TP53 mutations in chronic lymphocytic leukemia

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The prognostic and predictive value of del(17p)/TP53 mutation in patients with chronic lymphocytic leukemia (CLL) is well established [1, 2]. An abnormality in TP53 independently predicts rapid CLL progression and shorter survival, even in the era of novel agents. In addition, patients with TP53 abnormalities or 17p(del) demonstrate significantly decreased time to treatment initiation than those without TP53 aberration [3]. Although CLL patients with leukemia cells characterized by del(17p) and/or TP53 mutation have a poor prognosis when treated with fludarabine-based chemotherapy [1], they do significantly better when treated with non-chemotherapeutic agents such as small molecule inhibitors of Bruton’s tyrosine kinase (BTK), phosphatidylinositol 3-kinase (PI3K), or B-cell lymphoma 2 (BCL-2) inhibitors. Such TP53 abnormalities are now included in the IPI-CLL (International Prognostic Index for Chronic Lymphocytic Leukemia) prognostic model for CLL: patients with 17p deletion, TP53 mutation, or both, are considered to be at high risk [4].

For many years, the standard of care has been based on the detection of TP53 locus (17p deletion) by fluorescent in situ hybridization (FISH) [1]. As monoallelic mutations of TP53 equally affect treatment results, novel methods such as next-generation sequencing (NGS) and functional assays have been developed to improve detection of TP53 abnormalities. In several European countries, and in North America, molecular tests for TP53 abnormalities are routinely used as a part of CLL prognostication. Most Polish centers have only used the FISH method to identify TP53 locus removal (i.e. 17p deletion); however, as monoallelic mutations also have significant negative prognostic impact, it is also recommended to screen for both TP53 mutations and deletions. The most common approach to such screening is NGS, and this is the most convenient option for routine analysis. In addition, ultra-deep NGS permits the detection of minor clones with TP53 mutations, even below 1% [5].

Pepek et al. [6], in this issue of “Acta Haematologica Polonica”, report the results of a study examining the use of NGS in identifying TP53 mutations in relapsed and refractory chronic lymphocytic leukemia (CLL) patients in Poland. The study was initiated by the Polish Adult Leukemia Group (PALG) as an observational study and educational project aimed primarily at providing Polish hematologists with the possibility of testing TP53 mutations by NGS. Additional objectives were to provide laboratory and clinical experience on TP53 mutations in CLL, and to identify subclonal TP53 mutations and other selected gene abnormalities which play a possible pathogenic and prognostic role in CLL.

TP53 abnormalities are less common in previously-un-treated CLL patients than in relapsed or refractory patients. In addition, while no more than 5% of CLL patients are believed to carry the 17p deletion at diagnosis, it has been recorded in over 40% of patients with refractory CLL [7]. It is well established that TP53 mutation analysis should be performed in CLL patients before treatment initiation, and that patients with TP53 mutation should be considered for alternative treatment approaches. In the recent guidelines regarding the detection of tumor protein p53 expression, Eichhorst et al. [2] for the first time have recommended the use of FISH to identify chromosome 17 deletion [del(17p)]; if del(17p) is absent, TP53 sequencing should be performed to detect the presence of TP53 gene mutation. In such cases, it is recommended to test at least exons 4–10, but exons 2–11 should be evaluated. As additional genetic abnormalities can be acquired during the course of the disease, genetic analyses for del(17p)/TP53 mutations should be repeated before the onset of any subsequent treatment in relapsed patients [8–10].

In conclusion, NGS analysis represents a sensitive and reproducible technique for the screening of TP53 gene mutations, and should be performed routinely in CLL patients before each treatment initiation.

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None.

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**Ethics**
The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for Manuscripts submitted to Biomedical Journals.

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