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes” (2009) stated that based on data and expert opinion, a HLA-matched allogeneic donor (sibling, other family member, unrelated individual, or cord blood) SCT is recommended if an appropriate donor is available. If an allogeneic donor is not available, and CR is achieved with induction therapy, then an autologous SCT can be considered in the context of a clinical trial. The National Cancer Institute’s guideline on “Myelodysplastic Syndrome Treatment” (2011) stated that “Allogeneic bone marrow transplantation (BMT) for young patients with MDS offers the potential for long-term DFS. In two large studies, 45% to 60% of patients with de novo MDS were projected to be long-term disease-free survivors. Outcome tends to be better in younger patients with fewer bone marrow blasts, but long-term benefit has been noted in all FAB classification types, and in patients with marrow fibrosis, a variety of karyotypic findings, and different preparative regimens. A retrospective review of outcomes of allogeneic BMT according to pre-transplant IPSS score showed that the IPSS score predicted relapse rate and DFS. The 5-year DFS rates were 60% for the low-risk and intermediate-1 risk group, 36% for the intermediate-2 risk group, and 28% for the high-risk group. A review of 118 young MDS patients (median age of 24, age range of 0.3 to 53 years) who received allogeneic BMT from matched unrelated donors reported an actuarial survival of 28% at 2 years. Transplant-related mortality was influenced by the age of the patient (18 years or younger, 40%; age of 18 to 35 years, 61%; 35 years or older, 81%). Relapse rate was influenced by FAB classification. This study included patients who received transplants as early as 1986, which may have influenced the patient survival data. Outcomes may not be as good for patients with treatment-related MDS (5-year DFS of 8% to 30%) …. Allogeneic stem cell transplantation with non-myoeloablative conditioning is under clinical evaluation for treatment of MDS. A retrospective analysis of 836 allogeneic transplants for MDS using HLA-matched sibling donors was performed and included 215 patients who received non-myoeloablative conditioning regimens. The 3-year probabilities of progression-free survival and overall survival were similar in both groups (39% after myeloablative conditioning versus 33% in reduced intensity conditioning and 45% versus 41%, respectively; these differences were not significant). Relapses were more common in the reduced intensity group, but non-relapse mortality was decreased"
Deeg and Bartenstein (2012) noted that ASCT offers potentially curative therapy for patients with MDS. However, as the majority of patients with MDS are in their 70s or 80s, only few of these patients were transplanted following high-dose conditioning regimens. The development of RIC has allowed ASCT to be used in older patients and those with clinically relevant co-morbid conditions. Dependent upon disease status and the type of clonal chromosomal abnormalities present at the time of ASCT, 25 % to 75 % of patients will be cured of their disease and attain long-term survival. Furthermore, recent results with HLA-matched unrelated donors are comparable to those with HLA genotypically identical siblings.

Luger et al (2012) stated that although RIC and NMA-conditioning regimens have been used for over a decade, their relative effectiveness versus MA approaches to ASCT in patients with AML and MDS is unknown. These investigators compared disease status, donor, graft, and recipient characteristics with outcomes of 3,731 MA with 1,448 RIC/NMA procedures performed at 217 centers between 1997 and 2004. The 5-year uni-variate probabilities and multi-variate relative risk outcomes of relapse, TRM, DFS and OS were reported. Adjusted OS at 5 years was 34 %, 33 % and 26 % for MA, RIC and NMA transplants, respectively. Non-myeloablative conditioning resulted in inferior DFS and OS, but there was no difference in DFS and OS between RIC and MA regimens. Late TRM negates early decreases in toxicity with RIC and NMA regimens. The authors concluded that these findings suggested that higher regimen intensity may contribute to optimal survival in patients with AML/MDS, suggesting roles for both regimen intensity and graft versus leukemia in these diseases.

An UpToDate review on “Hematopoietic cell transplantation in myelodysplastic syndromes” (Negrin, 2012) states that “a subset of patients with MDS can be cured following allogeneic hematopoietic cell transplantation (allo-HCT). Allo-HCT may be considered for patients with MDS less than 60 years of age with an HLA-matched sibling donor or a well matched unrelated donor. The decision to pursue this aggressive form of therapy depends upon a number of criteria including the original or revised International Prognostic Scoring System MDS risk category, risk of disease progression, risk of infection, overall health of the patient, and the willingness of the patient to take on the risks associated with allo-HCT … Non-myeloablative allogeneic HCT appears promising for patients with MDS who are not candidates for myeloablative allo-HCT. Early results are encouraging in terms of reduced treatment-related mortality, although significant problems remain (e.g., increased relapse risk)”.

