enrolled in the study (10 of 23) had to discontinue treatment within the first 3 cycles of therapy due to 4 early deaths, 3 adverse events, and 3 other causes. The level of cardiac biomarkers accurately predicted which patients were most likely not to complete 3 cycles of therapy.9

Clearly with these poor outcomes, there is a need for improved therapy. Recently, bortezomib has been reported to have activity in light chain amyloidosis.10 However, this agent has not been extensively tested in patients with class III or class IV New York Heart Association cardiac failure.11

What are the take-home messages? First, therapy for the treatment of light chain amyloidosis remains a challenge. Those patients who need treatment most benefit the least. Second, it is dangerous to make treatment-based decisions simply on the outcomes of single-institution phase 2 trials because patient selection plays as much a role in outcome as the specifics of therapy. Third, the introduction of the free light chain level helps facilitate assessment of responses following treatment and the introduction of cardiac biomarkers will help stratify future studies so their comparability is improved. As noted in the study by Dietrich et al, only 9% of their patients were stage I amyloidosis while 53% were stage III, which likely accounts for the poor reported outcomes. Although melphalan and dexamethasone is the current standard of therapy, its ability to provide benefit is highly dependent on selection of the correct patients. A multinational study comparing melphalan and dexamethasone to melphalan, dexamethasone, and bortezomib is scheduled to begin this year. Enrollment in studies of treatment remains the only way to advance our knowledge in this field where improvement in outcomes remains a major therapeutic challenge.

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long been accepted as a critical factor for progression of solid tumors, where vascular supply needs to keep up with tumor growth. The role of angiogenic factors in hematopoietic cancers has been more controversial from a conceptual standpoint, given that leukemia cells in the marrow presumably have a less restricted access to blood and its nutrients. However, the recent emphasis on the microenvironment’s influence in leukemia progression and drug resistance is also nurturing the interest in angiogenesis and in interactions between leukemia and endothelial cells. Normal marrow hematopoiesis requires intimate contact of hematopoietic elements with a heterogeneous population of adherent cells collectively referred to as “stroma.” These accessory feeder cells form specialized “niches” that are close to the marrow vasculature (vascular niche) or to the endosteum (osteoblast niche). Leukemia cells usurp these niches, causing hematopoietic dysfunctions. Intimate contact between leukemia cells and ECs in marrow niches and the increased microvesSEL density in marrows infiltrated by CLL cells support the concept of crosstalk between CLL and ECs via the VEGF and the Ang-2/Tie2 axes, and indicate that such interactions are an integral part of the marrow microenvironment.

Besides the fascinating insights into the role of Ang-2 in CLL pathophysiology, Maffei et al emphasize that Ang-2 is an independent prognostic marker and could potentially become clinically useful for risk assessment. The large number of other prognostic factors in CLL, and the fact that none of these established prognostic markers has yet changed our clinical practice (observation in early disease stages, treatment in advanced stages) raise the question whether and why we need yet another prognostic marker in CLL. Early intervention studies in CLL patients have not been beneficial in the past, and a trial by the German CLL study group (CLL7) in which high-risk patients are randomized to receive FCR chemo-immunotherapy either at an early stage or at an advanced stage is ongoing, with data from the trial not yet available. Several other angiogenic factors, such as VEGF, basic fibroblast growth factor (bFGF), and Ang-2 in smaller series have previously been identified as prognostic factors in CLL, but never became widely used. Possible overlap with other angiogenesis-related markers and unique features of Ang-2 needs to be better defined in future studies to establish a solid rationale for measuring Ang-2 in CLL. On a more technical note: the cut-off for Ang-2 of 2459 pg/mL to distinguish high-versus low-risk patients seems impractical and should be rounded for future studies. Overall, Ang-2 is likely to be primarily used in correlative research studies in the near future. However, this may change once we better understand the source(s) and regulation of Ang-2 expression in CLL and/or once we have drugs available to therapeutically target this axis.

What makes Ang-2 different from other prognostic markers is the fact that Ang-2 is related to angiogenesis and probably reflects complex interactions between CLL cells and their microenvironment. In contrast, the most prominent other prognostic markers in CLL, the IgVH mutation status, cytogenetic abnormalities, and expression of CD38 and zeta-associated protein of 70-kD (ZAP-70), use intrinsic features of the leukemia cells as prognostic indicators. This raises question about Ang-2 regulation and the source(s) of elevated Ang-2 levels in patients with higher-risk CLL. The authors state that their prior work and the immunohistochemistry data in this paper suggest that CLL cells are the principal source of elevated Ang-2 levels in CLL patients. Surprisingly and in contrast to patients with multiple myeloma, the authors did not find any correlation between the degree of marrow infiltration and Ang-2 levels, nor did they find any changes of Ang-2 levels in patients undergoing treatment, indicating that the disease burden may have no impact on Ang-2 levels. Studies about the regulation of Ang-2 expression by CLL cells, for example, the effect of coculture of CLL cells with endothelium on Ang-2 expression, may help to clarify this important issue. As such, this paper encourages more exploration of function and significance of angiogenic factors in CLL. Such studies will help to determine whether or not Ang-2 will play in the premier league of prognostic markers in CLL.

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REFERENCES
Angiopoietin-2 in CLL

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