

ADVANCES IN LLM

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

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Current Status of Acute Myeloid Leukemia Treatment in the Elderly

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H&O What is the current status for treatment in elderly patients with AML?

GS There really is no standard of care. The management of elderly patients with acute myeloid leukemia (AML) is complicated by 2 major features: comorbid medical conditions and the individual biologic features of acute leukemia.

The biologic features of AML in the elderly differ dramatically from those typically identified in acute leukemia in younger patients. AML in older patients is known to be associated with a higher incidence of multidrug resistance, an increased cellular resistance of chemotherapy, unfavorable cytogenetics such as a higher frequency of karyotypes associated with poor prognosis—notably AML characterized by clonal deletions of chromosome 5 or chromosome 7, or parts of chromosomes 5 and 7.

The definition of the term “elderly” is up for discussion. In an attempt to make an inherently heterogeneous disease more homogeneous, the term “elderly” is typically referred to as age over 60. However, some studies use age over 55, other studies use age over 65, and the strongest predictor for adverse outcome with conventional therapies is ages over 70. Consequently, “leukemia in the elderly” is a very imprecise term. To most leukemia specialists, the term brings to mind the aforementioned biologic features and comorbid medical conditions, but chronologic age is a surrogate—a poor surrogate for those features.

Generally, older AML patients are said to achieve lower rates of complete response (CR), and relapse-free response. The Medical Research Council's (MRC) 8th AML trial compared therapy in AML patients of different ages and found that whereas patients who were 50 years or younger had a 70% CR rate, those who were 60–69 years old had a CR rate of 52%; and those who were 70 years old or older had a CR rate of 26%.¹

Another study conducted by the Cancer and Leukemia Group B (CALGB) showed a similar trend. When comparing AML patients who were younger than 60 years to those who were 60 years or older, the CALGB 8525 study saw that a higher CR rate (73%) was reported in the former group than in the latter group (47%). The same inclination could be seen in the disease-free survival rates in the 2 groups: 31% and 14%, respectively.²

H&O What are the unmet needs of current therapy?

GS There are many and large unmet needs. The current standard of infusional cytarabine for 7 days with an anthracycline for 3 days is not available to many patients with comorbid conditions and poorly addresses disease biology. We need different kinds of chemotherapy and more of the currently available cytotoxic chemotherapy. We need different approaches in treating AML in elderly patients, including novel cytotoxic/myelosuppressive approaches, disease-modifying approaches through

epigenetics, differentiation treatment (which we really do not have), and we need access to these different types of treatment in a more disease-specific way. The diagnosis of AML in the elderly, as mentioned before, is very vague and imprecise.

Unfortunately, it is impossible to determine whether or not a single elderly patient will benefit from chemotherapy. You can only identify response rates, complications, and survival for the aggregate, and it is very hard to prognosticate for the individual because there is too much disease-related and patient-related variability. We have a pretty good amount of diagnostic accuracy in identifying subtypes of AML, and we have a reasonable amount of accuracy in determining response to induction chemotherapy, but we have a less accuracy in determining survival based on prognostic features.

H&O Are there new agents being investigated in this patient population?

GS This is a very hot area. However heterogeneous they might be, elderly patients with AML are an ideal group for clinical trials testing novel and emerging treatment strategies, and there are many drugs that are being investigated.

Targeted Therapies

Clofarabine

Clofarabine (Clolar, Genzyme) is a purine analog that induces cell death through the inhibition of DNA synthesis. A phase II study investigated clofarabine as frontline monotherapy and showed its activity in AML patients who were 65 years or older: the drug produced a 44% overall response rate.³ A more recent study, presented at the 2008 American Society of Hematology annual meeting, showed a CR rate of 38% in AML patients 60 years or older who were given clofarabine.⁴