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

In a review on “Current therapy of myelodysplastic syndromes”, Zeidan and, Linhares (2013) noted that the approval of azacitidine, decitabine, and lenalidomide in the last decade was a major breakthrough. Nonetheless, the responses to these agents are limited and most patients progress within 2 years. Allogeneic stem cell transplantation remains the only potentially curative therapy, but it is associated with significant toxicity and limited efficacy.

Saber et al (2013) stated that allo-HCT from HLA- MRD and MUD produces similar survival for patients with AML. Whether these results can be extended to patients with MDS is unknown. These
investigators performed analysis of post-HCT outcomes for MDS. Outcomes of 701 adult MDS patients who underwent HCT between 2002 and 2006 were analyzed (MRD [n = 176], 8 of 8 HLA-A, -B, -C, -DRB1 allele matched MUD [n = 413], 7 of 8 MUD [n = 112]). Median age was 53 years (range of 22 to 78 years). In multi-variate analyses, MRD HCT recipients had similar DFS and survival rates compared with 8 of 8 MUD HCT recipients (relative risk [RR] 1.13 [95 % CI: 0.91 to 1.42] and 1.24 [95 % CI: 0.98 to 1.56], respectively), and both MRD and 8 of 8 MUD had superior DFS (RR 1.47 [95 % CI: 1.10 to 1.96] and 1.29 [95 % CI: 1.00 to 1.66], respectively) and survival (RR 1.62 [95 % CI: 1.21 to 2.17] and 1.30 [95 % CI: 1.01 to 1.68], respectively) compared with 7 of 8 MUD HCT recipients. The authors concluded that in patients with MDS, MRD remains the best stem cell source followed by 8 of 8 MUD; transplantation from 7 of 8 MUD is associated with significantly poorer outcomes.

An UpToDate review on “Hematopoietic cell transplantation in myelodysplastic syndromes” (Negrin, 2014) states that “Patients with MDS are at high risk for relapse (as much as 40 percent at five years) following allo-HCT. Small numbers of patients who have relapsed have undergone donor leukocyte infusions in an attempt to utilize the graft-versus-disease effect. Durable responses are not attained in most patients with MDS, and grade II to IV GVHD is common. Alternative approaches are clearly needed”. The review does not mention repeat/second allo-HCT for patients who have relapsed.

The British Committee for Standards in Haematology’s guidelines for “The diagnosis and management of adult myelodysplastic syndromes” (Killick et al, 2014) states the following:

- Early allogeneic stem cell transplantation with or without prior AML-type induction chemotherapy should be considered for eligible patients with high-risk MDS.
- Patients who fail to respond to pre-transplant induction therapy should not undergo allogeneic stem cell transplantation and should be considered for experimental therapy or supportive care alone.
- Autologous stem cell transplantation for MDS is not recommended outside of clinical trials.

Moreover, the guidelines do not mention repeat/second allo-HSCT.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Myelodysplastic syndromes” (Version 1.2015) indicates that for MDS patients who relapse after allo-HSCT, azacitidine/decitabine or “clinical trial” is the next step.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met :

38205
38230
38240
38242

CPT codes not covered for indications listed in the CPB:

38206
Hematopoietic Cell Transplantation for Myelodysplastic Syndrome

Other CPT codes related to the CPB:
- 38204, 38207
- 38221
- 86813
- 86817
- 86821
- 86822

Modifier 4A - 4Z

HCPCS codes covered if selection criteria are met:

S2150 Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

ICD-9 codes covered if selection criteria are met:

238.72 â€“ Myelodysplastic syndrome (MDS)
238.75

The above policy is based on the following references:


11. Negrín RS. Hematopoietic cell transplantation in myelodysplastic syndromes. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2012.


18. Negrín RS. Hematopoietic cell transplantation in myelodysplastic syndromes. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2014.


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