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Myelodysplastic Syndrome after Allogeneic Hematopoietic Stem Cell Transplantation: Diagnostic and Therapeutic Challenges

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A 25-year-old female with a history of Ewing sarcoma presented with leukopenia (920/μL), neutropenia (180/μL), thrombocytopenia (147,000/μL) and macrocytic anemia (hemoglobin 12.2 g/dL, mean corpuscular volume (MCV) 90.3 fL). Metastatic Ewing sarcoma of the right gluteal muscle with pulmonary metastases had been diagnosed 7 years previously. Prior treatment had included chemotherapy, radiation therapy, and allogeneic hematopoietic stem cell transplantation (alloHSCT).

In any patient previously treated with chemotherapy, radiation, and/or stem cell transplant, cytopenias and/or a rising MCV should prompt further investigation with myelodysplastic syndrome (MDS) as a consideration in the differential diagnosis. The incidence of secondary hematologic malignancies in pediatric cancers treated with standard therapies has risen with the risk linked to the intensity of therapy. (3) Specifically, there is a 2–9% cumulative

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[1]The National Cancer Institute (NCI) International Workshop on the Biology, Prevention, and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation (alloHSCT) was organized to identify, prioritize, and coordinate research activities related to the biology, natural history, prevention, and treatment of relapse after alloHSCT. (1, 2) As a part of that effort, a multidisciplinary tumor board was established at the NCI to review cases and provide guidelines for the diagnosis and management of post-transplant relapse of hematologic malignancies. This report summarizes a review of post-transplant myelodysplastic syndrome conducted in November 2010 at the NCI, Bethesda, Maryland.

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incidence over 5 years of treatment-related MDS (t-MDS) or acute myelogenous leukemia (AML) after treatment of Ewing sarcoma. (4, 5)

The patient had been treated in a clinical trial at the National Institutes of Health (NIH) for the treatment of high-risk pediatric sarcomas with non-myeloablative alloHSCT. (6) Pre-transplant conditioning consisted of fludarabine, cyclophosphamide, and melphalan. The donor was an HLA-matched sister and the graft source was filgrastim-mobilized peripheral blood stem cells. Graft-versus-host disease (GVHD) prophylaxis was with cyclosporine, which was discontinued on post-transplant day (Day +) 65. 100% donor engraftment was demonstrated on Day +14. The patient developed late-acute GVHD of the skin and the gastrointestinal tract, followed by chronic GVHD with involvement of the liver, skin, mouth, vagina and eyes. Subsequently, the patient sustained multiple recurrences of Ewing sarcoma beginning on Day +100, treated with chemotherapy, radiation, surgery, investigational monoclonal antibody against the insulin-like growth factor receptor-1 (CP751871, figitumumab), and an investigational tumor lysate dendritic cell vaccine.

Secondary malignancies, such as solid tumors and carcinomas, are relatively common after alloHSCT with a reported incidence of 2–20%. (7–9) The risk of therapy-related acute myelogenous leukemia (t-AML) and t-MDS after high-dose therapy with autologous stem cell rescue is also significant with a reported incidence ranging from 1–24%. (10, 11) In contrast, the risk of t-MDS/AML and other hematologic malignancies after alloHSCT is extremely rare with only 4 cases of t-AML observed in 4,749 patients. (12)

Cumulative doses of post-transplant therapy were etoposide 900 mg/m^2, vincristine 7 mg/m^2, cyclophosphamide 3,375 mg/m^2, doxorubicin 525 mg/m^2, irinotecan 1,500 mg/m^2, temozolomide 4,000 mg/m^2, and radiation 3,500 cGy. Cytopenias and macrocytosis developed at 71 months post-transplant.

