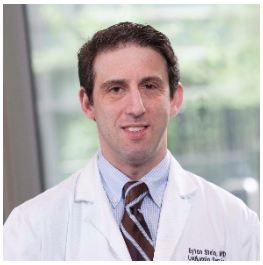
Surveying the Treatment Landscape: Therapeutic Advancements Affecting Treatment Decisions in AML



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Program Overview

Join Dr. Eytan Stein as he explores the evolving treatment landscape for acute myeloid leukemia (AML). Topics to be discussed include new uses of hypomethylating agents and venetoclax, targeted therapies for specific mutations, and investigational low-intensity treatment combinations. Dr. Stein will also extrapolate on expanding concepts such as patient 'fitness,' measurable residual disease, and maintenance therapy for AML.

What is considered standard therapy for AML and how is this standard evolving?

There are two main approaches that we consider for patients with newly diagnosed AML. One option is intensive induction chemotherapy with potent chemotherapeutic agents like cytarabine and anthracycline drugs (known as 7+3). The other option we may consider is the combination of hypomethylating agents (HMAs) with the BCL-2 inhibitor venetoclax. This combination is approved for newly diagnosed patients aged 75 or older, or younger than 75 in the presence of comorbid medical conditions that preclude the use of intensive induction chemotherapy.

Recently, there has been a trend where physicians are utilizing HMAs plus venetoclax in populations that fall outside this indication. These patient populations have very high-risk disease such that intensive chemotherapy is unlikely to work; for example, a 60-year-old patient with a complex karyotype and a P53 mutation. In this patient, the anticipated remission rate with intensive induction chemotherapy is in the range of 20%. However, the anticipated CR rate with a strategy like HMAs plus venetoclax is closer to 50% or 60%. Where it used to be that younger patients traditionally received intensive chemotherapy and older patients traditionally received low-dose chemotherapy with an HMA or HMA plus venetoclax, now that line is starting to blur. We are beginning to give some of our younger patients an HMA and venetoclax because it seems to lead to higher remission rates than intensive chemotherapy.

What are some of the new and upcoming therapies for AML? How do they work and what is the latest evidence on them?

In newly diagnosed AML, there are newer therapies that can be added to intensive induction chemotherapy. For FLT3-mutated AML, we add on the FLT3 inhibitor midostaurin to 7+3. In patients with favorable risk core binding factor AML, some physicians might add the anti-CD33 antibody-drug conjugate gemtuzumab ozogamicin to 7+3. Some patients have AML that has evolved from a prior myelodysplastic syndrome (MDS) or AML that is therapy-related (ie, secondary AML). For those patients, we might consider a liposomal formulation of cytarabine and daunorubicin called CPX-351.

For patients with newly diagnosed AML who are not candidates for intensive chemotherapy, one of the biggest advances has been the introduction and the use of HMAs with venetoclax. The efficacy of this approach was demonstrated in the randomized phase 3 VIALE-A study, which confirmed a 14.7-month median overall survival (OS) in the group of patients who got an HMA and venetoclax compared to 9.6 months in patients who got an HMA alone.[1] There is also data supporting the use of low-dose cytarabine with venetoclax. In a randomized study, low-dose cytarabine with venetoclax was superior to low-dose cytarabine alone in newly diagnosed AML patients who were ineligible for intensive chemotherapy.[2] In patients who cannot receive azacitidine and venetoclax for any reason, we now offer them low-dose cytarabine plus venetoclax, instead of low-dose cytarabine alone.

Finally, in the low-intensity treatment population, there is evidence supporting the hedgehog inhibitor glasdegib in combination with low-dose cytarabine (LDAC). In the phase 2 BRIGHT AML 1003 study, newly diagnosed AML or high-risk MDS patients who were not candidates for intensive chemotherapy were randomized to receive low-dose cytarabine with glasdegib versus low-dose cytarabine therapy alone.[3] The glasdegib plus low-dose cytarabine treatment group had a median OS of 8.8 months compared to 4.9 months in the low-dose cytarabine group.

In newly diagnosed AML, the evidence for 7+3 plus midostaurin stems from the randomized placebo-controlled phase 3 RATIFY trial, which randomized patients to receive standard chemotherapy (7+3) plus either midostaurin or placebo.[4] In this trial, the patients who received 7+3 and midostaurin had a 5-year OS benefit compared to the patients who got 7+3 and placebo. Evidence supporting the CPX-351 compound consists of a randomized non-placebo controlled open-label study of CPX-351 versus 7+3 in patients with secondary AML, which led to a median OS of 9.56 months in the CPX-351 group versus a median OS of 5.95 months in the patients who received 7+3.[5]

What factors affect your decision to use one particular therapy over another?

