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Review

Allogeneic Stem Cell Transplantation for MDS

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Abstract: Myelodysplastic syndromes are clonal disorders with morphological dysplasia, a variable degree of cytopenia and a risk of transformation to acute myeloid leukemia. Prognosis is very variable and is defined by blast count, cytopenia, cytogenetics and more recently by somatic mutations, with IPSS or revised IPSS score being the most widely used to assess disease risk. HSCT remains the only curative treatment to date, with high-risk patients obtaining the biggest benefit. However, NRM should be carefully assessed before indicating the transplant in this usually old population, where organ toxicity and comorbid conditions are to be considered. Multi-domain assessment tools, such as CGA (comprehensive geriatric assessment) and EBMT score, are useful in this context and might guide physician decisions regarding the transplant. Indeed, with the development of reduced intensity conditioning regimens, the number of patient candidates for an HSCT has increased. Regarding pre-transplant treatment, patients with a blast excess > 10% might be treated with HMAs or chemotherapy, although there are no randomized trials confirming the benefit of this approach, even when achieving a complete response. Concerning donor choice, matched sibling donors continue to be the first option, although matched unrelated donors, and more recently haploidentical donors, have proven to be valid options and should be offered in the absence of a related donor. Relapse remains the main cause of transplantation failure. MRD assessment and pre-emptive or prophylactic use of HMA or other targeted inhibitors with or without DLI are accepted strategies to reduce relapse risk, but the prognosis in this context remains dismal, and is the subject for several ongoing clinical protocols.

Keywords: myelodysplastic syndromes; stem cell transplantation; IPSS score; cytogenetic risk group; relapse; organ toxicity; co-morbid conditions

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1. Introduction

Myelodysplastic syndromes (MDS) are characterized by dysplastic morphology of hematopoietic cells associated with clonal hematopoiesis, peripheral blood cytopenia, and a propensity to progress to acute myeloid leukemia. The disease course is variable, mainly conditioned by molecular alterations, marrow blast count, and cytopenia [1–5]. Transformation into acute leukemia is the main cause of death in patients with higher risk MDS. Hematopoietic stem cell transplantation (HSCT) remains, to date, the only potentially curative therapy, albeit with a treatment-related mortality between 15 and 50%, according to specific risk factors [6–8]. Furthermore, only young and fit patients can be candidates for HSCT, due to higher mortality in the elderly and in patients with major comorbidities. The optimal timing of HSCT should take into account life expectancy without HSCT and quality of life. Some low-risk patients with persistent disease might live for years with supportive therapy and a relatively good quality of life. Hypomethylating agents (HMAs) have been reported to increase median survival and decrease transformation into leukemia in higher risk patients, and should be balanced with the potential effect of transplantation [9]. On the other hand, the development of less toxic conditioning regimens has expanded the indication to HSCT to older or more fragile patients previously not eligible for transplantation. Pre-transplant therapy remains a matter of debate. Indeed,

marrow blast percentage is a risk factor for disease progression, but there is no randomized trial demonstrating a benefit for pre-transplant cytoreduction. This review will detail the current evidence for transplant strategies in MDS patients.

2. Patient Consideration

Chronological age alone is not reliable enough to consider HSCT eligibility. Some relatively old patients have a relatively good outcome after HSCT, and some authors have reported that this is not an obstacle to transplantation [8,10]. As MDS patients are usually older than 60 years, the probability of non-relapse mortality (NRM) in this fragile population should be precisely estimated. In the EBMT study including 1245 MDS patients [8], older age and a higher number of comorbidities were associated with higher mortality. Comorbidity index has shown to impact the outcome in all categories of age, including the elderly [11,12]. Recently, multi-domain assessment tools have also been tested, especially in patients older than 50 or 60 years, to better estimate the risk of post-transplant morbidity and mortality [13]. Domains usually assessed include physical fitness, auto-nomy and dependence, cognitive performance, social and professional insertion, moods and psychological well-being, nutrition, and inflammation. This multi-domain assessment has been regularly tested in the geriatric setting and is called "comprehensive geriatric assessment" (CGA). CGA has been reported to be associated with mortality in cancer patients and, more recently, in transplanted patients, and could guide physicians in their decisions regarding invasive treatments. This CGA is also applied to younger patients in the setting of transplantation, thus CGA may be useful to determinate a physiological age and help the physician take the decision for transplantation.

