CONTEMPORARY THERAPY FOR HL:
Where Are We Now?

Key proceedings from a live symposium held at the 13th International Conference on Malignant Lymphoma (ICML) in Lugano, Switzerland

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This activity has been designed to offer you the latest therapeutic insights for the management of Hodgkin lymphoma (HL) from current practice to the status of ongoing clinical trials. As participants, you will have the opportunity to share your professional experiences with us and engage in discussion related to current and future management of this disease.

Target Audience

This activity is designed for physicians, pharmacists, physician assistants, nurses, and other health care professionals who have an interest in enhancing their clinical skills in Hodgkin lymphoma.

Learning Objectives

Upon completion of this educational activity, participants should be able to:

- Summarize clinical considerations in the upfront treatment of Hodgkin lymphoma variations in options and standards of care
- Identify current approaches to the treatment of relapsed/refractory HL and evolving approaches in ongoing clinical trials
- Identify key data from ongoing trials in the spectrum of HL disease

Agenda

Introduction - Franco Cavalli, MD, FRCP

Optimal Treatment Approaches to Frontline Treatment of Hodgkin Lymphoma –Tim Illidge, PhD, MRCP, FRCR, FRCPath

Relapsed/Refractory Hodgkin Lymphoma: Changing Treatment Paradigms? – Peter Borchmann, MD

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INTRODUCTION

Franco Cavalli, MD, FRCP

Significant advances in the diagnosis, treatment, and management of Hodgkin lymphoma (HL) have occurred since its discovery in 1832. These advancements have led to significant reductions in the mortality rate attributable to HL.[1] Despite these significant advances, challenges remain in treatment and management of HL — as a result, questions regarding therapy abound.

Currently, three key therapeutic questions are under investigation:

1. What is the role of radiotherapy for patients with early stage HL?
2. Which is the better treatment option for patients with advanced HL — doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP)?
3. What is the role of fluorodeoxyglucose-positron emission tomography (FDG-PET) in adaptation of therapy?

This activity summarizes current knowledge about the treatment of HL.

OPTIMAL TREATMENT APPROACHES TO FRONTLINE TREATMENT OF HODGKIN LYMPHOMA

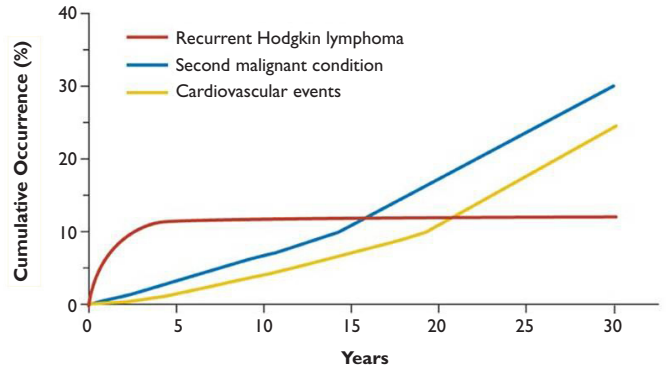
Tim Illidge, PhD, MRCP, FRCR, FRCPath

In today's clinical practice, the selection of first-line treatment for patients with HL should balance potential cure with the fewest complications and optimal survivorship. One of the biggest challenges with HL is the quality of the survivorship and that the lifespan of cured patients is not equivalent to that of aged matched controls. Patients who are cured of HL oftentimes die prematurely from secondary malignancies and complications of the therapy (Figure 1).[2] As Figure 1 shows, 5 years after receiving chemotherapy in combination with radiation therapy, the risk of recurrent HL is no longer a concern. However, there is significantly increased risk for secondary cancers and cardiovascular events. Importantly, the curves are based on older data using radiation fields that are no longer applicable. Modern data confirms that avoiding irradiation to the breasts and heart reduces the risk for radiation-induced heart events or second cancers. Although these modifications to the way we treat HL have reduced some of the late effects, late effects remain a significant and very important event to patients.

