Current status of reduced intensity conditioning allogeneic stem cell transplantation for acute myeloid leukemia

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ABSTRACT

Allogeneic stem cell transplantation (allo-SCT) is the most efficient antileukemic treatment for acute myeloblastic leukemia (AML). However, elderly patients can rarely benefit from standard myeloablative allo-SCT because of an unacceptable rate of procedure-related toxicities. This point is critical when considering AML patients in first complete remission. The development of the so-called reduced-intensity conditioning (RIC) regimens appears to decrease allo-SCT-related toxicities, and has emerged as an attractive modality in AML patients not eligible for standard allo-SCT. Such RIC regimens aim primarily to provide the immune graft-versus-leukemia effect while causing little toxicity. Of note, treatment-related toxicity appears to be lower with RIC regimens as compared to standard myeloablative regimens. Nevertheless, toxicity might represent only one aspect of the problem, since AML encompasses a group of chemosensitive diseases, raising concerns that significant reduction of the intensity of the preparative regimen may have a negative impact on long-term leukemic control. Furthermore, no prospective studies have been reported thus far establishing RIC allo-SCT as the preferred option in AML. Investigators are currently faced with a dilemma on how to optimize the potential role of RIC allo-SCT in AML patients, while delivering minimal myeloablation and maximizing allogeneic immunotherapy. The aim of this review is to analyze the available research evidence in this field.

Key words: allogeneic stem cell transplantation, acute myeloid leukemia, reduced intensity conditioning, GVHD, transplant-related mortality.

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In selected patients with acute myeloblastic leukemia (AML) allogeneic stem cell transplantation (allo-SCT) is the most efficient antileukemic treatment.[1] While complete remissions (CR) can be achieved with induction chemotherapy in almost 65% of adult patients with *de novo* AML,[2-4] the rate of post-remission disease-free survival (DFS) remains poor, usually being under 50% at 5 years. Despite new progresses,[5] it is well established that the overall outcome in AML can be predicted by simple biological risk factors (such as specific cytogenetic abnormalities),[6] but also older age (>60 years),[7] since most elderly patients with AML have more adverse prognostic features than younger patients, and will ultimately relapse and die from their disease within 2 to 3 years in the best cases.[2,7] Better results can be achieved by intensive post-remission chemotherapy including high dose cytarabine, autologous stem cell transplantation, and eventually allo-SCT, which has the greatest curative potential. However, elderly patients can rarely benefit from intensive treatments, including standard myeloablative allo-SCT because of an unacceptably high risk of procedure-related toxicity. This point is especially critical when considering AML in first CR (CR1).[8] Finally, most of the patients lack a human lymphocyte antigen (HLA)-identical donor further precluding an allo-SCT strategy. The development of so-called non-myeloablative or reduced-intensity conditioning (RIC) regimens appears to decrease allo-SCT-related toxicities. In contrast to standard-dosed myeloablative allo-SCT, RIC allo-SCT is relatively well tolerated by patients with high-risk clinical features such as advanced age or associated co-morbidities. Nevertheless, toxicity might represent only one aspect of the problem, since AML encompasses a group of chemosensitive diseases, raising concerns that significant reduction of the intensity of the conditioning may have a negative impact on long-term leukemic control.[9,10] This concern is particularly relevant in patients with high-risk leukemic features. Indeed, the importance of dose intensity has already been shown in myeloablative allo-SCT. However, the beneficial effect of more

intensive conditioning, which was associated with a reduced risk of relapse, was offset by an increased transplant-related toxicity.[11] The latter may be even more complex since the relative benefit of myeloablation as part of the conditioning regimen also depends on the patient and disease status at the time of allo-SCT (e.g. CR1 vs. beyond CR1 or advanced disease). Thus, investigators are currently faced with a dilemma on how to optimize the potential role of RIC allo-SCT in patients with AML, while delivering minimal myeloablation and maximizing allogeneic immunotherapy. The aim of this review is to analyze the available research evidence in this field.