3. MDS Consideration

HSCT is an established curative treatment in MDS patients. However, the risk of disease progression without such a treatment and the NRM after transplantation should be carefully balanced before indicating this procedure. According to standard or revised international prognostic scoring system (IPSS), different categories distinguished patients from low risk, with median survival longer than 10 years, to very high risk, with median survival of a few months [1,2]. The indication for transplantation relies on the estimation of mortality with or without HSCT. The NRM post-transplantation is usually greater than 15% in the best series and mortality mainly occurs within the first 2 years post-transplantation. Higher risk MDS patients (intermediate-2 and high) have an estimated mortality much higher than 15% at 2 years, suggesting that they may have a better outcome with HSCT. Registry studies raised the question of the potential benefit of transplantation comparing transplant and non-transplant cohorts. Specific statistics have been carried out to overcome all bias due to registry studies. Of note, transplant cohorts include patients who received transplantation only, meaning that patients had to be alive between diagnosis and transplantation, which is a major bias. Patients who are transplanted usually have a higher risk, but a better general performance status, than non-transplanted patients. Furthermore, the disease risk in main comparative studies is usually assessed by IPSS, but does not take into account other risk factors such as somatic mutations, marrow fibrosis, heavy transfusion requirement, previous infections, or complications, which have an impact on prognosis. The first comparative study published in 2004 by Cutler et al. included relatively young patients, transplanted from HLA matched sibling donors after a myeloablative conditioning regimen. It was shown that there was a survival benefit in higher risk patients (intermediate-2 and high risk according to classical IPSS) when transplantation was performed upfront, while there was a detrimental effect in lower risk patients (low and intermediate-1) [14]. It has been reported later that this was also true for older patients receiving a reduced intensity conditioning regimen in comparison to patients who received HMA [15,16]. In addition, a national prospective study including patients at the time of transplantation indication has reported a significant advantage of

survival in higher risk patients who received transplantation, especially after 2 years of follow up (Figure 1) [17].

