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Reduced-intensity conditioning allogeneic hematopoietic-cell transplantation for older patients with acute myeloid leukemia

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***Abstract*:** Elderly patients (>60 years) with acute myeloid leukemia have a poor prognosis with a chemotherapy-alone approach. Allogeneic hematopoietic-cell transplantation (HCT) can improve overall survival (OS). However, myeloablative regimens can have unacceptably high transplant-related mortality (TRM) in an unselected group of older patients. Reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) conditioning regimens preserve the graft-*versus*-leukemia effects but reduce TRM. NMA regimens result in minimal cytopenia and may not require stem cell support for restoring hematopoiesis. RIC regimens, intermediate in intensity between NMA and myeloablative regimens, can cause prolonged myelosuppresion and usually require stem cell support. A few retrospective and prospective studies suggest a possibility of lower risk of relapse with myeloablative HCT in fit older patients with lower HCT comorbidity index; however, RIC and NMA HCTs have an important role in less-fit patients and those with significant comorbidities because of lower TRM. Whether early tapering of immunosuppression, monitoring of minimal residual disease, and post-transplant maintenance therapy can improve the outcomes of RIC and NMA HCT in elderly patients will require prospective trials.

Keywords: acute myeloid leukemia, allogeneic hematopoietic-cell transplantation, graft-*versus*-leukemia effect, myeloablative transplant, nonmyeloablative transplant, older patients, reduced intensity conditioning transplant

Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults, with an estimated 20,000 new cases of AML in 2016 [Siegel *et al.* 2016]. It is particularly common in older patients and has a median age of 65–70 years at diagnosis [Siegel *et al.* 2016]. Most of the institutional registries, including the Cancer and Leukemia Group B (CALGB) have defined old age in the context of AML and hematopoietic-cell transplantation (HCT) as more than 60 years [Devine *et al.* 2015; Giles *et al.* 2007; Wallen *et al.* 2005]. The management of AML in older individuals can be particularly challenging due to the presence of multiple comorbidities, inability to tolerate intensive chemotherapy [Schiffer, 2010], and a higher incidence of unfavorable cytogenetics and drug resistance [Appelbaum *et al.* 2006]. Most of the reported trials involving older patients with AML have resulted in complete remission (CR) rates ranging between 35% and 70% [Ferrara *et al.* 1998; Gardin *et al.* 2007; Leoni *et al.* 1997; Lowenberg *et al.* 2009; Vey *et al.* 2004]. After a CR is achieved, AML relapse may occur in most cases within 4–6 months in the absence of HCT. Postremission therapy aims at reducing such relapses by destroying any leukemia cells that may have survived induction therapy. This involves the use of either consolidation chemotherapy or allogeneic HCT. The use of standard-dose consolidation chemotherapy in older patients is limited by a high incidence of

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treatment-related toxicities, with dose modification or reduction required in most cases [Gardin *et al.* 2007; Mayer *et al.* 1994; Lowenberg *et al.* 1998]. The use of HCT, by its graft *versus* leukemia (GVL) effect, has the advantage of offering long-term disease-free survival (DFS), especially in patients with high-risk disease [Blaise *et al.* 1992; Chang *et al.* 2007; Vicente *et al.* 2007].

Myeloablative regimens incorporate alkylating agents with or without total body irradiation (TBI) at doses that will not allow autologous stem cell recovery [Bacigalupo *et al.* 2009]. In older patients, the use of myeloablative chemotherapy regimens can lead to a high transplant-related mortality (TRM) of approximately 20% at 100 days and 40% at 3 years [Wallen *et al.* 2005]. The risk of TRM depends on HCT comorbidity index, which is higher in older patients [Sorror *et al.* 2005]. This has led to an increasing interest in utilizing nonmyeloablative (NMA) and reduced-intensity conditioning (RIC) regimens that preserves GVL effect but reduces TRM. The use of NMA regimen causes minimal cytopenias but is immunosuppressive to the extent that it results in full engraftment of donor stem cells [Bacigalupo *et al.* 2009]. By strict definition, NMA regimens do not require stem cell support. Conversely, RIC regimen, intermediate in intensity between myeloablative and NMA regimens, causes prolonged cytopenia and requires stem cell support. In RIC regimens, the dose of alkylating agents or TBI is reduced by at least 30% [Bacigalupo *et al.* 2009]. The definition of Center for International Blood and Marrow Transplant Research (CIBMTR) for RIC regimens includes the use of less than 500 cGy of TBI as a single fraction or 800 cGy in fractionated doses, a busulfan dose of less than 9 mg/kg, a melphalan dose of less than 140 mg/m^2, or a thiotepa dose of less than 10 mg/kg [Giralt *et al.* 2009]. Both NMA/RIC regimens allow the use of allogeneic HCT in older patients [Bacigalupo *et al.* 2009]. Despite the availability of NMA/RIC regimens, older AML patients are infrequently referred to transplant centers, and HCT is underutilized in this population. This article aims to review the existing evidence on the role of NMA and RIC HCT in older patients with AML.

History of nonmyeloablative and reduced-intensity conditioning regimens in acute myeloid leukemia

In allogeneic HCT, antitumor effect is mediated by donor lymphocytes as well as chemotherapy [Childs and Srinivasan, 2002]. Syngeneic HCT has a lower incidence of graft-*versus*-host disease (GVHD), thereby resulting in a higher incidence of relapse. NMA and RIC regimens, compared with myeloablative regimens, rely more on the GVL effect and less on chemotherapy-mediated destruction of leukemia cells. NMA and RIC regimens use conditioning regimens intense enough to prevent rejection, but allow preservation of the GVL effect [Storb, 2007]. Some of the retrospective registry analyses have shown encouraging results with such approaches. In 2006, a multicenter study of 122 AML patients from various centers in the United States and Europe utilized low-dose TBI with or without fludarabine as an RIC prior to allogeneic HCT. Of 122 patients, 18 had secondary AML, 51 were in first CR (CR1), 39 were in second CR (CR2), and 32 were beyond CR2. The use of RIC HCT resulted in 2-year overall survival (OS) of 48%, with TRM of 22% and 10% at 2 years for unrelated and related recipients, respectively [Hegenbart *et al.* 2006]. Another retrospective registry-based analysis from the European group for Blood and Marrow Transplantation (EBMT) comparing 361 RIC allogeneic HCT to autologous HCT, demonstrated less risk of relapse with the former [relative risk (RR), 0.77; 95% CI, 0.63–0.95; $p = 0.013$). In a multivariate analysis, RIC allogeneic HCT was shown to have a better DFS and OS as compared with autologous HCT in patients who achieved CR2 [Herr *et al.* 2007]. However, the reduced risk of relapse associated with allogeneic HCT in patients in CR1 did not translate into a survival advantage, likely secondary to increased TRM.

