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Dual Immunotherapy Adds Value in Relapsed/Refractory Hodgkin Lymphoma

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Three of every 4 people diagnosed with Hodgkin lymphoma (HL) will achieve cure with frontline combination chemotherapy supplemented as appropriate with radiotherapy. Standard of care salvage regimens for the 1 in 4 with relapsed or refractory (R/R) HL comprise further cycles of cytotoxic chemotherapy, usually including a platinum-based agent and/or gemcitabine, consolidated in younger, fitter patients by autologous stem cell transplantation (ASCT). A variety of salvage regimens are used, which appear to have similar overall response rates (ORR) of 70% to 90% and complete remission (CR) rates of 50% to 75%, although none have been compared in randomized controlled trials.

The advent of promising immunotherapeutics for this disease raises the prospect of improving outcomes in R/R HL. Abolishing traditional cytotoxic agents from salvage regimens might reduce the long-term morbidities of second primary malignancies, cardiovascular disease and infertility, which are particularly impactful in this relatively young patient group. More effective salvage approaches might enable more patients to benefit from potentially curative ASCT, or even abrogate the need for ASCT altogether.

Herrera and colleagues have recently published data pertaining to such a potential immunotherapy "dream ticket" in HL, namely a combination of the immune-checkpoint inhibitor nivolumab, an anti-PD-1 monoclonal antibody, and the CD30-targeted antibody–drug conjugate brentuximab vedotin (BV).[1] This approach attempts to exploit 2 hallmark features of this disease, overexpression of PD-L1 and universal expression of CD30 by the malignant Hodgkin Reed–Sternberg cell (Fig. 1).

Single agent BV, used in the first salvage setting in R/R HL has a CR rate of 27% to 35%, with 27% to 48% able to proceed directly to ASCT.[2,3] In heavily pretreated patients following both BV and ASCT, single agent nivolumab has a 73% ORR and 23% CR rate.[4]

Study design

In a phase 1/2 open label, single arm, multicentre study, 62 adults were enrolled (median age 36 years, range 18–69) at 12 centers over a 13-month period. All had failed frontline therapy for classical HL, having received Adriamycin, Bleomycin, Vinblastine, Dacarbazine in 56 cases (90%), incorporating radiotherapy in 9 cases (15%). None had received prior BV, immune checkpoint inhibition, ASCT, or allogeneic stem cell transplantation. Twenty-eight patients (45%) had primary refractory HL, 22 patients (35%) had relapsed within 12 months of frontline therapy.

The treatment schedule comprised a first cycle of BV 1.8 mg/kg on Day 1 and nivolumab 3.0 mg/kg on Day 8 of a 21-day cycle followed by 3 further cycles of both drugs given on Day 1 of each 21-day cycle.

A CT scan at cycle 2 screened for early disease progression followed by an end of treatment PET-CT at Day 30 to 37 following the last dose of drug. A Deauville 3 response or less on PET-CT was classified as a CR. The primary end points were end of treatment CR rate and ORR, being a combination of partial response and CR.

Results

One withdrawal of consent before receiving any treatment left 61 patients assessable for response, of whom 58 completed all 4 planned cycles of combination immunotherapy. The ORR was 82% (50 of 61 patients) with a CR rate of 61% (37 of 61 patients). Forty-two patients (69%) proceeded

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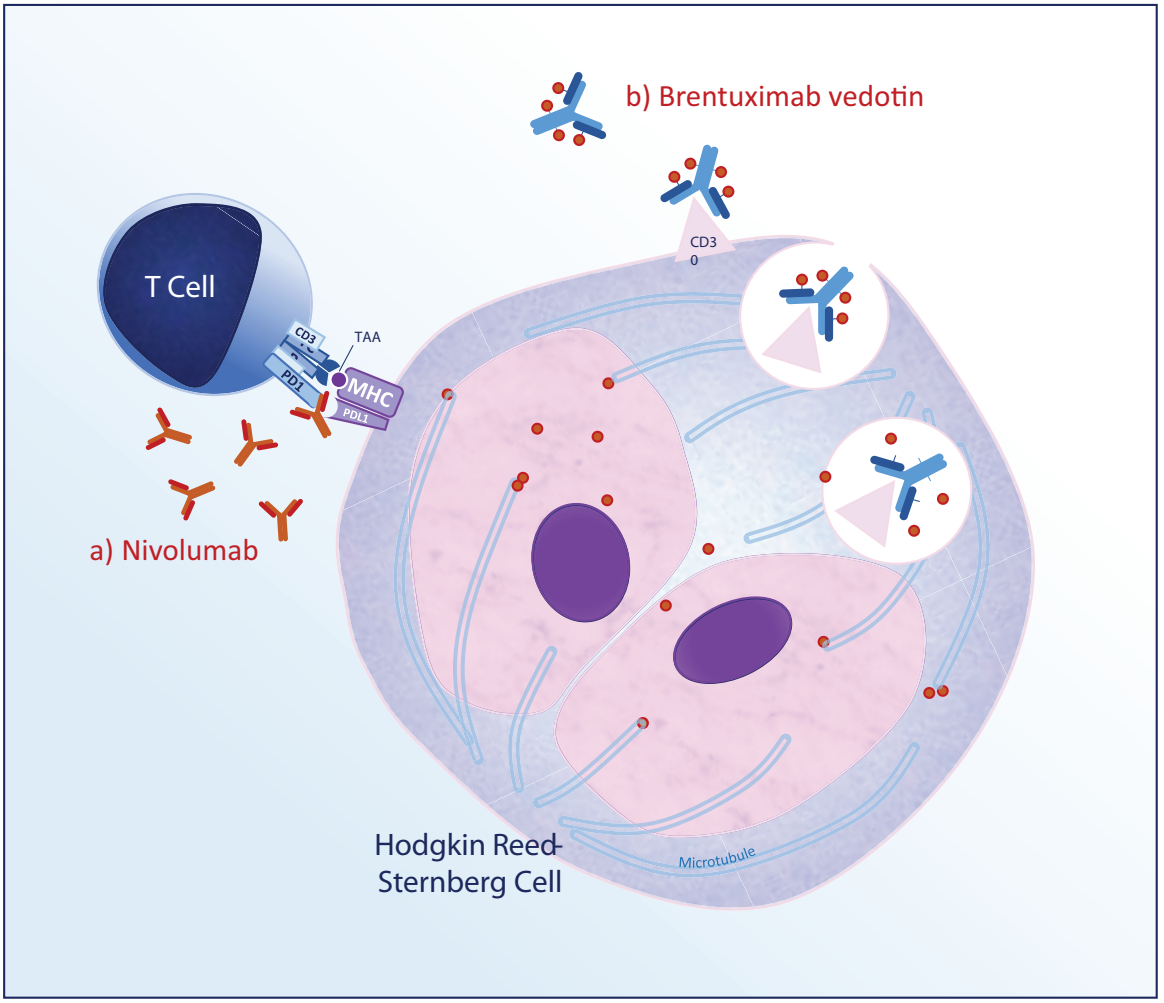