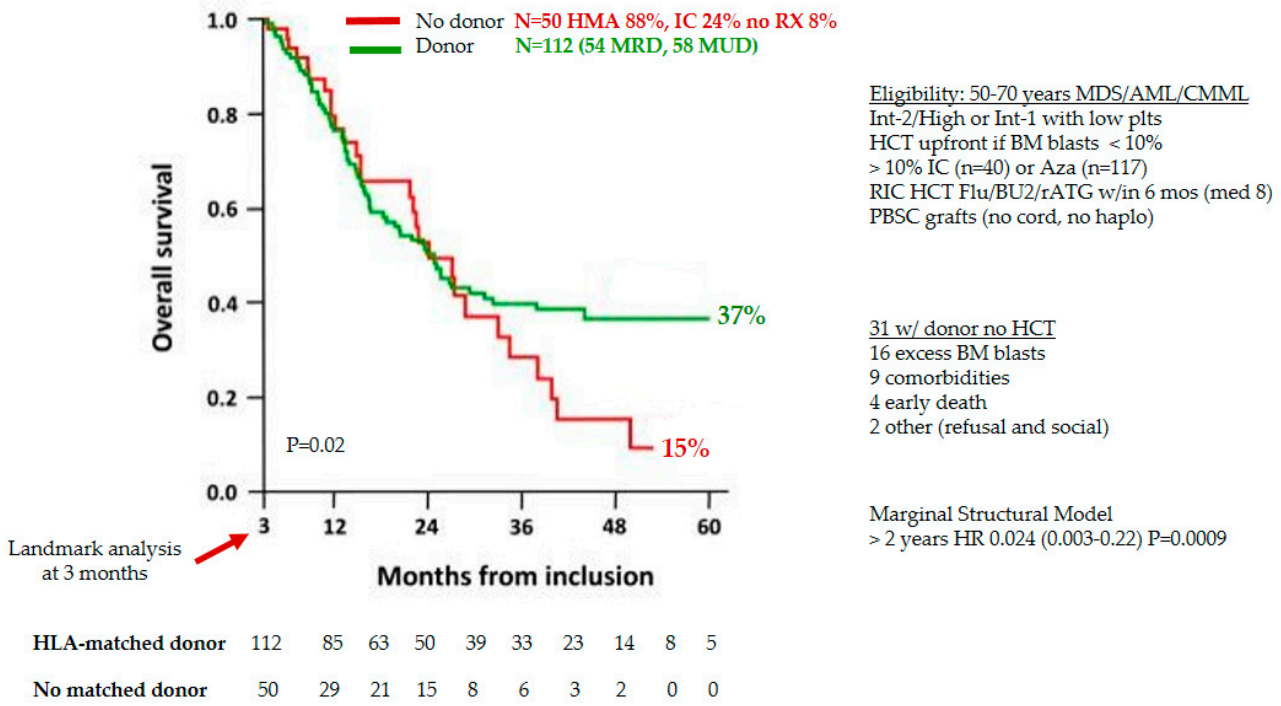

Figure 1. Overall survival in higher risk MDS patients with or without a donor. This is a prospective French study showing an advantage of survival in patients with a donor (Leukemia 2015. Robin et al.).

The role of somatic mutations in these comparative studies has not been evaluated, while their prognostic value has recently taken more and more room [5,18–21]. Somatic mutations have an impact in all categories of disease risk, especially for TP53, RUNX1, ASXL1, DNMT3A, TET2, and RAS-pathway mutations. Indeed, it has been reported that lower risk patients who harbored some poor risk mutations have superimposable survivals to higher risk patients. Some prognostic classifications have integrated somatic mutations in order to better assess patients risk, but had not been widely reproduced yet [22,23]. In higher risk patients, it has been reported that patients harboring very poor cytogenetics (complex or monosomal karyotype) or TP53 mutations have a very high probability of relapse after transplantation, leading to a poor survival rate of less than 15% at long-term [20,21,24,25]. That is an additional issue to think about when considering transplantation strategies in these patients to improve their outcome.

Transplantation in Lower Risk MDS

In lower risk patients, allogeneic transplantation indication is still controversial, as there are no prospective studies regarding this issue [26]. In this group of patients, NRM remains the main cause of treatment failure [27]. However, in young patients with pejorative factors, HSCT might be indicated. These factors are mainly somatic mutations (TP53, ASXL1, and RUNX1), marrow fibrosis (grade 2 or more), very poor cytogenetics, relapse or refractoriness to standard therapies, therapy related MDS, and profound or symptomatic cytopenia [26]. Nevertheless, more studies are needed to explore the role of HSCT in these patients.

4. The Role of Pre-Graft MDS Therapy

International recommendations, based on registry studies, have highlighted that marrow blast count, especially if higher than 10%, is a risk factor of post-transplant relapse

and mortality [28]. Many efforts have been made to reduce this marrow blastosis with chemotherapy or HMA. Nevertheless, there is no randomized trial showing that pre-graft therapy reduces relapse risk in MDS patients. One can argue this is because patients do not frequently achieve complete remission (CR), but even when patients are in CR, the prognosis is not improved [29,30]. The role of pre-transplant remission in acute myeloblastic leukemia (AML) has been largely demonstrated, as well as molecular remission, but this is not the case in MDS [31,32]. Minimal residual disease in MDS patients is unfrequently measurable and unfrequently negative when measured, even in patients in CR, as shown by the persistence of somatic mutations detection before HSCT, including patients in CR [20,21,25]. One hypothesis may be that the persistence of molecular disease is associated with an increased relapse risk in patients, whatever the disease status before transplantation. Of note, the HSCT procedure often takes several weeks to organize, especially when an unrelated donor is recruited, so a therapy to reduce the risk of AML transformation before HSCT may be justified in higher risk patients. Indeed, HSCT in overt AML is followed by a very poor outcome with high risk of relapse [33]. The issue appears similar using intensive chemotherapy (IC) or HMA [29,30,34].