One of the largest retrospective studies from the CIBMTR registry analyzed 545 AML and 535 myelodysplastic syndrome (MDS) patients who underwent RIC HCT. All patients with AML were between the ages of 40–79 years and underwent allogeneic HCT in CR1. Multivariate analysis revealed no impact of age on TRM, DFS, and OS. The 2-year OS in age groups 40–54, 55–59, 60–64, and 65 years or over were as follows: 44% (95% CI, 37–52%), 50% (95% CI, 41–59%), 34% (95% CI, 25–43%), and 36% (95% CI, 24–49%), respectively ($p = 0.06$) [McClune *et al.* 2010]. Unfavorable cytogenetics, poor pre-HCT performance status, and greater human leukocyte antigen (HLA) disparity were associated with worse survival in this study. Sorror and colleagues conducted a large multicenter study of 372 patients aged 60–75 years with various hematologic malignancies ($n = 109$ for acute leukemia)

who underwent HCT using NMA regimens. The 5-year cumulative incidences of TRM and relapse were 27% (95% CI, 22–32%) and 41% (95% CI, 36–46%), respectively, leading to 5-year OS and progression-free survival (PFS) of 35% (95% CI, 30–40%) and 32% (95% CI, 27–37%), respectively [Sorror *et al.* 2011]. Moreover, these outcomes were not statistically significant when stratified by age. However, like many other retrospective studies, this study might have the potential for selection bias and does not examine AML patients specifically. Nevertheless, it points out that old age should not be a sole factor for excluding the use of HCT.

A small prospective study assessed the outcomes of 50 patients (30 AML and 20 MDS patients) with a median age of 57 years, who underwent NMA allogeneic HCT using fludarabine and cyclophosphamide [Nelson *et al.* 2010]. A total of 43% of the patients were in CR1, 30% in CR2, 23% were not in remission, and 3% in relapse at the time of HCT. The study estimated 4-year DFS and OS to be 37% and 41%, respectively [Nelson *et al.* 2010]. In another EBMT study, clofaribine was used as a component of the RIC regimen in 69 AML patients (median age 43; age range 18–69 years). This study demonstrated a 2-year leukemia-free survival (LFS) of 30%, OS of 35% and TRM of 31% [Chevallier *et al.* 2012]. In a British study, the investigators attempted to reduce the TRM by reducing the dose of alkylating agent that was used in prior trials [Davies *et al.* 2013]. A total of 56 patients with AML (n = 41) and MDS (n = 15) were treated with a reduced dose of cyclophosphamide (~45 mg/kg *versus* 120 mg/kg in earlier trials). After a median follow up of 5 years, the DFS was reported to be 45% (overall) and 55% (patients transplanted in remission), whereas TRM was 9%. These data are encouraging for the use of NMA or RIC regimens for older patients who may have several comorbidities.

A recent prospective multicenter phase II trial from CALGB assessed the role of RIC HCT in AML patients between the ages of 60 and 74 years (median age 65 years), who were transplanted in CR1. Of 114 total patients, 52% received unrelated donor HCT. At 2 years, DFS and OS were 42% and 48% respectively for the entire cohort, and 40% and 50%, respectively, for the unrelated donor group. The 2-year cumulative relapse rate and TRM for the entire group were 44% and 15%, respectively [Devine *et al.* 2015]. This recent study demonstrates promising results of RIC HCT in older AML patients in CR1.

Chemotherapy *versus* reduced-intensity conditioning or nonmyeloablative conditioning

When assessing the role of RIC or NMA conditioning in elderly AML patients, it is imperative to compare it with postremission chemotherapy. In the past, chemotherapy was the preferred postremission therapy for many older patients, partly secondary to increased TRM with HCT. A retrospective study from the CIBMTR registry compared the outcomes of 190 older patients (60–70 years) with AML receiving RIC HCT in CR1 with patients who received consolidation chemotherapy. [Farag *et al.* 2011] The patients who received HCT were younger (63 *versus* 65 years) and had a longer duration from diagnosis to CR1 (44 *versus* 38 days). At 3 years, the study demonstrated that RIC allogeneic HCT was associated with a significantly lower risk of relapse (32% *versus* 81%; $p < 0.001$), higher TRM (36% *versus* 4%; $p < 0.001$), and longer LFS (32% *versus* 15%; $p = 0.001$). However, the study was able to show only a trend towards increased OS in patients who received HCT (37% *versus* 25%; $p = 0.08$) [Farag *et al.* 2011]. The retrospective design with potential selection bias and differences in the characteristics of the two groups may limit the conclusion of the study.

Kurosawa and colleagues retrospectively compared outcomes in 152 older Japanese AML patients (50–70 years) who received allogeneic HCT (myeloablative or RIC) after achieving CR1 with patients who received chemotherapy alone (n = 884) [Kurosawa *et al.* 2011]. The HCT group had a lower cumulative incidence of relapse as compared with the chemotherapy group at 3 years from CR1 (22% *versus* 62%; $p < 0.001$), but a higher incidence of TRM (21% *versus* 3%; $p < 0.001$). The 3-year relapse-free survival (RFS) (56% *versus* 29%; $p < 0.001$) and OS (62% *versus* 51%; $p = 0.012$) were also higher in the HCT group [Kurosawa *et al.* 2011]. In a subgroup analysis among HCT recipients, 37% underwent myeloablative conditioning and 61% underwent RIC, with no significant OS difference, however, the number of patients was relatively modest. A prospective trial from MD Anderson Cancer Center for patients with AML and unfavorable cytogenetics utilizing RIC in first CR was conducted in patients over 50 years of age. The transplant team

evaluated 53 eligible patients who achieved CR, but only 14 patients underwent HCT. These patients were compared with 43 matched patients who received postremission chemotherapy alone. The study suggested that RIC HCT was associated with increased RFS but not OS. [Estey *et al.* 2007]