Non-myelablative allo-SCT for AML

Allo-SCT procedures are currently undergoing a profound evolution. The spectra of patients and diseases for which this approach is now considered have increased considerably over the past years. Despite the development of new potent anti-leukemic drugs, outcome still remains poor for a large proportion of patients. Also, given the peak age incidence of AML (the median age of patients with AML at diagnosis is 68 years, and the age-adjusted incidence of AML is 1.8 per 100,000 for subjects less than 65 years old, increasing to 16.3 for those older than 64 years; SEER data: Surveillance, Epidemiology and End Results; *http://seer.cancer.gov/*), the vast majority of AML patients are excluded from high dose or intensive chemotherapy, thereby precluding access to standard allo-SCT for the majority of the patients in need. On this background, several groups have launched RIC allo-SCT programs for AML. The main findings from the principal studies focused on RIC allo-SCT for AML (reports including more than 25 cases of AML) are summarized in Table 1. Unfortunately, most of these studies reported on small heterogeneous groups of AML patients, with respect to disease status at time of allo-SCT (CR1, beyond CR1 or more advanced disease). Most importantly, in these studies, the indications for RIC allo-SCT with respect to the patients' disease risk status and eligibility for RIC allo-SCT are not clearly delineated. Also, few data are available to weigh the risk of transplant-related mortality (TRM) and morbidity versus risk of AML relapse. The comparison between different series often blurs these distinctions. In general, the median age was within the fifth decade, although some were in the sixth and seventh decades. In addition to the heterogeneous demographic and disease features, complexity in data interpretation is illustrated, for instance, by the large study by Sayer *et al.*[12] for the Cooperative German Transplant Study Group. This study included data from more than ten different centers employing at least six different RIC regimens, five different graft-versus-host disease (GVHD) prophylaxis regimens and different inclusion criteria for 113 AML patients. In these studies, the RIC regimen usually included a purine analog (mainly fludarabine) administered with or without low-dose irradiation and antibodies such as alemtuzumab or antithymocyte globulin (ATG). The source of the graft was also variable with studies mixing data on grafts from related and unrelated donors. Some of the trials also included an alkylating agent such as melphalan or busulfan. Of note, TRM was generally relatively low, in the 5–25% range, although some trials reported a rate as high as 66% in cases of advanced disease.[12] Conclusions related to the incidence or severity of GVHD are very difficult to draw from these studies, though it is likely that rates were not very dissimilar from those observed with standard myeloablative regimens. On the other hand, it is well established from these studies that RIC regimens including fludarabine can secure engraftment. Notably, engraftment failure rates in these series were very low, and the overall rates ranged from 0 to 10%, especially in the case of the sole use of low dose total body irradiation (2 Gy).[13] While relapse rates were variable and difficult to interpret, one can conclude that leukemia-free survival and overall survival rates were reasonable given the fact that many of these patients had high risk disease features and significant co-morbidities.

The largest prospective experience in the field was published by the Seattle consortium.[13] This study included 122 patients with AML who were conditioned with 2 Gy total-body irradiation (TBI) on day 0 with or without fludarabine (30 mg/m^2/day from days -4 to -2), and given post-grafting cyclosporine A (CSA) and mycophenolate mofetil. This study extended previous reports from the same group on the use of this fully and truly non-ablative regimen in patients with various hematologic malignancies. All patients from this study, but five, were ineligible for conventional myeloablative allo-SCT because of age and/or medical contraindications. More than half of the patients (58%) were in >CR2, 15% had secondary AML, and 17% had adverse cytogenetic risk factors. Durable engraftment was observed in 95% of the patients. The cumulative incidences of acute GVHD grades 2 to 4 at 6 months were 35% after related and 42% after unrelated allo-SCT. The cumulative probability of extensive chronic GVHD at 2 years for all patients was 36%. No differences in acute and chronic GVHD incidences were observed between patients with related and unrelated donors. With a median follow-up of 44 months, 51 patients were alive, of whom 48 were in CR. Cumulative TRM rates were 10% and 22%, and cumulative death rates from disease progression were 47% and 33% at 2 years for recipients of grafts from related and unrelated donors, respectively. Overall, 2-year survival was 48%, and DFS was 44%. Patients transplanted in CR1 had a 2-year overall survival of 44% after allo-SCT from related donors and 63% after allo-SCT from unrelated donors. In this study, the anti-leukemia effect relied virtually entirely on the graft-versus-leukemia effect (GVL). The success rates of 44% and 63% for patients in CR1 compared favorably with previous results in patients given continuous chemotherapy alone.[14] As for patients in CR2 or in more advanced diseases, 68% of patients receiving a graft from a related donor and 57% of those grafted from an unrelated donor

Table 1. Results of principal studies evaluating RIC allo-SCT for AML.

