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Relapsed Hodgkin disease: Should all patients receive an autologous stem cell transplant? - the CON

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Case:

A 26 yo woman presents to discuss options for treatment of relapsed Hodgkin lymphoma (HL). Five years ago, she was diagnosed with stage IIA HL involving non-bulky lymphadenopathy in the right cervical, anterior mediastinal, and hilar regions. She was treated with ABVD and achieved a complete metabolic response (CMR) after 2 cycles. She received a total of 4 cycles of treatment without radiation. She remained well until recently when she self-palpated an enlarged right supraclavicular lymph node. An excisional lymph node biopsy of the right supraclavicular lymph node confirmed relapsed HL. PET imaging showed non-bulky FDG-avid lymphadenopathy in the right cervical, anterior mediastinal, and right paratracheal regions. She feels well and denies fevers, night sweats or weight loss.

She is aware that the standard treatment for relapsed HL typically includes consolidation with high dose therapy followed by an autologous stem cell transplant (HDT/ASCT) however she is interested avoiding a transplant if possible.

Why avoid HDT/ASCT?

Although the standard treatment of relapsed or refractory HL involves second-line therapy followed by consolidation with HDT/ASCT, this is based upon 2 fairly historic studies that were conducted before novel agents, such as brentuximab vedotin (BV) and programmed death-1 (PD-1) blockade, were available.[1,2] Both studies showed significant improvement in event free survival (EFS) or freedom from treatment failure (FFTF), however neither demonstrated a survival benefit of HDT/ASCT. Based upon those studies, the chance of cure in the second line setting for HL was about 50%, however since the introduction of PET-adapted salvage as well as BV and PD-1 blockade, cure rates for relapsed/refractory (rel/ref) HL have been much higher. In fact, salvage regimens incorporating BV and/or PD-1 blockade produce CMR rates ranging from 67-95% and result in nearly 90% of patients achieving cure after HDT/ASCT.[3-7] With such impressive results, it is reasonable to ask whether such an aggressive approach is needed for all patients.

High dose therapy followed by ASCT has the potential to cause significant long-lasting toxicity such as infertility, cardiac dysfunction, pulmonary compromise, and secondary malignancies, therefore it would be desirable to avoid it if not absolutely necessary.[8,9] When the only treatments available for HL were traditional chemotherapy and radiation, it made sense to treat with high-intensity therapy such as HDT/ASCT; however, now that better agents are available for HL, a more personalized approach for rel/ref HL is warranted.

Is cure possible without HDT/ASCT?

Low risk patients

One of first studies to demonstrate the potential of a non-transplant approach to cure relapsed HL was the Children's Oncology Group AHOD0431 trial.[10] On this study, patients with newly diagnosed stage IA or IIA nonbulky HL received 3 cycles of AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide). Those with CMR were observed while those with partial response received involved field radiation therapy (IFRT). An important part of the study was inclusion of reduced-intensity second-line treatment for patients with low-risk relapse, defined as stage IA or IIA nonbulky disease relapsing after AVPC x3. Patients with low-risk relapse were treated with 2 cycles of IV (ifosfamide, vinorelbine), 2 cycles of DECA (dexamethasone, etoposide, cisplatin, cytarabine), and IFRT, 21 Gy. Among 278 patients treated with AVPC, 175 had CR, of which 37 experienced a relapse. Thirty-two patients had low-risk relapses of whom 20 received protocol-specified treatment with IV/DECA and IFRT. Among the 20 patients treated with a non-transplant approach, the 8-year EFS was 78.5%, demonstrating the likely potential of cure of select patients with relapsed HL eligible for radiation consolidation.

Building on the concept of risk-adapted treatment of rel/ref HL, the EuroNET-PHL-R1 study used baseline risk factors and response to salvage therapy to direct patients to either non-transplant or transplant strategies.[11] All patients received 2 cycles of IEP (ifosfamide, etoposide, prednisolone) alternating with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) followed by consolidation with either radiation (low-risk disease) or BEAM (carmustine, etoposide, cytarabine, melphalan) and ASCT +/- radiation (high-risk disease).

Low-risk patients were defined as those with late relapse (more than 12 months from end of first-line treatment) after initial early-stage disease and treated with only 2 cycles of chemotherapy. High-risk patients consisted of patients with disease progression up to 3 months after first-line treatment. Intermediate-risk patients consisted of all other patients with relapsed disease; these patients were further stratified into the low- or high-risk groups based upon response after 1 cycle of IEP-ABVD (Deauville ≤ 2 response designated as low-risk therapy and all others were high-risk).