Randomized trials comparing postremission chemotherapy *versus* HCT regardless of the donor availability are difficult to conduct. However, a French study utilized a 'genetic randomization' technique, wherein donor-*versus*-no-donor comparison was made in an intention-to-treat trial based on the availability of an HLA-identical sibling donor [Mohty *et al.* 2005]. The study included 95 AML patients in CR. The median age of the patients was 52 years (26–65 years). RIC regimens included fludarabine, busulfan and antithymocyte globulin. LFS was significantly higher in the 'donor' group as compared with the 'no donor' group that received conventional chemotherapy (54% *versus* 30% at 4 years; $p = 0.01$). The difference in LFS attained greater significance when patients who actually received HCT were compared with those who did not (62% *versus* 31% at 4 years; $p = 0.001$) [Mohty *et al.* 2005]. Additionally, OS was significantly higher (approximately 15%) in the 'donor' group as compared with the 'no donor' group ($p = 0.04$). However, in 25 patients who actually received allogeneic HCT, 13 patients had received high-dose cytarabine and autologous transplantation prior to the allogeneic HCT (details unavailable). Additionally, this study included many younger patients and patients with less comorbidities.

A recent time-dependent analysis of four prospective phase III trials in AML from Dutch-Belgian Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research (HOVON-SAKK) collaborative study group compared outcomes of various postremission strategies in AML patients aged 60 years and over, who had achieved CR following induction chemotherapy. In a multivariate analysis, the use of RIC allogeneic HCT resulted in better 5-year OS as compared with other nonallogeneic HCT therapies (such as chemotherapy, autologous HCT, or no further therapy) [hazard ratio (HR), 0.71; 95% CI, 0.53–0.95] [Versluis *et al.* 2015]. Taken together, the above studies suggest a superiority of RIC allogeneic HCT over consolidation chemotherapy alone in terms of RFS and disease control.

Alternative donor transplant in older patients

Availability of a matched donor is an important barrier to allogeneic HCT. This has led to an increasing interest in the evaluation of alternate donor sources such as partially HLA-mismatched (haploidentical) donors or unrelated umbilical cord blood. In a prospective study from Minnesota, 98 patients with AML or MDS aged 55 years or over underwent RIC HCT using matched-sibling donor ($n = 38$; median age 63 years) or cord blood ($n = 60$; median age 61 years). There were 26 AML patients in the sibling donor group (14 in CR1, 12 in CR2–3) and 44 AML patients in the cord blood group (27 in CR1, 17 in CR2–3) [Majhail *et al.* 2012]. Of the patients receiving cord blood HCT, 22 were 5/6 antigen matched and 31 were 4/6 antigen matched. On a multivariate analysis, there was no difference with the use of cord blood HCT in OS (RR, 1.3; 95% CI, 0.8–2.3], LFS (RR, 1.2; 95% CI, 0.7–2.1), relapse rate (RR, 0.7; 95% CI, 0.3–1.3), and TRM (RR, 1.2; 95% CI, 0.6–2.7), compared with sibling donor HCT. In addition, cord blood HCT recipients had a lower incidence of chronic GVHD at 2-years post-transplant (61 *versus* 33%, $p = 0.04$) [Majhail *et al.* 2012]. Another small retrospective study from Minnesota assessed the use of cord blood RIC HCT in very old patients (age $\geqslant 70$ years) with AML ($n = 7$) or MDS ($n = 3$). This was compared with nine patients (age $\geqslant 70$ years) with AML ($n = 6$) or MDS ($n = 3$) who received RIC HCT using matched-sibling donor [Sandhu *et al.* 2016]. The study demonstrated comparable 2-year TRM (20% *versus* 24%) and OS (30% *versus* 49%) outcomes with the use of cord blood *versus* sibling donor HCT. A recent Japanese registry analysis compared outcomes in 2091 patients aged over 50 years with AML ($n = 1346$), acute lymphoblastic leukemia (ALL, $n = 308$), and MDS ($n = 437$) who underwent matched-sibling donor marrow HCT ($n = 319$) [Konuma *et al.* 2016], matched-sibling donor peripheral blood HCT ($n = 462$), or unrelated cord blood HCT ($n = 1310$). The study demonstrated similar relapse rates among all three donor groups, but lower overall mortality in the marrow HCT (HR, 0.67; $p < 0.001$) and peripheral blood HCT (HR, 0.75; $p = 0.002$) as compared with cord blood HCT.

In a recently reported large retrospective study from Johns Hopkins ($n = 271$), 65 AML patients aged between 50 and 75 years received NMA haploidentical donor HCT with post-transplant

high-dose cyclophosphamide [Kasamon *et al.* 2015]. In AML patients aged 60 years and over, the 3-year relapse rate, PFS and OS were 60%, 31%, and 38%, respectively. The overall cumulative incidence of 1-year TRM for the entire study population of 271 patients with various hematological malignancies were as follows: 10% for patients aged 50–59 years, 14% for those aged 60–69 years and 11% for those aged 70–75 years ($p = 0.20$). This indicated that the NMA haploidentical HCT might be well tolerated in older patients regardless of age [Kasamon *et al.* 2015].

These studies demonstrate good outcomes of older AML patients who undergo alternative donor HCT. Hence, in older patients without matched donors, haploidentical and cord blood HCT are acceptable alternative donor strategies.

