Allogeneic Stem Cell Transplantation to cure Acute Myeloid Leukemia in elderly patients

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ABSTRACT

Outcomes for elderly patients with acute myeloid leukemia (AML) remain poor with standard therapies. Historically this age group has been excluded from treatment with allogeneic stem cell transplantation (allo-SCT) due to worries of excessive treatment related morbidity and mortality. However, transplantation outcomes have dramatically improved in the last decade due to the widespread use of less ablative conditioning regimens, improved supportive care, and improved patient selection based on prognostic tools such as the hematopoietic cell transplant specific comorbidity index. These have all led to an increasing acceptance of allo-SCT as a potential treatment modality in elderly patients with AML. This review addresses current strategies for patient selection and efficacy data for allo-SCT in elderly patients with AML.

INTRODUCTION

According to SEER data approximately 12,000 cases of acute myeloid leukemia (AML) were diagnosed in the United States in 2010.[1] AML is a disease with a peak incidence that occurs at 67 years of age. As healthy individuals at 70 years of age have a life expectancy of at least another 10 years,[2] consideration should be given to curative therapies whenever possible. Prognosis of elderly patients is poor and clearly inferior to that of young patients with AML.[3-6] This is not only due to host factors such as performance status but also due to a higher rate of disease related adverse prognostic signs such as poor risk karyotype and antecedent hematologic disorder.

Allogeneic stem cell transplantation (Allo-SCT) is one of the most effective strategies in the management of AML. The potent anti-leukemic effect of allo-SCT must be weighed against the possible risk of post transplant complications such as infection, graft versus host disease and organ dysfunction as a result of the conditioning regimen which all contribute to non relapse mortality (NRM). It is for this reason that allo-SCT has traditionally been reserved for patients under the age of 50 years. NRM has been reduced markedly over the last 15 years with the advent of reduced intensity preparative regimens and improved supportive care.[7]

With these facts in mind, the question of whether a curative option with Allo-SCT may be offered to elderly patients needs to be addressed. Here we outline recent advances in transplantation regimens, discuss the selection criteria and make the argument that elderly patients should be considered for allo-SCT whenever possible.

Importance of assessment of comorbidities in stem cell transplant

The term comorbidity, defined as a distinct additional clinical entity that coexists with an index disease was introduced by Feinstein in 1970.[8] Used to define the weight of additional diseases on a patient, comorbidities became of interest in stem cell transplant when non myeloablative conditioning widened the pool of patients eligible for Allo-SCT. Elderly patients often present with comorbidities causing increased post HSCT morbidity and mortality. It is accepted that the presence of comorbidities and not chronologic age alone should be one of the major considerations when deciding whether a particular patient is eligible for transplant.
Therefore, the development of a method to reliably assess pre-transplant comorbidities is important for clinicians to estimate the risks of undergoing HSCT.

Single organ comorbidities including cardiac, pulmonary and hepatic were initially studied and failed to predict transplant outcome.[9-18] Furthermore as many patients have at least one comorbidity, a more comprehensive tool was required. Several scoring system had been developed for the use in other patient populations. The Charlson comorbidity index (CCI)[19] is a weighted scoring system which was first reported in 1980 based on the one year mortality of general medicine patients admitted to a single hospital.[20] The CCI evaluates for

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Table 1. **Comorbidity definition, assigned score and incidence of comorbidities in University of Illinois cohort**

Comorbidity	Definition	Score	Prevalence (%)
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome or ventricular arrhythmias	1	0
Cardiac	Coronary artery disease*, congestive heart failure, myocardial infarction or EF < 50%	1	5 (10%)
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1	1 (2%)
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1	6 (12%)
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1	1 (2%)
Psychiatric	Depression or anxiety requiring psychiatric consult or treatment	1	5 (10%)
Hepatic (mild)	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN or AST/ALT > ULN to 2.5 x ULN	1	16 (32%)
Obesity	Patients with a body mass index > 35 kg/m2	1	6 (12%)
Infection	Requiring continuation of antimicrobial treatment after day 0	1	14 (28%)
Rheumatologic	SLE, RA, polymyositis, mixed CTD or polymyalgia rheumatic	2	2 (4%)
Peptic ulcer	Requiring treatment	2	0
Renal	Serum creatinine > 2 mg/dL, on dialysis or prior renal transplantation	2	0
Pulmonary (moderate)	DLco and/or FEV1 66%-80% or dyspnea on slight activity	2	16 (32%)
Prior solid tumor	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3	2 (4%)
Heart valve disease	Except mitral valve prolapsed	3	1 (2%)
Pulmonary (severe)	DLco and/or FEV1 < 65% or dyspnea at rest or requiring oxygen	3	11 (22%)
Hepatic (mod/ severe)	Liver cirrhosis, bilirubin > 1.5 x ULN or AST/ALT > 2.5 x ULN	3	0

