Bridging to Transplant in Older AML Patients: Old Notions and New Evidence

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Program Overview
In this activity, Dr. James M. Foran discusses new concepts in bridging therapy and stem cell transplant in older AML patients. He reviews the safety and efficacy data regarding stem cell transplant in this patient population and explores a number of agents and therapeutic strategies that have been evaluated for bridging to transplant in older AML patients, including midostaurin, CPX-351, decitabine, venetoclax-based regimens, gilteritinib, and the investigational agent Iomab-B.

How has standard therapy for AML evolved in recent years, specifically regarding older adults?

Until a few years ago, the standard algorithm for acute myeloid leukemia (AML) would involve evaluation of the patient to see if they were eligible for intensive therapy based on their age, performance status, comorbidities, cytogenetic/molecular risk profile, and personal preferences. For younger or fitter patients, the goal would be to induce remission and achieve cure with intensive induction and consolidation strategies, potentially followed by transplant. For older, less fit patients, the goal was to induce remission to prevent progression, improve survival, and maximize quality of life rather than achieve a cure. To that aim, lower intensity treatment would be delivered via low-dose cytarabine or hypomethylating agents such as azacitidine or decitabine, best supportive care, and clinical trial enrollment when available.

In the last three years, this algorithm has evolved considerably. There are now more than 10 agents that have been approved, many in the last three or four years, for AML. In response, patients are now strongly encouraged to undergo molecular and cytogenetic assessment of their leukemia prior to the initiation of therapy to determine if they have a mutation that can better direct therapy. Although the largest group of AML patients is over the age of 70 and therefore are typically ineligible for intensive therapy, stem cell transplant is playing an increasing role in these patients. In those older adults who are not candidates for intensive therapy, there are now low-intensity treatment strategies that can improve survival for as long as they continue to

respond to therapy. Importantly, some low-intensity patients may ultimately become eligible for curative therapy if their performance status improves, they achieve remission, and they have a suitable donor. Transplant is also considered after second remission. So for those who may be considered for allogenic transplant – those over age 60 who do not achieve long-term remission or cure with standard therapy, or select patients who improve after low-intensity therapy – it is important to recognize the role of these treatments as a bridge to transplant. Meaning induction is not the end-goal, but a path to transplant with curative intent.

What intensive therapeutic approaches have been evaluated for use in the 'bridge' setting?

There have been multiple studies looking at bridging therapy, some of which have included older adults. In the RATIFY study, in which older patients represented about 15% of the cohort, those with FLT3 mutations received midostaurin or placebo.[1] While this treatment was moderately effective for reducing the risk of death, it was particularly beneficial in patients who were randomized to receive 7+3 induction therapy with midostaurin and then went on to undergo transplant at first remission. About 70% of patients were alive at three years, suggesting that this is a favorable strategy for older patients with FLT3 mutations.

CPX-351 is an agent containing liposomal daunorubicin and cytarabine. In the phase 3 study that led to the approval of this therapy, CPX-351, given on Days 1, 3, and 5, was compared to standard 7+3 chemotherapy among older patients aged 60-75.[2] CPX-351 induced remission in 48% of the treatment arm, versus just 33% in the standard therapy arm. In a landmark five-year analysis of patients who achieved remission and went on to get allogeneic transplant, more patients in the CPX-351 treatment arm underwent transplant compared to standard therapy.[3]

Decitabine has been found to be particularly beneficial in patients with TP53 mutations.[4] Further, it appears to offer a significant survival advantage in patients who undergo transplant after 10-day decitabine therapy compared to those who do not receive decitabine. Older, fit patients who achieve remission and have a donor should be considered for this type of therapy.

What low-intensity regimens are useful in this setting?

While most older adults with AML are not candidates for intensive therapy, low-intensity treatment can provide a survival advantage. Venetoclax was shown in the phase 3 VIALE-A trial to be beneficial in this setting, particularly when combined with azacitidine, and is now considered to be the new standard of care for older adults with AML.[5] A recent study by Pratz, et al., evaluated the effects of venetoclax-based regimens in older and/or less fit adults (aged 75 or older or under age 75 if the patients had comorbidities or were not candidates for intensive therapy).[6] Of the patients who went on to get transplant, the 12-month survival was 68%, and 71% maintained remission at two years or more. Venetoclax-based regimens therefore may provide a path to curative stem cell treatment, even in patients who cannot receive intensive therapy.

What is the efficacy of high-intensity therapy and stem cell transplant in older adults compared with younger patients?

That question was evaluated in the E2906 study, where intensive induction therapy was evaluated in older fit adults aged 60 years and older. The median survival was nearly 14 months, although the high risk of relapse remained a significant barrier to curative therapy.[7] Allogeneic transplant was found to be feasible in this population following intensive therapy, with results revealing a 48% survival rate and 42% disease-free survival rate at two years with low incidence of acute graft-versus-host disease.[8] In short, transplantation toxicity, relapse, and survival for older adults are not significantly different than those for younger adults undergoing similar intensive therapy and allogeneic transplant. This has also been shown to be true in older adults after reduced-intensity conditioning.[9,10]

Knowing this, it is critical that therapeutic decision-making be centered on the individual patient. Although older patients are not necessarily as fit as younger patients, they have as much to lose from the disease and as much to gain from transplant, including significant reduction in risk of relapse. Patients over age 60 should be referred for consultation with a transplant center so they can be fully evaluated for candidacy, and all treatment options can be considered.

What treatment options should be considered for older relapsed/refractory (RR)-AML patients?

The goal of treatment in this setting is to induce remission or establish disease control, followed by consolidation with allogeneic transplant. Although quantifying the benefit of allogeneic transplant in RR-AML is difficult, an older 2009 retrospective study demonstrated a clear advantage in overall survival of RR-AML patients in the transplant groups compared with chemotherapy-based regimens.[11] However, without transplant, it is difficult to achieve long-term survival, particularly for those with early relapse.

There is no clearly superior salvage regimen in RR-AML. Comparative analysis has found no significant differences between mitoxantrone/etoposide/cytarabine (MEC), fludarabine/cytarabine/idarubicin/ granulocyte colony-stimulating factor (FLAG-Ida), and cladribine/arabinoside/cytosine/mitoxantrone/ granulocyte colony-stimulating factor (CLAG-M).[12] Venetoclax plus a hypomethylating agent is also acceptable in this setting. Patients with a targetable mutation may have more options. For example, those with FLT3-positive RR-AML may receive gilteritinib, which was found in the ADMIRAL study to produce a superior complete remission rate and median survival rate (9.3 months) compared with salvage chemotherapy (5.6 months).[13]

There is also an investigational therapy called Iomab-B, an I-131-tagged murine anti-CD45 antibody that works by delivering radiation to targeted lymphohematopoietic cells. In a phase 2 study, this treatment achieved an approximate 35%-40% overall survival at two years.[14] The

phase 3 SIERRA trial is currently assessing Iomab-B prior to hematopoietic stem cell transplant compared with chemotherapy.[15]

In conclusion, it is clear that some of the factors that were traditionally viewed as barriers to transplant are not necessarily so. There is a perception that all older adults are not candidates for allogeneic transplant, but more recent research is demonstrating that a certain percentage of that population does well with this treatment approach. Still, older AML patients tend to have higher comorbidity scores and be less tolerant of salvage therapy, and there is a need for therapies for this population that are more tolerable and effective at establishing disease control. Fortunately, research on this topic persists, and we are optimistic that outcomes in these patients will continue to improve.

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