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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-untreated 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.

Authors' contributions

TR — sole author.

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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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