with a higher rate of significant lymphopenia, whereas R-CHOP/R-CVP was associated with increased neutropenia. BR was also associated with a slightly increased risk of opportunistic infections and nausea but decreased neuropathy and alopecia compared with R-CHOP/R-CVP. Follow-up is ongoing, and progression-free survival/overall survival data were not reported.

This report by Flinn et al confirms that the future of therapy for indolent NHL and MCL is increasingly bright, and bendamustine and rituximab are effective agents adding to the armamentarium of resources for patients with untreated disease. However, the potential superiority of a given combination will not be evident without longer follow-up and a comparison of progression-free survival, overall survival, and the incidence of long-term toxicities. Although complete and overall response rates were similar between combinations, each regimen was associated with its own unique toxicity profile. Furthermore, differences between the German StiL study and the current report possibly stem from differences in toxicity reporting and the use of an independent review committee. While we wait for the next report, the management of symptomatic indolent NHL and most MCLs should remain individualized, with continued emphasis on trial entry and management decisions based on close attention to comorbidities, cost, tolerability, and goals of therapy.

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

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Comment on Middeke et al, page 2960

Abnl(17p) in AML: who will guard the guardian?

Minoo Battiwalla

In this issue of Blood, Middeke and colleagues highlight the poor outcome of the abnormal (17p) [abnl(17p)] subgroup of cytogenetically adverse-risk acute myeloid leukemia (AML) even after allogeneic hematopoietic stem cell transplantation (HSCT).1

Metaphase cytogenetics at the diagnosis of AML is routinely used to establish favorable, intermediate, and unfavorable prognostic categories. Unfavorable-risk cytogenetics is a standard indication for HSCT in first complete remission (CR1) for subjects with an available donor. Further dissection of the impact of individual cytogenetic abnormalities within the unfavorable-risk group is ongoing by retrospective analyses of registry studies. Eventually, it will be possible to identify patients who would unequivocally benefit from HSCT.

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REFERENCES
than 1000 different somatic mutations have been described, defying drug development. Mutational effects range from recessive loss of function (with an intact functional copy of the wild-type [WT] allele) to dominant-negative mutations (which dimerize to inactivate WT TP53). TP53 works as the critical mediator of a network that senses cellular stress and, in turn, regulates many other genes. TP53 activation either halts cell proliferation in order to facilitate DNA repair or kills the cell when damage is irreparable (see figure). Loss of TP53 function has been associated with invasion, proliferation, and metastasis. Importantly, TP53 mutation also confers resistance to genotoxic agents, which translates into refractoriness to cytotoxic chemotherapy and irradiation. Conventional small-molecule approaches to restore the functional loss of a defective tumor suppressor have not been successful but there are several promising therapies in development. It is therefore notable that the modest benefit of HSCT in abnl(17p) AML probably suggests that there is residual susceptibility to the graft-versus-leukemia (GVL) effect. Definitive evidence for GVL against abnl(17p) AML, such as responses to donor lymphocyte infusions, is still lacking. However, this does support exploring immunotherapeutic approaches against what is currently an “undruggable” target. Given the critical importance of TP53 mutation in oncogenesis and the absence of a US Food and Drug Administration (FDA)—approved therapeutic, there is an urgent need for strategies that may restore the “guardian of the genome” to its guard post.

**REFERENCES**


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Comment on Steward-Tharp et al, page 2978

**The right “Job” for STAT3 mutant mice!**

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In this issue of *Blood*, Steward-Tharp et al report the generation of a murine model of the human primary immunodeficiency autosomal dominant hyper-immunoglobulin E syndrome (AD-HIES) and reveal novel insights and therapeutic outcomes for this fascinating human monogenic disorder.1

"So Satan went forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown." This quote from the book of Job prefaced the subject of a clinical report by Davis et al that, in 1966, provided the first description of a new primary immunodeficiency. It was named Job’s syndrome after the biblical figure Job who..."
Abnl(17p) in AML: who will guard the guardian?

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