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Allogeneic hematopoietic stem cell transplantation in elderly patients with acute myeloid leukemia

Kazimierz Hałaburda

Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Abstract

The incidence of acute myeloid leukemia (AML) significantly increases with age. Most AML patients are elderly and rarely receive curative treatment. Even those who eventually achieve complete remission have a grim prognosis due to the high risk of relapse. In elderly patients, allogeneic hematopoietic stem cell transplantation (allo-HSCT) increases the probability of prolonged survival compared to standard treatment. The decision as to whether to refer a patient for transplantation must be preceded by a careful risk assessment based on the patient's remission status, comorbidities, and type of available donor. Although allo-HSCTs are routinely performed in the seventh decade of life, they are not common in those aged over 70. In recent years, the results of allo-HSCT in the elderly have improved, mainly thanks to refined conditioning regimen techniques and better supportive care. It can be anticipated that with growing data on allogeneic transplants in older AML patients, the proportion of this population among transplant recipients will continue to rise.

Key words: acute myeloid leukemia, elderly patients, allogeneic hematopoietic stem cell transplantation

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Introduction

Current life expectancy at birth in the European Union is 81 years according to Eurostat data [1]. It is better for women with 83.7 years than for men with 78.2 years. The steady increase of predicted life duration over the last 20 years raises the question as to how to define elderly and old populations. The recent World Health Organization definition describes persons over the age of 65 as old [2]. The process of ageing or senescence in an individual starts anywhere between 45 and 65 years of age and proceeds at different paces depending on genetic, ethnic and biological factors as well as on socio-economic circumstances. Thus, an exact age definition of an elderly patient is lacking. Usually those above 60 years are considered to be elderly. Epidemiology data shows that the median age of patients diagnosed with AML is between 64 and 70 [3–5]. Therefore, the majority of newly diagnosed AML patients fall into the elderly population category.

Diagnosis and risk factors in acute myeloid leukemia

According to the 2017 European LeukemiaNet (ELN) guidelines, AML is diagnosed based on leukemic blasts in the bone marrow in excess of 20% with the exception for AML with recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) [6]. Patients who are diagnosed with AML are stratified into low-, intermediate- or high-risk groups according to genetic abnormalities in line with ELN recommendations. However, the prognosis in AML strongly depends also on other factors such as age, performance status, sex, comorbidities, pre-existing hematological conditions, previous cancer treatment, and response of the disease to therapy [7].

Address for correspondence: Kazimierz Hałaburda, Institute of Hematology and Transfusion Medicine, Indira Gandhi 14, 02–776 Warsaw, Poland, e-mail: khalaburda@ihit.waw.pl

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AML in the elderly

The prognosis in elderly patients with AML is dismal. Five-year disease-free survival in the elderly is c. 5%, while in young patients it is c.40% [8, 9]. Poor outcomes in older patients are both disease- and patient-related. Among these patients, there is a distinct high-risk subgroup with therapy-related AML after previous exposure to radiotherapy or chemotherapy as well as secondary AML after antecedent myeloproliferative neoplasm or myelodysplastic syndrome (MDS) [10]. Adverse cytogenetic and molecular abnormalities affect 50–60% of older patients compared to 30% of those younger than 60 [11, 12]. Older age is frequently associated with comorbidities and frailties which preclude intensive (or even any) anti-leukemic treatment. Only about 55% of patients aged 65+ receive specific therapy for AML, and the proportion of treated patients is decreasing with age. This translates into median survival of 2 months in untreated vs. 6 months in treated patients [13]. Published data indicates that allogeneic hematopoietic stem transplantation (allo-HSCT) as post-remission therapy yields the best results in terms of survival benefit in elderly AML patients [13, 14].

