Acute Myeloid Leukemia in the Elderly: A Unique Disease

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Acute myeloid leukemia (AML) is a disease of the elderly, with the majority of patients diagnosed in their 6th and 7th decade of life. Older patients with AML are less likely to achieve complete remission after induction chemotherapy, and they suffer from higher rates of leukemia relapse compared to younger cohorts. Suboptimal outcomes are the result of adverse biologic characteristics of leukemia in the elderly, as well as the presence of medical comorbidities and patient or physician preferences as to initiating treatment. In addition, there is a distinct lack of randomized, prospective data to guide management decisions for the treatment of AML in the elderly. Patients who are over age 75, with poor performance status, multiple comorbidities, or poor prognostic features, should be considered for a clinical trial or palliative therapy. Elderly patients who are candidates for standard induction chemotherapy and achieve complete remission are unlikely to benefit from intensive postremission therapy and should be referred to a clinical trial when possible. Further prospective trials are needed to identify a tolerable, effective treatment regimen for older patients with AML.

In this well written and comprehensive article, Dr. Melchert covers the relevant characteristics of acute myelogenous leukemia (AML) in the elderly and describes the difficulties facing physicians and patients in regard to the best therapeutic approach to this disease in older adults.

AML in the elderly is a unique disease because of intrinsic characteristics such as a higher proportion of patients with unfavorable karyotypes, a higher incidence of antecedent hematologic disorders and secondary AML, and also because blasts of older patients are more often resistant to chemotherapy through the expression of a multidrug resistant phenotype. The host also presents a unique situation. Elderly patients often have comorbidities—the median number of relevant comorbidities in patients older than 65 is four—and compromised renal function. Therefore, the tolerance to chemotherapy and the ability to metabolize individual agents differ from what we find in a younger population.

Assessment and Treatment Initiation

The approach to an older adult with AML should start with a comprehensive geriatric assessment. Unfortunately, this is not possible in daily clinical practice because of the lack of sufficient time and resources as well as the urgency of initiating medical management for this severe condition. The development of simple, rapid, and reliable screening tools is therefore a field of current investigation. For example, in our retrospective experience of 177 patients with AML who received induction chemotherapy with idarubicin and cytarabine, patients with a hematopoietic stem cell-specific comorbidity index equal to or higher than 3 had a high early death rate (29%).[1] Once the patient has been considered suitable for induction therapy, the treatment decision should be guided by disease characteristics. A large proportion—up to 35% of patients—carry a poor-risk karyotype. Patients with AML carrying such cytogenetic features have been reported to be resistant to treatment with standard chemotherapeutic agents such as cytarabine. Therefore, this group should be offered an investigational program. Occasionally, fit and younger patients with an intermediate-risk karyotype and the rare patient with a favorable cytogenetic profile may benefit from standard induction with a combination of anthracyclines and cytarabine. Nevertheless, in these patients, particular attention must be paid to optimizing support with the use of growth factors and laminar flow rooms, and a shorter intensification program will need to be included in the treatment plan.

New Treatment Options

Treatment options for older adults with AML are evolving. Novel strategies are being explored thanks to a closer collaboration between oncologists and geriatricians, to the development of novel agents, and to an increasing emphasis on quality of life. Targeted therapies such as farnesyl transferase inhibitors and monoclonal antibodies (such as gemtuzumab [Mylotarg]) are offered to elderly
patients with AML by several facilities such as M. D. Anderson Cancer Center, and by many cooperative groups. These agents are being investigated both as monotherapy and in combination with "classic" chemotherapy. Novel chemotherapy agents, such as the modified alkylator cloretazine and the purine analog clofarabine (Clolar), have shown promising results in phase II studies. In a study of cloretazine used as a single agent in 104 patients over age 60 with AML or high-risk myelodysplastic syndrome (of which 39% had a borderline performance status), the drug produced a complete response rate of 32% with an early mortality of 17%. Induction therapy with clofarabine in combination with low-dose cytarabine in patients older than 60 years has shown an encouraging overall response rate of 60% and median remission duration of 9 months. Other agents such as methyltransferase inhibitors and histone deacetylase inhibitors are also undergoing clinical evaluation in this setting. Similarly to what has been seen in solid tumors, the endpoints of treatment for AML in older adults are changing; control of the disease, reduced dependency on blood support, and prolonged survival are becoming as relevant for this population as the attainment of a complete remission.

Conclusions

I strongly agree with Dr. Melchert's conclusion that progress in this field can only be achieved through clinical trials. In the years to come, a better understanding of disease biology, combined with thorough assessment of the patient and integrated with the results of ongoing clinical programs, will translate into an improved outcome for older patients with AML.

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References:


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