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CLINICAL TRIALS AND OBSERVATIONS

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The next frontier: enter PD-1 and exit PET scans?

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In this issue of *Blood*, Lynch et al present compelling results of a single-arm study of concurrent pembrolizumab, doxorubicin (Adriamycin), vinblastine, and dacarbazine (APVD) in newly diagnosed classic Hodgkin lymphoma (cHL).[1] In addition to demonstrating this regimen to be both safe and highly effective, 2 other important findings were noted: a high rate of false-positive positron emission tomography (PET)/computed tomography (CT) scans was observed, and circulating tumor DNA (ctDNA) assessment was highly correlated with treatment outcome.

Until recently, the management of untreated cHL has evolved very gradually. For decades, the prevailing debate had been between various chemotherapeutic regimens, use of PET scans to guide therapy modification, and the role of radiation therapy. The CD30-directed antibody-drug conjugate brentuximab vedotin (BV) was the first targeted therapy to obtain Food and Drug Administration approval for cHL, followed a few years later by the anti-programmed cell death-1 (PD-1) monoclonal antibodies nivolumab and pembrolizumab. As all of these agents are highly effective as monotherapy, it seemed to be merely a matter of time until they made their way into the treatment algorithm for patients with newly diagnosed cHL. The first blow was struck when the ECHELON-1 trial demonstrated that treatment with Adriamycin, BV, vinblastine, and dacarbazine (AAVD) was associated with a superior modified progression-free survival as compared with Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with untreated advanced stage cHL[2]; with longer follow-up, an overall survival difference has since emerged.[3]

What about PD-1 blockade? Results of the randomized SWOG S1826 trial (clinicaltrials.gov: NCT03907488), now fully accrued, comparing AAVD to Adriamycin, vinblastine, dacarbazine, and nivolumab, are eagerly awaited. In the interim, multiple smaller studies have been conducted examining various combinations of PD-1 blockade with Adriamycin, vinblastine, and dacarbazine, all of which feature very low rates of disease progression albeit with relatively short follow-up.[4-6] The APVD data presented by Lynch and colleagues here continue to support the excellent efficacy of PD-1 blockade combined with chemotherapy as initial therapy for cHL. Of the 30 enrolled patients, 18 of whom had advanced stage disease, only 1 experienced biopsy-proven progressive disease after a median follow-up of 2.1 years. Although the safety was consistent with the known toxicity profiles of PD-1 blockade and combination chemotherapy, immune-related toxicities were observed at a rate (nearly half of patients with rash and 5 of 30 patients with transaminitis requiring pembrolizumab modification and corticosteroids, including 10% that discontinued pembrolizumab) that merits note, though these were reversible. Thus, even though the authors' concurrent therapy approach may have hoped to avoid early immune-related toxicity with sequential immunotherapy followed by chemotherapy, it did not ultimately have that effect. Notably, the febrile neutropenia rate was higher than is typically observed with ABVD, though that did not translate into more infections as it appears to with AAVD.

This trial also highlighted the ongoing challenges of using PET/CT scans to measure disease response in cHL. Although the prognostic value of an interim PET/CT scan after 2 cycles of ABVD therapy (PET2) is clear,[7,8] PET/CT scan results do not appear to be as reliable for informing therapeutic adaptation in regimens that include novel immunotherapies, especially PD-1 blockade. For instance, although 89% of patients receiving AAVD in ECHELON-1 had a negative PET2 scan, patients with a positive PET2 still had a 6-year progression-free survival of 61%, suggesting limited predictive value for the PET2 when AAVD is used.[3] Meanwhile, Lynch and colleagues found that the PET2 negativity rate was only 57% with APVD, far below what has been reported with either ABVD or AAVD, and the end-of-treatment PET negative rate was 82%. Given only a single case of confirmed relapsed disease, this suggests a worryingly high incidence of false-positive PET/CT scans with APVD. There appears to be limited utility of interim PET/CT when using frontline PD-1 blockade and chemotherapy, and even end-of-treatment PET scans are problematic.

How then can we dependably measure therapy response in a future that may include frontline chemoimmunotherapy for cHL? The authors evaluated ctDNA in patients treated with APVD, and ctDNA dynamics were strongly associated with treatment outcome. Although cancer personalized profiling by deep sequencing (CAPP-Seq), a next-generation sequencing technique, had previously been shown to correlate with treatment response in cHL,[9] this study used phased variant enrichment and

detection sequencing (PhasED-seq), a newer methodology with improved detection capacity compared with CAPP-Seq.[10] The investigators showed that baseline ctDNA correlated with disease stage and total metabolic tumor volume, and ctDNA cleared quickly in the large majority of patients treated with APVD. When assessed at cycle 3 day 1 and again at end of treatment, 81% and 92% of patients, respectively, had undetectable ctDNA. The only patient with disease relapse had detectable ctDNA at both time points. Although the numbers are small, the results are provocative and suggest a potential role for ctDNA in response assessment and possibly therapeutic adaptation for patients with cHL treated with frontline PD-1 blockade + chemotherapy.

Lynch and colleagues have made an important contribution to the growing body of evidence supporting the efficacy of incorporating PD-1 blockade into frontline treatment of cHL. Since PD-1 blockade when given as monotherapy for cHL is associated with prolonged responses, yet is rarely curative, longer follow-up of this and other similar trials will be important to ensure that remissions are truly durable. Also, further work needs to be done to establish the best way to monitor disease response with these novel regimens given the suboptimal predictive value of PET/CT scans during and following treatment. The use of ctDNA to monitor disease response will need validation in a larger cohort, and the optimal timing of ctDNA sampling also still remains to be determined. Finally, if the striking efficacy results with APVD and other novel anti-PD1-based regimens are maintained in long-term follow-up, then studies of de-escalation of therapy, potentially driven by dynamic ctDNA results, could be considered.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Biondi et al, page 2587

CXCR4 to improve both T cell homing and function

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In this issue of *Blood*, Biondi et al[1] show that enforcing CXCR4 expression on CD33-targeting chimeric antigen receptor (CAR) cytokine-induced killer (CIK) cells enhances their homing to the bone marrow (BM) and improves their activity against acute myeloid leukemia (AML).

CXCR4 is a chemokine receptor that binds to CXCL12, also known as SDF-1, which is produced by BM stromal cells. Binding of CXCR4 to CXCL12 plays an important role in retention of hematopoietic stem and progenitor cells (HSPCs) in the BM. This is most evident by the use of plerixafor, a CXCR4 receptor antagonist, in clinical practice for HSPC mobilization.

AML is a malignancy that is derived from HSPCs, and CXCR4 expression is also observed on AML and is associated with poor prognosis.[2] One can presume that the mechanisms used to support HSPCs in their BM niche can also support AML, particularly the leukemic stem cells (LSCs) that serve as a nidus for disease relapse. Therefore, expressing CXCR4 on immune effector cells can bring them into close proximity with LSCs and increase the probability of achieving durable remissions in AML.

Initially, the authors examined CXCR4 expression on CD33-targeting CAR-CIK cells. Of note, the CIK cells used by the authors refer to a particular composition of effector lymphocytes that harbor a mixed T and natural killer (NK) cell phenotype and so are somewhat