The most commonly implicated agents in the etiology of t-MDS/AML include etoposide and alkylators (e.g., cyclophosphamide, ifosfamide) with a recently recognized association of temozolomide with MDS. (13–15) The cumulative dose thresholds that significantly predispose to t-MDS have been estimated to be 2,000 mg/m^2 for etoposide, 8,000–10,000 mg/m^2 for cyclophosphamide and 18,000–20,000 mg/m^2 for temozolamide. The latency periods to t-MDS/AML development range from 1–10 years depending on the specific drug and exposure. (15) Although the total doses of these agents used after transplant in the presented case did not reach these single-dose thresholds, there may be cumulative impact of multiple agents. Additionally, a case of temozolomide-induced MDS has been reported in a child who received only 2,100 mg/m^2 cumulative dose, suggesting that lower doses may be leukemogenic. (13) Recent reports have also suggested an increased rate of t-MDS following fludarabine-based regimens. (16)

Given the laboratory abnormalities, further evaluation with bone marrow aspirate and biopsy was performed revealing 16% blasts, hypocellularity (20–40%), and multilineage dysplasia leading to the diagnosis of MDS. Dysplastic changes were most prominent in the myeloid lineage (hyposegmented pseudopelgeroid neutrophils, hypogranular forms, and maturation asynchrony) and megakaryocyte lineage (small hypolobated megakaryocytes). Flow cytometry of the marrow aspirate revealed abnormal myeloid blasts as well as dysplastic granulocytic and monocytic lineages. Myeloid blasts were arrested with homogeneous CD13, CD34 and CD45 expression, and abnormal partial CD11b, bright CD33, partial dim CD38, dim to negative HLA-DR and dim to negative CD117 expression. Granulocytes were left shifted with decreased side light scatter consistent with hypogranularity, abnormal dim CD11b, and aberrant CD14 expression. Monocytes demonstrated abnormal bright CD15 and

dim HLA-DR. A diagnosis of refractory anemia with excess blasts-2 (RAEB-2) was assigned.

Patients with RAEB (5%–19% marrow blasts) generally have a relatively poor prognosis, with a median survival of 5 to 12 months. In contrast, patients with refractory anemia (RA) (< 5% blasts) or those with refractory anemia with ringed sideroblasts (RARS) (< 5% blasts plus > 15% ringed sideroblasts) have a median survival of 3 to 6 years. The proportion of individuals whose disease transforms to AML ranges from 5% to 15% in the low-risk RA/RARS group to 40% to 50% in the RAEB groups. (17, 18) The prognosis and likelihood of progression to AML for t-MDS has not been validated using this classification system.

In suspected cases of post-transplant MDS, bone marrow aspirate and biopsy should be performed for diagnostic confirmation. (19) (20) (21) In cases without blast increase, a suspicion for MDS after alloHSCT may be less obvious than in the de novo setting, due in part to the common occurrence and/or persistence of post-transplant cytopenias, macrocytosis, and bone marrow hypocellularity. For example, common medication-associated abnormalities may confound the diagnosis (e.g., trimethoprim-sulfamethoxazole associated erythroid macrocytosis and myelosuppression). Van Marion et al. reviewed bone marrow histopathology in the post-transplant period and noted frequent dyshematopoiesis with cytoplasmic and nuclear abnormalities in the first months after transplantation. (22) Therefore, additional techniques are required to assess the diagnosis of MDS in the post-transplant period.

Cytogenetics revealed a normal 46, XX female karyotype in 20 of 20 metaphases analyzed, which was confirmed on two subsequent bone marrow aspirates performed over a 24-week period.

Chromosome banding analysis should be performed whenever MDS is suspected to help to confirm the diagnosis and differentiate between de novo and therapy-related disease. (23) Complex and hypodiploid karyotypes are seen more frequently in t-MDS/AML in comparison to de novo disease, as are specific aberrations such as 5q-, monosomy 7, and 11q23/*MLL* abnormalities. (24) Conventional metaphase cytogenetic analysis detects aberrations in less than 50% of patients with de novo MDS. (25, 26) In a recent study by Tiu et al., the addition of single nucleotide polymorphism arrays led to detection of chromosomal defects in 74% in patients with MDS (*versus* 44% with conventional cytogenetics alone). (27) Fluorescence in-situ hybridization (FISH) may be used to monitor specific cytogenetic alterations that were present prior to transplantation or for confirmation of results of chromosome banding analysis. (28) In the event that the mitotic index is insufficient for that analysis, interphase FISH can be used to identify previously known cytogenetic alterations. Multiparameter flow cytometry can be helpful in the diagnosis of MDS (29) and in the detection of minimal residual disease (MRD). (30) Nonetheless, monitoring for MDS after alloHSCT is often limited by the lack of specific markers, (31) although this is expected to improve with the increasing panel of molecular markers in MDS. (32) (33)

Peripheral blood chimerism studies utilizing short-tandem repeat (STR)-PCR analysis revealed 100% donor origin of both the T cell (CD3) and the myeloid (CD33/CD66b) components. These findings were consistent with a donor-cell myelodysplastic syndrome, presumed related to the extensive post-transplant therapy.

