cyclosporine, is the mainstay of treatment of children and adults younger than age 40 years with severe aplastic anemia who lack a histocompatibility locus antigen-matched related donor. However, as reported for the proband in the Guo article and suggested by numerous cases in the literature, severe aplastic anemia resulting from a constitutional defect in telomere length maintenance is not responsive to immunosuppressive therapy. Thus, the prompt recognition of an underlying telomere biology disorder can spare patients from ineffective and risk-associated immunosuppressive therapy. In addition, if a matched related donor is available, he or she can be screened for the underlying telomere biology disorder, thereby avoiding transplantation with similarly affected hematopoietic stem cells.

Telomere length testing at the time of BMF presentation may provide the laboratory-based data needed to arrive at a telomere biology disorder diagnosis. Multiple methods for telomere length testing have been developed, and an assay that combines flow cytometry with fluorescent in situ hybridization (Flow-FISH) is available as a clinical test. When examined using the Flow-FISH assay, individuals with DC have very short telomere length across leukocyte cell types, with “very short” defined as telomere length less than the first percentile for age. Specifically, very short telomere length in 3 or 4 of total lymphocytes, naive T cells, memory T cells, and B cell subsets, as determined by Flow-FISH, is both highly sensitive and specific for DC. Whereas some patients have profoundly short telomeres, others may have telomere lengths that hover around the first percentile, as did the proband in Guo et al. Additionally, telomere length slightly below the first percentile across lymphocyte populations has been observed, albeit rarely, in patients with inherited bone marrow failure syndromes other than DC, such as Fanconi anemia, Diamond-Blackfan anemia, and Shwachman-Diamond syndrome. Thus, short telomeres and BMF alone may be insufficient to arrive at a diagnosis of an underlying telomere biology disorder.

Ultimately, gene mutation data, as obtained by Guo et al., can provide the essential support for an underlying telomere biology disorder. Thus, continuing efforts to arrive at the full repertoire of genes associated with the telomere biology disorders is of particular importance as we strive to accurately diagnose and provide optimal care to patients with BMF.

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

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CLINICAL TRIALS & OBSERVATIONS

Comment on Scheinberg et al, page 2820

Cyclophosphamide in severe aplastic anemia?

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In this issue of Blood, Scheinberg et al investigate moderate-dose cyclophosphamide (120 mg/kg) in treatment-naïve patients with severe aplastic anemia (SAA). The study was stopped for safety reasons.

SAA is a rare but serious form of bone marrow failure related to an immune-mediated mechanism that results in severe pancytopenia, a high risk of life-threatening infection, and hemorrhage. Allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling donor is the treatment of choice for young patients, leading to an 80% to 90% chance of survival, with no or few complications in the long term. In the absence of an HLA-identical sibling donor or in older patients, excellent outcomes can be achieved with the current gold standard first-line immunosuppressive therapy (IST) consisting of antithymocyte globulin (ATG) plus cyclosporine (CsA; 60-70% response rate and 70-80% long-term survival). After IST, only one-third of the patients are cured, one-third are dependent on long-term administration of CsA, and one-third will either relapse or develop a clonal disorder (myelodysplastic syndrome or acute myeloid leukemia); the latter complications are usually rare after BMT. Additional immunosuppressive drugs (ie, high-dose corticosteroids, mycophenolate mofetil, or sirolimus) have been added to the ATG/CsA backbone with the objective of decreasing relapse and secondary clonal disease, but thus far, no improvement in outcome has been observed. The use of rabbit ATG, a more potent immunosuppressant drug than horse ATG, did not improve the rate of hematological recovery and was associated with a detrimental effect on overall survival, justifying the recommendation to prioritize horse ATG in this setting.

Cyclophosphamide is as an alternative immunosuppressive drug in treatment-naïve patients with SAA, which may improve outcome but has already generated considerable controversy. A single phase 2 study conducted at the Johns Hopkins University testing high-dose cyclophosphamide (200 mg/kg) was updated in 2010 and an editorial in this journal
commented on the update. The reported high-level range results were of an overall actuarial survival rate of 88% (response rate of 71%) and an actuarial event-free survival rate of 58% in 44 treatment-naive patients at 10 years. Unfortunately, this procedure was associated with long-lasting neutropenia and severe fungal infections occurring at a rate of 18.2%. Moreover, in a randomized study conducted at the National Institutes of Health, directly comparing high-dose cyclophosphamide and horse ATG/CsA in treatment-naive patients, excess toxicity and death from invasive fungal infections were observed in the cyclophosphamide arm, which led to early termination of the protocol. A Chinese trial of moderate doses of cyclophosphamide (30 mg/kg per day for 4 days) appeared attractive when presented at a specialty conference several years ago and is now available in print, with an abbreviated period of neutropenia, little morbidity and mortality, and a response rate comparable to rabbit ATG. Those results combined with the recent drastic improvement of antifungal drugs justified further investigation of moderate doses of cyclophosphamide in patients with SAA.