In addition to reducing or eliminating late events, it is also important to consider the toxicities of the treatment. These include the treatment's impact on fertility, induction of second cancers, cardiac toxicity, pulmonary toxicity, and an area that is very neglected — quality of life. For many survivors of HL, the quality of life can be quite poor.

Thus, the challenge is to increase the number of patients with durable remissions while decreasing the likelihood of long-term side effects. This is even more important for young adults with HL, as these patients have many productive years ahead of them.

Figure 1. Approximate Cumulative Risk of Recurrent Hodgkin Lymphoma, Second Malignant Conditions, and Cardiovascular Events Patients Receiving Radiotherapy + Chemotherapy for Early Stage Hodgkin Lymphoma[2]



Adapted from: Armitage, 2010[2]

Current management of HL should focus on optimizing therapy for the individual patient. For patients with early stage disease, recent studies have focused on moving away from simply assessing clinical risk to integrating FDG-PET response-adapted therapy in avoiding radiotherapy in patients who are PET negative after initial chemotherapy. While for patients with advanced disease, the focus has been on escalation and deescalation of therapy — guided by early FDG-PET response to chemotherapy; as well as integrating new drugs into modified established regimens.

Risk Stratification Is Key to Appropriate Treatment Selection

An accurate assessment of the stage of disease in patients with HL is critical for the selection of appropriate therapy. Figure 2 shows the current German Hodgkin Study Group (GHSG) clinical risk allocation paradigm.

Figure 2. German Hodgkin Study Group Clinical Risk Allocation

	Stage (Ann Arbor)			
Risk Factors	**IA, IB, IIA**	**IIB**	**IIIA, IIIB**	**IVA, IVB**
None	**Early Favorable**		**Advanced**	
≥ 3 LK-Areas				
Elevated ESR				
Large Med Mass				
Extranodal Disease				

Early favorable disease presents with none of the risk factors, while early unfavorable disease includes those patients with early stage disease that have one risk factor. Lastly, advanced disease includes those patients with multiple of the risk factors.

Treatment of Early Stage Favorable Hodgkin Lymphoma

Currently, the standard of care for early stage disease is 2 cycles of ABVD plus 20 Gy radiation therapy.[3] The pivotal trial by the GHSG compared 4 cycles of ABVD plus 30 Gy radiation therapy with 2 cycles of ABVD plus 20 Gy radiation therapy and showed that the freedom from treatment failure (FFTF) was almost identical in the two groups, suggesting that reducing the intensity of the regimen did not lead to loss of efficacy.[3] In this large (n = 1370), well-conducted study with a median follow-up of 7.5 years, the lower intensity treatment was associated with a 90% cure rate with first-line therapy, and 95% of patients were still alive at 5 years. Since it is unlikely that further improvements on survival and cure are possible, the current focus should perhaps now shift to that of minimizing late toxicity events. Several strategies are attempting to achieve this goal.

Three potential strategies for reducing late events while maintaining high cure rates are:

1. Eliminate radiotherapy with more chemotherapy
2. Eliminate "toxic and less effective" drugs within ABVD as part of combined modality therapy
3. Reduce number of patients receiving radiotherapy using response-adjusted therapy with FDG-PET