My choice varies depending on the overall treatment goal. If the ultimate goal is allogeneic stem cell transplant, I am personally willing to accept a bit more treatment toxicity in the hopes of a potentially curative transplant. If the goal of therapy is to simply improve a patient's blood counts, I try to avoid therapy that is toxic enough to significantly impact quality of life (QOL). This is the more nuanced aspect of AML treatment; providers should consider not only the disease characteristics, but also the patient's values and goals. In many cases, the goal of therapy is to maintain the best QOL for the longest period of time possible, particularly in patients who are unwilling or unable to go through intensive chemotherapy.

How do you determine 'fitness' for chemotherapy?

Although there are scoring systems to help determine patient fitness, most physicians also rely on clinical judgment: how the patient appears when they walk into the office, what their comorbid medical conditions are, etc. I think the question of fitness is less important in this day and age. Historically, there was a clear-cut approach wherein fit patients got intensive chemotherapy while unfit patients did not get intensive chemotherapy. With widespread use of HMA/venetoclax which seems to have response rates that are similar to intensive chemotherapy, we sometimes will give "fit" patients HMA/venetoclax over more intensive therapy.

How does the concept of measurable residual disease (MRD) apply to therapy today and moving forward?

MRD is defined as the presence of leukemic blasts at a threshold less than 5% of marrow cellularity. The presence of MRD following intensive induction chemotherapy typically translates to poorer outcomes in the post-transplant setting. Therefore, MRD negativity is often a goal of therapy. The concept of MRD is perplexing in practice because one, we have yet to determine the optimal way to achieve MRD negativity, and two, some patients who are MRD positive will become MRD negative without further therapy. The randomized QUAZAR AML-001 study provided some insight.[6] In this study, patients received either a maintenance drug called CC-486 (an oral formulation of azacitidine) or placebo. What is interesting in that trial is that nearly 20% of patients in the placebo arm converted from MRD positivity to MRD negativity without any further therapy. This is likely the result of the timing of MRD measurement, wherein patients progressing towards MRD negativity were simply measured too early.

A third conundrum is that about 30% of patients who are MRD negative prior to transplant will relapse in the post-transplant setting and, likewise, about 30% of patients who are positive prior to transplant will *not* relapse after transplant. This demonstrates that the positive predictive value of our current approach to MRD testing is lacking. Clearly, we are in need of

improved MRD testing to more accurately identify residual leukemic cells. We also need improved understanding of the kinetics of MRD and how MRD status changes in patients, as well as well-designed trials to determine if elimination of MRD actually translates into a survival benefit.

How does maintenance therapy fit into the framework of AML treatment?

The goal of maintenance therapy is to prevent a relapse once a patient is in remission. Maintenance therapy has been successfully used in several hematologic malignancies, such as multiple myeloma and lymphoma. In AML, the role of maintenance therapy has historically been less clear. But we now have data from the QUAZAR study demonstrating a survival benefit derived from CC-486 maintenance among AML patients who were ineligible for transplant.[6] The median overall survival in the QUAZAR study in the patients who got CC-486 was 24.7 months, compared to 14.8 months in the placebo patients. So maintenance appears to be beneficial in this population. The other setting where maintenance therapy has had success is in FLT3-positive AML patients who are in remission and who are ineligible or unwilling to undergo transplant.

In your opinion, what investigational approaches hold the most promise for future treatment of AML?

The combination of azacitidine and venetoclax looks very promising for all AML, not just for patients who are 75 and older. This combination could potentially emerge as the new backbone of AML therapy, especially for intermediate- or unfavorable-risk disease. Adding targeted agents to this backbone – such as FLT3 inhibitors in FLT3-mutated AML – will likely improve outcomes for select patient groups. Menin inhibitors are also being developed. There is very promising clinical data showing that these drugs can be quite effective for mixed-lineage leukemia (ie, KMT2A translocations) and NPM1-mutant acute leukemias.[7] A variety of menin inhibitors are in phase 1 clinical studies.

We are lucky to now have many treatment options for AML. There is often a tendency to start combining these treatment options without the support of clinical data. Rather than attempt this approach, I would encourage community physicians to enroll difficult-to-treat patients in clinical trials that are investigating different combinations. This way, we will soon have more answers regarding optimal therapy for each AML patient.

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Provided by MediCom Worldwide, Inc.
This activity is supported by educational grants from Bristol Myers Squibb, Genentech, Helsinn, and Jazz Pharmaceuticals.