Donor cell leukemia (DCL) and donor cell myelodysplastic syndrome (donor-cell MDS) represent hematologic malignancies that arise in donor cells following alloHSCT. Detection of donor-cell MDS requires both a high index of suspicion as well as a way to distinguish between cells derived from recipient *versus* donor origin. This is especially important when

trying to differentiate from relapse of the primary disease, which has implications in regard to treatment. Suspicion for donor-cell MDS is often first raised when there is a discrepancy between the detection of pathologic morphologic findings, such as blast increase or dysplasia, in the setting of full donor engraftment without evidence for recipient cells or when the new abnormalities differ from the original diagnosis for which the recipient was transplanted. Importantly in this regard, in 72% (18 of 25) of reported cases of donor-cell MDS or DCL with likely antecedent donor-cell MDS, transplantation was performed for diagnoses other than AML or MDS. (34, 35) Chimerism analysis serves as the primary method by which donor-cell MDS can be distinguished from relapse of host origin. The various methods and indications for use include XY-FISH (in case of sex-mismatched HSCT) and different molecular methods including PCR for variable number tandem repeats (VNTRs: repeats of 10–100 base pairs) or short tandem repeats (STRs) (repeats of 2–6 base pairs), real-time PCR for donor/recipient specific polymorphisms, or restriction fragment length polymorphisms (RFLP). (36–38) Given the inherent genetic instability found within leukemic cells and limited sensitivity in detection, multiple methods may need to be applied in the evaluation of donor-cell MDS. In comparison to relapsed disease, which almost always occurs before 2 years post transplant, DCL is commonly diagnosed later, with a median time to DCL of 31 months (range: 2–312 months). (35)

Discussion

Myelodysplastic syndrome that develops after alloHSCT can represent relapse or de novo disease, the latter of which can be of recipient or donor origin. Relapse rates of MDS after alloHSCT range from 5–60% depending on the stage of disease at presentation and the intensity of conditioning. (39, 40) Combined, 84 cases of DCL and donor-cell MDS have been reported. (34, 35, 38, 41–47) Donor-cell MDS appears to be less common than DCL, with only 21 cases previously reported (34, 35, 44, 45, 47–57) with several additional cases of DCL arising from an antecedent MDS phase. (35, 44, 50, 58–64) Prior cases of donor-cell MDS have been reported after alloHSCT for hematologic malignancies and bone marrow failure syndromes. However, this represents the first known case of donor-cell MDS after alloHSCT for a solid tumor and it (50, 53)likely represents therapy-related MDS (t-MDS) induced by exposure of donor cells to the toxic effects of chemotherapy and/or radiation administered after transplantation.

Pathobiologic Considerations

In patients previously transplanted for AML/MDS, relapse of the original disease is far more likely than MDS arising in donor cells. In contrast, MDS is more likely to be of donor origin in patients transplanted for other conditions, although recipient-derived t-MDS may be related to pre-transplant exposure to chemotherapy and/or radiation. Proposed mechanisms leading to donor-cell MDS include occult leukemia in the donor, abnormal or defective stroma and/or bone marrow microenvironment, genetic susceptibility, immune-mediated phenomenon, infection, transmission of an oncogene from the host's original disease into donor cells, toxicity of post-transplant therapies, and possibly GVHD. (7, 35, 38, 43, 45, 50, 53, 54, 59, 65–69) In this reported case of MDS developing in a patient transplanted for a solid tumor, exposure of donor cells to the effects of the chemotherapy and radiation used to manage recurrent Ewing sarcoma is the most plausible etiology of donor-cell MDS. Consistent with this, 36 of 74 (49%) of previously reported cases of DCL had cytogenetic abnormalities typical of therapy-related disease, including abnormalities involving 11q23, 21q22, and chromosomes 5, 7, 8 and 21, and three of these cases were known to have had a history of post-transplant radiation or pre-transplant exposure to chemotherapy in the donor. (35, 47)

Management Considerations

The optimal management of MDS that recurs or develops after stem cell transplantation is not well defined. The options to be considered are usually extrapolated from the treatment of MDS in patients who have not undergone alloHSCT. The recommended approach after transplant varies depending on case-specific details (Figure 1, Table 1) and the rapidity of progression to AML.

