Standard therapy of advanced Hodgkin lymphoma

John Kuruvilla[1]

[1]*Division of Medical Oncology and Hematology, Princess Margaret Hospital, Department of Medicine, University of Toronto, Toronto, Canada.*

ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) continues to be the standard of care for patients with advanced-stage Hodgkin lymphoma (HL). Consolidation of primary chemotherapy with radiation or autologous stem cell transplantation (ASCT) has not demonstrated an improvement in overall survival in randomized controlled trials. Regimens such as escalated BEACOPP have more acute and late toxicities and survival benefits have yet to be confirmed.

Despite effective therapy, ultimately 30% to 40% of patients with advanced HL will relapse. ASCT has become the standard of care for patients with relapsed or refractory HL based on two randomized trials. The optimal salvage chemotherapy and high dose therapy regimen are not known. Similarly, non-ASCT strategies including salvage radiotherapy or non-ASCT chemotherapy strategies have been reported and have a potential role in selected clinical scenarios.

This review summarizes recent clinical trial results in the initial treatment of advanced HL and will focus on second-line treatment strategies for patients with relapsed or refractory disease.

Hodgkin lymphoma (HL) is a highly curable disease with the majority of patients presenting with localized disease. Advanced HL (defined as presented with bulk > 10 cm, the presence of B symptoms and/or stage III/IV disease) has typically been associated with failure rates as high as 30% to 40% with anthracycline-based polychemotherapy. Trials have systematically evaluated multi-agent chemotherapy regimens and the use of consolidation strategies with a focus on improved disease control.

Relapsed or refractory HL constitutes another common problem for clinicians who treat lymphoma. Second-line chemotherapy followed by autologous stem cell transplantation is the standard of care based on randomized trial data. However, there is a lack of consensus about the type of salvage chemotherapy employed prior to the transplant as well as the potential role of other strategies in non-transplant eligible patients.

Primary Therapy of Advanced Hodgkin Lymphoma

Primary Chemotherapy

The treatment of advanced HL has been advanced and refined by the conduct of numerous large multicenter randomized controlled trials (RCTs). There is clear consensus that anthracycline-based chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) is the gold standard because of its equivalent response rate to therapy and progression-free survival (PFS) and its more favorable toxicity profile compared with alternating MOPP/ABVD or MOPP/ABV hybrid chemotherapy.[1,2] Many groups have developed alternate regimens for advanced HL based on two principles—either to incorporate dose intensive/dose dense chemotherapy or to use a similar approach that dose intensifies certain agents while minimizing leukemogenic or gonadotoxic agents. These strategies led to promising phase II or institutional experiences that required testing in large phase III trials. A summary of recent RCTs in advanced Hodgkin lymphoma is provided in **Table 1**.

Despite the failure of multi-drug regimens in previous RCTs, the German Hodgkin Study Group (GHSG) developed the BEACOPP regimens (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) based on principles of dose density/intensity and mathematical modeling.[3] The GHSG HD9 trial was a large (n = 1195 evaluable) randomized trial comparing COPP/ABVD with BEACOPP and an escalated dose version of BEACOPP (escBEACOPP).[4] The primary endpoint of the trial was freedom from treatment failure (FFTF), defined as progression during treatment, lack of complete remission at the end of protocol treatment, relapse or death. EscBEACOPP was shown to reduce rates of early progression and resulted in a statistically significant improvement in overall survival (OS) compared with COPP-ABVD.

Table 1. Recent randomized trials of chemotherapy in the treatment of advanced Hodgkin lymphoma.

Regimen	No. of patients	CR, %	FFS, %	OS, %	Heme toxicity grade 3-4, %	RAD,* %
MOPP/ABV	419	80	66 (5 y)	82	74.6	0
ABVD[66]	433	76	63	81	63.6**	0
COPP/ABVD	260	85	69 (5 y)	83	71	64
BEACOPP	469	88	76	88	73	71
EscBEACOPP[4]	466	96	87	91**	98**	71
Mod Stanford V	107	76	54 (5 y)	82	29	66
MOPPEBVCAD	106	94	81	89	51**	47
ABVD[10]	122	89	78	90	21	62
Stanford V	259	ns	76 (5 y)	92	NS	53
ABVD[12]	261	NS	74	90	56	38
MDR	394	67	75 (3 y)	88 (3 y)	65**	40
ABVD[9]	394	68	75	90	56	38
BEACOPP	102	91	81 (5 y)**	92 (5 y)	54	44
CEC	102	83	78	91	48	43
ABVD[8]	103	84	68	84	34**	46

