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

Chathuri Abeyakoon,[1-3] and John Kuruvilla[4]

[1]Monash Haematology, Monash Health, Melbourne, Australia; [2]Epworth HealthCare, Melbourne, Australia; [3]Department of Medicine, School of Clinical Sciences at Monash Health, Monash University, Melbourne, Australia and [4]Division of Medical Oncology and Haematology, Princess Margaret Cancer Centre, Toronto, Canada

Correspondence: J. Kuruvilla
john.kuruvilla@uhn.ca

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High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) has long been the cornerstone of curative therapy for eligible patients with relapsed or refractory Hodgkin lymphoma (HL) who demonstrate treatment-sensitive disease.[1-3] Over the past decade, the therapeutic landscape of HL has evolved substantially. The incorporation of the CD30-directed antibody-drug conjugate brentuximab vedotin (BV) and immune checkpoint inhibitors (CPI) targeting programmed cell death protein-1 (PD-1) into frontline, salvage, and post-transplant settings has significantly improved outcomes. These advances have ignited debate regarding the ongoing role of ASCT: does high-dose therapy remain necessary for all patients with relapsed or refractory HL, or can selected subgroups be safely spared this intensive approach?

While this question is timely and important, the available evidence strongly supports the continued central role of ASCT as consolidative therapy for the majority of patients with relapsed or refractory HL in the current era.

The curative paradigm and historical evidence supporting autologous stem cell transplantation

Contemporary frontline strategies cure approximately 80-95% of patients with early- and advanced-stage HL.[4-9] Modern clinical trials in the primary treatment setting have sought to improve or maintain high cure rates while attempting to minimize treatment exposure to reduce rates of both acute and delayed toxicities. Cure remains the overarching goal for patients' management even in the relapsed/refractory setting. For the 10-20% of patients who are not cured with primary therapy, historical data have demonstrated that approximately 50% of patients can expect durable remission and cure with salvage therapy followed by consolidative ASCT.[10-14]

The role of ASCT is supported by two randomized controlled trials conducted in the era before the introduction of novel agents, which consistently demonstrated superior freedom from treatment failure or event-free survival compared with conventional-dose chemotherapy alone, albeit without a clear overall survival (OS) advantage.[10,11] The largest of these, the German Hodgkin Study Group (GHSG) HD-R1 trial, randomized 161 patients aged 16-60 years to receive two cycles of dexamethasone, BCNU, etoposide, cytarabine, and melphalan (Dexa-BEAM) followed by either two additional cycles of Dexa-BEAM or high-dose BEAM with ASCT. Among the 117 patients with chemosensitive disease, 7-year freedom from treatment failure was significantly improved with ASCT (49% *vs*. 32%; *P*=0.02) at a median follow-up of 83 months.[10] It is important to highlight that these trials were not powered to look at OS as the primary endpoint and that maintained event-free survival or freedom from treatment failure (ongoing longer term disease remission) is indicative of cure as relapse following second-line therapy is uncommon beyond 2 years.[15] Patients in the non-ASCT arm of these trials would have gone on to receive additional therapy (radiation, further chemotherapy, etc.) which may provide the potential for some disease control but treatment typically would no longer be given with curative intent.

These findings are reinforced by pooled analyses from GHSG trials, which demonstrated superior long-term outcomes among patients able to proceed to ASCT. Ten-year progression-free survival (PFS) and OS were 49% and 62%, respectively, in transplanted patients, compared with 31% and 41% in those unable to undergo ASCT.[13] A retrospective analysis of 501 patients treated on three prospective phase II trials and prospectively registered in the database at the MD Anderson Cancer Center demonstrated a 5-year PFS and OS of 55% (95% confidence interval [95% CI]: 50-59%) and 73%, respectively, with improvements in both endpoints over time.[14] Collectively, these data established ASCT as the standard

consolidative strategy for chemosensitive relapsed or refractory HL.