**One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft*

the presence of 19 diseases and assigns a score to each. Charlson et al noted that scores of 1 to 2 and 3 or higher were associated with increasing risks of mortality. This score was subsequently validated in a number of malignancies including breast, head and neck and lung cancer.[21-23] When applied to patients undergoing Allo-SCT, investigators found that the risk of overall grade 4 toxicity and NRM increased with increasing CCI. Notably patients who underwent NMA transplant had significantly less grade 4 toxicities despite being an older cohort. In an effort establish a comorbidity scoring system more appropriate to stem cell transplant the same investigators reported the hematopoietic cell transplantation specific comorbidity index (HCT-CI).[24] This tool was derived from over 1000 patients utilizing many of the same comorbidities in the CCI. Hazard ratios for NRM were obtained in order to develop a weighted score. The result was a new 17 point score which predicted NRM and OS (Table 1 along with prevelance of comorbidities as reported by the authors[25]). Patients were stratified into 3 groups based on HCT-CI score (0, 1-2, >3).

The HCT-CI has now been studied in several different diseases, conditioning regimens and donor types with varying results. The Seattle group reported that high HCT-CI predicted outcomes (NRM and OS) in patients with AML, MDS, CLL and lymphoma conditioned with both MAC and NMA regimens.[26, 27] Similar results were obtained when the Seattle data on AML patients in first complete remission was combined with data from the MD Anderson cancer center.[28]

Although by far the most comprehensive review of comorbidities in patients undergoing stem cell transplant, data regarding the utility of the HCT-CI has been mixed. A Canadian group reported that they found no association between HCT-CI and TRM or OS in a variety of conditioning regimens and disease.[29] In umbilical cord transplant registry data, HCT-CI did not consistently predict NRM or OS.[30] Similarly in patients with NHL conditioned with fludarabine and cyclophosphamide there was no association between HCT-CI and TRM or OS.[31]

Several investigators have reported that although HCT-CI may be useful, it lacks the sensitivity to predict outcome as stratified by the 3 original groups described. Farina et al[32] reported that in patients with myeloma or lymphoma who underwent RIC or NMA conditioning, HCT-CI of 0 was associated with a significantly improved OS and NRM when compared with both of the other groups. NRM was

not different between patients with HCT-CI of 1–2 and HCT-CI of >3 (P=0.48). Therefore in this population the HCT-CI lacked sensitivity to predict outcomes in patients with HCT-CI score >1. Conversely in patients conditioned with fludarabine/ oral busulfan and i.v. alemtuzumab although TRM seems to show linear increase with increasing HCT-CI score (16% vs. 24% vs. 42%), the difference was not statistically different between patients with 0 score and 1-2 but was significantly increased in patients with HCT-CI >333. Similarly a single center Japanese experience showed that patients with high HCT-CI score had statistically worse OS and NRM than low score patients. The same was not true for patients with intermediate score HCT-CI.[34]

Attempts have been made to increase the sensitivity of the HCT-CI. The original investigators have reported that the addition of Karnofsky performance score or disease risk at time of transplant enhances the stratification and gives incremental increases in non relapse mortality.[35] Barba et al reported that in patients conditioned with fludarabine/ melphalan or fludarabine/ busulfan (8-10mg/kg) there was no association between HCT-CI and NRM or OS36. However when the same investigators analyzed patients compartmentalized in a different manner they found this new flexible HCT-CI was a strong predictor of NRM and OS.

In addition to HCT-CI the PAM score has been described.[37] The PAM scores predicts mortality after transplant. Although it captures some comorbid conditions it is not specifically designed to evaluate comorbidities alone but rather all aspects associated with transplantation outcome that may contribute to increased morbidity and mortality. For example the PAM score includes disease related risk and type of donor.

REDUCED INTENSITY AND NON MYELOABLATIVE CONDITIONING

Myeloablative (MAC) transplantation refers to conditioning which leads to severe and long lasting cytopenias which would not recover without stem cell infusion.[38] These regimens lead to rapid full donor chimerism but are generally thought to lead to greater NRM. The realization that "immune-ablation" and not myeloablation was required for successful transplantation has lead to reduced intensity (RIC) and non myeloblative (NMA) transplant.