Figure 1. (A) Nivolumab is a PD-1 receptor blocking antibody, which disrupts the inhibitory PD-1 signaling pathway and restores T cell mediated antitumor immunosurveillance. (B) Brentuximab vedotin is an anti-CD30 antibody conjugated to monomethyl auristatin E (MMAE). On binding to CD30, the antibody–drug conjugate is internalized, the linker protein attaching the drug is cleaved by cell proteases, and MMAE is released, leading to microtubule disruption and apoptosis.

directly to ASCT. A further 12 patients underwent ASCT following additional salvage therapy, such that 54 patients of an assessable 61 (89%) receiving combination immunotherapy in this study were ultimately able to receive ASCT with curative intent.

The most common treatment emergent adverse events (AEs) were nausea (49%), fatigue (41%), and infusion related reactions (44%), none of which resulted in treatment discontinuation. Peripheral neuropathy was experienced by 20% of patients, which was grade 1 severity in all except the 1 individual coming off study for this reason. Of particular interest, given the conceptual risks of combination immunotherapy, were immune-related AE. Fifty of 61 patients (82%) experienced rash, gastrointestinal, liver, or lung inflammation that was potentially due to drug-related immune-phenomena. Of these, only 5 episodes (8%) warranted systemic steroids, and none resulted in study withdrawal.

Commentary

In a high-risk population enriched for primary refractory HL and early relapses, a combination of BV and nivolumab was well tolerated and effective in providing a bridge to ASCT in the majority of subjects. Response rates to these agents in combination appear superior to their single-agent activity, without generating intolerably high rates of severe immune-related AEs, and similar to established salvage regimens. Randomized controlled trials are needed to reliably determine comparative efficacy with established salvage regimens. Correlative laboratory studies are needed to identify biological markers predictive of response, to enable this and other immunotherapy regimens to be part of a more effective personalized medicine approach to R/R HL.

The low hematologic toxicity of this combination enables outpatient care and is likely to improve patient experience compared to traditional chemotherapy based salvage. It remains to be seen if the avoidance of cytotoxic chemotherapy has any discernible impact on late-effects, particularly if subsequent myeloablative conditioning and ASCT is still required for cure.

The cost savings from reduced blood product support and hospital admission is currently far outweighed by the vastly increased drug cost of this regimen. Combined with the pressing need for head-to-head efficacy studies with established salvage regimens, the listed drug price differential surely rules out BV plus nivolumab as the new standard of care first salvage regimen for HL in almost any economic setting? Innovative drug

reimbursement strategies might provide a way forward, reinforced by more mature and robust efficacy data and identification of patients most likely to benefit and potentially avoid the physiological and financial costs of ASCT.

This study is illustrative of the direction of travel in management of R/R HL, with an increasingly crowded field of drugs and combinations vying for primacy. This regimen will have to demonstrate greater advantages to justify its financial costs. There are also further promising innovations entering the field. CAR-T cell technology is being applied to HL in early phase studies. New-novel molecules are emerging such as AFM13, a first in class bispecific antibody incorporating an NK cell-activating element with a CD30 engaging epitope to direct cytotoxic NK cell responses against Hodgkin Reed–Sternberg cells. Data will soon be available from a phase 1 study combining this agent with the immune-checkpoint inhibitor pembrolizumab.

The data from this trial support pursuing further research into BV plus nivolumab in the R/R setting, with potentially significant gains for our patients from reduced toxicity with maintained efficacy. A study of BV plus nivolumab in patients with R/R HL ineligible for ASCT is ongoing and may further inform the role for this combination. Demonstration of durable responses with immunotherapy alone would be a significant breakthrough.

It is clearly a daunting challenge to define best treatment from an ever-increasing range of options, and then find a way to meet the huge financial costs of new immunotherapies. Nonetheless, this study gives further genuine cause for optimism that scientific progress in cancer immunotherapy will soon deliver tangible benefits to our patients.

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