sporadic cases of pediatric ALL demonstrated that signatures did not reflect the nature of the specific *ETV6* variants, but rather the presence of other genetic features including the ploidy status of the leukemia. Indeed, the authors show that damaging diploid cases cluster with ETV6-RUNX1 ALL cases, which are also enriched in recurrent *PAX5* and *ETV6* copy number losses (see figure). The ability to discriminate damaging from WT-like *ETV6* germline variants was fruitful in defining a transcriptional program activated in the presence of these variants. This signature comprises 94 putative ETV6 target genes, including the Chloride Intracellular Channel 5 (*CLIC5*), which was recently reported as being directly repressed by ETV6.[6] It is difficult to predict with complete confidence, a mechanism contributing to *ETV6*-driven malignancy without further validation, but one possibility worth considering is that the overexpression of *CLIC5* in *ETV6*-mutated cases could impart resistance to oxidative stress, permitting accumulation of DNA damage and acquisition of secondary leukemia driver events.[6]

More broadly, the study by Nishii et al emphasizes the complexity associated with predisposing genes for inherited hematological malignancies, including *CEBPA*, *GATA2*, *SAMD9L*, or *RUNX1*,[7-9] where the type or location of the germline variant and/or the acquisition of an additional mutation in the same gene appears to determine the penetrance and progression of disease. The functional annotation of gene mutations forms an increasingly important component of genetic counseling for inherited disorders, together with an assessment of clinical presentation and family pedigree. The American College of Medical Genetics, in conjunction with the Association for Molecular Pathology and the College of American Pathologists, have developed a consensus framework for the interpretation of sequence variants.[10] Critically, as achieved here by Nishii et al, functional studies showing the deleterious effects of a given variant in a gene previously associated with disease pathogeny, bolster the classification of such a variant to a "likely pathogenic" status, which is particularly valuable for informing medical decisions.

As demonstrated by this study, it is important not to assume that all variants are damaging; for many loci, the absence of a rigorous assessment of the effect of germline variants on gene function necessitates their classification as "unknown significance," thus limiting their diagnostic value. It is certainly reasonable that all variants should be presumed WT-like until proven otherwise, but equally we should remain cognizant that 50% of *ETV6* WT-like variants were not reported in the gnomAD dataset and could conceivably be influencing ETV6 function by as-yet-undetermined means.

Altogether, it is sensible that we encourage more studies like the one described here by Nishii et al, where a rigorous assessment of function is undertaken on the spectrum of variants affecting a given gene. There is a tacet acceptance among researchers that all variants are not created equally, and indeed damaging variants themselves may differ in their penetrance and severity. Although we should be heartened at the increasing awareness of germline predisposition to hematological malignancies, it remains the subject of healthy debate how germline information should be incorporated most effectively into the clinical management of a patient and their family. Confirmation that a variant is deleterious would seem like a good place to start.

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LYMPHOID NEOPLASIA

Comment on Evens et al, page 374

The balancing act in Burkitt lymphoma

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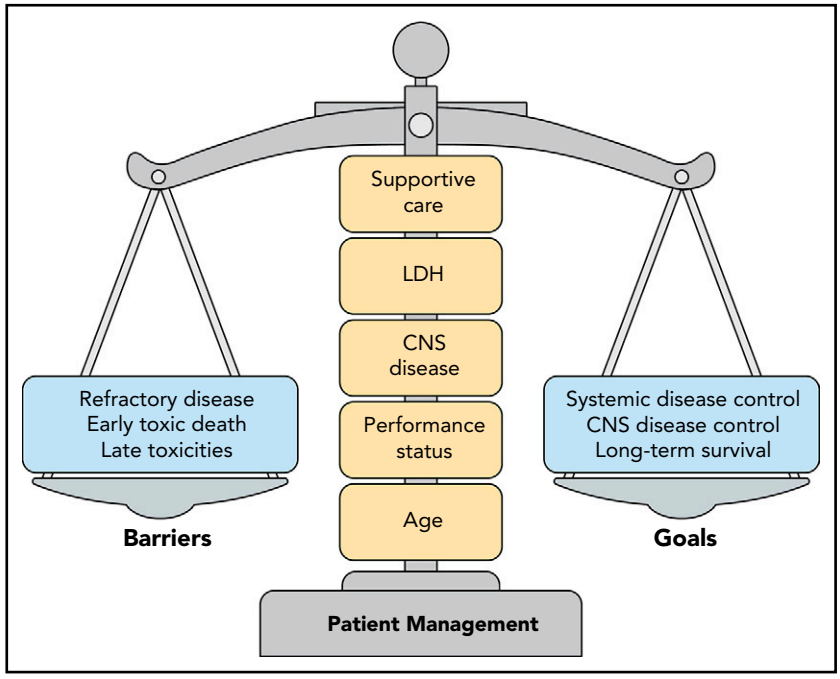
In this issue of *Blood*, Evens et al highlight critical prognostic factors that drive outcomes across the full continuum of adult patients with Burkitt lymphoma (BL) in the United States.[1]