Author (Ref.)	*N*	*Diagnosis*	*AML in CR1 (%)*	*Age (range)*	*HLA-identical sibling donor (%)*	*Conditioning Regimen (%)*	*Acute GVHD (grade 2-4) / chronic GVHD*	*TRM/NRM (years) TRM/NRM*	*% Relapse*	*Overall survival*
Hegenbart[13]	122	AML (prospective)	51 (42)	58 (17-74)	58 (48)	TBI-2Gy.(16) Flu-TBI-2Gy. (84)	40%/ extensive 36%	Total: 16% 10% if CR1 and Sib.; 21% if CR1 and MUD	Total: 39% 50% if CR1 and Sib.; 16% if CR1 and MUD	Total: 48% (at 2 y.) 44% if CR1 and Sib.; 63% if CR1 and MUD.
Blaise[17]	33	AML (prospective)	33 (100)	52 (26-60)	33 (100)	Flu-Bu-ATG (100)	24%/64%	Total: 9% (all in CR1)	Total: 18% (all in CR1)	Total: 79% (at 18 m.) (all in CR1)
De Lima[19]	94	AML: 68 MDS: 26 (prospective)	11 (12)	58 (22-75)	51 (54)	Flu-Mel (66) Flu-Cyt-Ida (34)	36%/34%	Total: 30% (at 1 y.)	Total: 40%	Total: 34% (à 3 y.)
Tauro[22]	76	AML: 56 MDS: 20 (retrospective)	22 (39)	52 (18-71)	35 (46)	Flu-Mel-Alem (100)	28%/11%	Total: 19% (at 1 y.) 13% if Sib. 24% if MUD	Total: 36%	Total: 41% (at 3 y.) 48% if CR1
Sayer[12]	113	AML (retrospective)	25 (22)	51 (16-67)	50 (44)	Flu-Bu-ATG (82) Flu-Bu-Cy (1) Flu-TBI (4-8 Gy.; 17)	42%/33%	Total: 53% (at 2 y.) 33% if CR or PR 66% if advanced disease	NA	Total: 32% (at 2 y.) DFS: 52% if CR1
Van Besien[23]	52	AML: 41 MDS: 11 (prospective)	9 (17)	52 (17-71)	23 (44)	Flu-Mel-Alem (100)	33%/18% (at 1 y.)	Total: 33% (at 1 y.)	Total: 32%	Total: 48% (at 1 y.)
Schmid [33]	75	AML: 65 MDS: 10 (prospective)	8 (11)	52 (18-66)	31 (41)	Chemo. with flu-Amsa-Cyt, followed in 3 days by 4 Gy TBI-ATG-Cy; prophylactic DLI in 12 patients	49%/35%	23% if Sib. 50% if MUD.	DFS at 2 y.: 40%	Total: 42% (at 2 y.)
Shimoni[25]	112	AML: 95 MDS: 17 (retrospective)	27 (24)	50 (17-70)	59 (53)	IV Bu-Cy (40) Flu-Bu (myeloab.; 23) Flu-Bu (red.; 37)	36%/47%	IV Bu-Cy: 22% Flu-Bu (myeloab.): 8% Flu-Bu (red.): 8%	IV Bu-Cy: 33% Flu-Bu (myeloab.): 43% Flu-Bu (red.): 49%	IV Bu-Cy: 50% (at 2 y.) Flu-Bu (myeloab.): 49% (at 2 y.) Flu-Bu (red.): 47% (at 2 y.)

AML: acute myeloid leukemia; CR1: first complete remission; TRM: transplant-related mortality; NRM: non-relapse mortality; TBI: total body irradiation; Sib: HLA-identical sibling donor; MUD: matched unrelated donor; Flu: fludarabine; Bu: busulfan; ATG: anti-thymocyte globulin; MDS: myelodysplastic syndrome; Mel: melphalan; Cyt: cytarabine; Ida: idarubicin; Alem: alemtuzumab; Cy: cyclophosphamide; PR: partial remission; NA: not available; DFS: disease-free survival; Amsa: amsacrine; DLI: donor lymphocyte infusion; myeloab: myeloablative; red: reduced.

in second CR have become long-term survivors; the corresponding figures for patients beyond second CR are 25% and 29%, respectively, also comparing favorably with results from similar patients treated with chemotherapy alone.[15]

Timing of RIC allo-SCT for AML

While the overall results from the approach pioneered by the Seattle group are relatively good, better results are achieved in patients in CR1 or CR2 than in those with more advanced disease stages,[13,16] emphasizing that RIC allo-SCT should be considered earlier in patients with AML. The impact of disease status at the time of allo-SCT was documented in the German multicenter analysis that included 113 AML patients not eligible for standard myeloablative allo-SCT. Here, the probabilities of DFS (median follow-up: 12 months) were 49% for patients with less than 5% blasts in the marrow, 24% for patients with 5-20% blasts and 14% with >20% blasts. In multivariate analysis, a higher number of blasts in the marrow, alternative donors and low Karnofsky performance score were shown to be independent adverse prognostic factors for DFS.[12] This is the reason why we chose, in our group, to perform RIC allo-SCT after a rather intensive induction-consolidation chemotherapy schedule in AML CR1 patients, including high-dose cytarabine and/or high-dose melphalan. Our RIC regimen included fludarabine, busulfan (8 mg/Kg total dose), ATG, and CSA alone for GVHD prophylaxis. In our initial cohort that included 33 patients, three patients died from non-relapse causes for a cumulative incidence of TRM of 9%, while six relapsed for a cumulative incidence of 18%. With a median follow-up of 18 months, 26 patients were alive, of whom 24 remained in CR1 for 2-year overall survival and DFS probabilities of 79% and 76%, respectively.[17] The latter may suggest that the sequential combination of intensive chemotherapy prior to allo-SCT, but also the inclusion of some form of myeloablation (busulfan) as part of the RIC regimen, might offer relatively low TRM and leukemia relapse rates even in high-risk patients.