Myeloablative *versus* reduced-intensity or nonmyeloablative conditioning regimens

There is a relative scarcity of well-designed studies comparing the outcomes of myeloablative conditioning regimens to NMA or RIC regimens. A retrospective study from Seattle analyzed the outcomes of 150 patients with MDS or AML, transformed from MDS, who underwent myeloablative or NMA HCT [Scott *et al.* 2006]. The NMA regimen used in 38 patients included 2 Gy TBI ($n = 2$) or fludarabine at a dose of 90 mg/m^2 ($n = 36$). Other patients received myeloablative regimens including busulfan and cyclophosphamide. The patients who received the NMA regimen were older (median age of 62 *versus* 52 years; $p < 0.001$), had higher-risk disease by International Prognostic Scoring System (53% *versus* 30%; $p = 0.004$), and a higher comorbidity index (68% *versus* 42%; $p = 0.01$). The study demonstrated similar outcomes in both myeloablative and NMA conditioned groups in terms of 3-year OS (48% *versus* 27%; $p = 0.56$), PFS (44% *versus* 28%; $p = 0.60$), and TRM (34% *versus* 41%; $p = 0.94$) [Scott *et al.* 2006]. This suggests that the GVL effect can play an important role in reducing the risk of relapse in older patients with MDS and possibly AML.

In a large retrospective EBMT study of AML patients aged over 50 years in CR1, the outcomes of 315 RIC HCT were compared with 407 myeloablative HCT [Aoudjhane *et al.* 2005]. The most common RIC regimens were fludarabine in combination with either busulfan (53%) or low-dose TBI (24%). After a follow up of 13 months (median), acute GVHD (grade II–IV) and TRM were significantly less ($p = 0.01$) in the RIC group. However, DFS was similar in both groups, and relapse risk was significantly higher ($p = 0.003$) in the RIC group. The patients in the RIC group were relatively older, suggesting the probable role of RIC in decreasing the overall mortality at the possible expense of increased relapse risk [Aoudjhane *et al.* 2005]. Dana Farber Group published a large retrospective study that analyzed outcomes in AML patients aged over 50 years, who received NMA or myeloablative conditioning. A total of 71 patients (21 with high-risk AML) received the NMA regimen that consisted of fludarabine (120 mg/m^2) and intravenous busulfan (3.2 mg/kg); 81 patients (13 high-risk AML) received myeloablative conditioning with cyclophosphamide and TBI. [Alyea *et al.* 2005]. Despite the adverse characteristics, such as active disease and prior myeloablative HCT, there was a trend towards higher OS in the NMA group at 1 (51% *versus* 38%; $p = 0.06$) and 2 years (39% *versus* 29%; $p = 0.06$). There was no difference in PFS (27% *versus* 25% at 2 years; $p = 0.24$) or incidence of grade II–IV acute GVHD (28% *versus* 27%). At median follow up of about 40 months, the NMA group had a lower cumulative rate of TRM (32% *versus* 50%; $p = 0.01$) but at the cost of higher relapse rate (46% *versus* 30%; $p = 0.052$) [Alyea *et al.* 2005].

The role of modified-dose intensity HCT was studied further in a prospective study from Israel involving 112 patients with AML ($n = 95$) and MDS ($n = 17$). A total of 45 patients in CR were eligible to receive myeloablative regimen with intravenous busulfan (12.8 mg/kg) and cyclophosphamide (60 mg/kg for 2 days) [Shimoni *et al.* 2006]. Other patients received RIC with fludarabine (150–160 mg/m^2) and intravenous busulfan (6.4 mg/kg; $n = 41$) or a modified myeloablative regimen with fludarabine (150–160 mg/m^2) and intravenous busulfan (12.8 mg/kg; $n = 26$). Patients who received modified-myeloablative (median age 51 years) or RIC (57 years) regimens tended to be older than the myeloablative group (42 years). The study showed similar 2-year OS and risk of relapse in all three groups. The myeloablative, compared with modified-myeloablative and RIC arms, had a higher incidence of TRM (22% *versus* 8% *versus* 8%, respectively; $p = 0.05$) [Shimoni *et al.* 2006]. Long-term follow-up results showed similar OS in all three groups when the HCT was performed at disease remission. However, the 5-year OS was

42%, 19% and 0% for patients with active disease at HCT, conditioned with myeloablative, modified-dose intensity and RIC HCT, respectively ($p = 0.01$), thereby highlighting that NMA may be a reasonable option in older patients who are in remission [Shimoni *et al.* 2010].

A large retrospective EBMT analysis compared outcomes in older AML patients with RIC ($n = 252$; median age 57; range 50–76 years; 31% in CR1, 37% in CR2–3 and 32% with advanced disease) or myeloablative conditioning ($n = 182$; median age 54; range 50–70 years; 41% in CR1, 27% in CR2–3 and 32% with advanced disease) [Ringden *et al.* 2009]. Patients receiving RIC were older, had a trend for longer interval between diagnosis and transplant in patients in CR2, received peripheral blood stem cells more frequently, and were treated less often with TBI. The most common indications for selecting RIC in older patients were advanced age (77%), infection (7%), special protocol (7%), and prior transplant or heavy treatment (7%). In patients older than 50 years, RIC was associated with decreased TRM (HR, 0.64; $p = 0.04$), similar relapse risk (HR, 1.34; $p = 0.16$) and LFS (HR, 1.04; $p = 0.79$) as compared with myeloablative conditioning [Ringden *et al.* 2009].

A prospective trial conducted in Barcelona compared two strategies of allogeneic HCT from HLA-identical siblings in 75 adults with poor-risk AML or MDS (refractory anemia with excess blasts) in CR1 [Martino *et al.* 2008]. The patients aged 50 years and less received myeloablative conditioning with cyclophosphamide and TBI whereas patients aged over 50 years received RIC with fludarabine and busulfan. The myeloablative group had a significantly higher percentage of AML patients (94% *versus* 56%, $p < 0.01$) and a lower probability of HCT the comorbidity index being at least 3 (26% *versus* 46%; $p = 0.002$). At a median follow up of 4 years, there was no difference in the TRM between the RIC and myeloablative groups (19% *versus* 20%; $p = 0.80$) [Martino *et al.* 2008]. This suggests that RIC regimens can reduce the risk of TRM in older patients.

