review

Use of molecular markers to determine postremission treatment in acute myeloid leukemia with normal cytogenetics

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Most patients with acute myeloid leukemia can be induced into complete remission, but postremission treatment is required for cure. The choice of postremission therapy in a majority of nonelderly patients, between intensive chemotherapy and allogeneic hematopoietic cell transplantation, is largely determined by the results of conventional cytogenetic analysis. In 45% of patients with a normal karyotype, the presence or absence of specific molecular mutations should be used to determine the prognosis and postremission treatment. In addition, the identification of mutations may indicate a role for targeted intervention, including following transplantation.

KEYWORDS: Molecular markers; Acute myeloid leukemia; Cytogenetics

Acute myeloid leukemia (AML) is a disease of older adults; however, half of patients with AML are ⩽65 years of age at presentation.[1] The incidence of AML has increased to nearly 20,000 new cases per year, in a large part due to more patients surviving longer periods following chemotherapy and radiation treatment for other malignancies, and longer survival in general.[2] Older and treatment-exposed patients are at higher risk than the general population. While patients with AML fare poorly overall (<20% leukemia-free survival [LFS] at 5 years), nonelderly patients (<65 years of age) have better outcomes than their older counterparts, and most have a substantial chance for cure. Cytogenetic analysis is used to risk stratify patients, and is the most important factor in determining postremission treatment. The identification of specific molecular mutations is important in patients with normal cytogenetics for their appropriate risk categorization and for help in determining the postremission treatment. In addition to improvements in treatment and supportive care, which have significantly lowered the treatment-related mortality (TRM) with chemotherapy[3] and with allogeneic hematopoietic cell transplantation (allo-HCT),[4] these advances in risk stratification and in the development of evidence-based guidelines for choice of postremission treatment are responsible for improving outcomes.

TREATMENT OF AML

Induction

The modern treatment of AML in the nonelderly includes induction therapy, which achieves complete remission (CR) in >70% of patients, followed by postremission therapy designed to cure the patient. For most patients ⩽65 years of age and many healthy patients older than 65 years, the standard aggressive induction therapy in North America consists of 7 + 3, shorthand for 7 days of cytarabine and 3 days of an anthracycline. Some centers add etoposide or other drugs to this regimen, although prospective

studies have not demonstrated long-term benefits over 7 + 3. Recent trials have demonstrated improved outcomes with more intensive anthracycline dosing.[5,6]

POSTREMISSION THERAPY

The two main choices for postremission therapy in those patients who achieve CR following induction therapy are intensive chemotherapy, usually with three to four cycles of high-dose cytarabine (HiDAC), and allo-HCT. Patients who achieve CR with induction therapy, but who do not receive postremission therapy, are almost never cured because they retain leukemic stem cells that are not detectable by standard measures. In many instances, the use of sophisticated techniques (e.g., multiparametric flow cytometry[7] or next-generation sequencing[8,9]) may identify residual disease in patients in CR.

Autologous transplantation was performed frequently in AML as recently as a decade ago. Favorable outcomes have been reported with this approach, particularly in young patients with favorable-risk AML.[10,11] A meta-analysis has demonstrated no prolongation of survival after autologous transplantation compared to standard chemotherapy.[12] Thus, intensive chemotherapy and allo-HCT are the main alternatives for postremission treatment.

HiDAC requires brief hospitalizations with regular outpatient follow-up, and is safer and less expensive than allo-HCT. It is curative in selected patients. Allo-HCT is the other commonly employed postremission therapy and exerts a more powerful antileukemic effect, first through its use of myeloablative chemotherapy or combined chemo- and radiation therapy, at doses which could not be tolerated without hematologic rescue by donor hematopoietic cells, as well as the potent antileukemia effect of the donor immune cells, termed the *graft-versus-leukemia effect*. Originally reported by Thomas et al.[13] to cure some patients with advanced acute leukemia, this approach is now more commonly and effectively used in patients in first CR.[14,15] Allo-HCT often requires hospitalization in excess of 4 weeks, followed by close outpatient monitoring. Compared to intensive chemotherapy, this approach is much more expensive. Allo-HCT is associated with significantly higher rates of nonrelapse mortality (NRM), and may be complicated by chronic graft-versus-host disease, which compromises the quality of life of some long-term survivors. It should be noted, however, that NRM following allo-HCT has been substantially diminished over the past two decades.[4] Whereas 1-year mortality rates with allo-HCT of ~30% were commonly cited a decade ago, a recent Center for International Bone Marrow Transplant Registry study of well over a thousand patients with AML in first CR performed at >100 international centers demonstrated a 1-year mortality rate of 12% using what is now the most widely administered pretransplant conditioning regimen, intravenous busulfan and cyclophosphamide.[15] The dose adjustment of busulfan, based on plasma levels following the first dose, could further improve NRM by avoiding the variation in plasma levels among different individuals. The optimal plasma levels of busulfan in specific situations are uncertain; it is likely that these may vary by disease, stage, comorbidities, and other factors, and require further investigation.

Further, the potential application of allo-HCT to virtually all patients ⩽65 years (and many older than that) using alternative donors has had a substantial impact. Only 30% of patients have human leukocyte antigen (HLA)-identical sibling donors. Matched unrelated adult donors, cord blood, and haploidentical family donors (using post-transplant cyclophosphamide to prevent graft-vs.-host disease) have all yielded results approaching those achieved in patients with fully matched sibling donors.[16]

In addition to the use of alternative donors, the application of allo-HCT has been enhanced by the development of reduced-intensity regimens with less toxicity than myeloablative conditioning. These regimens have extended transplantation to older patients and to those with significant comorbidities. The consensus criteria to define regimen intensity have been reported.[17] A regimen of fludarabine and low-dose total body irradiation has minimal toxicity, permits the engraftment of cells from HLA-identical sibling donors, and relies on the graft-versus-leukemia effect.[18] Additional donor lymphocytes can be infused within a few months of transplantation to augment the antitumor activity. More powerful (compared to fludarabine/low-dose total body irradiation) reduced-intensity regimens with less toxicity than myeloablative therapy have been developed, including widely used regimens with less than ablative doses of busulfan in combination with fludarabine.[19,20] These regimens result in lower NRM and less toxicity than myeloablative regimens, but are associated with higher relapse rates. Generally, survival has not been shown to be significantly different from that achieved with myeloablative regimens; however, a myeloablative busulfan/fludarabine regimen was associated with better LFS and overall survival compared to a reduced-intensity regimen using the same drugs in an analysis of patients allografted in second CR by the European