Among 118 patients enrolled, 12 were considered low-risk based upon having a late relapse after only 2 cycles of initial chemotherapy and all 12 received consolidation with radiation alone. Another 47 with intermediate-risk disease were later classified as low-risk group based upon achieving early CMR to IEP-ABVD. Of these 47 patients, 29 received consolidation with radiation alone, while 18 received BEAM and ASCT (off study). Altogether, 41 patients received consolidation with radiation alone which was associated with a 5-year PFS of 89.7% and OS of 97.4%. This represents the largest study demonstrating the potential of a non-transplant approach to cure select patients with relapsed HL.

The 2 studies described so far were conducted before novel agents for HL were available. Subsequent studies have incorporated BV and/or PD-1 blockade and expanded the definition of "low-risk". For example, in the Checkmate 744 study, low-risk patients with rel/ref HL were initially treated with 4 cycles of BV plus nivolumab.[12] Those with CMR (Deauville ≤3) received 2 more cycles followed by involved-site radiation (ISRT) while those with less than CMR receive 2 cycles of BV plus bendamustine followed by ISRT if CMR was achieved. This study defined "low-risk" as patients with either stage IA/IIA disease at initial diagnosis and relapse within 3 to 12 months from initial treatment (after 3 or fewer cycles of treatment and no RT) or stage IA/IB, IIA/IIB, or IIIA disease at initial diagnosis with relapse after more than 12 months from initial treatment. Furthermore, eligibility required no B symptoms at relapse, no extranodal disease at relapse, no extensive disease where RT was contraindicated at relapse, and no relapse in a prior radiation field.

28 patients enrolled on Checkmate 744, of whom 24 (86%) had stage I or II disease at relapse while 4 (14%) had stage III disease. 23 (82%) of 28 patients achieved CMR after 4 cycles of BV plus nivolumab; 6 patients proceeded to BV plus bendamustine of whom 3 achieved CMR. Overall, 26 (93%) of 28 patients achieved CMR before ISRT and the 3-year PFS was 95%. There was only 1 PFS event which was a patient with previous CMR who progressed 3 months after ISRT and was subsequently lost to follow-up.

Finally, a multicenter investigator-initiated study evaluating single-agent pembrolizumab followed by ISRT for low-risk rel/ref HL provided insight regarding how to best optimize reduced-intensity salvage. For this study, "low risk" was defined as patients with non-bulky stage IA or IIA at initial diagnosis with stage IA or IIA relapsed or refractory disease.[13] Patients were treated with single-agent pembrolizumab x 4 cycles followed by ISRT, where radiation dose ranged from 20-40 Gy depending upon PET and biopsy response following pembrolizumab. Among 22 patients enrolled, 2-year PFS was 61%. This was quite a bit lower than the Checkmate 744 study, primarily because 5 patients progressed on single-agent pembrolizumab while no progressions were seen on BV plus nivolumab. This suggests that although reduced intensity therapy with PD-1-based salvage followed by radiation is effective for select patients, it is best to use PD-1 based combinations to avoid potential progression on single-agent PD-1 blockade.

Non-selected rel/ref patients

The non-transplant studies discussed so far focused on selected patients considered to have "low-risk" relapsed disease. A phase II study of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin (pembro-GVD) followed by pembrolizumab maintenance for patients with CMR (Deauville ≤3) instead enrolled "all-comers" with

rel/ref disease (following 1 line of therapy).[14] This study enrolled 24 patients, including 58% with advanced stage, 21% with B symptoms, 46% with extranodal disease, and 54% with primary refractory disease. After a median follow-up of 30 months, the 2-year PFS was 60%. Among 24 patients, 10 patients relapsed either during or after pembrolizumab maintenance; 9 whom subsequently received additional salvage and HDT/ASCT consolidation. The 1 additional patient did not proceed to HDT/ASCT due to comorbidities but instead received palliative therapy with pembrolizumab plus gemcitabine resulting in CMR. After a median follow-up of 18 months post-ASCT, 2-year freedom from third relapse was 100%, as all patients were in remission at last follow-up.

To determine which patients were likely to relapse during or after pembrolizumab maintenance, and thus eventually need HDT/ASCT, standard clinical risk factors were assessed such as stage, time to relapse, extranodal disease, and B symptoms. The only factor that was predictive was stage IV disease. In fact, the 2-year PFS for patients with stage I-III disease was 72%.

A significant limitation of this study was its small size (24 patients); however, it again demonstrated that a select group of rel/ref patients can likely be cured without HDT/ASCT. Furthermore, it showed that for patients who are not cured with non-transplant approaches in the second-line setting, additional salvage and HDT/ASCT in the third-line setting is effective.