Eliminating Radiation Therapy with Increased Cycles of Chemotherapy

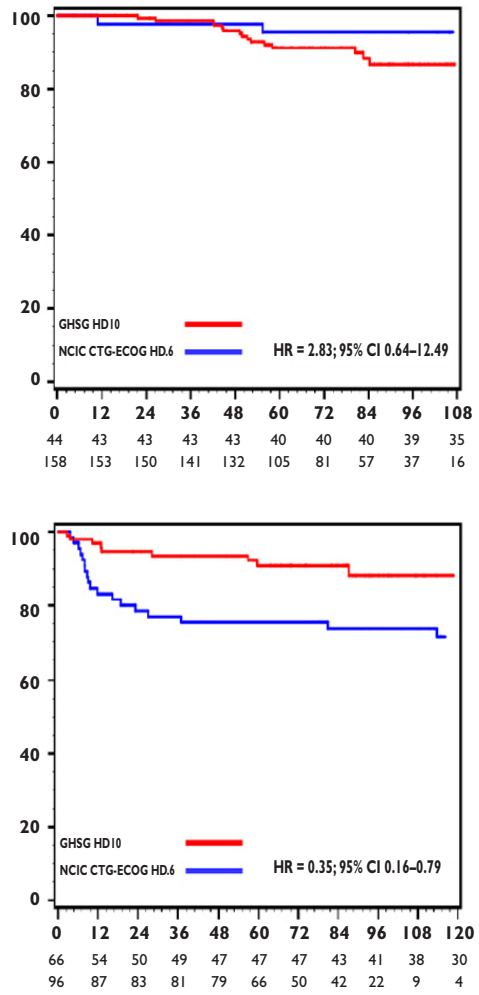
The National Cancer Institute of Canada (NCIC)/ Eastern Cooperative Oncology Group (ECOG) HD6 study was a randomized comparing ABVD chemotherapy alone with treatment that includes radiation therapy in patients with limited-stage HL.[4] The study was prematurely closed in 2002 having enrolled 399 patients following the favorable results achieved in the H8 trial, which showed excellent outcomes with a combined modality treatment using much smaller fields of radiotherapy with involved-field radiotherapy (IFRT). Non-bulky clinical stage I to IIA HL patients were stratified into favorable and unfavorable risk cohorts. Patients allocated to radiation-containing therapy received subtotal nodal radiation if favorable risk or combined-modality therapy if unfavorable risk. Patients allocated to ABVD received 4 to 6 treatment cycles. After a median follow-up of 4.2 years, the authors of the HD6 study concluded that in patients with limited-stage HL, no difference in overall survival (OS) was

observed between patients randomly assigned to receive treatment that includes radiation therapy or ABVD alone, but with a 5-year freedom from disease progression that was superior in patients receiving radiation therapy.[4] Subsequently, an analysis of longer follow-up (median 11.3 years) revealed that the patients in the ABVD arm had better survival compared with patients receiving radiation therapy (OS 94% vs 87%, respectively).[5] The higher rate of OS was attributed to a lower rate of death from other causes, including 5 deaths from unusual events. While including these unusual deaths I corrected from a statistical point of view – misleading information not attributable to radiotherapy. There was no reported death of "other" causes in chemotherapy alone group or in subtotal nodal irradiation (STNI) favorable group. The imbalance is misleading in favor of chemotherapy alone group. Without these unusual events, this would be a negative study without a survival difference for chemotherapy alone but with a significantly better tumor control for the radiotherapy group. The imbalance is most likely due to an undersized and incompletely recruited study with a small number of events.

The GHSG evaluated combined modality therapy (CMT) in two randomized controlled trials (RCTs) that included patients with favorable (HD10)[3] and unfavorable (HD11)[6] limited-stage disease. Based on disease control at median follow-up of 91 months, results of HD10 demonstrated that 2 cycles of ABVD plus 20 Gy IFRT was non-inferior to CMT that included 4 cycles of ABVD and 30 Gy IFRT. In HD11, 4 cycles of ABVD and 30 Gy IFRT remained standard treatment, when neither non-inferiority of 4 cycles of ABVD and 20 Gy IFRT, nor superiority of CMT that included standard doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) followed by 30 Gy IFRT were observed.

A subsequent analysis that combined data from the HD10/HD11 and HD6 studies revealed that CR after 2 cycles of ABVD was predictive of benefit from radiation treatment (Figure 3).[7] Importantly for the interpretation of the data , this is a non-randomized comparison, but nevertheless reveals interesting potential observation and hypothesis generating for the importance of radiotherapy in those patients who fail to achieve complete remission (CR) assessed by CT after 2 cycles of ABVD (see Figure 3).