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0901) recently presented a phase III randomized trial to compare outcomes by conditioning intensity in patients with AML ($n = 218$; 18–65 years) or MDS ($n = 54$) who had less than 5% marrow myeloblasts by morphology prior to HCT [Scott *et al.* 2015]. Among 272 patients enrolled of the planned 356 patients, 135 received myeloablative conditioning and 137 received RIC regimens. The study suspended enrollment based on an interim analysis. After a follow up of 18 months, RIC HCT, compared with myeloablative HCT, was associated with lower TRM (4.4% *versus* 15.8%; $p = 0.02$), higher risk of relapse (48.3% *versus* 13.5%; $p < 0.01$), and similar OS (67.7% *versus* 77.4%; $p = 0.07$) (Table 1) [Scott *et al.* 2015]. Although this study did not assess RIC HCT specifically in older patients or those with a high comorbidity index, this study indicates a lower risk of relapse with myeloablative HCT, but at the expense of higher TRM in patients who are fit to undergo a myeloablative transplant. In summary, the aforementioned suggest a possibility of lower risk of relapse with myeloablative HCT in fit older patients with lower HCT comorbidity index; however, RIC and NMA HCTs can reduce TRM in less-fit patients and those with significant comorbidities.

Impact of donor age

Donor age influences the outcomes of allo-HCT. Younger age of donors is associated with higher stem-cell yield and improved outcomes, particularly in RIC HCT [Mehta *et al.* 2006]. The question then becomes whether the older-matched sibling donor or the younger-matched unrelated donor is the preferred donor. A retrospective French study analyzed outcomes of 714 patients aged over 55 years with AML in CR1 after RIC HCT using matched-unrelated donors (median age 35 years) and matched-sibling donors (median age 61 years) [Peffault de Latour *et al.* 2015]. There was no significant difference in 3-year TRM (17% *versus* 23%; $p = 0.17$), relapse rate (37% *versus* 30%; $p = 0.12$), and OS (49% in both) between older sibling *versus* younger unrelated donor HCT. However, another retrospective study of AML ($n = 117$) and MDS ($n = 62$) patients from Spain who underwent allo-HCT from matched donors demonstrated conflicting results. The median age of patients was 51 years (range 18–69 years), and that of donors was 47 years (range 12–75 years), with 81 donors aged over 50 years [Bastida *et al.* 2015]. A total of 112 patients received RIC and 67 patients received myeloablative conditioning regimens. The patients who received HCT from donors aged over 50 years had worse OS (51% *versus* 73%; $p = 0.01$), TRM (20% *versus* 8%; $p = 0.038$) relapse rate (28%

Table 1. Studies comparing intensity of conditioning regimen prior with hematopoietic-cell transplantation.

Study [year]	*n*	Median age in years (range)	Type of conditioning	Regimen	Donor source	TRM	Relapse	RFS/ DFS/PFS	OS
Aoudjhane *et al.* [2005]	407	54 (50–64)	MA	Various	HLA identical sibling	32%	24%	44%	46%
	315	57 (50–73)	RIC			18% ($p < 0.0001$)	41% ($p < 0.0001$)	40% ($p = 0.8$)	47% ($p = 0.43$; 2 years)
Alyea *et al.* [2005]	81	54 (51–66)	MA	Mainly Cy/TBI	HLA matched related/ unrelated	50%	30%	25%	29%
	71	58 (51–70)	NMA	Bu/Flu		32% ($p = 0.01$)	46% ($p = 0.05$)	27% ($p = 0.24$)	39% ($p = 0.06$; 2 years)
Scott *et al.* [2006]	112	53 (40–65)	MA	Bu/Cy	HLA matched related/ unrelated	34%	23%	44%	48%
	38	62 (40–72)	NMA	TBI 2Gy ± Flu		41% ($p = 0.94$)	31% ($p = 0.43$)	28% ($p = 0.60$)	27% ($p = 0.56$; 3 years)
Shimoni *et al.* [2006]*	45	42 (22–58)	MA	Bu/Cy	HLA matched related/ unrelated	22%	33%	45%	50%
	41	57 (18–70)	RIC	Bu/Flu		8%	49%	43%	47%
	26	51 (18–64)	Modified MA	Bu/Flu		8% ($p = 0.05$)	43% ($p > 0.05$)	49% ($p > 0.05$)	49% ($p > 0.05$; 2 years)
Scott *et al.* [2015]*	135	18–65	MA	Bu/Cy, Bu/Flu, Cy/TBI	HLA matched related/ unrelated	15%	13%	67%	77%
	137	18–65	RIC	Flu/Bu or Mel		4% ($p = 0.02$)	48% ($p < 0.01$)	47% ($p < 0.01$)	67% ($p = 0.07$; 18 months)

Bu, busulfan; Cy, cyclophosphamide; DFS, disease-free survival; Flu, fludarabine; Mel, melphalan; *n*, number of patients; OS, overall survival; RFS, relapse-free survival; TBI, total body irradiation; TRM, transplant-related mortality; HLA, human leukocyte antigen; RIC, reduced-intensity conditioning; PFS, progression-free survival; MA, myeloablative; NMA, nonmyeloablative.
*The Shimoni study is a prospective study, and the Scott study is a prospective randomized trial. All other studies are retrospective designs.

versus 39%; $p = 0.03$) as compared with those who received HCT from donors aged less than 50 years. On a subgroup analysis, a 3-year OS, using matched-sibling donors aged over 50 years was worse in comparison with matched-unrelated donors aged less than 50 years (54% *versus* 72%; $p < 0.001$).

Role of minimal residual disease monitoring

The success of NMA or RIC HCT has been primarily demonstrated in patients who were transplanted in CR. Recently, multiparameter flow cytometry has allowed detection of minimal residual disease (MRD), and hence a more stringent remission status. In a retrospective study from Seattle, bone marrow aspirate from 241 adults receiving NMA ($n = 86$, median age ~62 years) or myeloablative HCT ($n = 155$, median age ~50 years) for AML in CR1 was analyzed for the presence of MRD [Walter *et al.* 2015]. The presence of MRD was associated with a higher risk of relapse rate in both NMA (HR, 2.83; 95% CI, 1.38–5.81) and myeloablative arms (HR, 7.22; 95% CI, 3.85–13.54). Another study from University of Minnesota analyzed the impact of the presence of MRD on outcomes in 203 AML patients who received RIC ($n = 123$, median age 61 years) or myeloablative ($n = 80$, median age 26 years) conditioning prior to HCT [Ustun *et al.* 2015]. On a retrospective analysis, MRD was present in 10 patients who received RIC and 15 patients who received myeloablative HCT. Among the RIC arm, the presence of MRD was associated with higher relapse rate (HR, 1.38; 95% CI, 1.7–8.7), DFS (HR, 2.9; 95% CI, 1.4–5.9), and OS (HR, 3.4; 95% CI, 1.7–7.0). A similar association was not seen in the patients who received myeloablative conditioning. This suggests a potential role for monitoring MRD to ascertain MRD-negative status prior to NMA or RIC allo-HCT.