*Patients receiving radiotherapy on protocol
**Statistically significant
Chemotherapy regimens: As referenced in article, escBEACOPP, escalated BEACOPP[4]; Modified Stanford V as by Gobbi et al; MDR, either ChlVPP/PABIOE (alternating) of CHlVPP/EVA (hybrid)[9]; CEC, COPPEBVCAD.[8]
NS indicates not stated

However, escBEACOPP was associated with increased hematologic and infectious toxicities although the non-relapse mortality was similar across all arms (7% for all patients in the trial). This regimen appears to carry a risk of gonadal failure in men and women that exceeds that reported for ABVD; follow-up is too short with regard to differences in other late effects such as cardiovascular complications and second cancers.[5,6] The GHSG HD9 Elderly trial prospectively compared standard dose BEACOPP with COPP/ABVD and found no difference in OS or disease-specific survival; however, the treatment-related mortality (TRM) of BEACOPP in the elderly population was 21%.[7]

The GISL HD2000 trial evaluated ABVD, BEACOPP (4 cycles of escBEACOPP and 2 cycles of BEACOPP baseline) and CEC (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin; COPPEBVCAD).[8] With a modest accrual of 307 patients that limited statistical power, the trial failed to discern a significant difference in OS between the arms, although BEACOPP was shown to have a significant advantage in PFS over ABVD. Once again, BEACOPP was associated with higher rates of grade III-IV hematologic toxicity and infection (anemia 16% vs 5%, neutropenia 54% vs 34% and infection 14% vs 2%).

Alternative multi-drug regimens have also been evaluated. The UK LY09 trial evaluated ABVD in comparison to two multi-drug regimens (ChlVPP/PABIOE and ChlVPP/EVA).[9] The UK multi-drug regimens were felt to be worthy of phase III testing as they were more dose intensive than ABVD but appeared to have less late toxicity than BEACOPP (lower rates of AML) and the potential for reduced pulmonary and cardiac toxicity by reducing doses of toxic agents. With a median follow-up of 52 months, the three arms had no statistically significant differences between them for event-free or overall survival.

The Stanford group developed Stanford V, a multi-agent abbreviated (12-week) chemotherapy regimen designed to intensify certain agents and de-escalate or omit more toxic agents. Stanford V emphasizes radiation to sites of bulky disease (at least 5 cm) and macroscopic splenic disease. Two recent RCTs have evaluated the Stanford V regimen. The Italian Intergroup published a three-arm randomized trial of 355 patients that compared a modified Stanford V regimen, MOPPEBVCAD and ABVD.[10] While the Stanford V chemotherapy was not modified, the radiation plan was limited to only two sites of disease and was not administered in patients achieving CR (91% patients in the Stanford series received radiation compared with 66% in the Italian trial). The 5-year OS was superior for ABVD over modified Stanford V ($P = .04$) with no significant survival differences between the other arms.[11] The UK NCRI randomized comparison of Stanford V and ABVD has only been presented in abstract form with a median follow-up of 49 months. PFS and OS were not statistically significantly different at this timepoint.[12]

Both the GHSG and the Italian Intergroup are testing strategies that reduce the toxicities of escBEACOPP. In the GHSG HD12 study, a 2×2 factorial design compares 8 cycles of escBEACOPP versus 4 cycles of escBEACOPP followed by 4 cycles of BEACOPP, while the second randomization has arms of consolidative radiotherapy or observation. At the early timepoint of 5 years and with 1571 eligible patients, OS and PFS were not statistically different, but importantly the TRM for all patients reached 5% (3% acute or salvage treatment toxicity, 2% due to secondary cancers).[13] The Italian Intergroup reported a

smaller trial of 321 patients comparing 4 cycles of escBEACOPP followed by 4 cycles of BEACOPP (the experimental arm of GHSG HD12) with ABVD for 6 to 8 cycles. Second-line therapy was pre-planned with the intent to deliver second-line chemotherapy along with BEAM high-dose therapy and ASCT.[14] Three-year freedom from progression was superior in the BEACOPP arm (87% vs 71%, $P = .01$) while OS and freedom from second progression were not statistically different between the two arms. Six (4%) treatment-related deaths were seen in the BEACOPP arm (4 during primary therapy and 2 during second-line treatment) compared with 1 patient receiving ABVD.