With the arrival of the CD30 antibody-drug conjugate BV and the first CPI developed in HL (nivolumab and pembrolizumab), agents with impressive single-agent activity in the palliative setting were identified. The goal of subsequent drug development was to incorporate these agents earlier into the disease course, particularly into the curative treatment setting.

Consolidation therapy after autologous stem cell transplantation

The confirmatory randomized trial for BV was the AETHERA study. This study randomized high-risk patients, defined as those with primary refractory disease, relapsed disease with an initial remission duration of less than 12 months or extranodal involvement at the start of pre-transplantation salvage chemotherapy, to receive up to 16 cycles of BV monotherapy *versus* placebo.[12] Long-term follow-up demonstrated a 5-year PFS of 59% (95% CI: 55-66%) with BV maintenance *versus* 41% (95% CI: 33-49%) with placebo.[16] These results demonstrate that in a modern cohort of patients with relapsed or refractory HL, BV maintenance improves outcomes after ASCT, with cure rates appearing superior to the approximately 50% reported in historical cohorts, even in patients with high-risk disease.

Prognostic importance of positron emission tomography response and optimization of salvage therapy

A key advance in the modern era has been the recognition of pre-transplant metabolic response as the strongest predictor of post-ASCT outcomes. Achievement of a complete metabolic response, most commonly defined as a Deauville score of 1-3 on ^{18}F-flurodeoxyglucose positron emission tomography (FDG-PET) imaging, is consistently associated with superior PFS and OS.[17-20] Importantly, the number of salvage regimens required to achieve FDG-PET-defined complete metabolic response does not appear to adversely affect transplant outcomes, underscoring the importance of response rather than regimen sequence.[19]

Traditional salvage chemotherapy regimens incorporating gemcitabine-, platinum-, or ifosfamide-based backbones historically yielded overall response rates of 60-70% and complete response (CR) rates of 20-25%, as determined by computed tomography (CT) criteria.[21] The integration of functional imaging has revealed substantially higher CR rates, even with conventional chemotherapy. Notably, the BeGEV regimen (bendamustine, gemcitabine, vinorelbine) achieved a PET-defined CR rate of 75%, with 5-year PFS and OS of 77% and 91%, respectively, among patients proceeding to ASCT.[22]

Given the central prognostic importance of PET-defined CR, novel agents have increasingly been explored and incorporated into salvage strategies to optimize pre-transplant disease control and improve subsequent post-ASCT outcomes.

Expected current outcomes with salvage and autologous stem cell transplantation strategies incorporating novel agents

Both BV and PD-1 inhibitors have been successfully integrated into salvage regimens and have produced high CR rates (Table 1). Initial experience with BV and CPI in the salvage setting involved the use of these agents as monotherapy in patients not responding to second-line (typically platinum-containing) regimens.[23,24] Although safe and effective, it was evident that using these agents as part of second-line therapy would likely lead to more favorable outcomes for patients. BV combined with conventional chemotherapy backbones, including ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin), IGeV (ifosfamide, gemcitabine, vinorelbine, prednisolone), and DHAP (dexamethasone, cytarabine, cisplatin), or with single-agent gemcitabine or bendamustine, has produced CR rates of 67-79%.[21] Similarly, CPI-based salvage regimens have yielded striking results. Pembrolizumab combined with ICE (ifosfamide, carboplatin, etoposide) or GVD (gemcitabine, vinorelbine, liposomal doxorubicin) has demonstrated CR rates of 86-95% and overall response rates approaching 100%.[25,26] It is important to highlight that these trials did not describe any concerning safety signals and, although grade 3-4 neutropenia was more common with BV combinations and immune-related adverse events can occur with CPI in the salvage setting, these complications are uncommon.[26-29]

Sequential strategies using BV or nivolumab monotherapy upfront to induce CR, reserving multi-agent chemotherapy for non-responders, has also been explored. CR rates of 28-77% with novel agents alone and 65-85% following subsequent chemotherapy have been described.[29-31] These trials highlight that approximately 25-75% of patients can proceed directly to an ASCT without exposure to chemotherapy-based salvage therapy. Novel–novel combinations have further expanded therapeutic options: BV plus nivolumab achieved a CR rate of 67%, while the triplet of nivolumab, BV, and ipilimumab yielded CR rates of 73%.[32-34] These regimens are also appealing as they do not include traditional chemotherapy agents but it remains unclear in the absence of randomized comparisons whether there is an optimal combination approach with the highest CR rate and most favorable toxicity profile prior to ASCT.