The potential benefit of reduced myeloablation

In our RIC approach we opted to include an intermediate dose of busulfan (in addition to fludarabine and ATG)

as part of the RIC regimen in order to provide some form of leukemic control, at least in the early period after RIC allo-SCT, while allowing for the establishment of the long term anti-leukemic immune control. The latter raises the issue of the dose intensity or myeloablation that should be incorporated in the RIC regimen prior to allo-SCT. In our experience, the 2-year cumulative incidence of TRM compared favorably with that allowing standard myeloablative allo-SCT[8,17] especially when taking into account that the majority of the patients were >50 years old. This favors the hypothesis that leukemic control in the setting of RIC allo-SCT may depend on the intensity of chemotherapy given prior to allo-SCT, but also during conditioning, without the overall beneficial effect of the whole procedure necessarily being hampered. The potential benefit of myeloablation intensity was also shown when investigated in an up-front approach of RIC allo-SCT early after diagnosis (median, 40 days) in 26 consecutive patients with high-risk AML characterized by poor-risk cytogenetics (n=19) or inadequate blast clearance by induction chemotherapy (n=7). During induction chemotherapy-induced aplasia after the 1st (n=11) or 2nd (n=15) cycle, patients received allo-SCT from related (n=11) or unrelated (n=15) donors following a fludarabine-based RIC regimen including either busulfan (3.3 mg/Kg IV) or melphalan (150 mg/m^2). Seventeen patients were not in remission before conditioning, with a median marrow blast count of 34%. The probability of DFS was 61% with only three patients relapsing 5, 6 and 7 months after allo-SCT, suggesting that up-front RIC allo-SCT as part of primary induction therapy may be effective, provided some form of myeloablation is included in the preparative regimen.[18] This issue of the intensity of myeloablation was also addressed by the MD Anderson group who retrospectively compared outcomes after a truly non-myeloablative regimen (120 mg/m^2 fludarabine, 4 g/m^2 cytarabine, and 36 mg/m^2 idarubicin [FAI]) and a more myelosuppressive RIC regimen (100 to 150 mg/m^2 fludarabine and 140 or 180 mg/m^2 melphalan [FM]).[19] With a median follow-up of 40 months, the FM regimen was associated with a significantly higher degree of donor cell engraftment, higher cumulative incidence of TRM, and lower cumulative incidence of relapse-related mortality. The relapse rate after FAI and FM was 61% and 30%, respectively. The actuarial 3-year survival rate was 30% after FAI and 35% following FM. In a multivariate analysis of patient- and treatment-related prognostic factors, DFS was improved after the semi-ablative FM regimen, especially for patients in CR at transplantation, and for those with intermediate-risk cytogenetics, suggesting that some form of *reduced myeloablation* (in contrast to truly non-myeloablative) regimen may provide better leukemic control though at a cost of increased TRM and morbidity.[19]