These factors include the age and condition of the patient, the extent of tumor burden as measured by the serum lactate dehydrogenase (LDH) level, and the presence of central nervous system (CNS) disease. Importantly, these prognostic factors do not include infection with human immunodeficiency virus (HIV). Although these factors have been recognized as critical determinants of outcome in both



Optimal patient management strategies for adults with BL require a careful evaluation of prognostic factors. The primary barriers to achieving disease control and long-term survival are primary refractory disease, early toxic deaths related to therapy, and the risk of late toxicities. Overemphasis of a single factor can unfavorably tip this delicate balance. The factors that require careful consideration are a combination of patient-related factors (age, performance status), biology-related factors (CNS disease, LDH level), and the resources available for prompt implementation of intensive supportive care.

children and young adults with BL, this large retrospective series of 641 patients captures the magnitude of barriers preventing the cure of older adults in real-world clinical practice settings, as the 3-year progression-free survival was only 64% in this cohort with a median age of 47 years.[2-5] An important, yet underappreciated, factor was where the treatment was delivered. The 12% of patients treated at community hospitals had an inferior overall survival compared with the patients treated at academic hospitals. This observation raises the question of whether the underlying reasons reflect patient referral bias, availability of supportive care resources, lack of expertise in complex disease management, or a combination of factors. The successful management of BL requires prompt implementation of intensive supportive care along with early institution of intensive chemotherapy. The optimal management strategy for individual adult patients requires delicate balancing of all these factors, to achieve long-term survival and avoid early toxic death (see figure). Most prospective clinical trials report high cure rates in adults with BL, often in the 75% to 85% range. However, this series shows that the cure rates are actually much lower in routine practice, suggesting that prospective clinical trials may not adequately capture the patients at highest risk of early death.

BL poses unique management challenges because it is a highly aggressive tumor with a predilection for involvement of extranodal sites, including the bone marrow and/or CNS.[6] In addition, because of rapid tumor proliferation, spontaneous tumor lysis syndrome may occur, even before initiation of therapy. Frequent gastrointestinal involvement increases the risk of perforation, and electrolyte disturbances may require hemodialysis early in the treatment course. Hence, early recognition of "possible BL" is a medical emergency that should lead to urgent diagnostic procedures and prompt initiation of aggressive supportive care designed to prevent organ compromise during the first few cycles of therapy. As an example, 27% of the patients in this series had LDH levels >5 times normal which should always prompt suspicion of possible BL. However, because BL represents only 1% to 2% of all lymphomas in adults, these clinical signs may not be fully appreciated by practitioners who are not focused on hematologic malignancies. Indeed, the treatment-related mortality (TRM) in this series was 10%, with the most common causes of death being sepsis (51%), intestinal perforation (15%), and respiratory failure (15%).

The first effective chemotherapy regimens for BL were pediatric: highly dose-intensive combination chemotherapy regimens that included agents that specifically penetrate the CNS.[7,8] In general, BL is considered a highly chemotherapy-sensitive tumor, and the complete remission rates of these pediatric regimens are very high. Yet, in this series, the primary refractory disease rate was 14%, suggesting a greater rate of intrinsic chemotherapy resistance than is commonly appreciated. Second, active CNS involvement is a known poor prognostic marker across all regimens used for BL. The rate of involvement at diagnosis is ~10% in most prospective clinical trials. In this series, the CNS involvement rate was 19%, including 3% of patients with brain parenchymal involvement, and was more common in patients with HIV infection ($P < .001$). These data support the notion that agents with good CNS penetration are critical. Further, the high rate of primary refractory disease suggest that chemotherapy agents alone may be inadequate to overcome treatment resistance.