Table 1. Salvage regimens incorporating novel agents.

Salvage regimen	Reference	N of patients	CR, %	PFS, %	OS, %
Salvage regimens incorporating BV					
BV + gemcitabine	56	45	57	NR	1-year: 95
BV + bendamustine	57 58	55 40	74 79	2-year: 63 2-year: 67	2-year: 94 3-year: 88
BV + ESHAP	59	66	70	30-month: 71	2-month: 90
BV + IGEV	27	28	70	2-year: 73.5	2-year: 87.1
BV + DHAP	28	67	81	2-year: 74	2-year: 95
BV + sequential augmented ICE	60	65	75 (28 after BV alone)	3-year: 82	3-year: 95
BV + sequential ICE/GVD	30	57	65	2-year: 67	2-year: 93
BV + sequential physicians' choice salvage regimen	31	37	61	NR	NR
Salvage regimens incorporating a CPI					
Pembrolizumab + ICE	25	42	86.5	Median: 26 months	2-year: 88.2
Pembrolizumab + GVD	26	39	95	1-year: 100	1-year: 100
Nivolumab + sequential NICE	29	43	71 after cycles of Nivo 98 after NICE	2-year: 72	2-year: 95
Salvage regimens incorporating BV in combination with a CPI					
BV + nivolumab	32	91	67	2-year: 78	2-year: 93
Nivolumab + BV + ipilimumab	33	64	BV-Ipi: 57 BV-Nivo: 61 BV-Nivo-Ipi; 73	1-year BV-Ipi: 61 BV-Nivo: 70 BV-Nivo-Ipi: 80	Median: not reached

CR: complete response; PFS: progression free survival; OS: overall survival; BV: brentuximab vedotin; NR: not reported; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, cisplatin; IGEV: ifosfamide, gemcitabine, vinorelbine, prednisolone; DHAP: dexamethasone, cytarabine, cisplatin; ICE: ifosfamide, carboplatin, etoposide; GVD: gemcitabine, vinorelbine, liposomal doxorubicin; CPI: checkpoint inhibitor; NICE: nivolumab, ifosfamide, carboplatin, etoposide; Nivo: nivolumab; Ipi: ipilimumab.

High CR rates achieved with novel salvage regimens appear to translate into favorable PFS outcomes after ASCT. BV-incorporating salvage regimens have demonstrated 2-year PFS rates of 63-78% and a retrospective analysis found superior 2-year event-free survival with CPI-based salvage therapy compared to conventional chemotherapy, BV and chemotherapy or BV monotherapy (79.7%, 49.6%, 62.3%, and 36.9%, respectively, $P<0.0001$).[21,35] As mentioned previously, patients with high-risk disease features at relapse can go on to receive post-ASCT BV maintenance with the aim of further improving PFS outcomes which can make interpretation of the impact of salvage therapy on post-ASCT PFS more challenging given the use of additional therapy. The only randomized controlled trial to date comparing novel salvage therapy against conventional chemotherapy is an ongoing Canadian Cancer Trials Group randomized study (CCTG HD.11, NCT05180097) comparing pembrolizumab-BV with GDP (gemcitabine, dexamethasone, cisplatin) followed by ASCT, which completed accrual in 2025.

Although long-term follow-up of these single-arm phase II or retrospective studies evaluating the efficacy of salvage regimens incorporating novel agents are relatively short (typically reporting 2-year time to event outcomes), the data remain encouraging. It will be important to review the long-term follow-up of these studies looking at late toxicities in order to better understand whether these approaches also have favorable impacts on secondary cancer rates and cardiovascular outcomes.

