blood advances

COUNTERPOINT Not all patients with AML over 60 years of age should be offered early allogeneic stem cell transplantation

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Introduction

The median age at diagnosis of acute myeloid leukemia (AML) is 68 years, and the prognosis worsens with increasing age. For many patients, allogeneic hematopoietic cell transplantation (HCT) is the only chance for cure, and HCT has been used with increasing frequency. For patients age 60 to 69 years and those age 70 years or older, data from the Center for International Blood and Marrow Transplant Research show 150 and 13 transplantations, respectively, for 1995 to 2000, and 3927 and 773 transplantations for 2011 to 2015.[1] There has been considerable progress in reducing toxicity and preventing graft-versus-host disease (GVHD),[2] but relapse after HCT has remained a major challenge.

The central questions regarding HCT for all age groups are: Is HCT indicated and when should it be performed? Should HCT be performed as consolidation therapy in the first complete remission (CR1) or as salvage therapy after relapse?[3] In older patients, other important questions pertain to medical comorbidities and fitness.[4,5] Older patients have a reduced tolerance for high-intensity (myeloablative) conditioning regimens, and reduced intensity conditioning (RIC) or non-myeloablative regimens are associated with an increased risk of relapse.[6]

Guidelines have been provided by the European LeukemiaNet (ELN) and by the National Comprehensive Cancer Network (NCCN) AML panel.[7] Widely accepted current recommendations are to provide transplantation for patients in the adverse-risk category and also for many patients in the intermediate-risk category (based on cytogenetics and a limited panel of mutations by ELN) while they are in CR1 after induction chemotherapy.[8,9] HCT is not recommended as standard consolidation for patients with favorable risk.[5] However, in view of expanding therapeutic options, a recent expert Commentary has proposed a more dynamic model.[10] This model proposes to define risk groups on the basis of expected 3-year overall survival (OS), taking molecular data and measurable residual disease (MRD) into consideration,[11-13] and to include patient-related factors such as age, which is a most relevant issue since recommendations by ELN and NCCN cannot easily be extrapolated to patients age 60 years old or older.

Novel non-transplant therapeutics

As indicated in the Commentary by Short et al,[14] highly effective chemotherapy regimens with good tolerability in older patients have become available over the past few years. In fact, a venetoclax-based regimen, generally in combination with a hypomethylating agent, is becoming the preferred first-line regimen for older patients with AML.[15] Of note, at least in 1 analysis,[16] treatment with venetoclax plus a hypomethylating agent rather than ELN risk classification predicted OS. The addition of an *FLT3* inhibitor to induction therapy has improved relapse-free survival,[17] with OS in some studies of >50%.[18,19] The lipid-encapsulated combination of daunorubicin and cytarabine (Vyxeos) has shown excellent tolerability in older individuals, and patients induced with this drug who then receive a transplant tend to experience superior survival after HCT,[20] possibly suggesting a deeper remission. This is an important aspect to consider when discussing MRD and its impact on relapse.

Transplantation

In parallel to the development of these new non-transplant treatment regimens, recommendations for HCT have evolved regarding donor selection, source of stem cells, conditioning regimens, and impact of disease pathophysiology which, of course, will also be incorporated into modified disease risk classification schemes. In principle, these considerations are relevant for patients of any age. However, the intensity of HCT conditioning is a major concern in older patients and is relevant in overcoming the disease burden and MRD. With the expansion of donor options, suitable donors can be identified for >90% of patients. Recent data suggest that success of HCT that uses an HLA-matched unrelated donor may be

superior to haploidentical transplants.[21] This seems to be true for older patients, but the issue requires further study.

Impact of cytogenetics

Cytogenetics has a significant impact on treatment outcome,[9] and the prevalence of high-risk cytogenetics increases with age.[22] Patients with t(8;21), inv(16), or t(16;16) (core-binding factor leukemias) are considered favorable risk, which does not require HCT in CR1. In 1 study, among 630 patients who received a transplant in their second CR (CR2) from 2000 to 2014, 5-year OS was 55% to 60%.[23] The incidence of relapse was 22.5% and nonrelapse mortality (NRM) was 23.3%. Adverse factors that had an impact on survival were ≥3 additional chromosomal abnormalities and a Karnofsky score <80. Survival was inferior among patients with t(8;21) who also had a *KIT* mutation. These patients should presumably receive their transplant while they are in CR1, although for older patients, the risks of HCT in CR1 may outweigh the benefit. Decisions should be made on an individual basis.