Thus, it would appear that the strategy of dose intensifying primary chemotherapy improves disease control but at the cost of acute toxicity; whether late effects (particularly second cancers) eliminate any potential survival advantage remains an important question. Results of RCTs involving Stanford V are awaited and the only published RCT involving Stanford V reinforces the importance of planned radiotherapy in this protocol to achieve cure. Escalated BEACOPP is the only regimen that has shown an OS advantage over ABVD in a large RCT. Current trials reported in abstract form suggest that it may be possible to reduce the number of escalated cycles of BEACOPP, but the impact of this strategy will require mature follow-up of these studies.

Consolidation Post Primary Chemotherapy

An alternative strategy to altering the primary chemotherapy for HL is to attempt to consolidate response. Both high-dose chemotherapy and autologous stem cell transplantation (ASCT) and radiation have been tested in phase III trials as consolidation following primary chemotherapy Two randomized trials were published earlier this decade that evaluate the role of ASCT as consolidation of high-risk HL. The Scotland and Newcastle Lymphoma Group HD3 trial compared 3 courses of a hybrid chemotherapy regimen followed by ASCT with 5 courses of hybrid chemotherapy.[15] Of 126 patients identified as high risk (using a prognostic index including age, clinical stage, lymphocyte count and hemoglobin), 65 (52%) of patients underwent randomization and both groups had a similar time to treatment failure (79% for the ASCT arm, 85% for the chemotherapy arm, $P = .35$) with no significant difference in OS.

A larger European intergroup trial randomized patients with unfavorable HL (defined as the presence of two poor risk factors consisting of high serum LDH, large mediastinal mass, > one extranodal site, low hematocrit or inguinal involvement) who achieved a CR or PR after 4 courses of ABVD (or similar) chemotherapy to either ASCT or 4 cycles of conventional chemotherapy.[16] After a median follow-up of 48 months, the 5-year failure-free, OS and relapse-free survival rates were similar. The trial concluded that there was no benefit for early intensification with ASCT in patients with unfavorable disease responding to anthracycline-based chemotherapy.

The H97-HR trial was a GOELAMS trial conducted between 1997 and 2004 involving high-risk stage IIB-IV patients (defined as the presence of at least 5 lymphoid sites, large mediastinal mass or at least 2 extranodal sites in stage IV disease).[17] This study examined an early intensive non-myeloablative chemotherapy (VABEM: vindesine, doxorubicin, carmustine, etoposide and methylprednisolone) and ABVD for 4 cycles followed by delayed myeloablative intensification (BEAM high-dose therapy and ASCT). The authors reported the results of 158 patients (82 in the VABEM arm, 76 in the ASCT arm) and compared FFTF (primary endpoint) and OS in a randomized phase II trial. Not surprisingly, the 5-year FFTF (VABEM: 79%; ASCT: 75%) and OS (VABEM: 87%; ASCT: 86%) were not statistically different given the lack of power. The authors did not feel this strategy warranted further study and concluded that ABVD remains the current standard for high risk HL.

Radiation is a more appealing consolidation therapy than ASCT as it has less acute toxicity and has more potential for general application. The EORTC has reported the results of the most recent trial of consolidative radiation. In this randomized trial, patients achieving complete remission following MOPP/ABV hybrid chemotherapy were randomized between involved field radiotherapy and observation.[18] Of 739 enrolled patients, 512 patients achieved a CR following chemotherapy and were randomized while 227 patients were in partial remission and received radiation. EFS and OS were similar in both patient groups randomized at CR. There may be a benefit in outcome in PR patients who went on to receive IFRT as part of protocol therapy as they appeared to have a similar survival to the patients in CR.

The GHSG HD15-PET study was designed to assess the negative predictive value of FDG-PET scanning after primary chemotherapy.[19] In the trial, patients with PET-positive disease following BEACOPP went on to receive consolidative radiotherapy; 311 patients with residual disease of at least 2.5 cm had a PET scan, with the PFS at 12 months for PET-negative patients being 96% and 86% for PET-positive patients ($P = .011$, indicating the inferior PFS in PET-positive patients). While HD15-PET is not a controlled trial, this is the only large prospective trial evaluating PET and consolidative radiotherapy and appears to confirm the benefit of radiation in PR patients. These data contrast with other reports, although these series are clearly not comparable and there are issues as described in a recent meta-analysis.[20]

Based on these controlled trials, there does not appear to be a clear role for consolidation treatment in advanced HL. There is no survival advantage in patients consolidated with ASCT as part of primary treatment. The currently available data do not demonstrate an overall survival advantage for consolidative radiotherapy in patients with advanced HL. There appears to be a role for radiation as a consolidation in patients who have achieved only a PR after primary chemotherapy, but this strategy has not been tested in a controlled trial. This type of strategy will require long follow-up to assess the incidence and significance of radiation-related late effects.