The role of partial in vivo T-cell depletion

Incorporation of *in vivo* T-cell depleting agents (such as ATG or almetuzumab) as part of a RIC regimen may prove useful in decreasing toxicity. ATG-containing RIC regimens can help to modulate the level of allo-immune reactions, and thereby the incidence and severity of GVHD,[20] without increasing the risk of infectious complications.[21] Such an approach was investigated in the British study which included 76 patients with high-risk AML or myelodysplastic syndrome (MDS) who received an allograft using a fludarabine/melphalan RIC regimen incorporating alemtuzumab for *in vivo* T-cell depletion.[22] In this series, no patient developed greater than grade 2 acute GVHD. With a median follow-up of 36 months, the 3-year actuarial overall survival and DFS rates were 41 and 37%, respectively, with these being even better in patients with AML in CR at the time of RIC allo-SCT .[22] In comparison to the FM RIC regimen used by the MD Anderson group, this alemtuzumab-containing regimen helped to decrease both GVHD and TRM, which was relatively lower (19% at 1 year): disease relapse was the most common cause of treatment failure.[19, 22] The University of Chicago group reported similar results in 52 patients with AML or MDS who were conditioned with fludarabine, melphalan, and alemtuzumab.[23] After a median follow-up of 18 months, 1-year survival was 48%, DFS was 38%, relapse rate was 27%, and TRM was 33%. Inclusion of alemtuzumab in the conditioning regimen allowed a relatively low cumulative probability of extensive chronic GVHD of 18%, which was only observed in recipients of transplants from unrelated donors. Performance score and disease status were the major predictors of outcome. High-risk disease (ie, active AML) or even modest decreases in performance status were associated with poor outcomes. Patients with standard-risk leukemia (CR1 or CR2) had excellent outcomes despite unfavorable disease characteristics.[23] In contrast to the complications seen with ATG,[21] infectious complications, especially cytomegalovirus reactivation (although cytomegalovirus disease was very rare), may be a matter of concern in patients receiving alemtuzumab.[22] Because both the source and the dose of stem cells are important determinants of immune recovery after RIC allo-SCT,[24] it is possible that tailoring graft characteristics will help to reduce the incidence of opportunistic infections.

The balance between dose intensity, toxicity and efficacy

This paradoxical picture of the balance between dose intensity, GVL and TRM was addressed by Shimoni *et al.* who attempted to better define the role of dose intensity in a cohort of 112 consecutive patients with AML/MDS.[25] A total of 45 patients met eligibility criteria for standard myeloablative conditioning and were given intravenous (IV) busulfan (12.8 mg/kg) and cyclophosphamide (IV Bu-Cy). A total of 67 non-eligible patients were given RIC with fludarabine and IV-busulfan (6.4 mg/kg, FB2, n=41) or a modified myeloablative regimen with fludarabine and myeloablative doses of IV-busulfan (12.8 mg/kg, FB4, n=26). As expected, TRM was significantly higher after IV

Bu-Cy, but relapse rates were lower.[25] As in other studies, active disease at the time of allo-SCT was the most significant predictor of reduced survival in multivariate analysis. Interestingly, patients treated with myeloablative or RIC regimens had similar outcomes when leukemia was in remission at the time of allo-SCT. However, patients with active disease could only be salvaged by myeloablative conditioning which was well tolerated in terms of toxicity when using an IV formulation of busulfan.[25]

This adds to the controversy surrounding preparative regimens. There is growing evidence that the use of novel growth factors, new drug formulations and targeted therapies adds to the safety of myeloablative regimens, while maintaining a higher degree of myeloablation that can optimize disease control and survival.[26-28] For instance, De Lima *et al*. showed that myeloablative doses of IV busulfan are an efficacious, reduced-toxicity, myeloablative-conditioning regimen for patients with AML or MDS undergoing allo-SCT.[27] The benefit from pharmacologically targeted therapies has already been proven in the context of standard myeloablative allo-SCT for chronic myeloid leukemia (CML), in which pharmacological targeting of busulfan (to reach a steady-state plasma concentration of at least 900 ng/mL) combined with cyclophosphamide minimized regimen-related toxicity while preserving anti-leukemic effects.[29] This targeted Bu-Cy regimen also proved to be effective for patients with MDS receiving allo-SCT from HLA-identical siblings or alternative donors, even those older than 60 years of age.[30] Moreover, targeted busulfan concentrations have also been used with fludarabine, the backbone component of RIC. To test the hypothesis that fludarabine can replace cyclophosphamide and facilitate donor engraftment with reduced toxicity, Bornhauser *et al*. used a conditioning regimen consisting of IV fludarabine, and oral busulfan, with doses adjusted to target plasma levels of 900±100 ng/mL at steady state. In this trial, which included 42 high risk patients (CML and MDS) with a median age of 52 years, the TRM at day +100 was 7%, and overall TRM did not exceed 24%, indicating that the combination of fludarabine and targeted busulfan is less toxic and sufficiently immunosuppressive to facilitate engraftment both from HLA-matched siblings and unrelated donors.[31] Taken together, these results suggest that it is possible that even patients who are eligible for myeloablative conditioning and are in CR1 may benefit from reducing toxicity with a RIC or truly non-myeloablative regimen without risking excess relapse rates. However, patients with more advanced or active disease at the time of allo-SCT will have a very high risk of disease relapse, which can be explained (at least in part) by relapse kinetics in a disease such as AML. In a context similar to AML, Martino *et al*. recently showed, in a multicenter retrospective study including 836 MDS patients, that the 3-year relapse rate was significantly higher after RIC allo-SCT than after standard myeloablative allo-SCT, although the 3-year TRM rate was decreased in the RIC group.[32] Indeed, induction of the immune GVL effect may require several months after allo-SCT to evolve, placing patients with active disease in a fragile situation with a high risk of disease progression that would outpace any further emergence of an effective GVL phenomenon. In order to circumvent this problem, a group from Munich tested the sequential use of intensive chemotherapy, RIC allo-SCT, and prophylactic donor lymphocyte infusions (DLI) in patients with high-risk AML and MDS.[33] This prospective study included 75 patients who received fludarabine (30 mg/m^2), cytarabine (2 g/m^2), and amsacrine (100 mg/m^2) for 4 days used for cytoreduction. After 3 days of rest, RIC consisted of 4 Gy TBI, ATG, and 80 to 120 mg/kg cyclophosphamide. Prophylactic DLI were given from day +120 in patients who were not receiving immunosuppression and were free of GVHD. With a median follow-up of 35 months, 2-year overall and DFS were 42% and 40%, respectively. Interestingly, the outcome of patients with refractory disease or with complex cytogenetic aberrations was identical to that of patients in better prognostic subgroups.[33] suggesting that a comprehensive treatment *package* including some form of high dose therapy prior to allo-SCT and/or semi-intensive little toxic cytoreduction/myeloablation incorporated within the RIC regimen may allow sufficient time for the GVL effect, while minimizing toxicity. Such *additional myeloablation* could be delivered in the form of an *increased* RIC intensity. These types of coordinated strategies may prove useful, especially in high risk or refractory AML patients. In a recent update, the Munich group confirmed their previous findings indicating the high anti-leukemic activity of their approach even in refractory AML.[34] Obviously, these findings merit testing in randomized, prospective studies, but such studies are not yet available.

