(12 mg/m² × 3 dose) as equivalent, if not, superior, substitutes for daunorubicin. More recently, a trial conducted by the Eastern Cooperative Oncology Group (ECOG) demonstrated that doubling the dose of daunorubicin to 90 mg/m² × 3 (cumulative dose 270 mg/m²) significantly improved survival in adults with AML under the age of 60 years. In the current study by the JALSG, daunorubicin 50 mg/m² × 5 (cumulative dose 250 mg/m²) was found to be equivalent but not superior to idarubicin 12 mg/m² × 3. Importantly, in both the ECOG and JALSG studies, the higher than standard doses of daunorubicin did not appear to increase the risk of infection or cardiomyopathy.

What conclusions can be made? Whether one should use high-dose daunorubicin (250-270 mg/m² cumulative dose) or either idarubicin, mitoxantrone (or even daunorubicin at 60 mg/m² × 3) is unanswered, but one point should be a clear: daunorubicin 45 mg/m² × 3 is no longer the standard of care in AML patients under the age of 65 years.

The rationale for the administration of high doses of ara-C is based on a multitude of clinical and pharmacodynamic studies conducted over the past 3 decades. The oft-cited Cancer and Leukemia Group B (CALGB) trial 8461 demonstrated that, in patients under the age of 60 years, repeated cycles of ara-C administered at a cumulative dose of 18 g/m² led to superior survival compared with lower cumulative doses of 2 g/m² or 500 mg/m². Further analysis of this trial, as well as others, showed that the benefit of the high-dose arm was observed, for the most part, in patients with a favorable karyotype; 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/m² to these patients or can we obtain similar efficacy with a dose somewhere between 2 and 18 g/m²? This is as yet unanswerable. Also unanswerable is the relevance of 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

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...
addition, myeloma cells with t(14;16) required progression and adhesion to the bone marrow stroma. In immunodeficient mice. To determine the path-tumors in nonobese diabetic–severe combined immunodeficient mice.

RAS can affect the PI3K and PI3 kinase, as well as the MAP kinase pathway. In the setting of myeloma, MEK inhibitors could kill cell lines resistant to conventional chemotherapy, including some expressing high levels of MAF. MEK inhibitors prolonged overall survival and decreased phosphorylation of ERK in a xenograft mouse model based on MAF overexpressing t(4;14) cell line OPM1. In addition, inhibition of MEK enhanced myeloma cell killing in the presence of dexamethasone, bortezomib, or lenolidomide, further suggesting that MEK inhibitors could enhance the efficacy of current myeloma therapy. In light of the current work, future clinical trials of MEK inhibitors in myeloma must be sure to include subsets of patients with MMSET and MAF rearrangements that collectively represent only one-third of all patients, lest a positive result be lost among the other two-thirds of patients who might not respond.

While gene expression profiling identifies 7 types of myeloma, currently therapy is based on empirical studies that predate the molecular classification of disease. Although it was clear that chromosomal anomalies and gene expression patterns have prognostic importance, the current study is one of the first to elucidate a therapy specific to molecularly defined subsets. Whether MEK inhibitors will prove effective in the clinic may also depend on the nature of other genetic changes found in myeloma. Besides the recurrent chromosomal translocations that represent initial genetic events, there are additional genetic events commonly found in myeloma, including activating mutations in RAS and NFkB pathways, rearrangements leading to MYC deregulation, and inactivating mutations in important cellular and epigenetic regulators such as p53 and UTX. With the cost of whole genome and exome sequencing rapidly declining, myeloma therapy in the next decade might involve genotyping of individual tumors and the use of rational therapy combinations to intervene with multiple affected pathways.
Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

THROMBOSIS & HEMOSTASIS

Comment on Acharya et al, page 2484

Unraveling hemophilic arthropathy

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In this issue of Blood, Acharya and colleagues provide evidence for the role of angiogenesis in the pathophysiology of hemophilic joint disease.1 Is this the linchpin that unravels this important clinical condition or merely a cog in a not so stepwise process?

Joint disease has always been the hallmark of severe hemophilia, but recent practice of regular infusions of intravenous factor VIII or IX (prophylaxis) from an early age has lessened its impact. Prophylaxis has now become the standard of care for children with hemophilia,2 but for those born in the preprophylaxis era or who demonstrate bleeding despite the regular infusion of factor concentrates, the treatment of established joint disease must include (alone or in combination) ongoing infusions of factor concentrate, radionuclide, or surgical synovecomy,3 or for those with end-stage arthropathy, chronic anti-inflammatory and pain management and/or joint replacement. Interestingly, it is well recognized that not all subjects with severe hemophilia will have joint bleeding and not all with joint bleeding demonstrate progressive joint disease. This paradox speaks to the role of factors other than the factor VIII/IX level and/or clinical bleeding as important to this process.

The hallmarks of hemophilic arthropathy involve joint bleeding, inflammation, synovial hypertrophy/villous formation, and cartilage/bony destruction; in essence, inflammation and cellular proliferation (angiogenesis). Iron deposition from joint bleeding, deep in synovial tissue, appears to be a key culprit. Iron has also correlated with increased c-myc expression,4 as well as overexpression of mdm2.5 The increased inflammatory response is a result of monocytes/macrophages recruited to the area along with accompanying inflammatory cytokines (interleukin-6 [IL-6], IL-1β, tumor necrosis factor α).6 The actual mediators of cellular proliferation and synovial hypertrophy are unknown, but evidence has partially implicated the previously mentioned cytokines and c-myc and mdm2 expression. In this issue of Blood, Acharya and colleagues provide evidence for the role of key angiogenic factors (vascular endothelial growth factor [VEGF], matrix metalloproteinase-9) in cellular proliferation.1

Several key experiments were performed to support the authors’ hypothesis that angiogenesis plays a major role in the pathogenesis of hemophilic arthropathy. First, proangiogenic growth factors (previously mentioned) and monocytes/macrophages (CD68+, CD11b+) were both significantly elevated in synovium and peripheral blood of hemophilic patients with joint disease compared with controls. Second, sera and peripheral blood monocytes from subjects with hemophilia caused endothelial cell and synovial cell proliferation, and these proliferative responses were down-regulated by blocking the effect of VEGF. Finally, the potential role of hypoxia in this angiogenic process was suggested by expression of hypoxia-inducible factor 1α from human synovial cells when incubated with sera from subjects with hemophilic arthropathy. The figure is illustrative of the pivotal role of monocytes and key angiogenic factors in synovial hypertrophy (see figure). It demonstrates (red arrow) by immunofluorescent staining, CD68+ cells coexpressing VEGF in the synovium of a subject with hemophilic arthropathy.

It is not surprising that angiogenesis plays a key role in hemophilic arthropathy.
MEK and MAF in myeloma therapy

Relja Popovic and Jonathan D. Licht