Current state and future directions

In the assessment of potential HCT recipients, clinicians should take into account the treatment strategy as a whole, including the induction chemotherapy used, and the degree of myeloablation achieved by the RIC regimen itself [Blaise *et al.* 2007]. A use of lower-intensity induction therapy such as 10-day decitabine, which is associated with a CR rate of up to 40–50% even in AML patients with complex karyotype, may preserve the performance status and organ function of patients as they proceed to HCT [Ritchie *et al.* 2013]. Early incorporation of multidisciplinary care, including attention to physical therapy, nutrition and psychosocial health may improve a patient's fitness to undergo and tolerate HCT in general. Additionally, in the selection of conditioning regimens, clinicians should take into consideration multiple factors, such as performance status and overall health status of an individual patient, a patient's preferences of accepted level of mortality risk, status of the disease and availability of clinical trials of novel agents. In 2005, an HCT comorbidity index was introduced as a tool to assess comorbidities in HCT recipients [Sorror *et al.* 2005]. This was further modified to form a composite comorbidity or age index where anyone aged 40 years or over was assigned a value of 1 in addition to the other parameters in the HCT comorbidity index [Sorror *et al.* 2014]. This tool demonstrated a higher predictive value for TRM and OS as compared with age alone. Similarly, comprehensive geriatric assessment can be utilized to determine the fitness of older patients [Stuck *et al.* 1993; Muffly *et al.* 2013]. Recently, a modified European LeukemiaNet classification for patients with AML undergoing HCT in CR1 has also been evaluated that utilizes molecular markers to stratify patients into four prognostic groups [Oran *et al.* 2015]. Utilization of such tools can guide better selection of conditioning intensity in an individual.

At the present time, the aforementioned studies indicate a lower risk of TRM with RIC or NMA HCT in older AML patients with a possibility of higher risk of relapse, compared with myeloablative HCT. Hence, NMA or RIC HCT may be utilized in older AML patients who achieve CR1 with induction chemotherapy, are less fit, or have a high HCT comorbidity index and hence are not candidates for myeloablative HCT. NMA or RIC HCT may also be the preferred approach in patients who are older than 70 years old. Conversely, myeloablative HCT may be considered in fit patients with a low HCT comorbidity index, aged up to 65–70 years, who have achieved remission and accept a higher risk of TRM. Frail older patients, or those with active disease should be encouraged to enroll in well-designed clinical trials of novel therapies. The current National Comprehensive Cancer Network (NCCN) Guidelines (available at http://www.nccn.org) recommend considering RIC allogeneic HCT at CR1 in patients aged 60 years and older with minimal comorbidities who have an available donor, and patients with low-volume disease who fail induction therapy (preferably in the context of a clinical trial).

A number of strategies, such as early tapering of immunosuppression, monitoring of MRD after HCT, pre-emptive therapy of impending clinical relapse and post-transplant maintenance with chemotherapy, immunotherapy or cellular therapy are being explored to reduce the risk of relapse after HCT [Wayne *et al.* 2013; Gress *et al.* 2013]. Whether such strategies can improve the outcomes of RIC and NMA HCT will require prospective trials. Recently, 'microtransplantation' has been reported as a novel HCT strategy in older patients without a matched-related donor. In this strategy, the infusion of granulocyte colony-stimulating factor–mobilized donor peripheral-blood stem cells following induction and consolidation chemotherapy in elderly patients resulted in higher CR rates and DFS without GVHD [Guo *et al.* 2011]. This emerging HCT technique should be further investigated. Finally, survivorship programs are integral to enhance long-term outcomes and quality of life of older transplant recipients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

Alyea, E., Kim, H., Ho, V., Cutler, C., Gribben, J., DeAngelo, D. *et al.* (2005) Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood* 105: 1810–1814.

Aoudjhane, M., Labopin, M., Gorin, N., Shimoni, A., Ruutu, T., Kolb, H. *et al.* (2005) Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia* 19: 2304–2312.

Appelbaum, F., Gundacker, H., Head, D., Slovak, M., Willman, C., Godwin, J. *et al.* (2006) Age and acute myeloid leukemia. *Blood* 107: 3481–3485.

Bacigalupo, A., Ballen, K., Rizzo, D., Giralt, S., Lazarus, H., Ho, V. *et al.* (2009) Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant* 15: 1628–1633.

Bastida, J., Cabrero, M., Lopez-Godino, O., Lopez-Parra, M., Sanchez-Guijo, F., Lopez-Corral, L. *et al.* (2015) Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome. *Leuk Res* 39: 828–834.

Blaise, D., Maraninchi, D., Archimbaud, E., Reiffers, J., Devergie, A., Jouet, J. *et al.* (1992) Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytoxan *versus* Cytoxan-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. *Blood* 79: 2578–2582.

Blaise, D., Vey, N., Faucher, C. and Mohty, M. (2007) Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica* 92: 533–541.

Chang, C., Storer, B., Scott, B., Bryant, E., Shulman, H., Flowers, M. *et al.* (2007) Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with *de novo* disease and disease following prior therapy or antecedent hematologic disorders. *Blood* 110: 1379–1387.

Chevallier, P., Labopin, M., Buchholz, S., Ganser, A., Ciceri, F., Lioure, B. *et al.* (2012) Clofarabine-containing conditioning regimen for allo-SCT in AML/ALL patients: a survey from the Acute Leukemia Working Party of EBMT. *Eur J Haematol* 89: 214–219.

Childs, R. and Srinivasan, R. (2002) Advances in allogeneic stem cell transplantation: directing graft-*versus*-leukemia at solid tumors. *Cancer J* 8: 2–11.