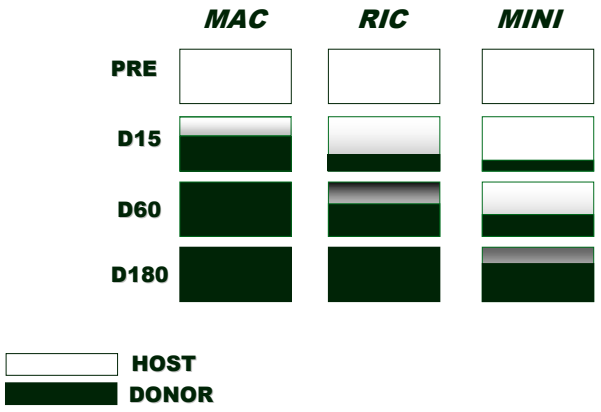

Figure 1. **Engraftment of donor stem cells after conditioning regimen with myeloablative, reduced intensity or non myeloablative therapy**

Conditioning regimens with myeloablative effect (MAC), or reduced intensity (RIC) or non-myeloablative doses of chemotherapy and/or radiation (MINI) produce a different rate of early engraftment of donor stem cells and thus allow the persistence of host cells for variable time. Over the time, donor stem cells are thought to progressively occupy the whole marrow of the host due to a graft-versus host reaction.

Although it is likely that RIC reduces antileukemic effect,[39] it is widely accepted that these regimens produce much less transplant related morbidity and mortality and therefore are often attractive in elderly and comorbid patients. In contrast to MAC, NMA conditioning cause minimal cytopenias which do not require stem cell support38. These regimens lessen NRM but still carry significant risk of acute graft versus host disease (aGVHD) which may be delayed in onset. If these 2 classes are considered at opposite ends of a spectrum then reduced intensity conditioning falls in the middle ground. For RIC, autologous reconstitution remains a possibility. There are now multiple phase II and retrospective studies with a multitude of NMA and RIC regimens. Although large prospective multicenter trials are ongoing, data on the full impact of these regimens or indeed whether any one is superior to another is currently lacking.

Table 2. **Comparison of EBMT and CIBMTR data in elderly patients**

	n	Median Age	RIC conditioning	OS	Relapse Rate	NRM
CIBMTR*						
40-54	208	50 (40-54)	78% (p=.07)	44% (p=0.06)	33% (p=0.87)	25% (p=0.26)
55-60	146	57 (55-59)	68%	50%	34%	22%
60-65	126	62 (60-64)	69%	34%	37%	32%
>65	55	67 (65-78)	65%	36%	33%	34%
EBMT**						
50-60	884	54 (50-60)	55% (p<0.01)	34% (p=0.23)	32% (p=0.02)	36% (p=0.39)
>60	449	63 (60-75)	78%	24%	41%	39%

**2 year estimates **4 year estimates*

Truly NMA conditioning with 2Gy TBI and fludarabine has been previously described. In patients with MDS or MPD conditioned with this regimen graft rejection was seen in 15% of patients.[40] The 3-year OS was 27%, with a relapse incidence of 41%. The 3-year NRM was 32%. In patients with AML 96% of patients had durable engraftment.[41] NRM was 25% for patients in CR1, 27% for those in CR2, 35% for those not in CR1 or CR2 and 28% for those with secondary AML. Relapse mortalities for these four patient groups were 36%, 36%, 42% and 46% respectively. Therefore even though the use of low dose TBI with fludarabine is well tolerated it often leads to failure to engraft as well as a high relapse rate in myeloid malignancies. The addition of a further 2 Gy to above described 2Gy/ fludarabine regimen has been attempted in an effort to decrease graft rejection and disease relapse. These data were compared with the authors data from previous experience with 2Gy TBI. Although fewer 4Gy TBI patients experienced graft rejection than that observed for the 2Gy TBI group, this did not reach statistical significance. No difference in relapse rate or survival were noted between the 2 groups, however many patients had indolent lymphoid malignancies rather than more aggressive myeloid malignancies. In subgroup analyses it appeared that patients with myeloid malignancies benefited most in terms of improved survival although patient numbers were small. Importantly the additional 2Gy was well tolerated.[42] An alternative NMA regimen has been proposed by the Stanford group involving total lymph node irradiation and antithymocyte globulin.[43] The analysis included 47 patients with myeloid malignancies. In total 34 patients were over the age of 60 years of age. 1 year NRM was less than 4%. 3 year OS was 60%. Therefore relapse remained a significant cause of death.