Fit patients with high-risk cytogenetics (ELN adverse risk), including t(6;9), t(v;11q23), t(9;22), inv(3), t(3;3), −5, del(5q), −7, −17, and complex karyotype, should probably undergo HCT in CR1. Yet, older patients with high HCT Comorbidity Index (HCT-CI)[24] scores would be conditioned with RIC regimens which, in turn, are associated with a higher probability of relapse, particularly if MRD is present.[25,26] Therefore, it might be preferable to treat those patients by using novel investigational protocols, for example, using cellular therapy modalities that are under development,[27-29] or new chemotherapy regimens[30] such as venetoclax plus hypomethylating agents rather than proceeding to HCT using current transplant strategies. In fact, Del Galy et al[31] observed comparable 2- and 3-year OS with HCT and non-HCT therapy among 174 consecutive patients age 60 to 74 years. There are additional data to support view.[32,33]

Other karyotypes will place patients into the intermediate-risk category. An analysis by Burnett et al[32] involved a cohort of 3919 patients, and the results suggested that for patients in the ELN intermediate-risk group who had not received a transplant in CR1, survival was similar to that for patients who received a transplant in CR1. They arrived at this result by combining data for patients who survived and were in a chemotherapy-induced remission and those who relapsed and underwent successful HCT in CR2. These were young patients, but older patients may not tolerate re-induction well. The availability of novel regimens (as outlined above) may render this strategy of re-induction after relapse and HCT in CR2 more attractive. Thus, despite the retrospective nature of those data, older patients with intermediate risk, particularly if comorbidities are present, might have the best outcome with HCT delayed until CR2.

The role of mutations

A recent review summarized the prognostic impact of mutations,[34] and Burd et al[35] tested the usefulness of prospective genomic profiling for therapeutic decisions in the Beat AML Master Trial. The bulk of published data focuses on *FLT3* and *NPM1* mutations. Patients with isolated *NPM1* mutation given chemotherapy and achieving a 4log or greater reduction have a low incidence of relapse.[13] However, if the mutation persists after 2 cycles of intensive therapy, the disease course resembles that of poor-risk patients with a relapse incidence of 82% in 1 study.[36,37] Therefore, while acknowledging the absence of consensus, those patients should undergo HCT[38] in morphologic CR1. *FLT3* mutations, specifically membrane-proximal internal tandem duplication (*FLT*-ITD), which are present in about 25% of patients with AML, are associated with treatment refractoriness, although survival is improved with FLT1 inhibitors.[17] The concurrent presence of *NPM1* mutations is favorable and is possibly dependent upon the allelic ratio of *FLT3*. For patients with an *FLT3:NPM1* ratio of <0.5 and mutated *NPM1*, survival was comparable to that for patients in other ELN intermediate-risk subgroups.[39] Although the idea is not without controversy, in patients with wild-type *FLT3* or low allelic ratios, HCT can be reserved for those who relapse, except possibly those with mutated *DNMT3A* in addition to *FLT3* and *NPM1*.[38] With higher *FLT3* ratios, however, HCT seems to offer an advantage over non-HCT consolidation, with relapse risks of 20% vs 80%, and 5-year OS of 70% vs 22%, respectively. But there may not be a critical cutoff.[40,41] In 1 study of 151 patients age 60 years or older, *NPM1* and *FLT3*-ITD mutations (present in 18%) did not have a significant impact on OS,[42,43] and if venetoclax-based regimens overcome the impact of those mutations in older patients,[16,44] this would support the recommendation to not provide a transplant to those patients in CR1. Conversely, the impact of *IDH* mutations may be different: in 1 study among 13 patients with mutated *IDH1*, 10 died early and 2 were refractory.[45] Thus, HCT would likely be futile, particularly in older patients. Further work with IDH inhibitors such as olutasidenib[46] may modify this recommendation.