Back to the case

We now return to our patient who is 26 and relapsing with non-bulky stage IIA HL about 5 years after initially receiving ABVD x 4 for non-bulky stage IIA disease. While there used to be 1 standard of care for this patient, we now have several potential options. The 5-year PFS of the phase II study of pembro-GVD followed by HDT/ASCT was 91% and therefore this approach can likely efficiently and effectively lead to cure.[7] This patient however has favorable features, such as long remission duration from initiation treatment, localized disease, and no prior radiation, which makes it possible to consider a less aggressive approach. Cumulative results from the AHOD0431 study, EuroNET-PHL-R1, and Checkmate 744 (summarized in Table 1) indicate that she has a good chance of cure with salvage therapy followed by ISRT. In fact, her clinical history most closely mirrors the eligibly criteria for the Checkmate 744 study with PET-adapted BV plus nivolumab, BV plus bendamustine, followed by ISRT.[12] Although larger studies are needed to confirm the results from non-transplant studies, she potentially has about an 80-90% chance of cure with salvage therapy followed by ISRT. The data from the pembro-GVD followed by pembrolizumab maintenance study also provides reassurance that if she is not cured with reduced-intensity second-line therapy, additional salvage

followed by high dose therapy and HDT/ASCT remains a curative option in the third-line setting.

Conclusion

When it comes to treatment of relapsed or refractory HL, it is no longer appropriate to use a “one size fits all” approach. In the front-line setting, we employ risk-adapted and response-adapted strategies to personalize therapy and optimize both efficacy and tolerability. Accumulating data indicate that similar concepts are now appropriate for second-line therapy. Several small studies evaluating salvage and radiation rather than transplant have demonstrated the potential of cure for patients with low-risk relapse. The cumulative results from these studies indicate that patients could consider one of these less aggressive approaches with the knowledge that if they experience a second relapse, additional salvage and HDT/ASCT consolidation is likely to be effective. Studies evaluating risk and response adapted strategies, such as the EuroNET-PHL-R1 study, serve as excellent models for future studies in this setting. Future studies need to adapt to the modern era where patients are receiving front-line nivolumab plus AVD (adriamycin, vinblastine, dacarbazine)[15] or BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, adriamycin, dacarbazine, dexamethasone)[16] and are then re-treated with novel agents in the second-line setting. These studies would help us understand the efficacy of salvage after modern front-line regimens and further identify which patients are appropriate for less aggressive second-line approaches. A proposed schema is shown in Figure 1.

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Table 1. Summary of non-transplant studies for relapsed and refractory HL

