

Overview of the Revised Response Criteria for Acute Myelogenous Leukemia

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What spurred the creation of the original response criteria in acute myeloid leukemia?

The 1990 criteria were published because there were many inconsistencies among clinical trials for patients with acute myeloid leukemia (AML). There was a clear need to standardize response criteria so that data could be interpreted and compared among trials. A relatively small group of US investigators met and drafted the original guidelines over a period of time. These guidelines have been applied internationally over the past 12 years or so to cooperative group and industry-sponsored studies, and the US Food and Drug Administration (FDA) has relied on these guidelines for drug evaluation and approval. A number of minor modifications have been made by individual investigators to the original guidelines, but in general, they have remained intact.

Why did the criteria for AML need to be updated?

One of the features of creating standard response criteria for a disease is that certain problems cannot be appreciated until the criteria are applied in the clinic. Over the years, practical experience informed us that some of the criteria required modification and clarification. In addition, much has been learned about the biology of AML. There are new technologies used to assess patients, and new agents being studied in the clinic. Also, when the original criteria was created, many of the definitions were arbitrary, not based on solid data. Therefore, we convened another group, this time including international participants, and developed revised response criteria that differ in many ways from the original guidelines.

What are some of the differences between the previous and new criteria?

Since a large number of correlative studies in patients with acute leukemias are now being conducted, we recommended the storage of viable blasts, so that studies could be done in the future. The distinction between de novo and secondary AML has been clarified. The improved information now

available about the implications of dysplasia in the bone marrow has been taken into account. The World Health Organization's additional definitions of AML and, for example, how to distinguish this disease from myelodysplastic syndromes (MDS), developed since the original criteria were published, have been accepted within these new recommendations. The importance of flow cytometry, bone marrow cytogenetics, and molecular findings are discussed. Notably, with the molecular remission that patients with acute promyelocytic leukemia (APL) are now experiencing, the new criteria support certain indications for central pathology review and offer new definitions for response. For example, there is a new response criterion called "leukemia-free state," which was not previously described. Anticipating future research needs, 2 new terms have been introduced: cytogenetic complete response (CRc) and molecular complete response (CRm). The threshold of neutrophils required for a complete remission has been lowered from 1,500 to 1,000, since generally patients who have over 1,000 neutrophils achieve a complete remission. The definition for relapse in the bone marrow has been altered. The requirement for cellularity in the bone marrow has been removed from the definition of complete response. In addition, late myelodysplasia is now considered a criterion for recurrence of disease. Leukemia-free survival and overall survival have been specified as the primary endpoints for most large clinical trials.

One of the major problems with the original criteria was that a complete response was required to last 4 weeks in order to be considered as such. However, many patients were being treated with consolidation therapy within that 4-week period of time, and therefore by the strictest definition, could not be considered to have achieved a complete remission. While the original guidelines did note that if a patient required another form of therapy per protocol, they would be considered to be in complete remission, most investigators felt uncomfortable with the 4-week waiting period. In the new criteria, this waiting period no longer exists.

What is the leukemia-free state?

The introduction of the concept of “leukemia-free state” was proposed in large part by Drs. Büchner and Hiddemann, from Germany. In the past, investigators would wait until a patient developed those criteria for complete response to confirm this level of response. However, we now know that it is possible to identify antileukemic activity earlier. A bone marrow aspirate sample is obtained about 7–10 days after completing the last dose of chemotherapy, and the sample is evaluated for its cellularity and number of residual leukemic cells. This approach has enabled investigators to confirm that patients no longer have evidence of leukemia much earlier than was previously thought. Therefore, the leukemia-free state was established, the criteria for which includes fewer than 5% blasts and a bone marrow aspirate that contains marrow spicules. In addition, there should be no blasts with Auer rods, and no persistence of extramedullary disease. If immunophenotyping is done by flow cytometry, no cells should retain the pretreatment phenotype. The presence of this phenotype should be viewed as persistence of leukemia.

What is the current definition of a disease-free state?

The term “disease-free state” carries the connotation of a patient who is in a remission, has no evidence of leukemia at that time, has normal blood counts, and has an improvement in bone marrow cellularity. As designated in the new criteria, the disease-free state is measured from the point that a complete remission is achieved.

What is the difference between CRc and CRm, and what brought about the need for this distinction?

We now know that cytogenetics are probably the most important prognostic indicator in the treatment of AML. In recent years, largely through the work of Dr. Bloomfield and others, we have come to understand the relationship between cytogenetics and patient outcome, and that one of the goals of therapy should be to eradicate that clone of cells that has the cytogenetic abnormality. In the past, the number of blasts in the bone marrow, with a threshold of 5%, has been the criteria to be considered a response. However, the 5% threshold is fairly arbitrary, and even in patients who meet this threshold, cytogenetic studies indicate that some will have a normal karyotype, whereas others will still have residual cytogenetic abnormalities. The latter group has a much poorer prognosis.