Eligibility of elderly AML patients for allogeneic stem cell transplantation

The achievement of complete remission of AML is the prerequisite for successful allo-HSCT. Treatment options in the elderly include intensive chemotherapy, demethylating agents, low dose chemotherapy, and palliative care. The choice of treatment depends on age, performance and comorbidities. Both the Charleston Comorbidity Index (CCI) and Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) have been proved useful in predicting outcomes of chemotherapy in the elderly. They are frequently employed to determine the optimal treatment modality in individual patients [15–17]. Complete remission rates are higher in those who receive intensive treatment compared to patients treated with azacitidine, decytabine or decitabine. According to different studies, patients receiving more intensive therapy tend to be younger with lower CCI or HCT-CI [18, 19]. Retrospective analyses show that expected CR rates with intensive chemotherapy in those patients can reach 50–60% [20, 21].

The recently published results of a study combining decitabine or azacitidine with venetoclax as first line treatment in elderly AML patients show promising outcomes, with CR rates of 65% and treatment-related mortality of 8% [22]. Despite relatively high CR rates among older patients receiving remission-aimed treatment, real-life data shows that only a fraction of newly diagnosed patients ever even enter the allo-HSCT procedure. A single-center French analysis showed that less than 20% of older patients actually receive allo-HSCT [23]. A large Center for International Blood and Marrow Transplant Research registry-based analysis indicates that only 6% of those aged 60–75 are offered transplantation [24]. Most elderly patients are deemed ineligible for the procedure by their treating physicians, decide themselves against this treatment option, or lack a suitable donor even if they achieve complete remission.

Allogeneic stem cell transplantation in older AML patients

Pre-transplant considerations

European Society for Blood and Marrow Transplantation (EBMT) annual reports consistently show AML as the main indication for allo-HSCT. The fraction of patients aged 65+ receiving allo-HSCT rose from <1% in 2000 to 6.7% in 2014 [25]. It is predicted that the proportion of older patients will increase in coming years in spite of emerging novel treatments for AML. Accepting older patients for allo-HSCT requires a specific approach apart from routine pre-transplant assessments including AML remission status or HCT-CI. Careful evaluation of performance status, as well as modified EBMT and pretransplant assessment of mortality (PAM) scores, are recommended [26, 27]. Functional geriatric tests or patient-reported functional history should be evaluated by qualified personnel.

Standard evaluation elements may include gait speed, grip strength, 6-minute walk test, independence in everyday life, psychosocial or cognitive tests as well as nutritional status and pharmacological treatment requirements. The Geriatric Assessment in Hematology (GAH) scale may be useful to determine a patient's eligibility for transplant [28]. Several studies have proved that Karnofsky Performance Score <80% and higher HCT-CI negatively influence transplantation outcomes [29, 30]. Cognitive impairment in elderly patients must be considered as an independent risk factor for increased non-relapse mortality and decreased survival after allo-HSCT [31]. A multidisciplinary team geriatric assessment before allo-HSCT may optimize patient selection for transplantation, and mitigate post-transplant morbidity and mortality [32].

Remission status before allo-HSCT

One of the most important factors determining overall and disease-free survival in patients transplanted for AML is complete remission of the disease before allo-HSCT. Not only the presence of overt leukemia, but even detection of minimal residual disease (MRD) before transplantation, negatively impact prognosis in AML. Regardless of the method used for the detection of MRD, those patients who are MRD positive have a significantly increased risk of relapse post-transplant [33]. The probability of obtaining CR in elderly patients is lower even with intensive treatment.

Thus, if medically fit, older patients may proceed to transplant with a partial response only. In a German study, AML patients aged 60 to 77 who received allo-HSCT in 1st CR had 3-year OS probability of 49%. But even those with active disease at transplantation had 3-year OS probability of 30% [34]. Nevertheless, elderly patients with AML who are MRD negative before transplant fare significantly better. In a study including 185 patients aged 65+, there was a substantial difference in 2-year overall survival (OS) and incidence of relapse between MRD negative patients and those with detectable leukemia. The results for OS were 76% vs. 8% in MRD negative and positive patients [35].