RIC vs. standard myeloablative allo-SCT

Currently, results from specific randomized studies comparing RIC and standard myeloablative allo-SCT for AML are not available. For this reason, the European Group for Blood and Marrow Transplantation (EBMT) compared, in a large retrospective analysis, outcomes of patients with AML older than age 50 years treated with HLA-identical sibling allo-SCT after regimens of reduced intensity or of myeloablative intensity.[35] Outcomes of 315 patients receiving RIC allo-SCT were compared with those of 407 standard myeloablative allo-SCT recipients. The majority of RIC regimens were fludarabine-based regimens associated with busulfan (53%) or low-dose TBI (24%). The median follow-up was 13 months. Cytogenetics, FAB classification, white cell count at diagnosis and disease status at transplant were not statistically different between the two groups. Despite the older age in the RIC group, grade 2-4 acute GVHD and TRM were significantly lower after RIC allo-SCT. However, DFS was not statistically different between the two groups. With regards to the disease status at transplant, the relapse rate of patients transplanted in remission (CR1

or CR2) was significantly higher after RIC than after a standard allo-SCT. In patients transplanted in an advanced disease phase, there was a trend for a higher relapse rate.[35] The impact of the shift from standard myeloablative allo-SCT to RIC allo-SCT was also evaluated by the Dana Farber group in a retrospective analysis of 152 patients older than 50 years.[36] Seventy-one patients (of whom 21 had AML) received a RIC regimen prior to allo-SCT consisting of fludarabine (120 mg/m^2) and IV busulfan (3.2 mg/kg). The remaining 81 patients (of whom 13 had AML) received fully ablative conditioning, consisting primarily of cyclophosphamide and full dose TBI. Despite more adverse characteristics (active disease, prior transplant and unrelated donors), overall survival was improved in the RIC group at 1 year (51% vs. 39%) and 2 years (39% vs. 29%). As in the EBMT study,[35] the RIC patients had a lower TRM rate, but a higher relapse rate (46% vs. 30%).[36] Curiously, a preliminary communication in the form of an abstract (*Herr et al., Blood, 2005; 17a, Abstract*) reported, but with little detailed infromation, a study involving nearly 1200 patients in which a higher TRM was found among those patients undergoing RIC allo-SCT as compared to those receiving standard myeloablative allo-SCT (5% vs. 8%). Obviously, such a low rate of TRM in the myeloablative setting is very surprising and warrants cautious interpretation. Therefore, in the absence of prospective randomized trials, it is still very difficult to draw conclusions from the comparisons between standard myeloablative allo-SCT and RIC allo-SCT for AML. There are several reasons for this. By definition, RIC regimens were designed to be applied in patients not eligible for conventional myeloablative preparative regimens due to advanced age or comorbid conditions. Additionally, AML risk factors such as cytogenetics and secondary versus *de novo* AML have not necessarily been taken into account in these elderly populations. Thus, comparisons between RIC and standard allo-SCT will likely be feasible (both from the medical and the patients' point of view) only in younger patients who are eligible for either a myeloablative or RIC allo-SCT, using homogeneous inclusion criteria.

