High-Dose Cytarabine Induction for Acute Myeloid Leukemia

To the Editor:

In a recent article, Bishop et al. state that high-dose cytarabine has not previously been used as induction for untreated acute myeloid leukemia (AML). In fact, high-dose cytarabine has been used by itself, with daunorubicin, and with daunorubicin in this role. Additionally, doses of cytarabine significantly above those considered standard had previously been used by other groups for initial induction with daunorubicin.

The report by Bishop et al builds on these previous experiences and clearly supports a role for high-dose cytarabine as initial therapy, as we and other groups have reported.

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Response: Induction Endpoints in AML

Shepherd et al are quite right. High-dose cytarabine has been used in a number of single-arm studies in the induction therapy of AML. However, our report is one of the first published papers of a phase III randomized study of high-dose cytarabine in the induction of de novo AML. The South-West Oncology Group (SWOG) is soon to publish its randomized study of high-dose cytarabine induction with similar results. We believe the distinction between phase III randomized and phase II single arm studies is important for the usual reasons that large randomized comparisons are the appropriate clinical trial methodology to avoid bias when comparing treatments. However, in addition, single-arm studies reporting high response rates in AML are difficult to interpret. A number of recent randomized trials of AML induction intensified with high-dose cytarabine or etoposide have shown no difference in complete remission (CR) rate but clinically important, statistically significant differences in remission duration, relapse-free survival, or survival.

An explanation for this discrepancy may be that most modern standard-dose induction chemotherapy is probably as successful as more intensive regimens in reducing marrow blasts to less than 5%. CR as measured by blasts in bone marrow on morphology (CR-BM) fails to detect clinically important residual disease in about 50% of patients who subsequently relapse. Thus, when reporting clinical trials it would be useful to routinely report cytogenetic CR (CR-C) or loss of a molecular marker (CR-M) to better understand the likely burden of residual subclinical disease.

The important observation that intensified induction therapy prolongs remission may also provide a useful clinical tool to evaluate a number of new induction therapies, all of which could produce high rates of CR. We have recently defined a new endpoint, time to failure, for evaluating induction treatment. This endpoint incorporates early deaths, failure to achieve CR, relapse after CR, and death in CR. This endpoint allows the individual types of failure to be studied as competing risks and is a valuable method for comparing induction regimens.

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REFERENCES


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