Davies, J., Taussig, D., Oakervee, H., Smith, M., Agrawal, S., Cavenagh, J. *et al.* (2013) Long-term survival with low toxicity after allogeneic transplantation for acute myeloid leukaemia and myelodysplasia using non-myeloablative conditioning without T cell depletion. *Br J Haematol* 162: 525–529.

Devine, S., Owzar, K., Blum, W., Mulkey, F., Stone, R., Hsu, J. *et al.* (2015) Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. *J Clin Oncol* 33: 4167–4175.

Estey, E., de Lima, M., Tibes, R., Pierce, S., Kantarjian, H., Champlin, R. *et al.* (2007) Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood* 109: 1395–1400.

Farag, S., Maharry, K., Zhang, M., Perez, W., George, S., Mrozek, K. *et al.* (2011) Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60–70 years with acute myelogenous leukemia in first remission. *Biol Blood Marrow Transplant* 17: 1796–1803.

Ferrara, F., Annunziata, M., Copia, C., Magrin, S., Mele, G. and Mirto, S. (1998) Therapeutic options and treatment results for patients over 75 years of age with acute myeloid leukemia. *Haematologica* 83: 126–131.

Gardin, C., Turlure, P., Fagot, T., Thomas, X., Terre, C., Contentin, N. *et al.* (2007) Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood* 109: 5129–5135.

Giles, F., Borthakur, G., Ravandi, F., Faderl, S., Verstovsek, S., Thomas, D. *et al.* (2007) The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. *Br J Haematol* 136: 624–627.

Giralt, S., Ballen, K., Rizzo, D., Bacigalupo, A., Horowitz, M., Pasquini, M. *et al.* (2009) Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant* 15: 367–369.

Gress, R., Miller, J., Battiwalla, M., Bishop, M., Giralt, S., Hardy, N. *et al.* (2013) Proceedings from the National Cancer Institute's second international workshop on the biology, prevention, and treatment of relapse after hematopoietic stem cell transplantation: part I. Biology of relapse after transplantation. *Biol Blood Marrow Transplant* 19: 1537–1545.

Guo, M., Hu, K., Yu, C., Sun, Q., Qiao, J., Wang, D. *et al.* (2011) Infusion of HLA-mismatched

peripheral blood stem cells improves the outcome of chemotherapy for acute myeloid leukemia in elderly patients. *Blood* 117: 936–941.

Hegenbart, U., Niederwieser, D., Sandmaier, B., Maris, M., Shizuru, J., Greinix, H. *et al.* (2006) Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol* 24: 444–453.

Herr, A., Labopin, M., Blaise, D., Milpied, N., Potter, M., Michallet, M. *et al.* (2007) HLA-identical sibling allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning compared to autologous peripheral blood stem cell transplantation for elderly patients with *de novo* acute myeloid leukemia. *Leukemia* 21: 129–135.

Kasamon, Y., Bolanos-Meade, J., Prince, G., Tsai, H., McCurdy, S., Kanakry, J. *et al.* (2015) Outcomes of nonmyeloablative HLA-haploidentical blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in older adults. *J Clin Oncol* 33: 3152–3161.

Konuma, T., Tsukada, N., Kanda, J., Uchida, N., Ohno, Y., Miyakoshi, S. *et al.* (2016) Comparison of transplant outcomes from matched sibling bone marrow or peripheral blood stem cell and unrelated cord blood in patients 50 years or older. *Am J Hematol.* doi:10.1002/ajh.24340 [Epub ahead of print].

Kurosawa, S., Yamaguchi, T., Uchida, N., Miyawaki, S., Usuki, K., Watanabe, M. *et al.* (2011) Comparison of allogeneic hematopoietic cell transplantation and chemotherapy in elderly patients with non-M3 acute myelogenous leukemia in first complete remission. *Biol Blood Marrow Transplant* 17: 401–411.

Leoni, F., Ciolli, S., Nozzoli, C., Marrani, C., Caporale, R. and Ferrini, P. (1997) Idarubicin in induction treatment of acute myeloid leukemia in the elderly. *Haematologica* 82: 13–18.

Lowenberg, B., Ossenkoppele, G., van Putten, W., Schouten, H., Graux, C., Ferrant, A. *et al.* (2009) High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 361: 1235–1248.

Lowenberg, B., Suciu, S., Archimbaud, E., Haak, H., Stryckmans, P., de Cataldo, R. *et al.* (1998) Mitoxantrone *versus* daunorubicin in induction-consolidation chemotherapy – the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. *J Clin Oncol* 16: 872–881.

Majhail, N., Brunstein, C., Shanley, R., Sandhu, K., McClune, B., Oran, B. *et al.* (2012) Reduced-intensity hematopoietic cell transplantation in older patients with AML/MDS: umbilical cord blood is a feasible option for patients without HLA-matched sibling donors. *Bone Marrow Transplant* 47: 494–498.

Martino, R., Valcarcel, D., Brunet, S., Sureda, A. and Sierra, J. (2008) Comparable non-relapse mortality and survival after HLA-identical sibling blood stem cell transplantation with reduced or conventional-intensity preparative regimens for high-risk myelodysplasia or acute myeloid leukemia in first remission. *Bone Marrow Transplant* 41: 33–38.

Mayer, R., Davis, R., Schiffer, C., Berg, D., Powell, B., Schulman, P. *et al.* (1994) Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med* 331: 896–903.

McClune, B., Weisdorf, D., Pedersen, T., Tunes da Silva, G., Tallman, M., Sierra, J. *et al.* (2010) Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol* 28: 1878–1887.

Mehta, J., Gordon, L., Tallman, M., Winter, J., Evens, A., Frankfurt, O. *et al.* (2006) Does younger donor age affect the outcome of reduced-intensity allogeneic hematopoietic stem cell transplantation for hematologic malignancies beneficially? *Bone Marrow Transplant* 38: 95–100.

Mohty, M., de Lavallade, H., Ladaique, P., Faucher, C., Vey, N., Coso, D. *et al.* (2005) The role of reduced intensity conditioning allogeneic stem cell transplantation in patients with acute myeloid leukemia: a donor *versus* no donor comparison. *Leukemia* 19: 916–920.