RIC allo-SCT vs. chemotherapy

Since chemotherapy alone is the standard of care in elderly AML patients, it is important to compare RIC allo-SCT and chemotherapy alone in order to evaluate the true benefit of RIC allo-SCT in AML. This latter prompted us to use a genetic randomization through a *donor* vs. *no donor* comparison, to assess the real benefit of RIC allo-SCT for adult AML and its impact on clinical outcome.[37] In our institution, it has been the treatment policy since 1999 to offer allo-SCT with a RIC regimen to all AML patients aged between 50 and 65 years or to patients aged under 50 years, but with a comorbidity precluding the use of standard myeloablative allo-SCT, if a sibling, related donor is available. In the context of a single center homogeneous population, in comparison to matched pair analysis or comparative studies,"*genetic* randomization can be a suitable way of comparing RIC allo-SCT with other treatment modalities, while eliminating potentially unknown selection biases.[38] It should be noted that we analyzed our results according to the *intention-to-treat* principle in order to avoid misleading interpretations and biased treatment effects.[39] In this intention-to-treat analysis, DFS was significantly higher in the group with a related donor than in the group with no such donor. Likewise, in the intention-to-treat analysis, overall survival was significantly higher in the group with a related donor than in the other group, suggesting that if a matched related donor is identified, RIC allo-SCT should be proposed for AML patients not eligible for standard myeloablative allo-SCT.[37,40] Naturally, such a conclusion should be confirmed in a strictly controlled fashion. However, for various reasons (not necessarily medical reasons, but sometimes reasons related to different health systems in different countries), many physicians are only weakly enthusiastic or may be even reluctant to study RIC allo-SCT in a controlled setting. Solutions to such problems can only come from the largest co-operative groups such as the Blood & Marrow Transplant Clinical Trials Network (BMT CTN) in the USA, and the major European co-operative groups. Prospective trials are being initiated, such as the one by the OSHO/HOVONS/ SAKK group in which elderly patients (age, 60–75 years) with a related or matched-unrelated donor, will receive a low dose TBI 2 Gy-based regimen after first consolidation. The outcome of these patients will be compared to that of patients given chemotherapy only on a *donor* vs. *no donor* basis.

Future directions: reducing toxicity and relapses after RIC allo-SCT

Despite the lack of randomized or controlled trials, several lines of evidence suggest that the assessment of the overall benefit of RIC allo-SCT for AML must not only take into account disease status at the time of allo-SCT, but also the *global* treatment strategy including any intensive chemotherapy (though the optimal regimen is yet to be determined) received prior to allo-SCT, and the level of myeloablation delivered within the RIC regimen itself. Nonetheless, one should bear in mind that the so-called level of myeloablation is somewhat arbitrary and a wide variety of regimens are now used by different groups, making the distinction between truly non-myeloablative and RIC regimens very difficult. Other potential confounding factors are related to immunologic senescence in the elderly, usually associated with a number of immunologic changes, most of which are likely to affect patients' outcome after RIC allo-SCT. Age-associated immune alterations (e.g decreased cellular immune functions) may lead to an increased incidence of infections, secondary tumors and autoimmune diseases.[41-45] The aging process also increases the prevalence of comorbid conditions, which are sometimes difficult to separate from clinical deficiencies exacerbated or triggered by the leukemic

process itself. The creation of indices aimed at measuring the influence of comorbidities on the outcome of allo-SCT is definitely a new field of investigation that will challenge investigators,[46] since the notion of *non-eligibility* for conventional or standard myeloablative allo-SCT is not clearly defined. Furthermore, the concept of non-eligibility is constantly evolving, e.g. perhaps a history of aspergillosis in the era of liposomal amphotericin, voriconazole, and caspofungin is not such a complete contraindication to allo-SCT as it used to be 10 or 15 years ago.[47]

