Relapsed Hodgkin lymphoma: should all patients receive an autologous stem cell transplant? – the CON

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Case scenario

A 26-year-old woman presents to discuss options for treatment of relapsed Hodgkin lymphoma (HL). Five years previously she had been diagnosed with stage IIA HL involving non-bulky lymphadenopathy in the right cervical, anterior mediastinal, and hilar regions. She was treated with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) and achieved a complete metabolic response (CMR) after two cycles. She received a total of four cycles of treatment without radiation. She remained well until recently when, on self-palpation, she found an enlarged right supraclavicular lymph node. An excisional biopsy of this lymph node confirmed relapsed HL. Positron emission tomography (PET) imaging showed non-bulky fluorodeoxyglucose-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 in avoiding a transplant if possible.

Why avoid high-dose therapy followed by an autologous stem cell transplant?

Although the standard treatment of relapsed or refractory HL involves second-line therapy followed by consolidation with HDT-ASCT, this is based upon two 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 or freedom from treatment failure; however, neither demonstrated a survival benefit from HDT-ASCT. Based on 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 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 as HDT-ASCT is needed for all patients.

HDT-ASCT has the potential to cause significant long-lasting toxicity such as infertility, cardiac dysfunction, pulmonary compromise, and secondary malignancies; it would, therefore, 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 relapsed/refractory HL is warranted.

Is cure possible without high-dose therapy followed by an autologous stem cell transplant?

Low-risk patients

One of the 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 non-bulky HL received three cycles of AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide). Those with a complete response were observed while those with a partial response received involved field radiation therapy. 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 non-bulky disease relapsing after three cycles of AVPC. Patients with low-risk relapse were treated with two cycles of IV (ifosfamide, vinorelbine), two cycles of DECA (dexamethasone, etoposide, cisplatin, cytarabine), and 21 Gy of involved field radiation therapy. Among 278 patients treated with AVPC, 175 had a complete response, of whom 37 experienced a relapse. Thirty-two patients had low-risk relapses of whom 20 received protocol-specified treatment with IV-DECA and involved field radiation therapy. Among the 20 patients treated with a non-transplant approach, the 8-year event-free survival was 78.5%, demonstrating the likely potential for cure of selected patients with relapsed HL eligible for radiation consolidation.

Building on the concept of risk-adapted treatment of relapsed/refractory 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 two cycles of IEP (ifosfamide, etoposide, prednisolone) alternating with ABVD followed by consolidation with either radiation (low-risk disease) or BEAM (carmustine, etoposide, cytarabine, melphalan) and ASCT with or without radiation (high-risk disease).

Low-risk patients were defined as those with late relapse (more than 12 months from the end of first-line treatment) after initial early-stage disease and treated with only two cycles of chemotherapy. High-risk patients were defined as 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 on their response after one cycle of IEP-ABVD (Deauville score ≤2: designated as low-risk; all others as high-risk).

Among 118 patients enrolled, 12 were considered low-risk based on having had a late relapse after only two cycles of initial chemotherapy and all 12 received consolidation with radiation alone. Another 47 with intermediate-risk disease were later assigned to the low-risk group based on having achieved an early complete response 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 progression-free survival (PFS) of 89.7% and overall survival (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 two studies described so far were conducted before novel agents for HL became 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 relapsed/refractory HL were initially treated with four cycles of BV plus nivolumab.[12] Those with CMR (Deauville score ≤3) received two more cycles followed by involved-site radiation therapy (ISRT) while those with less than CMR received two cycles of BV plus bendamustine followed by ISRT if CMR was achieved. This study defined "low-risk" patients as those with either stage IA/IIA disease at initial diagnosis and relapse within 3 to 12 months after their initial treatment (after ≤3 cycles of treatment and no radiotherapy) or stage IA/IB, IIA/IIB, or IIIA disease at initial diagnosis with relapse more than 12 months after their initial treatment. Furthermore, eligibility required no B symptoms at relapse, no extranodal disease at relapse, no extensive disease where radiotherapy was contraindicated at relapse, and no relapse in a previously irradiated field.