Scheinberg et al report on 22 consecutive treatment-naive patients with SAA who were treated with moderate-dose cyclophosphamide (120 mg/kg) plus low-dose CsA (recommended therapeutic range between 100 and 200 µg/L). Overall, 9 patients (41%, 95% confidence interval [CI], 20-62%) responded at 6 months (4 complete and 5 partial remissions). The average duration of severe neutropenia (<0.2 × 10^9/L) was 2 months. The average length of initial inpatient hospitalization was 47 days, and confirmed filamentous fungal infections were documented in 6 cases despite aggressive antifungal prophylaxis. With a median follow-up of 2.2 years, the cumulative incidence of clonal evolution was 22% (95% CI, 0-39%), the cumulative incidence of late events (clonal evolution + relapse) was 28% (95% CI, 4-46%), and the overall survival at 2 years was 72% (95% CI, 55-94%) (see figure). The Data Safety Monitoring Board eventually recommended termination of accrual due to unacceptable toxicity. Of course, differences exist between this study and the Chinese one that may explain the discrepancies in results (technical issues, ethnic considerations, and daily care). However, 2 (1 randomized) prospective controlled trials of cyclophosphamide at 200 mg/kg or at moderate doses (120 mg/kg) in treatment-naive patients with SAA are now published, both indicating unacceptable rates of toxicity with no benefit in term of relapse or clonal evolution.

Consequently, the real question is not whether we should continue to use cyclophosphamide in SAA (obviously not outside prospective clinical trials) but whether cyclophosphamide is a good investigational drug for SAA in 2014. Trials in the field are difficult to conduct mainly because of the rarity of the disease and the excellent outcome after standard treatment combining horse ATG and CsA. Moreover, one has to take into account other recent important insights in the field of SAA:

1. The outstanding results of the oral thrombopoietin mimetic eltrombopag in patients with refractory SAA with multilineage clinical responses in some patients. Eltrombopag has just been approved for this indication in the United States by the federal Food and Drug Administration, and preliminary results in previously untreated patients are promising. The drastic improvement of unrelated BMT with a recent presentation at the last European group for Blood and Marrow Transplantation (EBMT) meeting from the UK group using this procedure first line (whereas normally reserved to refractory patients after IST failure) and showing excellent results.

The SAA working party of the EBMT decided to prioritize a prospective randomized trial, which will compare horse ATG plus CsA with or without eltrombopag (http://clinicaltrials.gov/show/NCT02099747) in treatment-naive patients. At this time, unrelated BMT also seems very promising, yet the average 3-month delay between the diagnosis of SAA and BMT, mainly because of donor recruitment, renders such a procedure in patients with severe neutropenia at diagnosis difficult. Thus, cyclophosphamide does not appear to be a clinical research priority in treatment-naive patients with SAA.

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

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Comment on Krevvata et al, page 2834

Cellular thrust and parry in the leukemic niche

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In this issue of Blood, Krevvata et al show that osteoblasts duel with acute leukemia cells, each having adverse effects on the other.¹

The notion that cancer is a disease of tissues rather than that of a single rogue cell type has increasingly gained ground, particularly in the setting of hematologic malignancies. Although a single cell type generally exerts the pathologic consequences of malignancy, there is accumulating evidence that other cell types can contribute to the initiation, maintenance, and progression of the neoplasia. The report by Krevvata et al adds evidence that osteoblast loss is a necessary component of acute leukemic progression.² Reducing that loss mitigated the leukemia.

Tumor stroma has long been regarded as a coconspirator in the malignant process. Cancer-associated fibroblasts (CAFs) are not the same as fibroblasts from surrounding normal tissue in solid tumors like those of the breast, colon, or lung. The CAFs have been implicated in inducing neoangiogenesis, extracellular matrix reorganization, metabolic context, and growth factor milieu to enhance cancer progression.² These mesenchymal cells are not alone in the tumor-supporting cast because hematopoietic populations resident in tumors have become of central interest in tumor progression. Among these, macrophages are the most abundant and provide cytokines such as epidermal growth factor to enhance malignant cell growth and vascular endothelial growth factor and Tie2 to promote neoangiogenesis.³ They both respond to the presence of cancer cells and feedback to the cancer cells. This includes metabolites because cancer-cell lactate production induces M2 polarization of macrophages. These M2 cells have high levels of arginase-1 known to dampen lymphocyte activity, and perhaps also enhance polyamine synthesis needed by tumor cells for their propagation.⁴ Thus solid tumors have co-opted cells in their environment such that these stromal components enable cancer cell growth.

A similar paradigm has been shown in hematopoietic neoplasms where, for example, myeloproliferative neoplasm (MPN) cells induced increased osteoblastic cells and marked gene expression changes in mesenchymal stromal cells. Increased transforming growth factor-β and decreased CXCL12 and kit ligand (among other changes) compromised stromal cell support of normal hematopoietic cells in vitro, but not malignant ones.⁵ Tumor cells were preferentially supported over their normal counterparts in the coculture system.

However, the co-evolution of neoplastic cells and their stromal components also has a more hostile face in hematologic malignancies. Some cells of the bone marrow microenvironment appear to drop out in the presence of malignancy. Krevvata et al showed that this is true of osteoblastic cells in the setting of acute myeloid leukemia (AML) or myelodysplasia (MDS) among patients, and in
Cyclophosphamide in severe aplastic anemia?

Régis Peffault de Latour