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CLINICAL TRIALS AND OBSERVATIONS

Comment on Friedberg et al, page 786

Toward a cure for cHL without chemotherapy

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In this issue of *Blood*, Friedberg and colleagues present important long-term follow-up from a clinical trial of combinations based on brentuximab vedotin (BV) for untreated classic Hodgkin lymphoma (cHL) in older patients (aged ≥60 years) who are not fit for conventional chemotherapy.[1] Although the cohorts were small (part B, BV + dacarbazine, n = 22; part D, BV + nivolumab, n = 21), the response rates were high, and with a median follow-up of >4 years, nearly one-half of these responses were durable. This raises the question of whether a proportion of patients with cHL (old or young) can be cured without a standard combination chemotherapy approach.

Hodgkin lymphoma has long been associated as a disease of adolescents and young adults, but approximately 20% of patients are aged ≥60 years.[2] Traditional chemotherapy approaches for older patients in the E2496[3] and Echelon-1[4] studies were associated with inferior overall survival and increased treatment-related mortality. In addition, older patients were not well represented in the E2496 (6%) and Echelon-1 (14%) trials. Given the increased toxicity of concurrent administration of BV with AVD (Adriamycin [doxorubicin], vinblastine, dacarbazine) chemotherapy, a sequential approach was previously designed and evaluated.[5] Patients received 2 doses of BV and then received up to 6 cycles of AVD, with responding patients able to receive 4 additional doses of BV consolidation. With 48 patients enrolled, this regimen was highly effective (2-year progression-free survival [PFS], 84%), but it was still associated with increased toxicity ($G3^+$ adverse events, 42%; $G2^+$ peripheral neuropathy, 33%). Moreover, only 52% of patients were able to complete all study therapy. For the above reasons, there is currently no standard approach for the management of untreated older adults with cHL.

The study designed by Friedberg et al attempted to address this key gap by evaluating various BV-based combinations, including a combination with the PD1-inhibitor nivolumab. In recent months, we have learned exciting new data on the role of PD1 inhibition in the management of cHL. An interim analysis of the S1826 study in frontline advanced-stage Hodgkin lymphoma suggests that nivolumab + AVD will become the standard for untreated advanced-stage cHL.[6] We also learned from the 5-year follow-up of the KEYNOTE-087 study of pembrolizumab monotherapy in relapsed/refractory cHL that some patients have achieved a durable complete remission without additional therapy.

Both BV + dacarbazine (DTIC) (objective response rate [ORR], 95%; complete response [CR], 64%) and BV + nivolumab (ORR, 86%; CR, 67%) for up to 16 cycles were highly active in older patients with untreated CHL in the study performed by Friedberg et al. Toxicity was similar, but BV + DTIC had higher rates of peripheral sensory neuropathy (77% vs 48%). Overall, the most intriguing combination was that of BV + nivolumab. A previous study by Academic and Community Cancer Research United[7] had examined the combination of BV + nivolumab (only 8 cycles) in a similar population of older patients, and that study was closed early due to insufficient activity (ORR, 64%; CR, 52%) with a median PFS of only 18.3 months. Most events occurred shortly after study therapy was complete. In contrast, in the Friedberg et al study, 15 of 21 patients were treated beyond 24 weeks (median treatment duration, 42.9 weeks), and the median PFS was not reached, perhaps suggesting that the improved outcomes in the current study may be due to prolonged therapy.

BV + nivolumab represents an excellent treatment option for older, unfit patients with untreated Hodgkin lymphoma who are unable to tolerate chemotherapy. But there are still some open questions for how this should be used in real-world practice. First, all patients treated with BV + nivolumab on this study were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, so it is not clear how well this study represents very unfit patients (ECOG ≥2) at diagnosis. There are many reasons why an older patient may not be fit for chemotherapy, but in many cases a decline in performance status is due to the underlying disease itself and is potentially reversible. What is the correct approach in a situation in which a patient becomes eligible for combination chemotherapy as the lymphoma-related impairments resolve? Should a patient then transition to combination chemotherapy with, for example, AVD? Prednisone, vinblastine, doxorubicin, bendamustine[8]? Or even nivolumab + AVD? Subset analysis of patients 60 years of age and older who received nivolumab + AVD with limited follow-up looks impressive as well.[9] I think a transition to chemotherapy should be

discussed with a patient in this scenario, given the numerically better results seen in the sequential BV chemotherapy[5] approach. In the study by Friedberg et al, patients receiving BV + nivolumab received a median of 10 cycles of BV. In real-world practice, this can lead to significant cumulative toxicity, as illustrated by the high rates of grade 2+ peripheral sensory neuropathy. In patients opting for a chemotherapy-free approach, should BV be omitted at the first sign of neuropathy and the nivolumab treatment maintained? Given the excellent long-term results of PD1 inhibitor monotherapy, I do not believe the BV treatment should be prolonged as was done in the current study, as the responses can likely be maintained with nivolumab alone.

I also want to highlight the authors' discussion statement about cure without chemotherapy. Traditionally, the dogma has been that a cure can only come from some combination of an anthracycline, a vinca alkaloid, and a drug that rhymes with -carbazine. Personal anecdotes as well as emerging data from studies like this suggest there may be another way. Using noninvasive genotyping[10] and circulating tumor DNA[11] may help identify patients who are either at lower risk at baseline or perhaps cured far earlier during their treatment than anticipated. Given newer drugs and emerging technologies, we should resolve to design the next generation of studies with the goals of less or, dare I say, no chemotherapy at all, allowing us to reserve more toxic chemotherapy regimens for only those who truly need it.

In the end, I commend the authors for enrolling older patients who have been previously excluded from other frontline studies. More studies should help define optimal treatment combinations in this population, with greater emphasis in enrolling patients with poor performance status or comorbidities.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Cruz-Leal et al, page 807

AMIS RBC antigen loss: nibble or devour?

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In this issue of *Blood*, Cruz-Leal et al provide important new insights into the mechanism of red blood cell (RBC) antigen loss,[1] previously proposed by this group and others to be implicated in antibody-mediated immune suppression (AMIS) of erythrocyte alloimmunization independent of red cell clearance or epitope masking.[2,3] Cruz-Leal et al demonstrate that some AMIS-inducing antibodies targeting RBC antigens, including anti-RhD, can trigger antigen loss through a phenomenon of membrane-bound component transfer to macrophages called trogocytosis, without necessitating RBC clearance.

Alloimmunization against RBC antigens during pregnancy or transfusion can cause serious complications, including hemolytic disease of the fetus and newborn (HDFN) and hemolytic transfusion reactions. HDFN happens when maternal alloantibodies, most frequently anti-RhD, cross the placenta and destroy incompatible fetal RBCs, potentially leading to anemia, jaundice, and even neonatal death in severe cases.[4] The only prophylactic treatment currently available to prevent anti-RhD formation in RH:–1 pregnant women is the administration of human polyclonal anti-RhD. This prophylaxis is the sole example of AMIS used clinically to prevent alloimmunization and HDFN. However, alloimmunization can also be due to other non-RhD alloantigens, among which alloantibodies