Recent trials evaluating non-ASCT-based approaches provide some expectations for such an approach in the current era. A non-randomized phase II trial is assessing four cycles of pembrolizumab-GVD followed by 13 cycles of pembrolizumab maintenance with the omission of an ASCT in those able to achieve a CR after the initial four induction cycles. Interim results have demonstrated a 2-year PFS of 51% (95% CI: 33-80%) with higher risk of progression in patients with stage IV disease at trial enrollment.[36] These results highlight the importance of enrolling patients on well-designed prospective clinical trials as the impact on OS and cure for a non-ASCT-based approach remains an unanswered question.

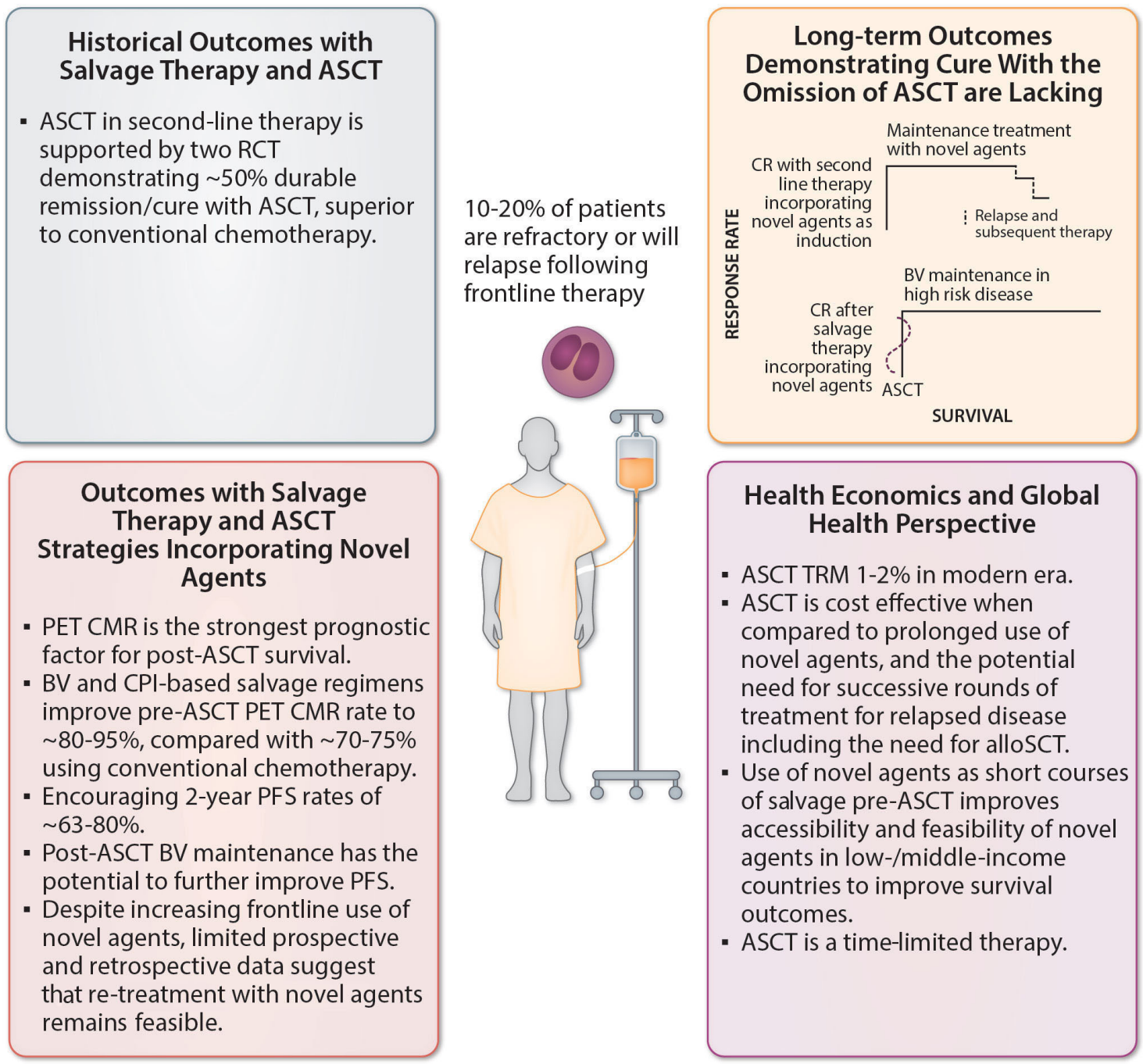


Figure 1. Autologous stem cell transplantation remains an important therapeutic modality in the management of relapsed or refractory classical Hodgkin lymphoma. ASCT: autologous stem cell transplantation; RCT: randomized controlled trials; PET: ^{18}F-flurodeoxyglucose positron emission tomography; CMR: complete metabolic remission; BV: brentuximab vedotin; CPI: checkpoint inhibitor; PFS: progression-free survival; CR: complete remission; TRM: transplant-related mortality; alloSCT: allogeneic stem cell transplantation.

Evolving primary therapy approaches and new questions

The incorporation of BV-AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine), N-AVD (nivolumab, doxorubicin, vinblastine, dacarbazine) and BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) into frontline therapy has further improved outcomes in HL.[8,9,37] While these advances represent a major success, they introduce new uncertainties in the relapsed/refractory setting. The impact of prior exposure to novel agents on response to salvage, transplant outcomes, and long-term cure remains largely unknown. These regimens were tested in stage III-IV patients and are typically approved/reimbursed (or pending approval and reimbursement) in many countries in this setting. Given traditional inclusion of patients with stage IIB bulky disease among those with advanced-stage disease, it would be reasonable to anticipate that many of these patients would also receive novel therapy in combination with chemotherapy. However, the role of BV and CPI in patients with stage I-II disease is less clear. Phase II data have demonstrated excellent results with the incorporation of novel agents in this setting.[38-40] Randomized controlled trials are currently underway.[41,42]

