Editorial

Revolutionary changes in salvage treatment for Hodgkin lymphoma: toward a chemotherapy-free future

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Recently, O'Connor *et al*. reported the high activity of the combination of brentuximab vedotin (BV) and bendamustine in relapsed/refractory Hodgkin's lymphoma (HL) patients (1). The study is notable for the heavily treated population and relatively large sample size.

Combined chemotherapy, with or without radiation, is considered highly effective in HL patients and provides a cure rate of over 80%. However, approximately 5–10% of cases suffer from primary refractory HL and a further 10–30% of patients relapse after their initial response. Treatment options for relapsed/refractory patients are quite limited. The current approach often involves high dose chemotherapy followed by autologous stem cell transplantation (ASCT) (2). However, even with ASCT, a significant proportion of patients experience further relapse. Furthermore, salvage treatment regimens prior to ASCT often include platinum-based combined chemotherapy, which is often highly toxic, and resistance is quite common, especially in patients with high risk factors or who have failed multiple lines of therapy (3). The need for an alternative approach for those patients is long unmet.

Fortunately, after more than 30 years without innovative new drugs registered for HL, the advent of BV, an antibody-drug conjugate comprising of an anti-CD30 antibody and the anti-microtubule agent monomethyl-auristatin-E, dramatically changed the outlook for relapsed/refractory patients. Since its approval by the Food and Drug Administration (FDA), many have explored its efficacy in various types of CD30 positive neoplasms (4-6). When it comes to relapsed/refractory HL, however, BV monotherapy provided a 2-year progression-free survival (PFS) rate of only 22% (7). The suboptimal response rate warranted exploration of combination options with BV. Adding BV to standard chemotherapy regimens is an obvious approach and proved to be highly effective. Hagenbeek *et al.* reported 12 patients who received BV in combination with DHAP chemotherapy, and all 12 patients achieved complete remission and were progression-free at 2 years (8). Similarly, in a larger cohort reported by Garcia-Sanz *et al.*, 46 of the 66 patients achieved complete remission, and 87% remained progression free at 2 years (9). While such combinations are highly effective, they are nonetheless very toxic. Furthermore, since both investigations were conducted only in first-time relapse patients, it remains doubtful whether real-world patients who often have failed multiple lines of treatment will be as responsive as those enrolled in clinical trials.

The study by O'Connor *et al.* investigated the activity of bendamustine plus BV in relapsed/refractory HL patients. The study enrolled a total of 64 HL patients, including 27 in phase I, dose-escalating trial and 37 in phase II trial. The phase I trial confirmed the safety of the combination, with the most common dose-limiting adverse effect being grade 4 neutropenia. In the phase II trial, the researchers utilized the standard doses of both drugs when given as single agent, which is 1.8 mg/kg for BV and 90 mg/m^2 for bendamustine. It is worth mentioning that the 37 patients enrolled in the phase II trial had failed a median of 3 lines

of previous treatment, including 29 (78%) patients who previously received platinum-based regimen, and 21 (57%) who underwent ASCT. The authors observed a complete response rate of 43% and an overall response rate of 78%. Considering patients in this cohort were heavily pretreated, the response rate is very impressive. The combination was also proven safe to administer, with the main adverse effect being neutropenia, and as a result, lung infections. The study has proven that BV plus bendamustine is highly effective even in heavily pretreated patients, and the favorable toxicity profile.

The combination of BV and bendamustine has comparable efficacy and far less toxicity, suggesting a strong potential of replacing the currently used platinum-based regimens. Some researchers went one step further and investigated the possibility of chemotherapy-free salvage regimen of BV plus immune checkpoint inhibitors. In a phase 1/2 study, Herrera *et al.* reported the efficacy and safety of the combination of BV and nivolumab as initial salvage therapy in patients with relapsed or refractory HL. With 61 patients treated, they observed a promising complete response rate of 61% and an objective response rate of 82%. This combination therapy was also well-tolerated: less than 10% of patients required systemic steroids for immune-related adverse events (10). Others explored cellular therapies including chimeric antigen receptor (CAR) T-cell therapy and autologous EBV-directed cytotoxic T-lymphocytes. In a recent study, 18 patients with relapsed/refractory HL were treated in a phase 1 trial of CD30 specific CAR T-cells. Seven patients (39%) achieved partial remission with a median PFS of 6 months (11). Another study investigated the efficacy of autologous EBV directed cytotoxic T-lymphocytes in EBV expressing lymphomas, including HL. The study demonstrated that 13 of 21 patients who had measurable disease at the time of cytotoxic T-lymphocytes infusion had responses, including 11 complete remissions (12).

Overall, the impressive results from the recent studies suggest it is time to revisit the current standard of care for relapsed/refractory HL patients. Novel agents provide a similarly effective option for those patients, and are proven to be less toxic. Future studies should focus on exploring the best approach to these patients by comparing the efficacy of various novel agents.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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