Laromustine

Laromustine (Clometazine, Vion Pharmaceuticals) is a novel sulfonylhydrazine alkylating agent that preferentially targets the O₆ position of guanine resulting in DNA cross-links. It is an agent that alkylates oxygen rather than the electron-rich nitrogen and is cytotoxic. A large, single-center trial in which older AML patients were treated with a single IV infusion of 600 mg/m² over 1 hour showed an overall response rate of 35%. Patients in this study had untreated de novo AML and one risk factor (ie, age >70, poor performance status, unfavorable blast karyotype, or organ dysfunction). When response rate was investigated based on risk factors, age of 70 years or above had no adverse impact, but only 23% of patients with an unfavorable blast karyotype achieved

a response. The drug had significant hematologic toxicity and 14% of patients in this study died within the first 30 days.⁵

At the 2008 ASH meeting, an analysis of 2 previous laromustine studies (CLI-033 and CLI-043 by Giles [2007] and Schiller [2008]) showed that the 30-day mortality for patients treated with laromustine compares favorably with published data of early death rates in older patients who receive induction chemotherapy. There was relatively long survival in a subset of older patients with multiple risk factors who achieved a response to single-agent, single-dose laromustine.⁶

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (Mylotarg, Wyeth), an anti-CD33 monoclonal antibody linked to the cytotoxic calicheamicin, is FDA approved for the treatment of AML patients 60 years or older who have relapsed or are intolerant to other therapies.⁷

As reported at the 2008 ASH meeting, results from a sequential phase II/III trial in AML patients aged 61 years or older with untreated AML showed that low dose gemtuzumab ozogamicin therapy is a tolerable and active therapy for older patients who are considered unsuitable for intensive chemotherapy. This AML-19 trial conducted by the EORTC-GIMEMA consortium suggested that upfront use of this drug might be superior to best supportive care in unfit patients. In the study, 2/3 of the patients were randomly assigned to receive a single induction course of either gemtuzumab ozogamicin 3 mg/m² IV on days 1, 3 and 5, or gemtuzumab ozogamicin 6 mg/m² IV on day 1 and 3 mg/m² on day 8. The investigators concluded that the latter 1+8 schedule is associated with a more favorable efficacy profile.⁸

DNA Methyltransferase Inhibitor

Decitabine

As decitabine (Dacogen, MGI Pharma) is a lower intensity therapy, it could be thought that it is better tolerated in older AML patients who are not candidates for standard induction chemotherapy. An open label, phase II trial presented at the 2008 ASH annual meeting showed that a popular schedule of decitabine (20 mg/m² IV over 1 hour for 5 consecutive days every 4 weeks) yielded a CR rate of 26%.⁹ The 30-day mortality rate in this trial was 4%, which compares favorably to the mortality rates typically seen in this population treated with standard induction therapy.⁹

Azacitidine

A pilot combination study evaluated azacitidine (Vidaza, Celgene) plus ozogamicin, finding this combination

safe and effective in elderly AML patients.¹⁰ A complete response was achieved in 55% of patients, with a median overall survival of 10 months. Notably, when studied in similar patient populations, the CR rate achieved was higher than that achieved with gemtuzumab ozogamicin alone (22%)¹¹ or azacitidine alone (18%).¹²

H&O How will new drugs be tested in this patient population?

GS Testing in this patient population is very hard to do. Trials are done to achieve remission. I think that setting the bar in trials for survival data is a little too much to ask for because there are things that happen in the post-remission period—unproven consolidation therapy, transplants, intercurrent infections, and organ problems—that may compromise survival. However, I do know that the only way to achieve long-term survival measured in years is to achieve remission.

Many elderly patients have comorbid medical conditions that make the conventional 3+7 treatment (7 day infusion cytarabine and 3 days anthracycline) impossible. They may have cardiac disease, which renders them ineligible for the anthracycline component. They may have issues that make it very difficult for them to receive cytarabine by continuous infusion, or they may have liver disease which makes it impossible for them to receive cytarabine. So there are a lot of issues with giving conventional therapy, and these issues make it difficult to do a randomized trial. Phase III trials are no longer useful in the AML setting because of time and the lack of a patient population available for randomization.

Therefore, we need the FDA to be more on board to give us more drugs that we can study in a phase IV fashion. Hopefully in the next 5–10 years, we will have more access to more drugs. I think that is what we are looking for.

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