Twenty-eight patients were enrolled on Checkmate 744, of whom 24 (86%) had stage I or II disease at relapse while four (14%) had stage III disease. Twenty-three (82%) of the 28 patients achieved CMR after four cycles of BV plus nivolumab; six patients proceeded to BV plus bendamustine of whom three achieved CMR. Overall, 26 (93%) of the 28 patients achieved CMR before ISRT and the 3-year PFS was 95%. There was only one event indicating progression, which occurred in 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 relapsed/refractory HL provided insight regarding how best to optimize reduced intensity salvage. For this study, low-risk patients were defined as those with non-bulky stage IA or IIA at initial diagnosis with stage IA or IIA relapsed or refractory disease.[13] Patients were treated with four cycles of single-agent pembrolizumab followed by ISRT, with the radiation dose ranging from 20 to 40 Gy depending upon PET- and biopsy-determined response following the pembrolizumab treatment. Among 22 patients enrolled, 2-year PFS was 61%. This was quite a bit lower than in the Checkmate 744 study, primarily because five 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 selected patients, it is best to use PD-1-based combinations to avoid potential progression on single-agent PD-1 blockade.

Non-selected relapsed/refractory patients

The non-transplant studies discussed so far focused on selected patients considered to have "low-risk" relapsed disease. In contrast, a phase II study of pembrolizumab plus GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) followed by pembrolizumab maintenance for patients with CMR (Deauville score ≤3) enrolled "all-comers" with relapsed/refractory disease (following 1 line of therapy).[14] This study enrolled 24 patients, including 58% with advanced-stage disease, 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 the 24 patients enrolled, ten relapsed either during or after pembrolizumab maintenance; nine of whom

subsequently received additional salvage and HDT-ASCT consolidation. The one additional patient did not proceed to HDT-ASCT because of comorbidities but instead received palliative therapy with pembrolizumab plus gemcitabine resulting in CMR. At a median follow-up of 18 months after 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 relapsed/refractory 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 years old and relapsing with non-bulky stage IIA HL about 5 years after initially receiving four cycles of ABVD for non-bulky stage IIA disease. While there used to be one standard of care for this patient, we now have several potential options. The 5-year PFS of the phase II study of pembrolizumab plus GVD followed by HDT-ASCT was 91% and therefore this approach would likely efficiently and effectively lead to cure.[7] This patient does, however, have favorable features, such as a long duration of remission from initiation of treatment, localized disease, and no prior radiation, which make 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 eligibility 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

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

Study	Patients eligible for non-transplant strategy	Treatment	N	EFS/PFS, %	OS, %
COG AHOD0431[10]	Stage IA/IIA, non-bulky, 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; Relapse >3 months from start of treatment and CMR (DS ≤2) after 1 cycle 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 initial 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-symptoms, extranodal sites Eligible for RT	BV-nivolumab x 4 then PET: PET-negative: (DS ≤3): BV-nivolumab 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; Relapsed or refractory stage IA or IIA disease; Eligible for RT	Pembro x 4 followed by ISRT. ISRT dose: -CMR (DS ≤3): 20 Gy -DS 4-5 and responding: 30 Gy if biopsy negative, 36-40 Gy if biopsy positive -DS 5 and progressing, biopsy negative: 36-40 Gy	22	2-year PFS: 61	2-year OS: 100
Pembro-GVD then pembro maintenance[14]	Any patient with relapsed or refractory HL after 1 line of therapy	Pembro-GVD x 4 then PET If DS ≤3: pembro x 13	24	2-year PFS: 60; 2-year third RFS: 100	2-year OS: 100

