In cases where asymptomatic ON is diagnosed by routine MRI, there is no evidence extant to suggest that any intervention such as reducing further steroid exposure or starting therapy such as a statin might decrease the incidence of progression to symptomatic ON. In the study by Kawedia et al, management of patients with symptomatic ON was not standardized, but left to the discretion of the treating physician. One could conceive of a possible trial design in which patients with high serum lipids and low serum albumin and/or decreased dexamethasone clearance might be eligible for an intervention such as statin therapy in an effort to reduce the risk of grade 3 and 4 ON.

In my opinion, this study does not provide evidence that screening asymptomatic patients for ON by MRI provides clinical benefit, and screening should not be performed outside the context of a well-designed clinical trial. If screening is performed, it will be critical to control how therapy is changed if asymptomatic ON is discovered, because this study suggests that a large percentage of patients will have such findings. Screening should not be performed on a routine basis in patients < 10 years of age. For older patients, one could consider screening only those patients at increased risk for developing symptomatic ON but, however, we lack clearly defined risk factors for symptomatic ON and we have no evidence that any intervention would be effective in patients identified by screening.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Comment on Ohtake et al, page 2358, and on Miyawaki et al, page 2366

Too much ara-C? Not enough daunorubicin?

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It seems strange, but after 40 years of experience using cytosine arabinoside (ara-C) and daunorubicin, leukemia doctors are still unsure as to how much of each drug they should use to treat their patients with acute myeloid leukemia (AML).

Most would agree that, as initial therapy for patients with AML, ara-C by continuous infusion, in combination with a topoisomerase II inhibitor (eg, daunorubicin, ida rubcin, mitoxantrone) is a standard of care around the world. In the postremission setting, administration of repeated cycles of escalated doses of ara-C is widely accepted as the optimal nontransplant treatment strategy. However, despite a farrago of studies, there continues to be debate on 2 points: (1) what is the optimal topoisomerase II inhibitor to use during induction therapy and at what dose, and (2) how much ara-C should be administered after remission and to which patients? In this issue of Blood, the results of a trial conducted by the Japan Acute Leukemia Study Group (JALSG) adds additional complexity to the debate. In a study (published as 2 separate papers) of more than 1000 untreated adults with AML under the age of 65 years, high doses of daunorubicin were compared with standard doses of idarubicin during induction, and high-dose ara-C was compared with a standard dose, ara-C–based multigagent regimen in the postremission setting.1,2

In the 1970s daunorubicin at a dose of 45 mg/m² × 3 (cumulative dose 135 mg/m²) combined with infusional ara-C for 7 days (“7 + 3”) was established as an effective regimen in adults with untreated AML.3 Studies conducted in the 1990s and reaffirmed in subsequent later trials, established both idarubicin (12 mg/m² × 3 doses) and mitoxantrone...
c-Kit mutations associated with the CBF AMLs. Do these patients benefit from the higher doses?

For AML patients with intermediate and poor-risk karyotypes, the benefit of postremission high-dose ara-C is less well established. A retrospective analysis by the CALGB showed that in AML patients with a normal karyotype, a significant disease-free, but not overall survival, advantage was observed in the intermediate-dose and high-dose ara-C cohorts compared with lower doses. The current JALSG study suggests that these patients do just as well with standard-dose regimens. None of the studies have demonstrated an advantage for ara-C dose escalation in poor-risk patients. Thus it can be argued that the routine use of high doses of ara-C may not be justified in patients other than those with a CBF mutation. It is unfortunate that data on NPM1 and FLT-3 mutations are not available from the JALSG study. Retrospective trials have demonstrated that patients with NPM1 mutations, without FLT-3 mutations, have similar outcomes to those of patients with CBF mutations, and it would be helpful to know if high-dose ara-C is an important factor in this outcome.

Conflict-of-interest disclosure: The author declares no competing financial interests.

**REFERENCES**


8. Bloomfield CD, Lawrence D, Byrd JC, et al. Frequency of t(8;21) and Inv (16)—the core binding factor (CBF) leukemias. The JALSG study published in this issue reaffirms the effectiveness of high-dose ara-C compared with standard doses in CBF mutated AML patients, but shows a lack of benefit over standard-dose ara-C—based consolidation therapy in the intermediate and unfavorable karyotypic subsets of AML.

Are we giving too much ara-C to patients with AML? The higher incidence of prolonged myelosuppression and serious infections observed in patients treated on the high-dose ara-C arm of the JALSG study should mandate a clearly proven clinical benefit for high doses to justify the risk of increased toxicity. For patients with CBF AML, the benefit of high-dose ara-C has now been demonstrated in multiple studies and this approach should be considered the standard of care. However, do we have to deliver up to 18 g/m^2 to these patients or can we obtain similar efficacy with a dose somewhere between 2 and 18 g/m^2? This is as yet unanswered. Also unanswered is the relevance of C-Kit mutations associated with the CBF AMLs. Do these patients benefit from the higher doses?

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**LYMPHOID NEOPLASIA**

Comment on Annunziata et al, page 2396

**MEK and MAF in myeloma therapy**

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Despite increased understanding of molecular pathogenesis of multiple myeloma and implementation of therapies such as bortezomib and thalidomide, only 10% of patients survive more than 10 years after diagnosis. Until recently, new therapies for myeloma have not been developed based on a detailed understanding of the molecular pathology of the disease. In this issue of Blood, Annunziata et al report a rationale for the use of mitogen-activated or extracellular signal-regulated protein kinase (MEK) inhibitors in the subset of myeloma patients expressing high levels of the MAF oncogene.

The molecular pathogenesis of multiple myeloma has become clearer with the identification of recurrent chromosomal translocations in approximately 40% of cases. These rearrangements represent aberrant class switching resulting in the linkage of the immunoglobulin promoter/enhancer to the Cyclin D1, Cyclin D3, MMSET, and FGFR3, c-MAF, or MAF-B genes. Gene expression profiling found that myeloma could be distinguished from
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