Hypomethylating agents—The hypomethylating agents azacitidine and decitabine have demonstrated efficacy in the treatment of MDS, but there are only limited data in the post-transplant setting.(70–72) These agents have associated toxicities, most notably cytopenias that limit the dose that can be safely administered after alloHSCT. (73) Maintenance therapy with low-dose azaciditine to prevent post-transplant recurrence is being tested in clinical trials. (74)

Allogeneic stem cell transplantation and donor lymphocyte infusion—AlloHSCT is the treatment modality with the highest curative potential for patients with newly diagnosed MDS and high-risk features. (75) Consequently, second stem cell transplant is considered for patients with MDS after alloHSCT, although data are somewhat limited and outcomes are guarded with second transplants in general. The Center for International Blood and Marrow Transplant Research (CIBMTR) conducted a retrospective study of alloHSCT in 868 patients with t-MDS/AML. Although none of these patients had undergone prior alloHSCT, 17% had undergone prior autologous stem cell rescue. (76) Other smaller studies have included patients with prior allogeneic transplantation. (77–79) Second alloHSCT for relapsed disease after reduced intensity conditioning was utilized for 10 patients with relapsed MDS with 17% OS, 21% relapse, and 23% TRM rates at one year. (80) Donor lymphocyte infusion (DLI) has been successfully employed, albeit with relatively limited efficacy and poor long-term survival. One series reported 3 complete remissions in 14 evaluable patients, but with the consequence of extensive chronic GVHD. (81)

Other therapeutic options—AML-type chemotherapy is commonly employed for patients with high-risk subtypes of MDS, although in general the results are poor.(75, 82–85) Furthermore, the expected toxicity of AML-type chemotherapy prohibits use after alloHSCT in most cases. (86) Thus, the use of chemotherapy for MDS after transplant is commonly limited to low-dose palliation. High-dose therapy with autologous stem cell rescue has been used in the treatment of newly diagnosed MDS with reduced TRM and no risk of GVHD in comparison to alloHSCT, but without the benefit of a graft-*versus*-leukemia (GVL) effect and with an associated increased risk of relapse. (87) (88) However, there is no known experience using “autologous” stem cell rescue in the management of MDS after alloHSCT. Other therapeutic approaches that have been utilized in the management of newly diagnosed MDS might be considered. For example, hematopoietic growth factors and transfusion support would be expected to be well tolerated and might be of palliative benefit. (89) Lenalidomide is active in the subgroup of patients with MDS with deletion of 5q, although the utility of this agent in t-MDS is unclear especially in the absence of deletion 5q. (90, 91). Finally, antithymocyte globulin (ATG) and cyclosporine have been associated with hematologic responses in some patients. (92, 93)

Specific considerations in the treatment of donor-cell MDS—Treatment of donor-cell MDS is challenging and carries a poor prognosis. In general, the treatment options to be considered are similar to those detailed above. In a recent analysis of 64 patients with DCL/donor-cell MDS, 34 patients had died at a median of 5.5 months after the diagnosis of DCL/donor-cell MDS was made. Median OS for treated patients was estimated at 32.8 months

(95% confidence interval 22.5–43.1 months). Re-induction chemotherapy with curative intent was attempted in 47 of 52 patients who received any therapy with a complete response achieved in 27 and a sustained response in 16 of these. (35) These data suggest that complete remission can be attained with re-induction chemotherapy in the setting of DCL. Second transplant is also an option for the treatment of donor-cell MDS and includes the possibility of using either the original donor or a new donor. Utilizing the original donor in the setting of 100% donor engraftment may reduce TRM and GVHD in comparison to a transplant from another donor and this approach has been successfully employed in a few cases of DCL. (35, 94) However, there would be no expectation of a therapeutic GVL effect given that the MDS is of the same donor origin. Transplantation from a different donor would have the potential to induce a therapeutic GVL effect, although this would carry additional risks (e.g., graft rejection, GVHD). In a recent review of DCL, 17 patients were identified as having undergone a second alloHSCT and 7 (41%) remained alive at a median of 29 months from the diagnosis of DCL. Five of these patients were known to have received a second transplant from the original donor, and 3 were reported with durable responses. (35, 50) As noted above, DLI has potential efficacy in the treatment of relapsed MDS after transplant. (81) Although unlikely to be curative, DLI in the setting of donor cell MDS has been reported to be associated with improvements in hematologic parameters. (45)