Donors

Most allo-HSCTs in older AML patients are performed from unrelated donors. Even if patients have HLA-matched siblings, they usually are of a similar age and have chronic medical conditions which preclude stem cell donation. In patients older than 65, only 28% of donors are siblings [36]. Particularly in older AML patients, there is an additional issue of whether an unrelated younger donor would be better over an older but matched sibling. This issue was resolved by a retrospective study form the EBMT published a few years ago which included AML patients whose median age was over 61.

This study found similar outcomes in terms of relapse, non-relapse mortality, leukemia-free survival (LFS), and OS of transplants from younger unrelated and older sibling donors [37]. According to the National Marrow Donor Program, there is a 74% chance of finding a fully human leukocyte antigen (HLA) matched unrelated donor (MUD) for a recipient of Caucasian European descent. Patients of Middle Eastern, African or Native American descent have a decreasing likelihood of finding a complete match. For AML patients in need of an allogeneic transplant, there is a possibility of finding an alternative donor: unrelated donor with acceptable HLA mismatch (mMUD), haploidentical family donor (Haplo) or cord blood (CB). Results of a retrospective EBMT analysis indicate that transplants from mMUD yield worse results than transplants from MUD in AML patients [38]. In a recently published large study from Japan in 1,577 AML patients aged 60+, the probability of OS at 3 years after single unit CB transplant was 31% [39]. Haploidentical transplants have recently generated great interest as an attractive option for patients who lack an HLA compatible sibling or an unrelated donor. Indeed, earlier papers indicated comparable results in AML for transplants from Haplo, MUD and matched sibling donors. Yet an evaluation from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the EBMT revealed higher non-relapse mortality, and overall mortality, after transplants from haploidentical compared to matched related donors in acute leukemia patients aged 55 to 76 [40]. Analysis from the CIBMTR comparing the results of transplants from young (18–40) MUD and Haplo donors in AML patients aged 50–76, showed probability of 5-year OS after young MUD and Haplo transplants of 42% and 32%, respectively [41].

Conditioning

Commonly, older patients with AML receive reduced intensity conditioning (RIC) that is composed of lower doses of alkylating agents or irradiation frequently combined with a purine analog replacing classical cyclophosphamide for immunosuppression. This is aimed at reducing toxicity and ultimately non-relapse mortality (NRM) while preserving anti-leukemic and immunosuppressive effects. Some regimens are non-myeloablative (NMA), based entirely on the immunosuppressive effect to ensure engraftment of donor cells but allow autologous hematopoietic recovery without transplantation.

A large registry-based study by the EBMT compared outcomes of allo-HSCT from sibling donors in 1,423 AML patients aged 50+ after myeloablative conditioning (MAC) and RIC. In a long-term 10-year follow-up, probabilities of OS and LFS were comparable in patients older and younger than 55. Results were also comparable with regard to intensity of the conditioning. Ten-year LFS was 31% and 32% after MAC and RIC. An advantage was observed with RIC compared to MAC in patients older than 55 who had 28% vs. 20% LFS probability respectively. Ten-year OS was also comparable, with 33% and 35% after MAC and RIC [42]. This study, along with other papers, has demonstrated lower risks of treatment-related mortality and graft-versus-host disease (GvHD) in patients receiving allo-HSCT after RIC, although the relapse incidence (RI) was higher [43]. Even though elderly AML patients are nearly universally transplanted after various RIC regimens, there is little data from prospective investigations. One such study from the Cancer and Leukemia Group B included patients aged 60–74 who received RIC consisting of 6.4 mg/kg total dose busulfan, fludarabine with or without anti-thymocyte globulin. Two-year probabilities of LFS and OS in the entire group were 42% and 48% respectively [44]. Similar efficacy was reported with other RIC regimens combining melphalan at doses of 100 mg/m^2, 140 mg/m^2 or 180 mg/m^2 with fludarabine or cladribine. In patients with high-risk AML or MDS whose median age was 55, such conditioning was efficacious even in those who entered transplants without CR. Two-year OS was achieved in 40% and 23% of patients with active disease and circulating blasts, respectively [45].