Although pediatric regimens are highly effective in children and young adults, older patients often cannot tolerate these regimens. In this series, the TRM was only 2% in patients aged <40 years of age, but jumped to 16% in patients aged ≥60 years. The lower intensity regimen, dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and rituximab (DA-EPOCH-R) has recently been shown to be highly effective in adults of all ages with BL. Careful examination for occult CNS disease is critical, because a risk-adapted approach is used with this regimen to treat and prevent CNS disease. Despite lower dose intensity, patients with active CNS disease treated with DA-EPOCH-R remain at risk for early toxic death caused by sepsis and multisystem organ failure.[2] Finally, all patients regardless of age remain at risk for late toxicities, including secondary malignancies.[9] In this series, 25 (6%) cases of secondary myelodysplastic syndrome or acute myelogenous leukemia were observed after a median of only 45 months and were almost

exclusively observed after highly dose-intensive regimens.

In summary, although this important dataset highlights the critical prognostic factors across the full spectrum of adult patients with BL, only prospective clinical trials can inform the selection of the optimal treatment regimen. Unsurprisingly, the patients treated with lower intensity regimens in this study were older and had a worse performance status than did those treated with highly dose-intensive regimens. Outcomes in adults with BL have significant room for improvement, because of intrinsic treatment resistance and risk of early toxic death. These factors must be carefully balanced when personalizing management strategies. If one is considering highly dose-intensive regimens, then both early and late toxicities should be part of the calculus. If one is considering lower intensity regimens, careful examination of the cerebral spinal fluid by flow cytometry should be performed to avoid undertreatment of CNS disease. The balance of risk factors should be the same in HIV$^+$ patients compared with those without HIV.[2,10] Finally, prompt recognition of possible BL represents a medical emergency that requires rapid diagnosis; intensive supportive care is mandatory for all patients. Practitioners at community hospitals should consider referral to an academic tertiary hospital if they lack sufficient expertise or adequate supportive care resources.

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MYELOID NEOPLASIA

Comment on Jäger et al, page 387

IFN: Jekyll and Hyde

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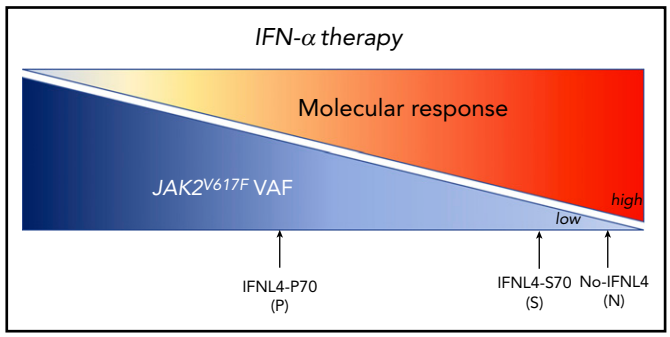
In this issue of *Blood*, Jäger et al report that interferon lambda 4 (*IFNL4*) is an important genetic determinant of interferon-α (IFN-α)–induced molecular response (MR) in myeloproliferative neoplasms (MPNs), allowing a better stratification of patients.[1]

BCR-ABL-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). They result from the transformation of a hematopoietic stem cell leading to the overproduction of mature cells (red blood cells, platelets, granulocytes). The 3 main drivers are *JAK2*^{V617F} in all three of the diseases, and mutations in the thrombopoietin receptor (*MPL*) and calreticulin (*CALR*) genes only in ET and PMF. They are generally treated with drugs that normalize the hematological parameters, ameliorate the symptoms, and decrease the splenomegaly, but have minor impact on eliminating *JAK2*^{V617F} or *CALR*-mutated cells. Type I IFN-α has emerged as an interesting therapy because it induces both a hematologic response (HR) in >70% of ET/PV patients and an MR in >50% of patients.[2,3] However, there is considerable room for improvement as only 20% of patients achieved a major MR response with a remission after treatment. In addition, long-term IFN-α therapy may induce significant side effects (flulike symptoms, tiredness,



The IFN-α therapy induces an MR on JAK2^{V617F} PV patients according to the IFNL4 functional status: very high MR for N: no IFNL4 and S: IFNL4-S70 and less MR for P: IFNL4-P70.