RIC has been described utilizing a fludarabine immunosuppressive backbone in addition to alkylator therapy with melphalan (<140mg/m2). The fludarabine/ melphalan regimen has now been described by several groups to have acceptable non relapse mortality[44-48] One of the initial descriptions of this regimen was by the MD Anderson group utilizing fludarabine (125mg/m2) and melphalan (140mg/m2 or 180mg/m2).[44] In patients with a median age of 52 years the NRM was 37.4% at 100 days. Overall survival was not adversely affected by increasing age. Other fludarabine-based RIC regimens combined this purine analogue with cyclophosphamide[49,50] and thiotepa[51] also in allo-SCT studies for patients with myeloid malignancies. Nevertheless, the 40 year-experience in stem cell transplantation of a conditioning regimen utilizing oral busulfan, and the development over the last 10 years of a more stable and practical intravenous formulation of this drug, have led the majority of transplant centers utilizing a combination of fludarabine and IV busulfan at very different doses.[52-55]

Fludarabine/IV Busulfan -
A reduced toxicity regimen with myeloablative effect

Initial use of busulfan was entirely oral. A stable IV formulation now exists with an oral to IV conversion of 1: 0.8. Busulfan containing regimens gained popularity when shown to have equivalent survival to TBI based regimens with decreased toxicity[56] In addition targeting of busulfan dose has gained acceptance as low busulfan levels have been shown to correlate with relapse.[57] The fludarabine/ busulfan regimen was described by Russel et al in 2002. The authors described a tolerable regimen with reliable engraftment58. We have described that a standard RIC regimen (Fludarabine/ Melphalan) and MAC (Fludarabine/ Busulfan) induced similar hematologic and minimal extrahematologic toxicity.[59] Furthermore, the outcome of patients at standard risk and high risk was comparable to other standard regimens, but with a reduced toxicity[60] An improving knowledge of busulfan pharmacokinetics has allowed many centers to design strategies using low, intermediate or full dose busulfan.[52-55,61-63] The optimal dose for reduced intensity regimens including busulfan has been addressed by in a study comparing 3.2mg/kg with 6.4mg/kg64. Median age of patients was 58 in the lower dose group and 62 in the higher dose group (p=0.0006). 2 year NRM was 3.7% in the low dose group and 11.1% in the high dose group (p<0.05). However relapse was significantly increased in the low dose group. New strategies targeting the dose of Bu according to PK studies at the time of transplant are currently addressing whether efficacy and toxicity may be optimized in each patient avoiding sub- or supratherapeutic levels of busulfan.

Clinical experience with transplantation
in elderly patients with AML

A number of small single center studies have shown safety of allo-SCT in elderly patients. However, evidence presented in large cohorts of patients (Table 2) now supports the safety and efficacy of allo-SCT in elderly patients with AML.[65,66] The European Group for Blood and Marrow Transplantation (EBMT) reported on 1333 MDS and secondary AML patients over the age of 50, including 34% over 60 years of age, who received a transplant after 1998. 62% were conditioned with RIC and 38% with MAC. In multivariate analysis age >60 did not impact overall survival or non relapse mortality. Advanced disease, RIC and unrelated donor were risks for non relapse mortality. The major independent variable for overall survival was disease stage at time of transplantation. A CIBMTR analysis included a total of 1080 patients. Of these 545 patients had AML (the remainder had MDS). Among patients with AML, 36% were older than 60 years of age, and 12% were ≥ 65 years old. In multivariate analysis recipient age was not an independent variable for non relapse mortality. 1 year non relapse mortality was adversely affected by lower KPS, worsening HLA disparity, MDS (whether cytogenetically good, intermediate, or poor risk), unfavorable-risk AML, and increasing donor age. Similarly overall survival was not significantly impacted by age but low KPS, mismatched donor and unfavorable cytogenetic all had a negative effect on survival.

In addition two recent studies have addressed this issue. Alatrash et al reported the outcome of patients > 55 years of age with AML or MDS conditioned with the myeloablative regimen of busulfan (130mg/m^2) and fludarabine.[67] Median age was 58 years. Using the median age as a cutoff the auhors showed that there was no significant difference between the 2 groups in terms of OS. Koreth et al analyzed the outcome of 158 patients aged between 60 and 71 who underwent RIC68. 44% of patients had AML. Two year NRM and relapse were 10% and 54.6%. 2 year OS was 46%. In multivariate analysis age >65 was not associated with increased NRM.

CONCLUSION

AML in the elderly has a poor prognosis with little change in the outcome over the last 30 years. A substantial amount of evidence now supports the potential curative effect of allo-SCT in the elderly patient. Patient selection using objective criteria analyzing comorbidities is important. Future avenues of investigation will include targeted therapies to intensify the anti-leukemic activity of the conditioning regimen while simultaneously limiting extrahematologic toxicity. This is already under investigation in phase I and II clinical trials including radiolabeled monoclonal antibodies and intensity modulated total marrow irradiation.

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