In another study, 36 patients at median age 57 received similar conditioning while in CR. Long-term follow-up of the entire cohort revealed 71% and 68% probabilities of OS and LFS, respectively [46]. A meta-analysis of seven studies with a total of 1,861 patients compared RIC regimens combining fludarabine with either 6.4 mg/kg busulfan (BuFlu) or 140 mg/m^2 melphalan (FluMel). The results

in AML and MDS significantly favored FluMel over BuFlu in terms of OS [hazard ratio (HR) 0.83]. The risk of clinically significant acute GvHD was lower after BuFlu (HR 0.71) as was the risk of NRM, even though the difference was not statistically significant in AML patients (HR 0.86). The risk of chronic GvHD was similar after the two regimens [47]. Among alkylating agents, treosulfan is recognized as myeloablative with a favorable toxicity profile, hence its use for reduced intensity conditioning in older patients. A meta-analysis determined long-term outcomes of busulfan vs. treosulfan based conditioning in AML and MDS patients. No significant differences were found for relapse, NRM, LFS and chronic GvHD. Treosulfan conditioning resulted in significantly decreased incidence of acute GvHD (HR 0.7) and improved OS (HR 0.8) [48]. Strictly non-myeloablative conditioning is frequently based on low-dose 2 gray total body irradiation combined with fludarabine (FluTBI). This modality was retrospectively compared to RIC BuFlu regimen in 1,088 AML patients in first CR aged 60+ reported to the EBMT. The results in this large group of elderly patients were nearly identical in terms of OS, LFS, NRM and risk of relapse. Patients who received FluTBI had a significantly higher risk of developing chronic GvHD, particularly when transplanted from unrelated donors [49].

Transplant versus non-transplant approach

The decision as to whether to refer a patient to allo-HSCT is based on meticulous assessment of the risk and benefit ratio. ELN guidelines recommend transplantation in high-risk AML patients or whenever the risk of relapse estimated on factors present at diagnosis exceeds 30% or 40% [50]. Additionally, in those who never achieve CR on treatment, or who have detectable MRD, allo-HSCT is the only potentially curative option, providing that patients are fit enough to withstand the procedure.

There is no doubt that fit elderly patients with AML who respond to therapy should be considered as potential candidates for allo-HSCT. Several retrospective studies have compared outcomes of allo-HSCT with chemotherapy as post-remission treatment. A registry-based study from the CIBMTR compared allo-HSCT in 190 patients aged 60 to 70 to those who received chemotherapy only. At 3 years, LFS was significantly improved in the transplant group (32% vs. 15%), and less relapse was noted (32% vs. 81%), at a cost of increased NRM (36% vs. 4%) with a trend towards increased OS (37% vs. 27%) [51]. A similar single center study from Japan compared 152 patients older than 50 (range 50–70) who received allo-HSCT to 880 patients in the same age range who received chemotherapy. Again, at 3 years RI was lower after transplantation (22% vs. 62%) with higher TRM (21% vs. 3%) but with statistically better both LFS (56% vs. 29%) and OS (62% vs. 51%) [52]. A multicenter Dutch-Belgian-Swiss study consortium (HOVON-SAKK) conducted a prospective trial in 640 AML patients aged 60+ who achieved remission after induction treatment. Ninety-seven patients proceeded to allo-HSCT with RIC. A time-dependent analysis was performed in which transplantation was compared to other post-remission treatment modalities. The results showed that patients after allo-HSCT had significantly higher probability of OS at five years than those after chemotherapy (35% vs. 26%), especially in intermediate and adverse risk groups [53]. A nationwide study from Denmark studied 1,031 AML patients who achieved CR with chemotherapy. Of those, 196 received allo-HSCT in first remission. Allo-HSCT was studied as a time-dependent co-variate and was associated with significantly superior OS compared to chemotherapy in cytogenetically intermediate- and high-risk patients. The positive effect of allo-HSCT was especially pronounced in patients aged 60+ (HR 0.42) [54].

