ONCOLOGY SCAN

International Journal of Radiation Oncology biology • physics

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Immune Therapies for Lymphomas: A Disruptive Technology With Opportunities for Radiation

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Received Mar 5, 2018, and in revised form May 24, 2018. Accepted for publication May 31, 2018.

Patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) have seen remarkable improvements in survival over the past 3 decades. However, relapsed/refractory (r/r) disease remains a significant challenge, despite the advent of new systemic regimens, allogeneic hematopoietic stem-cell transplant (allo-HSCT), and targeted/biologic therapies. More recently, programmed death-1 (PD-1)—inhibitory checkpoint blockade and chimeric antigen receptor T-cell (CART) therapy have emerged as promising strategies for the treatment of r/r HL and NHL.

External beam radiation therapy has an established role in the multimodal management of de novo HL and NHL (1-3). The use of checkpoint blockade and CART therapy in the r/r setting may offer an opportunity for the incorporation of radiation to improve outcomes, particularly in light of the promise of the "radiation vaccine" concept—exploiting the abscopal effect with checkpoint inhibitors—in a variety of disease sites (4, 5).

In this Oncology Scan, we review the pivotal KEYNOTE-013 phase 1B trial of pembrolizumab in r/r HL (6) and the recent ZUMA-1 phase 2 trial of CART therapy for r/r NHL (7). For patients with hematologic malignancies, radiation therapy is often marginalized in favor of more aggressive systemic therapies; it is, therefore, important for radiation oncologists to understand the changing landscape regarding these emerging biologic therapies for lymphoma. Finally, we speculate on the implications of checkpoint blockade and CART therapy for radiation therapy in the management of lymphomas.

Armand et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. *J Clin Oncol* 2016. (6)

Laboratory work has shown that in addition to immunoglobulin-related mutations (8), in nodular sclerosing HL, 9p24.1 chromosomal amplification leads to increased PD-L1 and PD-L2 expression (9). It is, therefore, unsurprising that HL sees a higher response rate to checkpoint inhibitors than other solid tumors (Fig. 1) (10, 11). NHL comprises a heterogeneous group of tumors, yet these too are responsive to a checkpoint blockade, albeit to a lesser extent than HL (10, 11). With results from the pivotal KEYNOTE-013 phase 1B trial, Armand et al reported very promising safety and efficacy results among patients with HL.

Summary: Thirty-one patients with r/r classical HL progressing through brentuximab vedotin received 10 mg/kg pembrolizumab every 2 weeks until disease progression. The average age was 32 years (range 20-67). All patients failed brentuximab. Ninety-seven percent of patients had received at least 3 to 5 prior therapies. Sixty-eight percent of patients were refractory to their latest treatment. Seventy-one percent of patients had undergone autologous stem cell transplant. All but 1 patient had treatment-related adverse events, the most common being hypothyroidism (16%), diarrhea (16%), nausea (13%), and pneumonitis (10%). Grade 3 toxicities were reported in 16% of patients and included nephrotic syndrome, colitis, joint swelling, back pain, axilla pain, and aminotransferase increase. No

Conflict of interest: none.

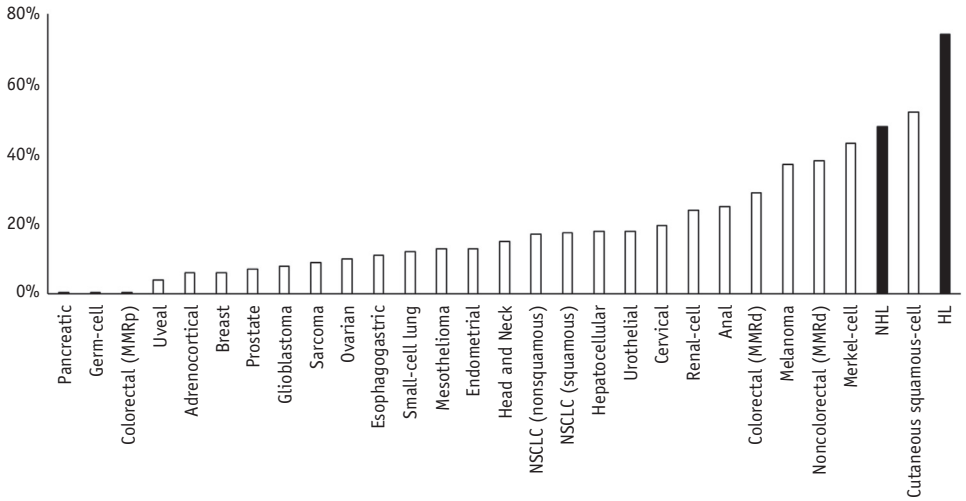

Fig. 1. Overall response rates to programmed death-1 inhibition in various tumor types, as summarized by Yarchoan et al (11) and Galanina et al (10).

