

Treating the Hodgkin's Lymphoma Variant of Richter's Transformation

Sir,

Golden *et al.* from Dublin, Ireland recently reported a case of Hodgkin's lymphoma (HL) arising from Richter's transformation (RT) in an elderly gentleman with chronic lymphocytic leukemia (CLL).¹ RT into aggressive non-Hodgkin's lymphoma (NHL) is a well-documented occurrence; however, HL arising from RT occurs in only 0.5% of patients and carries a poorer prognosis than *de novo* HL.² Given its rarity, the optimal treatment for this disease has not been systematized with most data limited to isolated patients or patient-series.

Commonly used regimens are ABVD, MOPP and CVPP. These regimens have been used with or without concurrent radiotherapy in the HL variant of RT (HL-RT). Regimens for aggressive NHL have also been used. Overall, these have shown < 50% response rates, with short overall survival (up to 1.7 years).² Detailed analyses for ABVD and MOPP regimens show only 27.3% complete response (CR) rates.³ CLL (and therefore, HL-RT) is a disease of the elderly. Elderly patients generally have several comorbidities such as kidney and liver diseases (with impaired metabolism and clearance of drugs), cardiovascular diseases and frailty. These factors make toxicities major concerns that limit treatment options and adversely affect survival; hence treatment regimens need to be selected carefully, weighing the benefits over adverse effects.⁴ Highly aggressive therapies, such as stem cell transplantation, are not suitable for elderly patients, such as the one discussed,¹ and have failed to show promise even in younger HL-RT patients who are suitable candidates.²

Prior treatment with purine-analogs, consequent reduction of cell-mediated immunity and reactivation of latent Epstein-Barr virus (EBV) are better predictors of RT and aggressive HL than poor-risk molecular/biological factors.³ Considering that a vast majority of patients with HL-RT are positive for EBV, the virus is believed to be a transforming agent, playing a crucial role in the pathogenesis of RT, especially in case of the HL variant.² This represents a potential biological factor for targeted therapy to improve outcomes. In *in vivo* studies, histone deacetylase (HDAC) inhibitors have shown to induce viral thymidine-kinase expression, sensitizing EBV+ lymphoma cells to nucleoside antivirals and showing significant activity against EBV-associated lymphomas.^{2,4} Incorporating EBV viral-load

monitoring during CLL treatment, especially with purine-analogs, and reduction with antivirals to reduce EBV-associated RT is another plausible, albeit debatable approach.³

Reed-Sternberg cells in nodular-lymphocyte-predominant HL are CD20+ as opposed to only 20% of classical HL cases showing CD20-positivity. Given that CLL cells are also CD20+, anti-CD20 monoclonal antibodies (like rituximab or ofatumumab) used in combination with other agents, may be reasonable options for CD20+ HL-RT.³

Brentuximab Vedotin (BV) is an anti-CD30 antibody-drug conjugate showing activity against HL, even in elderly patients. Able to produce notable responses in up to 75% patients (CR: 34%), the only notable adverse effect associated with BV is peripheral neuropathy, which is reversible in 50% of patients after discontinuing treatment. Bendamustine is another agent that has shown better tolerability in elderly HL patients, showing responses in 58% heavily-pretreated patients (CR: 33%). Based on these reports, BV and bendamustine are promising agents for treating *de novo* HL in elderly patients. Although not currently, but in the future, these agents may become therapeutic options for HL-RT, potentially showing both efficacy and tolerability with improving outcomes in this patient group.^{2,4}

In a developing country like Pakistan, treatment is limited by non-availability or high costs of different agents. HDAC inhibitors and ofatumumab are not available in the country. While BV and rituximab are available at several centers, their high cost makes them inaccessible to a vast majority of patients. Patients should be screened for positivity against EBV. Monitoring EBV viral-load during CLL treatment and therapy with antiviral medications, if positive, may prove to be a cost-effective and efficient strategy to reduce the risk of RT (both HL and NHL) in CLL patients. Since bendamustine is a relatively less costly and efficacious drug showing good tolerability, especially in elderly patients,⁵ novel chemotherapy regimens containing bendamustine or combining it with other drugs from conventional HL regimens, may prove to be beneficial in treating patients with HL-RT. Since HL-RT is a rare entity, it is difficult to conduct prospective studies and randomized clinical trials to propose the optimum treatment regimen. Before such a regimen can be devised, therapy should be decided based on the activity, effectiveness, and toxicity of these agents for each individual patient.

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