

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Advances in the Management of AML in the Elderly

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H&O What is the age demographic for acute myeloid leukemia?

EE It is difficult to compute the exact age demographic because there is a greater tendency to not report older patients compared with younger patients. However, the median age of acute myeloid leukemia (AML) patients is thought to be approximately 65 years, with a third of patients over 70 years old. AML is certainly a disease associated with aging.

It may be that the incidence stops increasing at a certain age, say 80 or 90 years. In addition, there are two types of AML and these correlate with age differently. AML characterized by chromosomal translocation appears to be constant with age and is associated with a better prognosis. The second type of AML, characterized by more complex chromosomal abnormalities, appears to increase with age and is associated with a relatively poorer prognosis.

H&O What is the biologic connection between AML and aging?

EE Though there is no definitive answer to this question yet, one common theory is that the development of AML is related to the accumulation of toxicity in a susceptible host. The chromosomal abnormalities seen in older patients with AML who have not been exposed to chemotherapy are the same as those seen in people who have received chemotherapy for breast cancer or lymphoma. In contrast, younger patients have different chromosomal

abnormalities. These observations suggest that cumulative exposure to chemotherapy-like toxins found in the environment leads to AML in older patients. One problem with this theory is that if it were true, the incidence of AML should be higher in the industrialized world, and it is not clear that this is so.

H&O What have been the principal challenges in treating AML in elderly patients?

EE There are two causes of death among patients with AML: the treatment or the treatment's lack of efficacy. It can be difficult to distinguish between these two causes. If a patient dies on the fourth day of treatment, then it can be clearly concluded that the death was treatment-related, as a response could not be expected by day 4. But if a patient dies of an infection on day 64, for example, this death may be due to the treatment, or it may not. As many patients are in remission by day 64, the death can be attributed as much to failure of the chemotherapy to produce a remission as to the treatment's toxic events, given that there is a strong correlation between achievement of remission and resolution of infection. Indeed essentially all patients who survive more than 2–3 years after a diagnosis of AML achieve remission, indicating that remission and survival are inextricably linked. The main challenge associated with treating older AML patients is that the majority of deaths are due to resistance to treatment (ie, the treatment does not produce a sustained remission) rather than directly due to treatment. Thus, even if less toxic treatments are developed, the mortality rate as measured at 1–3 years may not decrease if the less toxic treatments are not more effective than current treatments. The occurrence of resistance reflects a lack of effective therapies.

H&O What new agents are being developed for the treatment of AML?

EE There has been recent interest in clofarabine (Clofar, Genzyme) and clometazine (VNP40101M, Vion). It

appears that patients who receive these agents experience disease remission. However, the underlying question that remains to be answered is: what is the best therapy? There may be a 20–30% remission rate with a new agent, but how does this compare to standard therapy? The important issue for patients is not only whether a new drug is active, but also, and more importantly, how does it compare to other treatments. The current studies are not designed to address this issue. The fact that there are many active drugs for AML is encouraging, but we do not yet know which is associated with the greatest efficacy.

H&O What is the best way to proceed treating patients until these questions are answered?

EE There are two alternatives: standard treatment and investigational treatment, ie, a clinical trial. I believe that patients intuitively prefer standard treatment given that there is much more experience with it. However, this preference is conditioned on the effectiveness of the standard therapy. As suggested above, standard therapy for older patients with AML is generally highly ineffective. It is possible that investigational therapy could be worse than standard; the ethical basis for randomized trials comparing standard and investigational therapies rests on this assumption. However for the average older patient with AML, results with standard therapies are so poor that many patients, when apprised of these results, prefer investigational therapy. I certainly subscribe to this view and thus believe most older patients with AML should be placed in clinical trials. We may not know which investigational therapy is best, but we do know that standard treatments are poor. However, in view of the intuitive preference for standard therapy already noted, it is important to ask whether there are any characteristics that might make standard therapy a good choice. For example, an otherwise healthy 64-year-old patient with de novo AML and normal chromosomes may have a 20% chance of long-term survival with standard therapy and a 60% chance of remission. Some patients fearing that investigational therapy could be worse would choose standard therapy. Others would focus on the 80% chance of death with the standard therapy and choose the investigational therapy. Though this decision is more cultural than medical, it is incumbent on the physician to inform the patient of the likely outcome with standard therapy. In probably 80% of cases, the outcome with standard therapy is so poor (eg, chance of cure <10%) that the investigational option seems the only reasonable one.

In general, it is important to remember that age is not the only parameter to consider when presenting treatment options to a patient. All patients are not the same,

and other variables may have an important impact on treatment outcomes.

H&O Is it difficult to enroll older patients in clinical trials?

EE Yes, sometimes. Many clinical trials exclude patients with poor performance status; thus, a patient who is not ambulatory, for example, may not be able to be treated with a promising agent because he or she is ineligible. This is difficult to explain to patients. How does one explain that a therapy that they have just been told is promising is now out of their reach because it is assumed that they will do poorly due to their performance status? It may be that in time studies will be designed to compare more drugs earlier and that exclusion and inclusion criteria will be adjusted to more closely reflect real-world demographics.

H&O Could you further describe some of the promising new agents?

EE Clofarabine is a nucleoside analog and cloretazine is an alkylating agent. The response rates seen with both of these agents are promising and studies are ongoing. Other promising approaches include agents that affect multi-drug resistance (MDR), a protein that causes antileukemic drugs to be excluded from cancer cells. Tipifarnib (Johnson & Johnson), lestaurtinib (CEP701, Cephalon), and decitabine (Dacogen, MGI Pharma) are three “targeted therapy” agents being studied for the treatment of AML, although the evidence is less than fully compelling that there is a relationship between clinical response and either the pretreatment status of the presumed target or the ability of the drug to modulate the target.

So-called “minitransplants” are also being investigated. The use of minitransplants has extended the upper age limit for transplantation to 70–75 years. Furthermore, unrelated donor transplants have also increased the number of patients who can receive a transplant; results with unrelated donor transplants seems as good as results with transplants in whom the donor is a sibling. A study we conducted at The University of Texas M. D. Anderson Cancer Center seems to indicate that it may be best not to wait too long for remission to occur before administering minitransplants. For example, a patient may first be given a new agent while the logistics of the transplant are arranged. The transplant would be conducted once the response to the new agent is known, especially if remission were not observed.

A major improvement resulting from recent efforts is that there is currently less early death among older AML

patients than there was previously. However, the major problem with AML in the elderly has never been early death; the major problem is that patients do not go into remission and when remission is achieved, it does not last long. Whether newer agents achieve more and longer remissions remains to be seen.

Suggested Reading

Giles F, Rizzieri D, Karp J, et al. Cloretazine (VNP4010M), a novel sulfonylhydrazine alkylating agent, in patients age 60 years or older with previously untreated acute myeloid leukemia. *J Clin Oncol*. 2007;25:25-31.

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Estey E, de Lima M, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood*. 2007;109:1395-1400.



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