Is allogeneic transplantation the preferred therapy for older patients with acute myeloid leukemia?

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The treatment of acute myeloid leukemia (AML) has seen tremendous developments over the last few years, but treatment approaches and results are predominantly determined by selection based on age, karyotype, and molecular genotype. Treatment recommendations mainly follow the European LeukemiaNet (ELN) guidelines (1), especially the use of allogeneic hemopoietic stem cell transplantation (HSCT) as postremission consolidation therapy for adverse risk disease. However, these recommendations are category 2A only with low-level evidence but uniform panel consensus, since results from randomized clinical trials (RCT) are lacking (2). The deficits with the system, in addition, include a bias in that the data set for its establishment almost exclusively consists of treatment results in younger fit patients with de novo AML who were treated with intensive induction chemotherapy followed by high-dose cytosine-arabinoside or HSCT. Recommendations for postremission therapy in elderly AML patients have not explicitly addressed HSCT but point to the high degree of selection even with reduced intensity conditioning (RIC) (3).

Russell et al now present a considerable set of data on the outcome of older AML patients aged 60 to 70 years treated intensively within the NRCI AML 16 study with various induction regimens followed by RIC transplantation in case of non-favourable cytogenetics and the presence of a fully matched related or unrelated (at least 9/10 HLA-match) donor (4). Out of 932 patients treated between 2006 and 2012, 788 continued on some sort of chemotherapy, while 144 underwent HSCT (sibling n=52; MUD n=92). In transplanted patients survival was 37% at 5 years versus 20% in the chemotherapy arm (p<0.001). There was no significant difference in survival between sibling and MUD HSCT. Using the Wheatley risk group definition (5), all three risk groups benefitted from HSCT. Although the mutation status was not known in the majority of the patients, the benefit was also seen in patients with an FLT3-ITD and/or NPM1 mutation with no difference in genotypic subgroups. Thus, Russell et al conclude that “RIC transplant is an attractive option for older AML patients lacking favorable risk cytogenetics” (4).

Although the data are encouraging they do not fully solve the current problems in the elderly AML patient population with regard to the appropriate postremission therapy. In the NRCI AML 16 trial the patients had to be fit for intensive induction chemotherapy which only applies to the minority of the patients. The recent developments with new effective drugs and combination therapies are not yet addressed. These include, for example, the use of additional FLT3 inhibitors (6) or CPX-351 (7) in the fit patients who can be treated intensively, or combinations of hypomethylating agents plus venetoclax which now have become standard of care in the less fit AML patients. The latter combination is especially effective in AML with NPM1 and IDH1 mutations (8). These developments especially in the unfit population might even lead to a more dynamic approach, since patients unfit at the time of AML diagnosis might become fit for RIC HSCT once they have entered complete remission with restoration of normal hemopoietic function (9). The NCRI AML 16 data support the now common practice to offer RIC HSCT as postremission therapy to these patients. However, it would be
preferable to design RCTs to demonstrate the advantage of this approach compared to other postremission therapies including maintenance therapy, e.g. with oral azacitidine (10). The development of novel drugs will certainly lead to new risk stratification in AML and treatment recommendations which include HSCT also in older AML patients (11). Not only HSCT has undergone rapid progress, but the whole therapeutic landscape is in flux and it would be preferable to have data from RCT for informed decisions in patient care.

References


