The origins of the definition of complete remission in acute myeloid leukemia

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TITLE	Criteria for the evaluation of response to treatment in acute leukemia.
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The achievement of a complete remission (CR) for patients with acute myeloid leukemia (AML) has long represented the critical initial goal of therapy with the hope that it portends the likelihood of ultimate cure. How CR for AML is defined has evolved over the years. An early attempt to define CR was published as a letter to the editor in the journal *Blood* in 1956.[1] The letter came from the Clinical Studies Panel of the Cancer Chemotherapy National Service Center and was authored by Harry Bisel, MD, the executive secretary of the Panel. Dr. Bisel was an oncologist at my institution, the Mayo Clinic, where he founded the Department of Medical Oncology and served as its chair from 1963-1972. He was also one of the founding members of the American Society of Clinical Oncology. In the letter an excellent response to therapy or CR was defined as less than 5% marrow blasts and attainment, for more than 1 month, of a hemoglobin concentration greater than 12 g/dL, circulating granulocytes (or absolute neutrophil count) greater than 200/mm^3 (1,500/mm^3 for children) and return of platelet counts to greater than 100,000/mm^3 for adults and children. One wonders whether the granulocyte figure of 200/mm^3 may have been a typographic error and was truly meant to be 2,000/mm^3. Additionally, "subsidence of all evidence of leukemic infiltration" was required as part of a CR. Fair and poor responses were also described in the letter, representing attempts to define partial and no responses, respectively (Table 1). A definition of relapse was also provided.

These criteria were applied in a report by Freireich *et al*. in 1961 of 178 adult and pediatric patients with acute leukemia admitted to the Chemotherapy Service of the National Cancer Institute between October, 1953 and October, 1958.[2] Of the 178 patients, 63 had AML and 115 had acute lymphoblastic leukemia. Treatment consisted of 6-mercaptopurine, methotrexate and corticosteroids. However, by January of 1960, 171 (96%) of the patients had unfortunately died.

Table 1. Criteria for the evaluation of response to therapy of acute leukemia.[1]

Parameter	Complete remission[a]	Partial remission[b]	No response
Blasts	<5% adults, <10% children	<70%[c]	No improvement
Hemoglobin	≥12 g/dL adult, ≥11 g/dL children	≥9 g/dL adult & children	No change or less than criteria for partial remission
Granulocytes	>200/mm^3 adult; >1,500/mm^3 children	>200/mm^3 adult; >1,500/mm^3 children	No change or less than criteria for partial remission
Platelets	>100,000/mm^3	-	No change or less than criteria for partial remission
Extramedullary disease	Resolved	≥50% reduction	No change
Clinical symptoms	None	Improved	No improvement

[a]Complete remission requires that all criteria in this column be fulfilled. [b]Partial remission requires fulfillment of criteria in each row for either complete or partial remission. [c]Achievement of normal myelopoiesis for 2 weeks or longer to >30% of total nucleated cells and a reduction in the number of leukemic cells, lymphocytes and blasts to <70%.

Over the ensuing 70 years the definition of CR has undergone further revision with decreases in the absolute neutrophil count to ≥1.0x10^9/L, elimination of the hemoglobin level as a requirement for CR, maintenance of achievement of a platelet count ≥100x10^9/L, incorporation of cytogenetic and molecular data and, most recently, lack of evidence of measurable residual disease by flow cytometry or molecular techniques. These changes have been nicely summarized in a recent review article.[3]

In more recent years in the context of new drug approvals, particularly those related to less myelosuppressive drugs, CR with blood count recovery not meeting the levels defined in the preceding paragraph have been utilized as criteria for response and to support United States Food and Drug Administration approval of these agents. A recent publication from the Food and Drug Administration utilizing these less than CR criteria showed that they were associated with "clinical benefits consistent with clinically meaningful palliative effects for the treatment of AML with nonmyelosuppressive drugs, although less robustly than for CR." [4]

In summary, the landmark, brief, but seminal, report by Bisel in *Blood* in 1956 laid the groundwork for the definition of CR in AML and, although revised subsequently, has stood the test of time in defining this critical endpoint in the treatment of AML.

Disclosures

No conflicts of interest to disclose.

References

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