It is important to recognize that, over the coming years, clinicians will increasingly be required to manage two distinct populations of patients in the second-line relapsed/refractory setting: (i) patients without prior exposure to novel agents, and (ii) patients with prior exposure to novel therapies, including BV, CPI, or both. In light of the impressive safety and efficacy outcomes from the S1826 trial, it

is likely that many patients will have received N-AVD in the frontline setting, with a smaller proportion treated with BrECADD. Consequently, the results of second-line salvage strategies incorporating novel agents will primarily be applicable to patients who are novel agent-naïve at relapse. As disease progression typically occurs within 12-24 months of frontline therapy, large datasets (prospective or retrospective) evaluating second-line approaches in patients progressing after frontline BV or CPI exposure are not yet available.

Limited prospective and real-world data suggest that retreatment with BV or CPI monotherapy is feasible, with overall response rates of approximately 50-60% for BV and 75-100% for CPI in selected patients.[43-46] This is suggestive of the feasibility of retreatment in combination approaches from an efficacy perspective, but there are also important factors to consider in the clinic. Cumulative toxicities (particularly peripheral neuropathy with BV) and prior immune-related adverse events or history of autoimmune disease (for CPI) may be key factors when selecting second-line regimens in patients with prior exposure to novel agents. More importantly, the durability of responses achieved with novel salvage regimens alone remains uncertain. In a patient already treated with BV-AVD or BrECADD, a nivolumab- or pembrolizumab-based approach is rational. Conversely, in a nivolumab- or pembrolizumab-exposed patient, a BV-based approach is rational.

Can autologous stem cell transplantation be omitted in selected patients?