Additional case-specific considerations—The treatment of MDS in this reported case was complicated by two major factors: residual post-transplant toxicities including chronic GVHD and organ dysfunction; and continued recurrences of Ewing sarcoma. In the setting of progressive clinically symptomatic Ewing sarcoma that was treated with chemotherapy and radiation, the ability to administer any specific therapy for MDS was compromised. Only supportive care was administered for the MDS that consisted of intermittent filgrastim as needed to reverse severe neutropenia and antibiotics to treat and prevent infection. The patient remained transfusion independent and serial bone marrow biopsies revealed stable MDS with blast counts below 10% until her death from progressive Ewing sarcoma 13 months from the diagnosis of donor-cell MDS.

Conclusions

The development of a novel hematologic malignancy after alloHSCT is rare. In the setting of post-transplant MDS, it is important to determine the origin of the disease as this has implications for treatment. Treatment of post-transplant MDS is challenging and therapeutic options should be considered in relation to patient- and transplant-specific characteristics, as well as the origin of the MDS.

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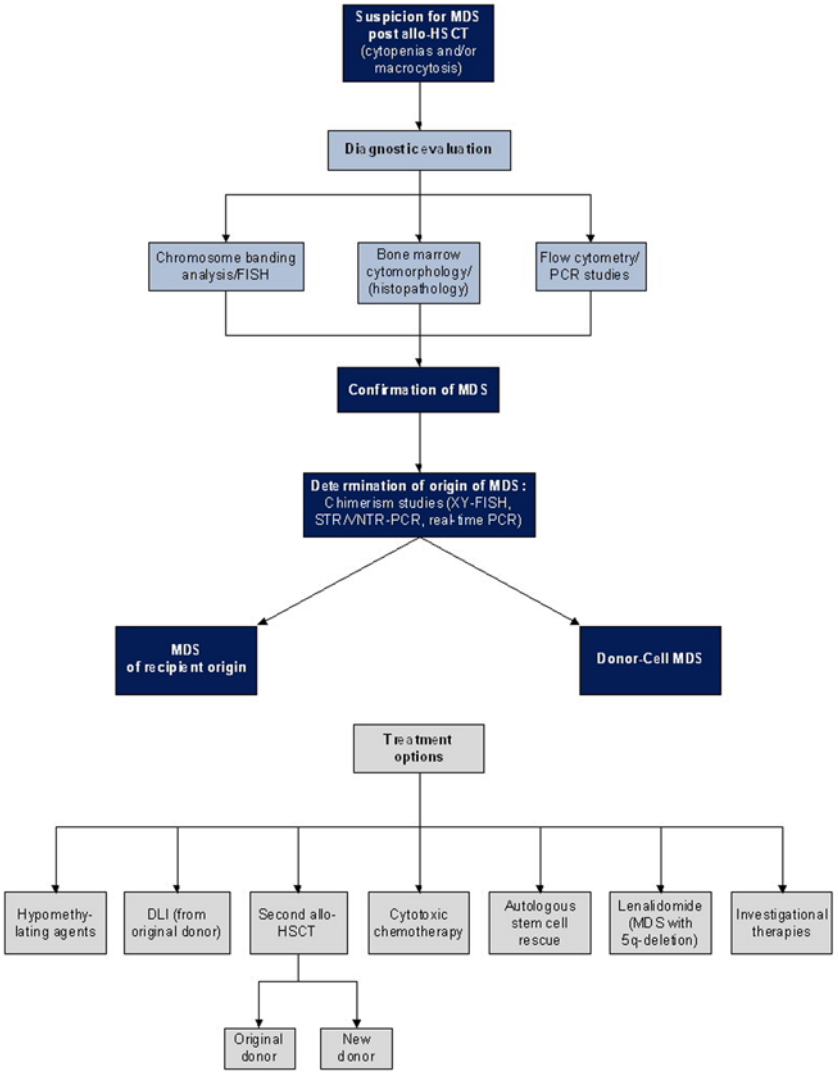

Figure 1. Algorithm for the evaluation and treatment of MDS after allogeneic hematopoietic stem cell transplantation

This algorithm provides general guidelines for the evaluation and treatment of MDS after allogeneic hematopoietic stem cell transplantation.