Muffly, L., Boulukos, M., Swanson, K., Kocherginsky, M., Cerro, P., Schroeder, L. *et al.* (2013) Pilot study of comprehensive geriatric assessment (CGA) in allogeneic transplant: CGA captures a high prevalence of vulnerabilities in older transplant recipients. *Biol Blood Marrow Transplant* 19: 429–434.

Nelson, R., Jr., Yu, M., Schwartz, J., Robertson, M., Hromas, R., Fausel, C. *et al.* (2010) Long-term disease-free survival after nonmyeloablative cyclophosphamide/fludarabine conditioning and related/unrelated allotransplantation for acute myeloid leukemia/myelodysplasia. *Bone Marrow Transplant* 45: 1300–1308.

Oran, B., Jimenez, A., De Lima, M., Popat, U., Bassett, R., Andersson, B. *et al.* (2015) Age and modified European LeukemiaNet classification to predict transplant outcomes: an integrated approach for acute myelogenous leukemia patients undergoing allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 21: 1405–1412.

Peffault de Latour, R., Labopin, M., Cornelissen, J., Vigouroux, S., Craddock, C., Blaise, D. *et al.* (2015) In patients older than 55 years with AML in first CR, should we search for a matched unrelated donor

when an old sibling donor is available? *Bone Marrow Transplant* 50: 1411–1415.

Ringden, O., Labopin, M., Ehninger, G., Niederwieser, D., Olsson, R., Basara, N. *et al.* (2009) Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. *J Clin Oncol* 27: 4570–4577.

Ritchie, E., Feldman, E., Christos, P., Rohan, S., Lagassa, C., Ippoliti, C. *et al.* (2013) Decitabine in patients with newly diagnosed and relapsed acute myeloid leukemia. *Leuk Lymphoma* 54: 2003–2007.

Sandhu, K., Brunstein, C., DeFor, T., Bejanyan, N., Arora, M., Warlick, E. *et al.* (2016) Umbilical cord blood transplantation outcomes in acute myelogenous leukemia/myelodysplastic syndrome patients aged ⩾70 years. *Biol Blood Marrow Transplant* 22: 390–393.

Schiffer, C. (2010) 'I am older, not elderly,' said the patient with acute myeloid leukemia. *J Clin Oncol* 28: 521–523.

Scott, B., Pasquini, M., Logan, B., Wu, J., Devine, S., Porter, D. *et al.* (2015) 'Results of a phase III randomized, multi-center study of allogeneic stem cell transplantation after high *versus* reduced intensity conditioning in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML): Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901', *57th Annual meeting and exposition, American Society of Hematology*, pp. LBA–8.

Scott, B., Sandmaier, B., Storer, B., Maris, M., Sorror, M., Maloney, D. *et al.* (2006) Myeloablative *versus* nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. *Leukemia* 20: 128–135.

Shimoni, A., Hardan, I., Shem-Tov, N., Yerushalmi, R. and Nagler, A. (2010) Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative *versus* reduced-intensity conditioning: long-term follow-up. *Leukemia* 24: 1050–1052.

Shimoni, A., Hardan, I., Shem-Tov, N., Yeshurun, M., Yerushalmi, R., Avigdor, A. *et al.* (2006) Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative *versus* reduced-intensity conditioning: the role of dose intensity. *Leukemia* 20: 322–328.

Siegel, R., Miller, K. and Jemal, A. (2016) Cancer statistics, 2016. *CA Cancer J Clin* 66: 7–30.

Sorror, M., Maris, M., Storb, R., Baron, F., Sandmaier, B., Maloney, D. *et al.* (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 106: 2912–2919.

Sorror, M., Sandmaier, B., Storer, B., Franke, G., Laport, G., Chauncey, T. *et al.* (2011) Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA* 306: 1874–1883.

Sorror, M., Storb, R., Sandmaier, B., Maziarz, R., Pulsipher, M., Maris, M. *et al.* (2014) Comorbidity–age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol* 32: 3249–3256.

Storb, R. (2007) Can reduced-intensity allogeneic transplantation cure older adults with AML? *Best Pract Res Clin Haematol* 20: 85–90.

Stuck, A., Siu, A., Wieland, G., Adams, J. and Rubenstein, L. (1993) Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 342: 1032–1036.

Ustun, C., Courville, E., DeFor, T., Dolan, M., Randall, N., Yohe, S. *et al.* (2015) Myeloablative, but not reduced-intensity, conditioning overcomes the negative effect of flow-cytometric evidence of leukemia in acute myeloid leukemia. *Biol Blood Marrow Transplant*.

Versluis, J., Hazenberg, C., Passweg, J., van Putten, W., Maertens, J., Biemond, B. *et al.* (2015) Post-remission treatment with allogeneic stem cell transplantation in patients aged 60 years and older with acute myeloid leukaemia: a time-dependent analysis. *Lancet Haematol* 2: e427–36.

Vey, N., Coso, D., Bardou, V., Stoppa, A., Braud, A., Bouabdallah, R. *et al.* (2004) The benefit of induction chemotherapy in patients age ⩾75 years. *Cancer* 101: 325–331.

Vicente, D., Lamparelli, T., Gualandi, F., Occhini, D., Raiola, A., Ibatici, A. *et al.* (2007) Improved outcome in young adults with *de novo* acute myeloid leukemia in first remission, undergoing an allogeneic bone marrow transplant. *Bone Marrow Transplant* 40: 349–354.

Wallen, H., Gooley, T., Deeg, H., Pagel, J., Press, O., Appelbaum, F. *et al.* (2005) Ablative allogeneic hematopoietic cell transplantation in adults 60 years of age and older. *J Clin Oncol* 23: 3439–3446.

Walter, R., Gyurkocza, B., Storer, B., Godwin, C., Pagel, J., Buckley, S. *et al.* (2015) Comparison of minimal residual disease as outcome predictor for AML patients in first complete remission undergoing myeloablative or nonmyeloablative allogeneic hematopoietic cell transplantation. *Leukemia* 29: 137–144.

Wayne, A., Giralt, S., Kroger, N. and Bishop, M. (2013) Proceedings from the National Cancer Institute's second international workshop on the biology, prevention, and treatment of relapse after hematopoietic stem cell transplantation: introduction. *Biol Blood Marrow Transplant* 19: 1534–1536.