Finally, a recent single-center study from the Netherlands confirmed survival benefit with allo-HSCT in elderly patients. Three-hundred and fifty-five individuals aged 60+ were included in the analysis. Of those, 68 proceeded to transplantation. Median OS for transplanted patients was 68 months compared to eight months for those who did not proceed. In patients who achieved CR with either intensive chemotherapy or demethylating agents, median OS after allo-HSCT was not reached vs. 25 months in those CR patients who were not consolidated with transplant. Of interest, the type of therapy that led to CR had no influence on survival post-allo-HSCT [55].

Maintenance therapy

Relapse of the original disease remains the major cause of allo-HSCT failure. The greatest risk for disease recurrence is observed in the first year after transplantation. Much interest is currently paid to possible prophylactic therapy in patients after transplant who have a significant risk of relapse. The idea of effective maintenance is particularly appealing after reduced intensity conditioning and in elderly patients. Today, only two therapies in acute leukemia after allo-HSCT are nearly universally recognized. One is dasatinib in BCR-ABL-positive acute lymphoblastic leukemia, and the other is multi kinase inhibitor sorafenib in FLT3-ITD-positive AML [56, 57]. No other tested maintenance therapy has yet emerged as standard. Initial interest focused on the hypomethylating agents azacitidine and decitabine. Small studies indicated a possibly beneficial effect of such maintenance, but a large randomized phase III trial showed contradictory results [58, 59]. Recently, the outcomes of a prospective trial with azacitidine administered as MRD guided preemptive treatment were published. In patients aged 52–69 who became MRD positive after allo-HSCT, azacitidine therapy resulted in 46% relapse-free survival at 12 months [60]. In a small phase I/II trial with oral azacitidine in high-risk AML or MDS patients, RI at 12 months was 21% with acceptable toxicity of maintenance

[61]. Apart from sorafenib, other FLT3 inhibitors are under investigation in clinical trials. In a phase III randomized trial, midostaurin provided 89% RFS at 18 months vs. 76% in non-maintenance FLT3-ITD+ patients (p =0.27) [62]. Also, a gilteritinib vs. placebo trial in FLT3-ITD+ patients is underway, although accrual is slow due to common usage of sorafenib for maintenance [63].

Of other drugs, venetoclax alone or in combination with azacitidine has been evaluated in high-risk AML and MDS patients. Preliminary results of a small single center study in elderly patients with median age 65 indicate an 87% probability of 6-month survival after allo-HSCT on venetoclax maintenance [64]. Early phase clinical trials with other targeted compounds such as isocitrate dehydrogenase, histone deacetylase and hedgehog inhibitors are being conducted, but so far very little information on their progress or results is available.

Summary and conclusions

Allogeneic stem cell transplantation in elderly AML patients has become the standard of care with improving outcomes over the years. To take full advantage of the curative potential of the procedure, careful individual estimation of the risk-benefit ratio is necessary.

Apart from routine pre-transplant evaluation, elderly patients require a specific geriatric assessment to avoid excessive non-relapse mortality. Treatment in transplant candidates should aim at achieving complete remission to maximize survival probability, but in some patients with a partial response survival benefit with allo-HSCT can be achieved. In most cases, patients aged 55+ will benefit from reduced intensity or reduced toxicity conditioning before transplantation, although in carefully selected patients a standard myeloablative conditioning may be considered. The best donors for elderly patients are either siblings or well-matched unrelated donors, because transplantation from alternative donors yields significantly inferior results.

Various post-transplant maintenance modalities are under investigation, and at present one of them, namely sorafenib, has become the standard of care for FLT3-ITD+ AML. There is growing evidence that allogeneic transplantations are feasible in older patients, with improving results over the last decade. Several studies confirm that in elderly patients, allo-HSCT as post-remission treatment prolongs survival compared to standard therapy. However, we must keep in mind that most of these studies are retrospective with a selection bias and that the majority of newly diagnosed elderly AML patients are still, at best, being offered palliative treatment.

Author's contributions

KH — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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