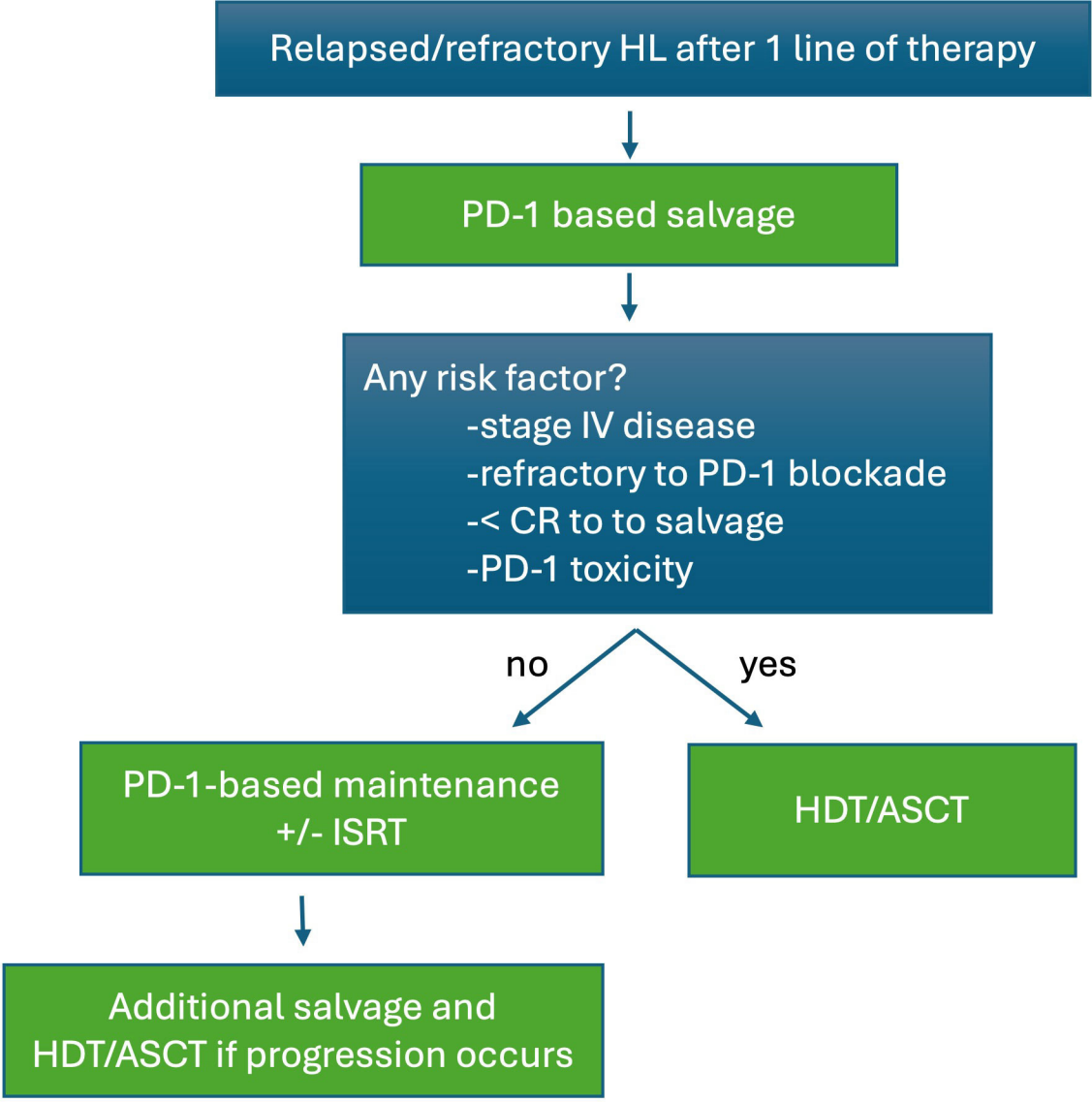
Study	Patients eligible for non-transplant strategy	Treatment	n	EFS/PFS	OS
COG AHOD0431[10]	Stage IA/IIA, nonbulky, relapse after AVPC x 3	IV/DECA x 2 followed by IFRT (21 Gy)	20	8-year EFS 78.5%	8-year OS 100%
EuroNET-PHL-R1[11]	Relapse > 12 months from treatment with 2 cycles of chemotherapy; Relapsed > 3 months from initiation treatment and CMR (Deauville ≤2) after 1 cycles of IEP-ABVD	IEP-ABVD x 2 followed by RT	41	5-year PFS 89.7%	5-year OS 97.4%
Checkmate 744[12]	-stage IA/IIA at initial diagnosis and relapse within 3-12 months from initiatial treatment of < 4 cycles and no RT OR -Stage IA/IB, IIA/IIB, IIIA at initial diagnosis with relapse after > 12 months from initial treatment AND -no B Sx, ENS -Eligible for RT	BV/nivo x 4 -> PET PET negative (Deauville ≤3): BV/nivo x 2 and ISRT PET positive: BV/bendamustine x 2 and ISRT (if CMR achieved)	28	3-year PFS 95%	3-year OS 100%
Pembro-ISRT[13]	-Non-bulky stage IA or IIA at initial diagnosis; rel/ref stage IA or IIA disease -Eligible for RT	Pembrolizumab x 4 followed by ISRT ISRT dose: -CMR (Deauville ≤3): 20 Gy -Deauville 4-5 and responding: 30 Gy if biopsy negative, 36-40 Gy if biopsy positive -Deauville 5 and progressing, biopsy negative: 36-40Gy	22	2-year PFS 61%	2-year OS 100%

Pembro-GVD-> pembro maintenance[14]	Any patient with rel/ref HL after 1 line of therapy	Pembro-GVD x 4 -> PET If Deauville ≤3: pembrolizumab x 13	24	2-year PFS: 60%; 2-year time to third relapse: 100%	2-year OS: 100%

Abbreviations: AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide; BV/nivo (brentuximab vedotin, nivolumab); BV/bendamustine (brentuximab vedotin, bendamustine); COG (Children's Oncology Group); EFS (event free survival); IEP-ABVD (ifosfamide, etoposide, prednisolone/adriamycin, bleomycin, vinblastine, dacarbazine); IFRT (involved field radiation therapy); ISRT (involved site radiation therapy); IV/DECA (ifosfamide, vinorelbine-dexamethasone, etoposide, cisplatin, cytarabine); pembro-GVD (pembrolizumab, gemcitabine, vinorelbine, liposomal doxorubicin); PFS (progression free survival); rel/ref (relapsed or refractory); RT (radiation therapy)

Figure 1. Proposed modern-era risk-adapted and response-adapted study for relapsed or refractory Hodgkin lymphoma

Abbreviations: CR (complete response); HDT/ASCT (high dose therapy and autologous stem cell transplant); HL (Hodgkin lymphoma); ISRT (involved site radiation therapy); PD-1 (programmed death-1)


Relapsed/refractory HL after 1 line of therapy
PD-1 based salvage
Any risk factor?
-stage IV disease
-refractory to PD-1 blockade
-< CR to to salvage
-PD-1 toxicity
no
yes
PD-1-based maintenance
+/- ISRT
HDT/ASCT
Additional salvage and
HDT/ASCT if progression occurs