Therapy of Relapsed or Refractory Hodgkin Lymphoma

Salvage Chemotherapy and Autologous Transplantation

Salvage chemotherapy followed by ASCT has become the treatment of choice in patients with relapsed HL or when the disease is refractory to initial chemotherapy. Two randomized phase III clinical trials have shown improved PFS in patients receiving HDCT compared with those treated with standard-dose salvage chemotherapy.[21,22] The GHSG/EBMT randomized 161 patients with relapsed HL to either dexa-BEAM or ASCT with chemosensitive patients able to proceed through the protocol. Although there was no difference in OS, FFTF was significantly improved in the ASCT group (55% versus 34%, $P = .02$).[22]

Although there have been many published phase II studies reporting results of salvage regimens for relapsed or refractory Hodgkin lymphoma,[23-33] there are no RCTs and no consensus on the most effective second-line chemotherapy regimen. If the ultimate goal of salvage chemotherapy is to enable patients to proceed to ASCT, an ideal salvage regimen should produce a high response rate with acceptable hematologic and non-hematologic toxicity, and not impair the ability to mobilize peripheral blood stem cells for autotransplant. The RCTs of ASCT only included chemosensitive patients, and only cohort and registry data speak to the benefit of ASCT for patients refractory to primary treatment or chemorefractory immediately prior to ASCT.[34-36]

A number of salvage therapy regimens have been reported in retrospective case series or prospective phase II studies, typically as part of an ASCT strategy. Several popular regimens are summarized in **Table 2**. These trials report overall response rates (ORR) between 60% and 87%, with overlapping 95% confidence intervals. Although these single-arm phase II trials enrolled different patient populations, there is no evidence to demonstrate that one is superior over the others. Calculated confidence intervals are also presented for rates of toxic death

The toxicity reported in these trials is largely hematologic, although nausea and vomiting are also common. While the Dexa-BEAM regimen had an ORR of 81% in the GHSG/EBMT phase III ASCT trial, the toxic death rate from salvage chemotherapy was 5%. Other trials have reported toxic death rates of between 0% and 2%, a more acceptable level given the young age and lack of comorbidity typically seen in patients with HL.

The efficacy of salvage chemotherapy for HL must be balanced by toxicity and the impact on subsequent PBSC mobilization. Success rates for PBSC mobilization have not been consistently reported in these trials. Some studies report that regimens containing melphalan such as Dexa-BEAM or mini-BEAM may result in reduced stem cell mobilization.[37-39] Available results for PBSC mobilization after treatment with these salvage chemotherapy regimens are presented in **Table 3**.

Despite numerous publications regarding salvage chemotherapy in relapsed or refractory HL, there is no clear standard, and factors such as response rate, toxicity and ability to mobilize stem cells should be considered. Similar consideration should be given to the intensive therapy regimen used as part of the autograft procedure as there are no RCT data to inform this decision. It is often only feasible to evaluate the salvage-ASCT as a whole, as published reports tend to emphasize response and toxicity data from salvage chemotherapy and OS and PFS post-ASCT.

Currently, the GHSG and EBMT are performing the HD-R2 trial, a randomized comparison of high dose sequential therapy (HDS) with the control arm consisting of standard chemotherapy and ASCT.[40] The GHSG reported on a multicenter phase II pilot trial that showed HDS to be feasible with acceptable toxicity.[41] The Cologne HDS protocol consists of an induction phase of 2 cycles of standard DHAP chemotherapy followed by a response assessment. Responders proceed to HDS, which consists of 4 g/m^2 of cyclophosphamide followed by granulocyte colony-stimulating factor (G-CSF) and subsequent PBSC collection, 8 g/m^2 of methotrexate with vincristine 1.4 m^2, etoposide 2 g/m^2 with G-CSF and an optional second PBSC collection and finally BEAM high-dose therapy and ASCT. With a median follow-up of 30 months, freedom from second treatment failure was 59% while OS was 78%. The randomized results are awaited.