MDS should be considered in the differential diagnosis of persistent cytopenias and/or macrocytosis that are not otherwise explained by medication effect or post-transplant complications. Diagnostic bone marrow aspirate and biopsy should be performed for morphologic evaluation and extra aspirate samples collected for possible additional studies as detailed below. If dysplasia, atypia and/or increased blasts are detected, samples should be sent for cytogenetic evaluation by means of chromosome banding analysis and/or FISH, flow cytometry, PCR studies specific to previously documented molecular markers of the underlying disease, and/or chimerism analysis. The origin of the MDS as either recipient- or donor- derived should be determined. In patients previously transplanted for AML/MDS, relapse is more likely than de novo donor-cell MDS. In patients transplanted for other conditions, donor-cell MDS is most likely. Methods for determining the origin of MDS include STR/VNTR PCR, real-time PCR, and XY-FISH (in sex mismatched transplants). Treatment options for MDS after alloHSCT include hypomethylating agents, DLI, second alloHSCT (from the original or a new donor), cytotoxic chemotherapy, high-dose therapy

with autologous stem cell rescue, and lenalidomide (for those with 5q-deletion). Enrollment in clinical trials should be considered. The decision regarding the best treatment for an individual patient is dependent upon the origin of the MDS (recipient *versus* donor), the rapidity of disease progression to AML, cytogenetic abnormalities, and co-morbidities. Treatment options should be weighed carefully and individualized with close considerations of such factors. Specifically, the origin of MDS plays an important role in determining the best therapy. For example, DLI may be a reasonable first choice to manage relapsed MDS of recipient origin, whereas a therapeutic GVL effect would not be expected in donor-derived MDS and thus an alternative treatment would be preferred in that setting. Although some treatment options have curative potential (e.g., second alloHSCT), these may be associated with high risk of treatment-related mortality. In contrast, other approaches are less likely to be curative, however, they may offer reduced toxicity and higher likelihood of improved short-term quality of life.

Table 1

Treatment options for relapsed MDS and donor cell MDS after allogeneic hematopoietic stem cell transplantation

Treatment Option	Primary Indication	Advantages	Disadvantages	Reference
Hypomethylating agents Azacitidine Decitabine	De novo MDS	• Survival benefit with azacitidine in de novo disease • Delays progression to AML • Likely less TRM and side effects compared to other treatment options	• Reduced efficacy in t-MDS • Survival benefit unclear in high-risk and t-MDS • Main anticipated toxicity is cytopenia, which may be worse after alloHSCT • No known data in donor cell MDS • One case report of CR in relapsed AML post-transplant for MDS	(70–72, 95)
Donor Lymphocyte Infusion	Relapsed primary disease	• Reduced risk of GVHD with original donor	• No anticipated GVL effect with original donor • Limited efficacy for post-transplant relapsed MDS • No known data in setting of t-MDS. • Transient hematologic response seen in 1 case of donor cell MDS	(45, 81)
Second Allogeneic Stem Cell Transplant	Relapsed disease or graft failure	• Curative option	• High risk of TRM • No anticipated GVL effect with original donor • Risk of GVHD, especially with new donor	(35, 94, 96)
Chemotherapy	De novo or t-MDS	• Standard of care for upfront therapy in low-risk disease	• Low remission rates for t-MDS • Transplant may be required for cure • No survival benefit with intensive chemotherapy in advanced disease • Anticipated side effects • No known data in post-transplant setting	(22, 23, (84)

Treatment Option	Primary Indication	Advantages	Disadvantages	Reference
Autologous Stem Cell Rescue	De novo or t-MDS	• Curative option • Reduced risk of TRM in comparison to alloHSCT	• Increased risk of relapse • No GVL	(87, 88)
Lenalidomide	MDS with 5q-deletion	• May reduce cytopenias and transfusion requirements	• Unclear benefit in t-MDS • No known data in donor-cell MDS or post alloHSCT	(90, 91)

Abbreviations: AML: acute myelogenous leukemia; DCL: donor cell leukemia; GVHD: graft-*versus*-host disease; GVL: graft-*versus*-leukemia; alloHSCT: allogeneic hematopoietic stem cell transplantation; TRM: treatment-related mortality