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.

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benefit from HSCT vs those who would be better served by participating in clinical trials with newer antileukemic therapies.

Abnl(17p) has emerged as one of the worst cytogenetic aberrations in AML. Although abnl(17p) may be conveniently identified by conventional metaphase cytogenetics or fluorescence in situ hybridization (FISH), it is only a part of the mutational spectrum in the tumor protein 53 (TP53) gene. TP53 is highly conserved across vertebrates and, in humans, is located on chromosome 17p. Most mutations in TP53 remain cryptic and are only identified by gene sequencing. What do we know about TP53 mutations in AML? Whereas cytogenetically defined abnl(17p) is seen in ~5% of AML, the frequency of TP53 mutations found by sequencing is 8% in de novo AML.2 TP53 mutation is the hallmark genetic aberration, rising to ~30%, in secondary AML.3 Significantly, TP53 mutations are driver mutations, in most cases correlated with a complex karyotype.2,4-6

In this retrospective analysis of pooled registry data, Middeke et al have reported on the outcomes of 201 AML subjects with abnl (17p) by cytogenetics or FISH, all of whom underwent allogeneic HSCT. This is the first large retrospective study to derive definitive conclusions about the value of HSCT with this cytogenetic abnormality. Overall survival (OS) was only 22% even in CR1, and early relapse was the greatest contributor to mortality with a cumulative incidence estimate of 49%.1 Such dismal outcomes are comparable to the monosomal karyotype2 and Flt-3 ITD8 mutations that confer OS of ~20% despite prompt HSCT in CR1. Although the OS with abnl(17p) after HSCT is certainly better than the OS of 0% described in another large series,4 it is clear that HSCT produces disappointing outcomes.

The poor prognosis of this subtype of AML is not at all surprising. TP53 is frequently referred to as the “guardian of the genome” based upon its crucial role as a tumor suppressor gene in protecting against mutations in the genome. TP53 mutations may occur infrequently in the germline (Li-Fraumeni syndrome) but more commonly as acquired somatic mutations that are involved in ~50% of all malignant conditions.9 More 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.10 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.

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

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