Another approach recently was tested by the GELA in the multicenter H96 trial; a risk-adapted approach by which

Table 2. Salvage chemotherapy regimens in relapsed or refractory Hodgkin lymphoma.

Regimen	No. of patients	CR,% 95% CI	PR,% 95% CI	ORR, % 95% CI	Grade 3/4 NEUT, %	Grade 3/4 TCP, %	Grade 3/4 VOM, %	Toxic deaths, % 95% CI
Dexa-BEAM[22]	144	27 20-34	54 46-62	81 75-87	NS	NS	NS	5 1-9
Mini-BEAM[25]	55	49 35-63	33 21-47	82 69-91	86	60	NS	2 0.1-10
ICE[67]	65	26 16-39	59 46-71	85 74-92	NS	NS	NS	0 0-5
DHAP q2wk[28]	102	21 13-29	68 59-77	89 83-95	88	69	26	0 0-4
GDP[29]	23	17 5-39	52 31-73	69 47-87	9	13	13	0 0-15
GVD*[68]	91	19	51	70	63	14	0	0
IEV[32]	51	76 60-88		84 71-93	100†	NS	NS	0
MINE[31]	157	NS 64-84	NS	75	NS	NS	NS	5
IV[33,69]	47	45 30-60	38 25-54	83 69-92	65	0	2	NS

*mucositis reported in 9%
†all patients experience grade IV neutropenia
‡5% toxic death rate included patients undergoing ASCT
Chemotherapy regimens: BEAM, BCNU, etoposide, ara-C, melphalan; ICE, ifosfamide, carboplatin, etoposide, DHAP, dexamethasone, ara-C, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin; GVD, gemcitabine, vinorelbine, doxil (liposomal doxorubicin); IEV, ifosfamide, etoposide, vinorelbine; MINE, mitoguazone, ifosfamide, vinorelbine, etoposide; IV, ifosfamide, vinorelbine.
NS indicates not stated; NEUT, neutropenia, TCP, thrombocytopenia; VOM, vomiting

Table 3. Efficacy of PBSC mobilization following salvage chemotherapy for relapsed or refractory Hodgkin lymphoma.

Regimen	N	% CD34 $\geq 2 \times 10^6$/kg	% CD34 $\geq 5 \times 10^6$/kg	% undergoing marrow harvest
GDP[70]	34	97	97	3
MB[70]	34	82	57	18
ICE[67]	65	86	67	14

Chemotherapy regimens: GDP, gemcitabine, dexamethasone, cisplatin; ICE, ifosfamide, carboplatin, etoposide, DHAP, dexamethasone, ara-C, cisplatin.

patients were assigned to a single or tandem autograft based on the presence of risk factors (primary refractory disease or at least two poor risk factors: time to relapse < 12 months, relapse in a prior radiation field, or stage III/IV disease at the time of relapse).[42] With a 6% TRM in the poor-risk group of patients and a 5-year OS of 46%, this trial has demonstrated feasibility but ideally should be tested in a controlled trial.

In summary, ASCT clearly remains the treatment of choice for patients with relapsed or refractory HL. The results of an RCT of HDS compared with a standard ASCT approach are awaited. There also may be a role of tandem ASCT in poor-risk patients but further investigation is warranted. However, ASCT may not be applicable to all patients due to comorbidity, advanced age or other patient factors. Alternate salvage strategies such as radiotherapy or chemotherapy without subsequent ASCT can be considered. It should be noted that the data from non-ASCT strategies in relapsed or refractory HL include patients treated before anthracycline-based primary chemotherapy became the standard of care, and prior to the emergence of phase III data showing superiority of ASCT over conventional chemotherapy.

Alternative Salvage Strategies

The GHSG reported the outcomes and prognostic factors of 422 patients with relapsed HL enrolled in their databases.[43] Salvage treatment was radiation in 13%, chemotherapy in 54%, and ASCT in 33%. Freedom from second failure and OS ranged from 33% to 81% and 46% to 89%, respectively, for each treatment. Unfortunately, there are few large or prospective series that study non-ASCT–based strategies in relapsed HL.