Because we are trying to increase the cure rate of patients with acute leukemia, it would be helpful to identify those patients who have minimal residual disease. One way to do that is to look at the cytogenetics of what is thought to be a remission bone marrow. In the future, there will be more risk-oriented therapy, and a patient who achieves a CRc, may receive standard postremission therapy, whereas a patient achieving a morphologic CR but retaining the cytogenetic abnormalities might receive further and perhaps more intensive therapy.

Patients are now achieving responses at the molecular level, which is deeper than a CRc. Using a variety of techniques such as polymerase chain reaction (PCR), it is possible to identify certain patients, for example those with APL, who achieve not only a morphologic complete remission and a

CRm, but in whom the specific genetic marker is now absent. Just as with CRc, the CRm criterion has prognostic implications for those patients who have a persistent marker versus those who no longer have that marker after treatment. Now that techniques to identify populations of patients at a good risk or a poor risk following therapy are available, and because we are learning an increasing amount about molecular abnormalities in acute leukemias, it seemed best to include these in the revised recommendations. As new molecular lesions are identified, it will be important to determine whether or not it is possible to eradicate these lesions.

In summary, there are now terms to define the various levels of remission: morphologic, then cytogenetic, then molecular. All of these terms indicate when the patient is in a complete remission, but the latter 2 give us a more accurate indication of the depth of that complete remission. These terms enable us to determine whether minimal residual disease has been eliminated. If it is possible to eliminate minimal residual disease, then it is likely that the quality and duration of remission will be better.

Is there a correlation between a patient's prognosis, as determined by genetic abnormalities, and the application of the response criteria?

There is clearly a correlation between genetic abnormalities and outcome, and cytogenetics is perhaps the strongest predictor of outcome. Some cytogenetic groups, such as those with APL and those with core binding factor leukemias, tend to do quite well. Intermediate groups include those patients with normal cytogenetics. Patients with an unfavorable prognosis, as predicted by cytogenetic analysis, include those with -5 and -7 abnormalities. With regard to the molecular responses, APL patients who receive induction therapy and have a persistently positive PCR have a much higher likelihood of relapse than do patients whose PCR is persistently negative.

What is the difference between de novo and secondary AML, and how has this been updated in the response criteria?

Most AML patients are thought to have de novo disease, that is, disease that occurs without any antecedent hematologic abnormality or without some form of toxin or drug exposure that is known to be leukemogenic. However, standardized definitions of de novo versus secondary AML have been lacking. The group of clinicians revising the AML response criteria proposed recommendations that are also consistent with the WHO guidelines. De novo AML refers to AML in patients without a prior myelodysplastic syndrome (MDS), myeloproliferative disorder, or exposure to any known leukemogenic agents. Secondary AML refers to patients who do have an antecedent hematologic abnormality, prior MDS or myeloproliferative disorder, or prior leukemogenic exposure. Determining whether a patient has de novo or secondary MDS is not always easy, particularly because very often patients do not know that they have had a leukemogenic exposure, environmental or otherwise. In addition, there may be leukemogenic agents that have not yet been identified. Therefore, the number of AML cases thought to be de novo is 80–90%, which may be a high estimate.

Are some of the revised criteria still arbitrary, and what data are still needed in these evaluations?

Many of the cut-off levels for response are still arbitrary. However, different to the meetings that led to the 1990 criteria, in making these revisions, we had data available to evaluate. Investigators from all over the world presented data, much of which was unpublished, showing what different thresholds reflected in clinical outcomes. The availability of data led us to lower the requisite number of neutrophils for a CR from 1,500 to 1,000, because there were data showing that patients whose neutrophils were over 1,000 almost uniformly obtained a complete remission, with all the other features remaining the same. It is likely that there will always be some degree of arbitrariness, but the need for standardization supersedes waiting for firm data. Recommendations that are still somewhat arbitrary will either be validated over time or will be modified. Hopefully, once the revised response criteria are incorporated studies, we will learn more and modify the criteria if needed.

How do the response criteria relate to the process of drug development?

The response criteria will hopefully continue to facilitate drug development. When it comes to drug development, the new leukemia-free state criteria will give an earlier indication of activity. However, in general, different responses to drugs are important at different points in the progress of a disease. New agents are usually studied in patients with relapsed or refractory disease, and now increasingly in the initial therapy of patients with adverse prognostic factors. In this setting, it is important to know simply if the treatment has activity. Here, the leukemia-free state and partial remission criteria may provide guidance as to whether to proceed with further development

of that agent or not. Later, when a drug is in phase II, and particularly phase III testing, other criteria are more meaningful. At that point, more important than response rates are the durability of responses, progression-free survival, leukemia-free survival, and overall survival.

Were any criteria removed from the guidelines?

No criteria were removed from the guidelines. However, the updated criteria emphasize that complete remission with low platelet count (CRp) should not be included as a true CR. Studies have been published that discussed CRp, such as phase II studies with new agents, most notably gemtuzumab ozogamycin (Mylotarg, Wyeth Ayerst), and the term needed clarifying. In the initial criteria, CRp was defined as a complete remission but with persistent thrombocytopenia. When revising the guidelines, longer-term follow-up data of those patients was available. Based on this data, it was reasonably clear that the eventual outcome of CRp patients is not the same as patients who have a complete morphologic remission with a normal platelet count.

Suggested Reading

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