grade 4 to 5 toxicities were reported. With median follow-up of 17.6 months, overall response rate (ORR) was 65% (16% complete response [CR], 48% partial response [PR]); of those, 70% had a durable response of at least 24 weeks. A total of 90% of patients saw an average 50% decrease in tumor burden. Among the 5 patients with a CR, 1 went on to have progressive disease (PD); among 15 patients with a PR, 6 went on to have PD. At 24 weeks, progression-free survival (PFS) was 69% and overall survival (OS) was 100%; at 1 year, PFS was 46% and OS was ∼87%.

Commentary: The results of the KEYNOTE-013 r/r HL cohort are exciting in that they establish the safety and efficacy of a checkpoint inhibitor for these patients. However, the trial failed to meet its CR endpoint of 20% improvement, underscoring the challenge that relapsed or refractory disease presents. In 2015, Ansell et al reported a phase 1 trial of nivolumab, with an r/r HL cohort of 23 patients with similar characteristics (12). As with pembrolizumab, nivolumab caused adverse events in all but 1 patient, largely rash and thrombocytopenia among others. Grade 3 toxicity was reported in 52% of patients (compared with 16% with pembrolizumab), and no grade 4 to 5 events were reported; the toxicity profile seen in these studies is generally shared across disease sites treated with checkpoint inhibitors. With a shorter median follow-up of 40 weeks (compared with 17.6 months for pembrolizumab), the ORR was greater at 87% (vs 65%), although the CR rate was similar at 17% (vs 16%). CR was substantially higher (3 of 5 patients; 60%) among those who had not received brentuximab pretreatment. All patients saw a reduction in tumor burden. Twenty-four-week PFS was 86% (vs 69%), and although median survival was not reached, OS was not reported. Ultimately, even in the absence of randomized data, these exciting early-phase trials led to the Food and Drug Administration's approval of both pembrolizumab and nivolumab as single-agent therapies for HL.

In both of these trials, many patients went on to receive allo-HSCT after PD1 inhibition (10% after pembrolizumab, 26% after nivolumab). Emerging evidence suggests that caution is warranted when combining checkpoint inhibition and allogeneic transplant. Merryman et al retrospectively reviewed 39 patients with HL (79%) and NHL (21%) who underwent all-HSCT after immune checkpoint therapy with nivolumab (72%) or pembrolizumab (28%) (13). With a median follow-up time of 12 months, they reported selected cumulative acute and chronic toxicities. At 1 year, they saw 21% grade 2, 10% grade 3, 13% grade 4, and 8% grade 5 (death due to) acute graft-versus-host-disease. An additional patient died of hepatic sinusoidal obstruction syndrome. Eighteen percent of patients developed fevers not due to infection and required long-term steroids, and 41% of patients had chronic graft-versus-host-disease. OS (95% confidence interval) was 89% (74%-96%), PFS was 76% (56%-87%), cumulative relapse-related mortality was 14% (4%-29%), and cumulative non—relapse-related mortality was 11% (3%-23%) at 1 year. The authors concluded that although allo-HSCT after PD-1 blockade is effective, prior use of PD-1 inhibitors may increase toxicity.

As has been the case for several malignancies, checkpoint blockade may be paradigm-shifting in the management of lymphoma. If so, because PD-1 inhibitors appear to increase the risks of allo-HSCT—a procedure that inherently carries high risks even in the absence of checkpoint inhibitor pretreatment—it is possible that allo-HSCT will fall out of favor in the management of relapsed or refractory disease. Although these trials demonstrate the promise of PD-1 inhibitors for r/r HL, there is clearly room for improvement. HL is exquisitely radioresponsive, even to relatively low doses of radiation, and radiation may have an expanding role in r/r disease—for instance, by using PD-1 inhibitors to potentiate the abscopal effect (14, 15). How radiation should be combined with checkpoint

blockade in r/r HL will be an ongoing challenge with regard to timing, dose, volume, and toxicity mitigation.

Neelapu et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med* 2017. (7)

In the midst of the excitement surrounding checkpoint blockade, perhaps even more exciting is the promise of CART therapy for the treatment of various cancers. By harvesting T-cells, retrovirally transducing them with a gene encoding a target receptor antigen attached to T-cell-activating proteins, and reinfusing them, a patient's own T-cells can be engineered to target cancer cells bearing a specific receptor (16, 17). In the case of lymphocytic leukemias and NHLs, a T-cell receptor specific to these cells, CD19, can be targeted (16, 18). On the heels of phase 1 and single-center trials, as well as recently published data suggesting that CART therapy may *cure* r/r NHL in some cases (19), Neelapu et al undertook the multicenter phase 2 ZUMA-1 trial that showed impressive rates of long-term CR.