The largest series of salvage radiotherapy is a retrospective review from the GHSG reporting the outcome of 100 patients enrolled in trials between 1988 and 1999 treated with radiation at the time of disease progression.[44] Eighty-five percent of the patients had progressed after COPP-ABVD or similar regimens, while 8% had received standard

or escalated BEACOPP. The remaining patients had received radiotherapy alone. The 5-year FFTF and OS rates for the entire cohort were 29% and 51%, respectively. In multivariate analysis, the presence of B symptoms and advanced stage at relapse were adverse predictors of overall survival. Review of the other smaller series demonstrates similar results.[45-49]

The data supporting re-treatment with standard dose chemotherapy following relapse after anthracycline-based chemotherapy are similarly limited. However, some patients with late relapse (defined as more than 1 year after completion of primary treatment) may experience long-term disease control with standard-dose second-line regimens. In the series from Milan reported by Bonfante et al,[50] 8-year freedom from second progression and OS were 53% and 62% for patients re-treated with MOPP-ABVD following a CR lasting more than 12 months. Some patients with very late relapse (for example, more than 5 years) following primary therapy and those who may be ineligible for ASCT due to age and/or comorbidity may possibly benefit from standard-dose chemotherapy.

Patients initially treated with radiation alone (a small group of patients currently) who relapse may experience long-term disease control with conventional-dose chemotherapy. A series of patients reported by the GHSG has demonstrated that treatment with COPP-ABVD or BEACOPP following relapse after initial extended field radiation therapy for limited stage disease may result in a freedom from second treatment failure of 81% and OS of 89% with a median follow-up of 45 months.[51] Multivariate analysis suggested that the type of salvage therapy was an important predictor of freedom from second treatment failure, favoring BEACOPP over COPP-ABVD a retrospective observation consistent with the prospective GHSG HD9 trial in untreated HL.[4]

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation (allo-SCT) has remained a treatment in advanced HL due to the relatively young age of many of these patients. Myeloablative allo-SCT in HL has been employed in advanced phases of the disease, but there have been significant concerns since the treatment-related mortality often exceeded 50% and relapses were not uncommon.[52-56] The role of myeloablative allo-SCT in HL appeared limited; while dose intensity can be delivered in the context of a myeloablative allograft and donor stem cells are free of tumor cell contamination, the presence of a clinically significant graft-versus-Hodgkin lymphoma (GVHL) effect has never been clearly demonstrated.

More recently, reports have demonstrated signs of anti-tumor effect following donor lymphocyte infusion.[57-60] In addition to this demonstration of immune-mediated anti-tumor effect, the safety of allogeneic transplantation has improved with the use of reduced-intensity allogeneic stem cell transplantation (RIC-allo) strategies. These approaches have become increasingly popular due to decreased rates of early TRM.[61-64] Despite early favorable results, mature results of RIC-allo available in the literature are consistent in demonstrating a lack of long-term disease control, with PFS estimates of approximately 25% to 30% and OS estimates of 35% to 60% at time points at least 2 years post-SCT.[59,61-64] It is clear that patient selection remains an issue in all allo-SCT reports (particularly in retrospective institutional or registry reviews), and the benefit of RIC-allo to patients with relapsed/refractory HL remains open to debate. Future trials may focus on strategies designed to reduce relapse post allo-SCT, but ideally allo-SCT should be tested in controlled trials in order to clarify these issues.

Conclusions

The standard treatment of advanced HL remains ABVD in most centers across the world and has not clearly been surpassed by other multi-drug regimens.[1,2,8,9,12] Escalated BEACOPP has improved OS in a large well-designed RCT (with increased acute and late toxicity), but a confirmatory positive trial remains to be completed. The ECOG and NCIC CTG have completed a large trial comparing Stanford V to ABVD, the results of which will soon be available. More recently developed trials are evaluating novel risk-adapted strategies using FDG-PET to define groups that following 2 cycles of ABVD are potentially at high risk of treatment failure and may be benefit from more intensive treatment.[65]

The optimal management of all patients with relapsed or refractory HL requiring salvage therapy is still somewhat controversial. Although ASCT is generally considered the standard of care, it is a treatment with significant acute and late morbidity and may be limited in application due to patient age and medical fitness. Current trials have evaluated high-dose sequential and tandem ASCT strategies. Future studies should focus on identification of patients who remain at high risk of treatment failure despite ASCT, such as those with residual positive FDG-PET scans, who may benefit from tandem transplants or other efforts to intensify therapy.

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Correspondence

John Kuruvilla, MD, FRCPC, Princess Margaret Hospital, Division of Medical Oncology & Hematology, 610 University Ave., Rm. 5-108, Toronto, Canada M5G 2M9; Phone: 416-946-4567; Fax: 416-946-6546; e-mail: john.kuruvilla@uhn.on.ca

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