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Evolving Strategies for the Management of Core-Binding Factor Acute Myeloid Leukemia



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H&O What are core-binding factors?

GB Core-binding factors are heterodimeric transcription factors that are necessary at different stages of hematopoiesis. Core-binding factor alpha has 3 subunits—RUNX1, 2, and 3—whereas core-binding factor beta has 1 subunit. The core-binding factor alpha and beta subunits form heterodimers to bind to DNA and regulate hematopoietic differentiation, cell cycles, and ribosome biogenesis. Translocation events creating fusion proteins alter DNA binding of the transcription factors. This changes the transcription program toward downregulation of differentiation genes and maintenance of stemness genes. The normal function of the core-binding factor is to promote differentiation, such as orderly maturation in the process of hematopoiesis. When this process is disrupted, the cells are arrested at an earlier state, which sets the stage for the development of leukemia.

H&O What are the translocation events in core-binding factor acute myeloid leukemia?

GB The events occur in translocation 8;21, involving the alpha complement; and in inversion 16 (or translocation 16;16), involving the beta component. These are the 2 translocation events that define core-binding factor acute myeloid leukemia (AML). The event in translocation 8;21 mostly impairs the function of the core-binding factor alpha (RUNX1). Inversion 16 impairs function of core-binding factor beta. Eventually, these transcription factors cannot bind to the right place in DNA, and they

may start to bind in alternate places. In the process, the genes that are necessary for maturation of these blood cells cannot function, and the cells are arrested at an earlier stage. The resultant differentiation block leads to the development of leukemia. Additional background genetic events—such as kinase, epigenetic, and cohesion mutations—also contribute.

Core-binding factor AML is defined by these unique translocation events and with lower mutational complexity compared with other AMLs. Most other types of AML do not have such a defining translocation event. (An exception is acute promyelocytic leukemia, which is defined by translocation 15;17 or mixed-lineage leukemia [MLL]-rearranged leukemia.)

The unique translocation events make core-binding factor AML amenable to serial and quantitative molecular monitoring of minimal residual disease (MRD) with quantitative polymerase chain reaction (qPCR) testing. Many of the other mutations or genetic events in AML may not be suitable for quantitative monitoring. The unique translocations in core-factor binding AML are possibly among the first events that occur in the development of the disease, and they can be measured quantitatively. This point is critical because quantitative reduction in MRD as measured by qPCR impacts long-term outcome, as shown by several research groups.

H&O What is the goal of management of patients with core-binding factor AML?

GB Core-binding factor AML has a good prognosis.

At MD Anderson, we strongly believe that the goal of management should be cure. Data from large groups in the past 15 years suggest that the rate of long-term overall survival is approximately 50%. However, a 50% survival rate should not necessarily define good risk in AML; a better rate would be higher than 70%. At MD Anderson, since we adopted the newer modalities of treatment for core-binding factor AML in 2007, overall survival has exceeded 75%. This rate can hopefully be improved even more. In acute promyelocytic leukemia—another good-risk AML—the rate of overall survival exceeds 90%. It should be possible to reach this rate in core-binding factor AML, too.

H&O What are the treatment options for core-binding factor AML?

GB Core-binding factor AML is defined by a high level of chemosensitivity, particularly to high-dose nucleoside analogues, such as cytarabine and fludarabine. Remission rates are much higher than in other types of AML, and long-term survival is better. These patients do not require stem cell transplant in first remission. Almost half of patients with core-binding factor AML at first relapse can achieve a second remission, which is not the norm in AML.

In other subtypes of AML, patients in first remission undergo stem cell transplant, which provides the best chance of long-term cure. Patients with core-binding factor AML do not usually undergo stem cell transplant in first remission. In the frontline setting, chemotherapy has better outcomes than stem cell transplant. For these patients, stem cell transplant can be considered among patients in second remission.

The traditional treatment of core-binding factor AML is induction chemotherapy, followed by several cycles of intensive cytarabine-based chemotherapy consolidation. Data from the Cancer and Leukemia Group B show that outcome is better with 2 to 4 consolidation cycles vs only 1 cycle. This strategy leads to a cure in approximately 50% to 60% of patients. Ideally, we would like to improve this rate to higher than 80%, which may be possible with newer treatment approaches.

The incorporation of gemtuzumab ozogamicin (Mylotarg, Pfizer) into the induction consolidation regimen improves outcome in patients with core-binding factor AML. This observation is supported by data from a meta-analysis of several randomized trials, as well as nonrandomized data from MD Anderson. Frontline treatment with gemtuzumab improves overall survival and relapse-free survival in patients with core-binding factor AML. Gemtuzumab does not necessarily improve outcome in patients with high-risk AML. Data from MD

Anderson, as well as from the Medical Research Council in the United Kingdom, suggest that induction consolidation with fludarabine and cytarabine may improve outcome vs the traditional 3-plus-7 regimen followed by consolidation with cytarabine.

Among patients with other types of AML who relapse, approximately 30% can achieve a second remission. Patients with core-binding factor AML may remain sensitive to chemotherapy even after relapse. A chemotherapy-based approach has the potential to bring approximately 50% of these patients back into remission and render them eligible for transplant.

In terms of treatment, the most important recommendation is to add gemtuzumab to the induction regimen.

H&O Are there ways to tailor treatment to particular patients?