Summary: One-hundred-one of 111 patients successfully received axicabtagene ciloleucel (axi-cel). The authors presented their data with a modified intention-to-treat analysis of the 101 patients who received axi-cel. The median age was 58 years (range 23-76); the majority of patients (76%) had diffuse large B-cell lymphoma, 16% had transformed follicular lymphoma, and 8% had primary mediastinal B-cell lymphoma. Sixty-nine percent of patients had received at least 3 prior therapies. All patients experienced toxicity, notably fever (85%), neutropenia (84%), and hypotension (59%). Cytokine release syndrome (CRS) was seen in 93% of patients, and neurotoxicity—chiefly encephalopathy, confusion, and tremor—was seen in 64% of patients. Grade 3 or higher CRS and neurotoxicity were seen in 13% and 28%, respectively. An additional 12 grade 3 toxicities and 1 grade 4 toxicity, primarily related to infection, were reported after the primary analysis data cut-off of 6 months. Tocilizumab, an anti-interleukin-6-receptor antibody, was needed in 43% of patients, and steroids were given to 27%; neither measurably affected treatment response. The authors noted that CRS and neurotoxicity rates improved with center experience. With median follow-up of 15.4 months, ORR was 82% (58% CR, 24% PR); of those, 42% had a durable response (40% CR) of at least 6 months. Three of 7 (43%) patients from the ZUMA-1 phase 1 arm had continued CR at 2 years. Notably, CR could take up to 15 months to be seen. At 1 year, PFS was 44%, OS was 59%, and median survival was not reached. Of the initial 111 patients enrolled, axi-cel generation failed for 1 patient, who ultimately died of PD. Four patients experienced serious adverse events after leukapheresis. One patient developed sepsis, and 1 patient died in the setting of pre-axi-cel conditioning chemotherapy. An additional patient died of PD before infusion. Two patients had disease that regressed to the point of immeasurability before infusion.

Commentary: Considering the fact that of the 10 patients who did not receive axi-cel, 7 had serious adverse events or died before infusion, it is clear that the cohort in this trial includes very sick patients, thus rendering CART therapy's durable response rate all the more impressive.

These results are mirrored by a companion paper in the same issue of the *New England Journal of Medicine* by Schuster et al, a single-institution case series of 28 patients with r/r NHL receiving a different anti-CD19 CART-based therapy, CTL019 (tisagenlecleucel) (20). Among 28 patients, 16 (57%) achieved a CR. Notable toxicities included neutropenia (79%), hyperglycemia (64%), CRS (57%), hyponatremia (54%), and "other" skin/subcutaneous toxicity (46%). Of the 16 patients (57%) with CRS, 5 had grade 3 to 4 toxicity. Neurotoxicity was reported in 39%, with 11% grade 3 or higher. At 28.6-month median follow-up, PFS was 57%, and median PFS was not reached. Though the median PFS was 3.2 months for the diffuse large B-cell lymphoma subgroup, responses in this subgroup were durable to the median 28.6-month follow-up time.

In the study reported by Schuster et al, patients were allowed bridging chemo- or radiation therapy between the time of T-cell harvest and infusion, at the discretion of the treating physician. This is in contrast to the multicenter ZUMA-1 trial, in which no intervening therapy was permitted after leukapheresis and before T-cell infusion. Because of differences in manufacturing and preservation techniques (axi-cel is generated from fresh lymphocytes only), the time between T-cell harvest and infusion was longer in the Schuster et al study (median 39 days, vs 17 days with axi-cel). It is notable that 1 patient died of progressive disease in the interim in the ZUMA-1 study.

Although these data are exciting on their own, they also suggest that there may be a role for radiation in the management of patients with lymphoma awaiting CART therapy. The patient populations that have received CART therapy on trial have remarkably refractory disease that is often highly symptomatic. In both the ZUMA-1 and JULIET trial, a number of patients enrolled did not go on to receive their infusion. In the intervening time between T-cell harvest and ultimate infusion, radiation may offer a low-toxicity approach to cytoreducing large or symptomatic sites of disease, maintaining locoregional control while CART-cells are being expanded. Because radiation may cause lymphodepletion (21, 22), radiation therapy should be approached with caution in potential CART candidates to ensure there is sufficient lymphocyte count for collection.

The best way to integrate radiation therapy into these powerful immune therapies is a work in progress. As in combined modality treatment for initial therapies for lymphoma, radiation therapy may provide a complementary

role when combined with immune therapies in the r/r setting.

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