Reducing toxicity without compromising the GVL effect could be of significant benefit to many patients, but more *intense* RIC regimens, despite the hazard of increased toxicity, may be necessary in others. Thus, the trade-off between dose intensity, toxicity, and disease control will remain to be assessed for each individual patient. In addition, the specific roles of matched unrelated RIC allo-SCT and transplants from alternate stem cell sources are yet to be investigated. In this regard, peripheral blood stem cells (PBSC), mobilized by granulocyte colony-stimulating factor, have been used in almost all cases in the setting of RIC allo-SCT. The focus on PBSC after a RIC regimen may be justified by the need to accelerate engraftment in elderly or unfit patients, but also because the use of allogeneic PBSC has been shown to be of greater benefit in patients with more advanced hematologic diseases.[48] In fact, a large percentage of AML patients receiving RIC allo-SCT are beyond CR1 at the time of transplantation or have secondary AML. However, this potential benefit should be weighed against the risk of TRM. Indeed, infusion of traditional bone marrow is feasible and can yield quick engraftment after an ATG-based RIC regimen.[49] In addition, it is now well established that the use of PBSC is associated with a significantly higher incidence of severe chronic GVHD both after standard myeloablative allo-SCT[50] and after RIC allo-SCT.[20] With long term follow-up, a higher incidence of extensive chronic GVHD will unavoidably increase toxicity and offset the overall benefit of the procedure. Therefore, and at least for patients with less advanced disease (e.g. AML in CR1), the debate related to the optimal stem cell source should not be abandoned without well controlled studies. Reduction of relapse rates after RIC allo-SCT while preserving patients' quality of life remains a major goal. This might eventually be achieved with a better understanding of the polymorphic minor histocompatibility antigens.[51] Indeed, T cells directed against hematopoietic-restricted minor histocompatibility antigens may mediate GVL reactivity without GVHD. Furthermore, T-cell responses against proteins solely expressed in hematopoietic cell lineages from which the malignancy is derived may be appropriate mediators of GVL reactivity without inducing GVHD. In parallel, the efficacy of RIC allo-SCT against AML may be improved by *in vitro* generation of T-cell responses directed against defined minor histocompatibility antigens. Characterization of clinical immune responses in patients treated for AML[52] and close monitoring of immune effectors after RIC allo-SCT may lead to the characterization of new minor histocompatibility antigens that can be exploited to generate tumor-specific immune responses. In addition, *active* modulation of immunosuppression early after RIC allo-SCT may also play a role in favoring the rapid expansion of both effector T lymphocytes,[53] and natural killer cells. Another important challenge facing investigators is the identification of the critical period when regular and close monitoring of minimal residual disease will show evidence of leukemia recurrence, since it is possible that the relapse risk may be determined by levels of occult residual disease. The serial use of lineage-specific chimerism to monitor the proportion of donor T cells may identify patients at risk of relapse (Mohty *et al.*; *unpublished observations*), in order to promptly initiate interventions aimed at reducing the risk of relapse. Prophylactic use of systematic DLI may be useful, but should be balanced against the risk of severe or fatal GVHD. However, one should bear in mind that the use of DLI was generally disappointing in AML patients (except in situations of minimal residual disease; *Dominietto et al., Blood 2005, Abstract N° 2012*). DLI manipulation (e.g depletion of regulatory T cells) is likely necessary, and may become a putative beneficial alternative.[54] On the other hand, early administration of biologically targeted therapies, such as flt-3 or farnesyl transferase inhibitors, or vaccinations (dendritic cells, peptides), after RIC allo-SCT may be an attractive strategy in certain biologically defined subgroups of patients.[55-59] Alternatively, the testing of radio-immunotherapy to intensify the anti-leukemic activity of the RIC regimen without increasing toxicity may be of interest.[60] Whereas the humanized anti-CD33 monoclonal antibody usually has only modest activity against overt AML, it can eliminate minimal residual disease detectable by reverse transcription-polymerase chain reaction in acute promyelocytic leukemia, making it a good candidate for maintenance therapy for AML after RIC allo-SCT. On the other hand, radio-immunotherapy with isotopes targeting CD33, CD45 and CD66 can potentially allow intensification of anti-leukemic therapy, and will likely prove useful when used in combination with standard chemotherapy in the treatment of AML before and after RIC allo-SCT. Overall, based on the current results in different high-risk AML populations, one can reasonably envision that if a matched related donor is identified, RIC allo-SCT should be proposed since it represents a valid option for AML patients not eligible for standard myeloablative allo-SCT. The immune-mediated GVL effect is usually stronger than any other form of salvage chemotherapy. However, identification of suitable donors remains an obstacle in the majority of cases. The use of alternative donors (matched unrelated donors, partially matched family member donors, and unrelated partially matched umbilical cord blood) for stem cell therapy is essential to ensure broad applicability of RIC allo-SCT. Although preliminary studies indicate that the use of alter-

native donors can provide reliable engraftment, GVHD and other toxicities remain matters of concern, and only controlled prospective trials will ultimately settle these issues, and establish the definitive benefit and appropriate use of RIC allo-SCT for AML and other malignant conditions.

Authors' Contributions

DB: performed the bibliographic search and wrote the manuscript; NV, CF: performed bibliographic search; MM: performed the bibliographic search, wrote and edited the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest.

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