The desire to reduce treatment intensity where safely possible is appropriate. Guidelines on the treatment of children and adolescents from the EuroNet group already recommend non-transplant approaches for carefully selected low-risk patients based on time to relapse, stage at relapse, prior therapy, and achievement of early PET-defined CR (after 2 cycles of salvage therapy).[47] Whether similar strategies can be safely extrapolated to adults remains an open question. Early-phase studies exploring ASCT omission are promising but immature. In the phase IIb BRESELIBET trial, BV-ESHAP (brentuximab vedotin, etoposide, methylprednisolone, high-dose cytarabine, cisplatin) improved CR rates compared with ESHAP alone, with patients who achieved CR receiving BV consolidation without ASCT.[48] A randomized controlled trial evaluating ASCT *versus* pembrolizumab maintenance in patients who achieved a CR to induction cycles of pembrolizumab-GVD is underway.[26,36] However, long-term PFS and OS data are not yet available, and these studies largely exclude patients treated with frontline novel agents.

Until mature randomized data demonstrate non-inferiority of ASCT-free strategies, omission of transplant should remain investigational and limited to carefully selected patients within clinical trials. Importantly, patients with high-risk features – early relapse, primary refractory disease, advanced stage, or extranodal involvement – are unlikely to be adequately treated without ASCT consolidation. Furthermore, patients who do not proceed to second-line ASCT consolidation and subsequently relapse will most likely go on to receive ASCT as part of third-line treatment strategies.

Health economics and global equity considerations

Historically, ASCT had risks even in younger patients, including a 100-day non-relapse mortality of approximately 5-6%.[49,50] However, the safety of ASCT has improved substantially given advances in supportive care and the routine use of peripheral blood stem cells, and the figure is now in the range of 1-2%, particularly in patients under the age of 60 years.[51,52] While cost analyses are complex, ASCT has been shown to be cost-effective compared to conventional chemotherapy and transplant is a time-limited therapy.[53] In contrast, multiple rounds of subsequent treatment, prolonged use of novel agents as maintenance or sequential therapy and the potential need for an allogeneic stem cell transplantation are likely to incur substantial cumulative costs, particularly in the absence of a definitive cure.

From a global perspective, access to BV and CPI remains limited and largely confined to high-income countries, with significant disparities even within these settings. Moreover, short-course exposure (2-4 cycles) to novel agents as salvage therapy to optimize ASCT outcomes represents a more cost-effective strategy than prolonged novel agent therapy, potentially improving feasibility and accessibility in low- and middle-income countries. Additionally, conventional chemotherapy and ASCT are available in most regions worldwide, underscoring their continued relevance and importance in achieving equitable HL-directed care.[54,55] A systematic review performed by Craven *et al*. exploring HL treatment patterns and outcome disparities in low- and middle-income countries demonstrated that ASCT is the most commonly used treatment modality in the relapsed/refractory setting (62%) in comparison to novel agents (29%).[55]

Conclusions

The modern therapeutic era has transformed outcomes for patients with HL, and novel agents have undeniably improved the efficacy of salvage approaches. However, these advances should be viewed as complementary to, rather than replacements for, ASCT. At present, ASCT remains the only consolidative strategy for which there is

robust long-term evidence for durable remission and cure in relapsed or refractory HL. Until prospective randomized data demonstrate equivalent long-term outcomes without transplant, ASCT should remain standard of care for the majority of transplant-eligible patients with relapsed disease (Figure 1). In the enthusiasm for therapeutic innovation, we must be careful not to discard a curative modality with decades of proven benefit.

Disclosures

CA has no conflicts of interest to disclose. JK has research interests with AstraZeneca, BeOne, Merck and Roche; has provided consultancy services for AbbVie, AstraZeneca, BeOne, BMS, Kite/Gilead, Merck, Roche and OmniaBio; has recieved honoraria from AbbVie, Amgen, Arvinas, Astra Zeneca, BMS, BeOne, Genmad, Incyte, Janssen, Kite-Gilead, Lilly, Merck, Novartis, Pfizer and Roche; and has participated in a Data Safety Monitoring Board for Karyopharm.

Contributions

CA and JK conducted the literature search and wrote the manuscript.

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