5. The Role of Conditioning Regimen

The intensity of the conditioning regimen has been guided by patient's age for a long-time, meaning that young patients received myeloablative conditioning (MAC) while older or young patients with comorbidities received reduced intensity regimen (RIC). RIC was developed to reduce NRM, but is followed by an increased progression/relapse risk. An EBMT phase 3 prospective trial has compared MAC and RIC in MDS patients [35]. There was no significant difference between the two arms, relapse risk being balanced by NRM risk. It was not confirmed in an American phase 3 trial including MDS and a majority of AML, which showed worse results with RIC. The minority of MDS patients in the American trial can explain why the results were different from the EBMT study [36]. Schmid and colleagues reported a new regimen combining two sequences of chemotherapy (SEQ): one AML targeted chemotherapy with Fludarabine, Amsacrine and Cytarabine (FLAMSA) followed by one RIC (4 Gy Total Body Irradiation and Cyclophosphamide) developed for high risk patients, especially not eligible for MAC [37,38]. Prophylactic donor lymphocyte infusions (DLI) were planned. All patients (total $n = 75$) included in the phase 2 trial were either progressive or refractory to chemotherapy, in second remission after early relapse, or in first remission with poor cytogenetics. The 2-year OS was 42% and 62.5% in primary chemotherapy refractory patients. However, a recent phase 3 randomized trial from United Kingdom (UK) has compared SEQ to RIC in 255 patients with AML ($n = 164$) or MDS ($n = 80$), and there was no advantage with SEQ on overall survival, event-free survival, NRM, or cumulative incidence of relapse [39]. Of note, disease characteristics from the phase 3 UK trial are very far from the original trial published by Schmid et al., with a majority of patients in remission at time of HSCT, and a minority of MDS at high risk. The exact room for SEQ remains debated and is a source of comparative studies.

In the last years, conditioning regimens with new drugs such as treosulfan [40] in the RIC setting have shown better results regarding NRM. These new approaches might offer better results and enlarge the number of patients who might be candidates for HSCT, such as more lower risk patients, or patients with comorbidities.

6. The Type of Donor

Apart from conditioning regimen, the donor type is potentially modulated by physician's choice. It is established that an HLA matched sibling donor (MSib), may be the first choice. However, the preference of a younger HLA matched unrelated donor has been questioned [41]. Indeed, an EBMT study reported that the outcome of MDS patients receiving transplant from a young unrelated donor (<30 years) may be better than patients receiving a transplant from an older HLA matched sibling donor. This issue is not spe-

cific to MDS, but it is particularly relevant in MDS where both recipients and donors are typically older [42].

Regarding the donor choice between MSib and unrelated (MUD), a CIBMT registry study reported that treatment failure (death or relapse) is similar among MDS patients who received a transplant from MSib as compared to MUD [43]. However, NRM remains significantly higher with MUD. Unfortunately, not all patients have an HLA matched donor, and in these cases, several alternative HLA mismatched donors are possible: unrelated cord blood, unrelated donor, or related haplo-identical (HAPLO) donor. CIMBTR and EBMT have reported that an HLA mismatched unrelated donor gives an inferior outcome as compared to an HLA matched donor [43–45]. HAPLO donors are being increa- singly used, mainly because new procedures, including intensive GVHD prophylaxis with post-transplant cyclophosphamide have considerably improved post-transplantation outcome. The EBMT registry study reported that outcome was better using HAPLO donor than unrelated cord blood [44,46], and it has been confirmed in a large meta-analysis [47]. Others have reported that outcome after HAPLO is close to outcome after matched related donor, and several meta-analyses have compiled this HAPLO effect, however they did not only include MDS. A meta-analysis including 1919 patients (publications searched until February 2017) has compared engraftment, GVHD, relapse, DFS, NRM, and OS after HAPLO or HLA matched sibling donor [48]. The authors found that outcomes were all better with MSib, except for NRM, which was similar. Another large meta-analysis including 11,359 patients (publications research until June 2017) confirmed that HAPLO gives similar acute and chronic GVHD, NRM, and relapse incidence than HLA matched donors [49]. However, patients who received a RIC-HAPLO, had higher risk of acute GVHD and NRM. Another more recent meta-analysis including 7806 patients (publications searched until June 2019) compared HAPLO to MSib. HAPLO lowered chronic GVHD risk but increased NRM. Relapse, OS, and DFS were similar. From these meta-analyses, not focused on MDS and sometimes overlapping, we conclude that HAPLO is a valid alternative donor, and gives close results as compared to HLA matched donor transplantation. Randomized trials are still ongoing to determine if HAPLO do better than HLA matched or HLA mismatched donor transplantation.