Figure 3. **Progression-free Survival for Combined Modality vs ABVD Alone in a Non-randomized Post-hoc Analysis of the NCIC-ECOG HD6 and GHSG HD10 Studies**[7]



Adapted from: Hay, et al.[7]

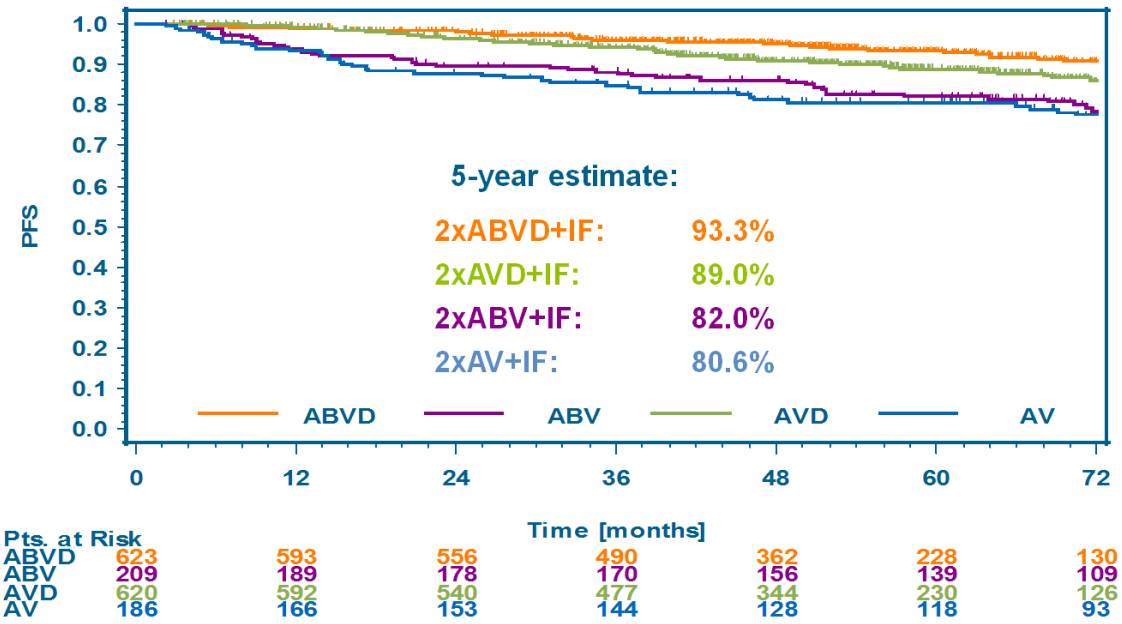
FDG-PET is emerging as a key tool for the management of HL in assessing the status of the disease before, during, and after treatment. While the use of PET itself in HL is well-established, several issues remain unresolved regarding the interpretation and routine integration of PET in the management of HL.[8] These include interim PET imaging that has been proposed as a useful prognostic tool integrated in a response-adapted therapy setting. A multitude of trials are currently underway to test the accuracy of FDG-PET as a marker of tumor chemosensitivity. However, whether a PET-adapted individualized treatment strategy leads to a long-term survival benefit compared with standard chemotherapy remains unknown for the HL population.