EFS: event-free survival; PFS: progression-free survival; OS: overall survival; COG: Children's Oncology Group; AVPC: doxorubicin, vincristine, prednisone, cyclophosphamide; IV-DECA: ifosfamide, vinorelbine - dexamethasone, etoposide, cisplatin, cytarabine; Gy: Gray; IFRT: involved field radiation therapy; CMR: complete molecular response; DS: Deauville score; IEP-ABVD: ifosfamide, etoposide, prednisolone - adriamycin, bleomycin, vinblastine, dacarbazine; RT: radiation therapy; BV: brentuximab vedotin; PET: positron emission tomography; ISRT: involved site radiation therapy; pembro: pembrolizumab; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; HL: Hodgkin lymphoma; RFS: relapse-free survival.

from non-transplant studies, she potentially has about an 80-90% chance of cure with salvage therapy followed by ISRT. The data from the pembrolizumab plus GVD followed by pembrolizumab maintenance study also provide reassurance that if she is not cured with reduced-intensity second-line therapy, additional salvage followed by 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 in which 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.

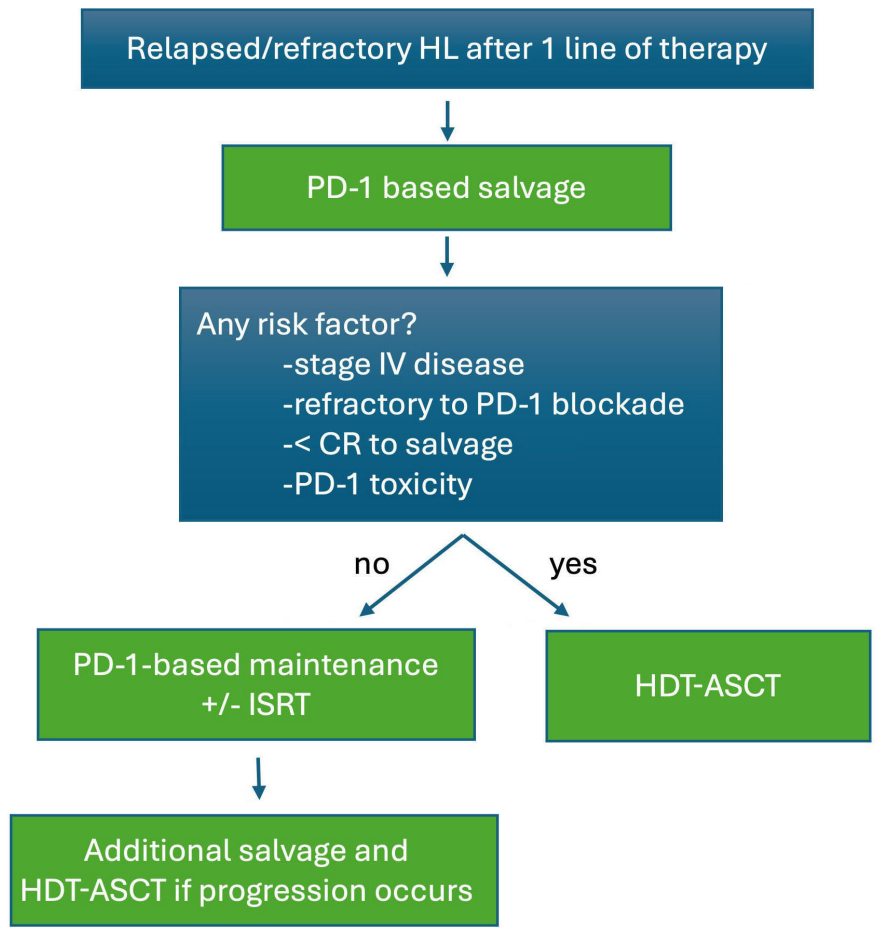


Figure 1. Proposed modern-era risk-adapted and response-adapted study for relapsed or refractory Hodgkin lymphoma. HL: Hodgkin lymphoma; PD-1: programmed death-1; CR: complete response; ISRT: involved site radiation therapy; HDT-ASCT: high-dose therapy and autologous stem cell transplant.

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