7. Outcome after Transplantation

Outcome after transplantation depends on patient characteristics; disease characteristics; transplantation-related factors including GVHD prophylaxis, type of donor, infectious prophylaxis; and the occurrence of post-transplant complications such as acute or chronic GVHD, infection, organ failure, comorbidities, or therapy side effects. Recent studies showed 3-year overall survival from 20% to 82% according to disease risk, age, and type of MDS (de novo vs. therapy-related) [25]. The majority of currently transplanted patients have intermediate/high risk, and 3-year OS in this category of patients ranges from 35 to 50% [50–52]. NRM, estimated in a large MDS EBMT cohort, ranges between 13% to 60% according to age, comorbidity, disease risk, and type of donor, and for the whole cohort is 28% at 2 years [8]. Relapse incidence ranges from 5 to 80%, mainly related to cytogenetics and somatic mutations prognosis [24,51]. Other risk factors for relapse are high blast count, marrow fibrosis, and refractoriness to pre-graft therapy. Scores taking into account potential risk factors have been developed and used to estimate outcome of transplanted MDS patients [50,51,53]. The optimized EBMT score considers CMV serostatus of the recipient, Karnofsky score, and age for patient characteristics, cytogenetics, platelet count and blood blast count as disease risk, and donor type as transplant procedure. This score is able to distinguish four groups of patients from lower to higher proportion of survival (Figure 2).

