The efficacy of ibrutinib in the treatment of Richter syndrome

Richter syndrome (RS) is defined as the transformation of chronic lymphocytic leukemia (CLL) to a more aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL). Traditional anthracycline- or platinum-based chemotherapy is associated with complete response (CR) rates of <20%, and median survival after transformation is <12 months. Although stem cell transplantation has been shown to improve outcomes in RS, fewer than 15% of patients are able to proceed to transplantation because of primary refractory disease.

Ibrutinib, a Bruton’s tyrosine kinase inhibitor, has shown remarkable efficacy in relapsed/refractory CLL. In a pivotal phase 1B/2 study of ibrutinib in 85 pretreated CLL patients, the overall response rate (ORR) was 71%. Despite this remarkable activity, 7 patients experienced RS at the time of progression. A subsequent phase 3 study (n = 391) comparing ibrutinib to ofatumumab in relapsed/refractory CLL found no difference in the rate of transformation to RS between treatment arms. Although some have interpreted these results to imply that ibrutinib has no activity in RS, we describe here the successful use of ibrutinib in patients with RS. The Mayo Clinic Institutional Review Board approved this study.

Table 1 shows the characteristics of 4 CLL patients who developed biopsy-proven DLBCL. The median time to transformation from CLL was 4.3 years (range, 3.1 to 11.4 years). In the only patient with available testing to determine clonality (patient 3), the DLBCL was clonally related to the underlying CLL. At the time of transformation, 3 patients were initially treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with a suboptimal response. Subsequent regimens in these 3 patients included rituximab, ifosfamide, carboplatin, and etoposide (R-ICE; n = 2); rituximab, cytarabine, cisplatin, and dexamethasone (R-DHAP; n = 1); and rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (R-EPOCH; n = 1) with no response. Because of a lack of efficacious standard treatment options for refractory RS, ibrutinib was initiated in these 3 patients. The fourth patient, with heavily pretreated CLL harboring a 17p deletion, was felt to be a poor candidate for anthracycline-based therapy and began treatment with ibrutinib at the time of RS diagnosis.

The median duration of ibrutinib therapy for these patients was 6.1 months (range, 2.8 to 10.8 months). All patients experienced an improvement in constitutional symptoms. According to the 2007 revised response criteria for malignant lymphoma, 1 patient had a CR and 2 patients had a partial response. The fourth patient was started on low-dose ibrutinib (140 mg per day) because of concomitant voriconazole use (metabolized through the CYP3A4 pathway); he subsequently died of pulmonary mucormycosis (diagnosed prior to ibrutinib initiation) after 15 weeks of therapy and prior to repeat imaging to allow for response assessment. The patient who achieved a CR is currently receiving ibrutinib (duration of therapy,
2.8 months). Of the 2 patients who achieved a partial response, 1 experienced progression of CLL after 11 months and the other experienced progression of DLBCL after 8 months of ibrutinib therapy. Ibrutinib was well-tolerated; no patient required discontinuation as a result of adverse events.

On the basis of gene expression profiling in de novo DLBCL, patients can be stratified according to the cell of origin of the tumor cells—germinal center B-cell (GCB) and activated B-cell (ABC) subtype.8 When treated with R-CHOP, de novo DLBCL patients with ABC subtype have a worse prognosis compared with those who have a GCB subtype. Constitutive activation of nuclear factor κB is observed in ABC DLBCL; this is in part related to chronic BCR signaling.9 A phase 2 study of ibrutinib in relapsed/refractory de novo DLBCL (n = 79) found an ORR of 23%. On subgroup analysis, the ORR was significantly higher in patients with the ABC subtype compared with those who had the GCB subtype.
Although the progression-free survival in these 4 patients was relatively short, it was nonetheless encouraging for a condition with a median survival of <12 months.2 Our experience with these patients suggests that ibrutinib has potential as a novel therapeutic approach for patients with RS, and future trials investigating its use, either as monotherapy or in combination, appear warranted.

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Acknowledgments: This work was supported by National Institutes of Health, National Cancer Institute grants K23CA160345 (W.D.) and CA95241 (N.E.K.). S.A.P. is a recipient of the Mayo Clinic Department of Medicine Career Development Grant for Scholarly Clinicians. T.D.S. is a scholar of the Leukemia and Lymphoma Society.

Conflict-of-interest disclosure: T.D.S. has received research funding from Genentech, GlaxoSmithKline, Cephalon, Hospira, Celgene, Jannsen, and Polyphenon E International. The remaining authors declare no competing financial interests.

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References

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