Some 10% to 20% of patients with AML present with mutations in CCAAT/enhancer-binding protein α (*CEBPA*).[47] Patients with monoallelic mutations, often accompanied by mutations in *FLT3*, *NPM1*, and *IDH2*, should be referred for HCT. Biallelic mutations, often with concurrent mutations in *TET2* or *GATA2*, carry a superior prognosis with induction chemotherapy, independent of the type of consolidation, including HCT. For older patients with such a presentation, HCT should be reserved for salvage treatment.

TP53 mutations, present in <10% of de novo AML and 20% to 30% of secondary or treatment-related AML, indicate high-risk disease.[48] In 70% of patients, *TP53* mutations are associated with complex cytogenetics.[41,49] Mutation frequency increases with age and is particularly prominent in patients with chromosome 5, 7, or 17 abnormalities.[34] The rate of chemotherapy-induced CR has been 25% to 30%, and median OS is about 6 months. In 1 study, 35% of patients survived beyond 1 after HCT.[41] In fact, data on 83 patients age 18 to 75 years (38% older than age 60 years) with *TP53* mutations, the presence of a low HCT-CI score, good performance score, and achievement of CR1 or CR2, showed a 1-year OS of 67%.[41] Of course, these qualifying parameters considerably narrow the pool of patients likely to benefit from HCT. Overall data would cause a physician to question the advisability of HCT for older patients with *TP53*-mutated AML and of conditioning those patients with RIC regimens because of the high incidence of relapse.[6] In addition, considering transplant-related complications, proceeding to HCT may not be the optimal choice for older patients with *TP53* mutations.

In fact, any mutation (other than possibly *DNMT3A*, *TET2*, or *ASXL1*[11]) persisting during morphologic CR (ie, representing MRD) has been associated with a 4-year incidence of relapse ≥50%.[11] Clearly, current HCT strategies are not satisfactory, and novel non-HCT strategies are preferable.

And back to age

AML biology changes with age[22,42,50] and so do patients. High-risk cytogenetics, myelodysplastic features, antecedent hematologic

disorders, and high mutation burden are more frequent. As the frequency of comorbidities increases (which affects survival even in patients who have not received HCT[33,51]), biological reserve declines,[52] and socioeconomic support is often tenuous. Nevertheless, a prospective phase 2 trial showed that HCT using RIC is well tolerated in selected patients age 60 years or older,[53] and data from 1 prospective study in patients age 60 years or older who were randomly assigned according to such terms as donor availability indicate superior survival with HCT.[54] However, non-transplant therapy in that era did not use modern modalities, which show markedly improved results without HCT. With high HCT-CI scores and Instrumental Activities of Daily Living scores showing impairment in 1 analysis, survival approached zero within 2 years after HCT.[55] High HCT-IC scores are also associated with an increased incidence of severe GVHD[24,56] and NRM.[57] Glucocorticoids, still the mainstay of therapy for GVHD, are poorly tolerated by older individuals. Finally, RIC regimens (as are used for most older patients) are associated with increased risk of relapse, particularly in the presence of MRD.[13,26] Thus, in older patients, more so than in younger patients, it is the combination of disease and patient characteristics and the non-HCT therapies that are now available[14] that determines the advisability and outcome of HCT.

Conclusions

All studies in older patient cohorts have involved highly selected patients who were considered eligible, and thus the results cannot be generalized.[24] Although the basic principles for recommending HCT in younger patients are also of value in older patients, disease characteristics differ, and patient characteristics as well as modified HCT strategies amplify the impact of disease parameters on relapse, morbidity, and NRM. In particular, the presence of MRD, high-risk cytogenetics, and certain mutational patterns should give pause for consideration in the discussion of HCT. Older patients should have an HCT consultation, but not all older patients with AML need to be referred for early HCT. Recommendations are typically based on statistics, but statistics disregard the needs of individual patients, which leads to considerable uncertainty.[58] And because different physicians have different degrees of uncertainty, this has an impact on the recommendations they offer. Best management, at times, means to not offer HCT while considering the patient's preference.

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