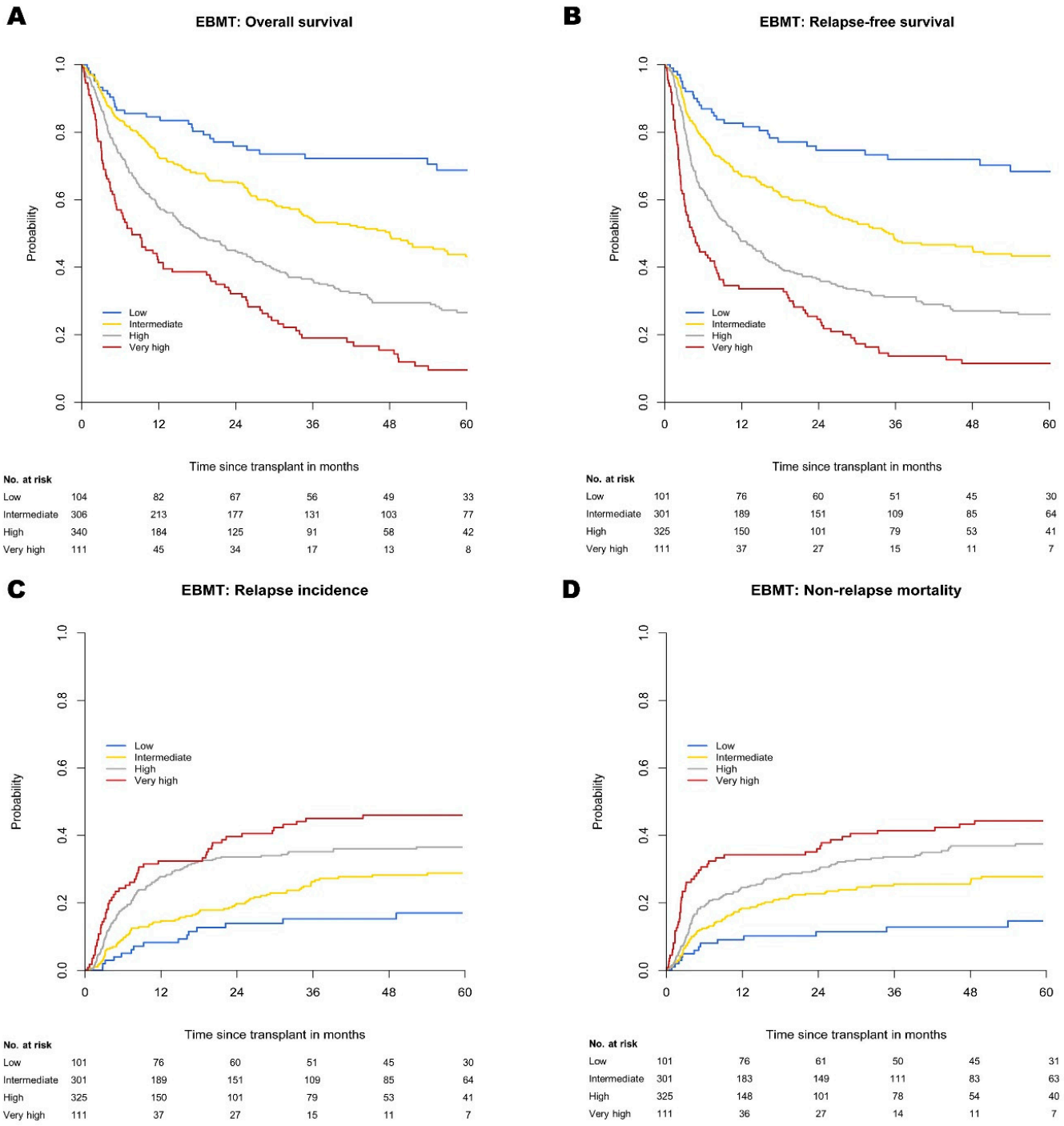

Figure 2. Outcome of MDS transplanted patients according to EBMT adapted score. This is a registry study from EBMT reporting a new score based on CMV serostatus recipient, Karnofsky score, and age for patient characteristics, cytogenetics, platelet count and blood blast count as disease risk, and donor type (Haematologica 2019, Gagelman [53]). The figure shows overall survival (**A**), relapse-free survival (**B**), relapse incidence (**C**), and non-relapse mortality (**D**) according to the EBMT adapted score.

8. Post-Transplant Relapse

Relapse remains the first cause of failure after HSCT. An EBMT study showed, in 698 patients relapsing after HSCT, that median OS is only 4.7 months after relapse. Poor risk factors in these patients were shorter remission after HSCT, MDS with blast excess before HSCT, older age, the use of an unrelated donor, and acute GVHD occurrence before relapse [54]. This study also analyzed the outcome after therapy. Using a 6-month

landmark post relapse, 2-year OS was 29.7% after second HSCT, and 27% after donor lymphocyte infusion (DLI). The German cooperative transplant group reported the outcome in 152 relapsing patients treated by AZA and DLI [55]. Two-year OS was 29%, and predictors for response were low percentage of marrow blast or molecular relapse. Recently, the SFGM-TC has reported 147 MDS patients relapsing after transplant. Only patients who received "cellular therapy" (DLI or second SCT) could achieve long-term survival (32% vs. 6% for chemotherapy alone) [56]. These results were not confirmed by another European study, showing that relapsing patients who responded to AZA had better OS, with or without DLI [57]. More recently, the addition of Venetoclax to DLI has shown to be feasible in a small retrospective trial [58], with ORR of 50%. Regarding AZA + Venetoclax combinations, a study of the German Cooperative group concludes that toxicity remains high, and responses might be better in molecular relapse and as first salvage therapy [59]. However, larger and prospective studies are needed in this setting [60].

Patients with lower disease burden respond better to post-transplant therapy. This observation led to the development of preemptive therapy. In MDS, there is no standardized method to monitor minimal residual disease (MRD) in all patients. Platzbecker et al. have conducted two prospective phase 2 trials based on preemptive AZA therapy [61,62]. In these two studies, markers of minimal disease were flow sorted CD34 positive donor cells, NPM1, or leukemia specific fusion genes. In the most recent study, 60 patients among 198 had MRD detection during follow-up, and 53 were eligible for the treatment. Among the 138 patients who stayed MRD negative, only five patients relapsed. After MRD-guided treatment, relapse-free survival was 46% at one year, which is very encouraging in patients with imminent relapse.

Preventive therapy is another option which has proven its efficiency in acute myeloblastic leukemia for FLT3 inhibitors in phase 3 trials [63,64]. In MDS, phase 2 studies have reported that reduced dose AZA or decitabine are feasible from day 40 after transplantation [59,65–67]. These preventive therapies are especially indicated in patients at very high risk of post-HSCT relapse.

9. Conclusions

HSCT is a curative therapy for MDS, but NRM remains a major obstacle to the success of this treatment. The risk of disease related mortality without the transplant should be balanced with the NRM. Higher risk patients have short life expectancy with chemotherapy, and will generally benefit from the HSCT. Risk for NRM should be carefully eva-luated, and relies on functional age assessment related to general performance status and comorbidities. When a patient has an indication of HSCT, a donor can be found either in the family (MSib or HAPLO) or in registry (matched unrelated or mismatched unrelated). The use of a mismatched donor increases the risk of NRM, but there is also evidence to suggest that an HAPLO donor is a valid choice, as general outcome appears to be at least similar to MUD. Outcome after HSCT is still disappointing in some situations, such as in patients harboring TP53 mutations or very poor cytogenetics. Protocols are ongoing to test new strategies in these patients, enabling us to overcome this poor prognosis and to prevent post-transplant relapse.

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