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Tp53 disruptions: is there a marker of poor prognosis in chronic lymphoproliferative disorders?

TO THE EDITOR: We read with great interest the paper by Göçer and Kurtoğlu about a real-life experience of 32 patients with chronic lymphocytic leukemia (CLL, 11/32 cases) or B-cell non-Hodgkin lymphomas (NHL, 21/32 cases) treated with ibrutinib [1]. The authors observed an elevated overall response rate (ORR) and complete response (CR) rate, consistent with available literature data. Overall toxicity was manageable without unexpected adverse events (AE). In all the 11 CLL patients, the deletion of 17p (del17p) mutation was assessed and 4 were positive. Interestingly, a survival curve for overall survival (OS) according to del17p status was performed and showed that in four mutated cases, one had early disease relapse, while the others were disease-free, despite the short follow-up period [1]. We agree with the authors that single-agent ibrutinib is a suitable option for patients with both CLL and NHL, regardless of prior therapies and disease subtype. We strongly appreciate the effort to present a real-world experience on ibrutinib use for NHL patients, including marginal zone lymphoma (MZL), an NHL subtype in which ibrutinib is not approved as treatment in most countries. However, we did not find any mention about del17p or TP53 mutations for NHL cases, even if the TP53 gene could have a prognostic significance in lymphoid malignancies other than CLL. It is interesting to assess TP53 disruptions (17p deletions and/or TP53 mutations) in NHL cases experiencing an early disease progression during or after ibrutinib therapy.

Chronic lymphoproliferative disorders such as MZL are characterized by an indolent course. Rituximab with bendamustine (BR) or alkylating agents as first-line regimens demonstrated long-term efficacy and mild toxicity. However, a small proportion of refractory patients exists and there is a lack of clinical trials to establish the optimal management for this subgroup [2]. Poor prognosis has been associated with TP53 disruptions in many solid tumors and hematological malignancies, including lung cancer and splenic MZL (SMZL) [3]. Noy and colleagues demonstrated the possibility of achieving a durable response with ibrutinib single-agent in relapsed/refractory (R/R) MZL in the PCYC-1121 phase II trial, leading to the Food and Drugs (FDA) approval of ibrutinib for previously treated MZL patients [4, 5]. However, in the PCYC-1121 study, only 14 SMZL cases were enrolled. Göçer and Kurtoğlu also did not specify the MZL subtype in their cohort. Moreover, to our knowledge, only a case of extranodal MZL and 5 cases with central nervous system MZL localization receiving ibrutinb were published. Thus, a real-life experience about SMZL is lacking [1, 4-7].

At our institution, we managed a 17p-deleted, rituximab-refractory SMZL patient with concomitant lung cancer. The patient started first-line therapy with BR and after 4 cycles, CT scan showed normal spleen size and a pulmonary lesion. Histological exam of the lesion after lobectomy demonstrated squamous lung cancer (pT2a-pN0, PDL1-negative, ALK-negative, EGFR not assessed). The patient stopped BR and underwent clinical follow-up for both malignancies. Nine months later, the patient relapsed. Due to this unusual behavior, FISH analysis was performed and revealed a 17p deletion. Karyotype did not show other alterations. We decided to administer a chemotherapy-free regimen using bortezomib and rituximab. A partial response was obtained after 3 cycles; however, CT scan showed lung cancer recurrence. The patient then received platinum-based therapy. However, at oncological restaging, he had lymphocytosis and thrombocytopenia, and CT scan demonstrated stable disease, an increase of spleen size, and enlarged lymph nodes suspicious for a lymphoproliferative disorder. Given the 17p deletion-positive status, we decided to treat the patient with ibrutinib. We obtained the drug for compassionate use after the approval of Institutional Review Board. The patient signed the informed consent form and received 560 mg ibrutinib orally once daily. Spleen size rapidly diminished during the clinical exam and platelet count improved. Although the SMZL clinically improved during the first cycle, the patient developed worsening respiratory failure and underwent sudden death at home, probably due to the concomitant pulmonary neoplasm; autopsy was not performed.

Lymphoproliferative disorders and solid neoplasms with 17p deletion are characterized by poor prognosis with no standard of care, representing an unmet need for clinicians [3, 8]. Interestingly, the presence of TP53 mutations was associated with response to anlotinib, a novel oral multi-targeted antiangiogenic tyrosine kinase inhibitor used in advanced,

non-small cell lung cancer [9]. Moreover, the selective antitumor activity of ibrutinib, an oral BTK inhibitor, was demonstrated in EGFR-mutant non-small cell lung cancer cells [10].

Ibrutinib is highly effective in CLL patients; however, long-term follow-up data showed that patients with TP53 disruptions tend to lose their response. A recently published paper demonstrated a lower capacity of inducing apoptosis on TP53-disrupted CLL cells compared to wild type CLL cells [11, 12]. For B-cell lymphoid malignancies with 17p deletion and/or TP53 mutations, different approaches are currently being tested, such as the use of BTK inhibitors, PI3K inhibitors, and BCL2 inhibitors. Thus, we strongly encourage to test del17p status in R/R patients with CLL or NHL [11-15]. The PI3K inhibitor duvelisib was successfully administered to patients with R/R indolent non-Hodgkin lymphomas (NHL), but it is not available for these malignancies in many countries outside clinical trials [13]. In a phase II trial by Noy and colleagues, ibrutinib gave promising results in previously treated MZL cases, whose responses were recently confirmed after a long-term follow-up analysis [4, 5]. The long-term analysis after a median follow-up of 33 months confirmed the efficacy and safety of ibrutinib in 63 R/R MZL cases; ORR was 58%, and median progression-free survival (PFS) and duration of response (DOR) were 15.7 and 27.6 months, respectively [4, 5]. Remarkably, in an exploratory analysis, even if TP53 was not mentioned, about 1400 cancer genes and 200 microRNA were investigated for a possible association with response and survival, including MYD88, A20, CARD11, KMT2D, and NOTCH-2. MYD88 mutation was associated with improved PFS, while mutations in KMT2D and CARD11 were associated with inferior DOR compared to wild type. NOTCH-2 did not show an association with response or survival [5].

In conclusion, ibrutinib achieved FDA approval for R/R MZL but it is not yet approved in most countries. It should be considered as a new treatment option, especially for MZL or other indolent NHL patients harboring 17p deletion and/or TP53 mutations which represent a subgroup characterized by dismal prognosis.

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