GB With core-binding factor AML, the average rate of survival is approximately 50%. Therefore, 40% to 50% of patients are still relapsing and dying from the disease. It would be ideal to identify these at-risk patients up front and modify their treatment. Two important risk factors are older age and persistence of MRD. These patients have a unique translocation that can be identified by qPCR. A group from the United Kingdom showed that substantial reduction in MRD by qPCR is associated with a better outcome. Studies at MD Anderson confirmed this observation. Patients who do not achieve an optimal molecular response have higher rates of relapse and death from disease. A nonrandomized study from China suggested that patients without an optimal qPCR response might benefit from allogeneic transplant rather than continued chemotherapy. This finding should be evaluated in a randomized study, or at least in a more prospective fashion in a multicenter analysis. The next step in treatment for patients without an optimal qPCR response is not known. These patients relapse more often. Stem cell transplant might be an option. If the patient is not a candidate for a stem cell transplant, then maintenance strategy might improve survival.

Recent retrospective data suggest that core-binding factor AML is associated with additional mutations—beyond the 8;21 translocation and inversion 16—such

as alterations in epigenetic modulators, the cohesion complex, or the spliceosome. The presence of these mutations may identify a patient at higher risk. Unfortunately, these retrospective analyses included patients treated with several different treatment regimens. A comprehensive study is needed to determine whether these mutations still define high risk if the patients are treated with the optimal induction regimens.

Several investigative groups have reported that the mutation in the *KIT* gene indicates high risk. Patients who have *KIT* mutations tend to relapse more often. At MD Anderson, we have not been able to confirm this finding in the context of fludarabine- and cytarabine-based regimens, and this observation was not borne out in the pediatric setting. Therefore, it is not yet known whether the *KIT* mutation necessarily indicates a higher-risk patient population that requires treatment modification.

H&O Are there any evolving treatment strategies for patients with core-binding factor AML?

GB The addition of gemtuzumab should be incorporated into the treatment of core-binding factor AML. This strategy should become the standard of care, based on data from MD Anderson, as well as other randomized trials. At MD Anderson, we believe that a regimen incorporating fludarabine, cytarabine, and granulocyte colony-stimulating factor is more effective than the standard 3-plus-7 regimen. Unfortunately, there are no randomized head-to-head comparisons. A randomized comparison from a UK group showed that a regimen of fludarabine, granulocyte colony-stimulating factor, cytarabine, and idarubicin improved relapse-free survival, but no difference was seen in overall survival. In this study, patients with core-binding factor AML who completed the planned treatment with the fludarabine-based regimen did exceptionally well.

Investigators at the Eastern Cooperative Oncology Group and in Germany have evaluated the possibility of targeting the *KIT* mutation. It appears that the *KIT* mutation predicts for early relapse and high-risk disease. The tyrosine kinase inhibitor dasatinib (Sprycel, Bristol-Myers Squibb) targets *KIT*. Data for these studies are not yet mature enough to unequivocally indicate whether dasatinib is an effective option.

At MD Anderson, we are evaluating an option for patients with persistent MRD after completion of standard chemotherapy: maintenance with a hypomethylating agent. We have used decitabine in this context. Some physicians might use decitabine or another hypomethylating agent in patients who have not achieved the optimal molecular response. Maintenance with a hypomethylating agent can lead to a better molecular response. It

is important to consider, however, that the data are still early. Oral hypomethylating agents are now becoming available for use as a maintenance strategy. Their role is not yet known, but they would be a great option for patients to improve long-term outcome.

H&O Are there differences in de novo vs therapy-related core-binding factor AML?

GB Most cases of core-binding factor AML develop de novo, in patients who had not received previous chemotherapy. A troubling observation, however, is that a small subset of patients previously treated with chemotherapy can develop therapy-related core-binding factor AML. Long-term prognosis is worse in therapy-related core-binding factor AML. Overall survival and relapse-free survival are shorter. A similar scenario occurs in therapy-related acute promyelocytic leukemia, but here the outcome is the same regardless of whether the disease arises de novo or after chemotherapy exposure.

In 2009, researchers at MD Anderson Cancer Center reported data comparing outcomes of de novo and therapy-related core-binding factor AML among their patients. In 2020, a multicenter, retrospective analysis of 351 patients was published. We found that outcome was poor among patients with therapy-related core-binding factor AML. It is not known why these patients have a poor prognosis. One hypothesis is that they may have secondary mutations that are absent from de novo disease. More research is needed to identify differences in the biologies of these subtypes.

H&O Do you have any other suggestions regarding the management of patients with core-binding factor AML?

GB In terms of treatment, the most important recommendation is to add gemtuzumab to the induction regimen. Gemtuzumab was redrawn from the US market several years ago. When the drug was reappraised in 2017, clinicians appeared reluctant to incorporate it into the frontline regimen for core-binding factor AML. Multiple studies suggest that gemtuzumab confers a substantial benefit.

Another important consideration is that the translocations of core-binding factor AML provide a unique opportunity to quantitatively monitor this disease through qPCR of the transcription. This strategy should be incorporated as a standard-of-care practice. A barrier is that the methods of qPCR are not standardized across institutions, although this is something that could potentially be done. Local resources can be used to monitor disease by qPCR. An optimal response translates into

optimal survival, so qPCR testing should be performed routinely. A question that arises is whether transplant should be considered for patients who do not reach an optimal qPCR reduction, as patients without a very good molecular response have a higher chance of relapse. In this particular high-risk patient population, transplant might provide a better outcome.

There are several potential collaborative projects for the community of physicians who treat patients with core-binding factor AML. The first would be to define whether the so-called high-risk mutations—whether *KIT*, epigenetic, or another type—remain high risk in the context of an appropriate treatment strategy. The answer to this question is important because it may be possible to identify patients with these mutations at diagnosis, and to therefore consider them for future stem cell transplant. Approximately 15% of all patients with AML have the core-binding factor subtype. Treatment centers may not see a large number of these patients. However, groups can share information to increase the database in order to address some of these questions.

It should be possible for MRD monitoring to become more standardized across institutions. It would be helpful to have comparable values across treatment centers.

Disclosure

Dr Borthakur has no real or apparent conflicts of interest to report.

Suggested Readings

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