Reducing Treatment Toxicity

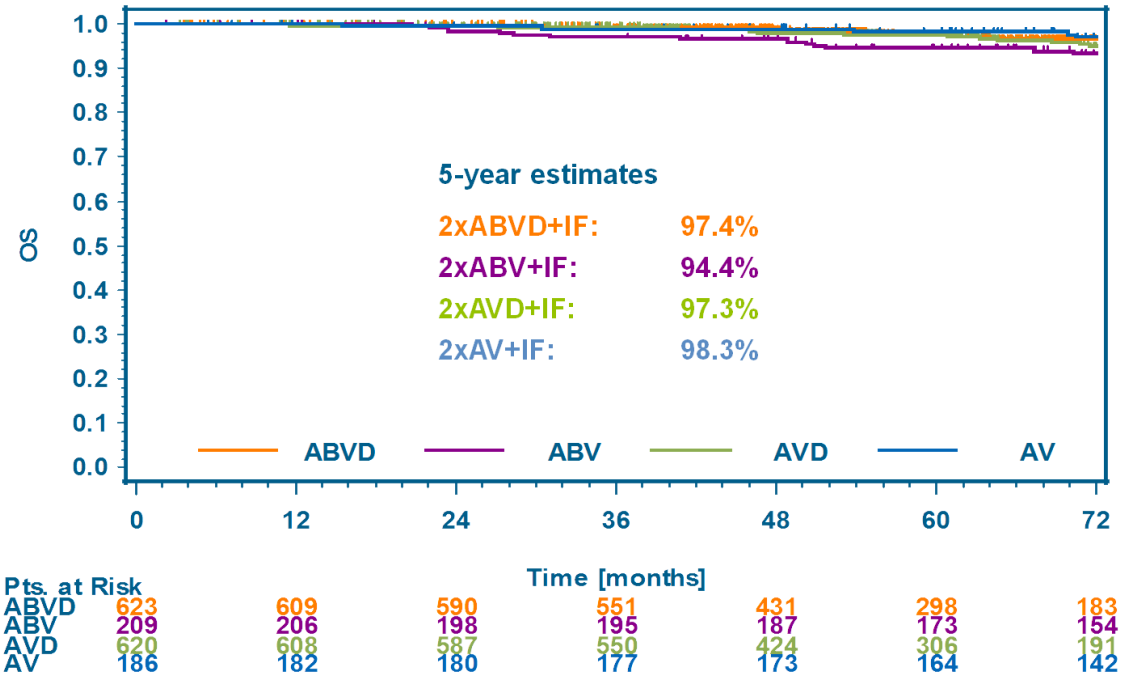
In the GHSG HD13 study, patients with stage 1 and 2A HL without risk factors compared standard ABVD to omission of dacarbazine (ABV), omission of bleomycin (AVD), or omission of both dacarbazine and bleomycin (AV).[9] This was an open-label, randomized, non-inferiority study. In addition to chemotherapy, all patients received 30-Gy of IFRT as the results from HD10 and 20 Gy radiotherapy consolidation were not known. While a decrease in progression-free survival (PFS) was observed as chemotherapeutic agents were omitted (Figure 4A), this did not translate into a decrease in OS (Figure 4B).

Figure 4. Progression-free Survival (A) and Overall Survival (B) in the GHSG HD13 Study[9]

A.



B.



Adapted from: Behringer, et al.[9]

Response-adapted Therapy

The aim of such response-adapted therapy is to use FDG-PET to potentially select the patients that would do well without radiation treatment. This has been the subject of intense investigation worldwide, leading to interesting results with somewhat controversial conclusions.

The recently published United Kingdom National Cancer Research Institute RAPID trial investigated 3 cycles of ABVD and subsequently underwent a PET scan. Patients were then randomized according to the PET findings: patients with negative PET findings were randomized to either IFRT or to no treatment. Patients with positive PET findings received a fourth cycle of ABVD and 30-Gy IFRT. There were 602 patients registered, and two-thirds of the patients had stage 2A disease, and using both the European Organisation for Research and Treatment of Cancer (EORTC) and the GHSG criteria, about two-thirds of the patients had early stage favorable with a third of the patients having early stage unfavorable. After 3 cycles of ABVD, approximately 75% of the patients were PET-negative (score 1 or 2 on the Deauville scoring system) while the remaining 25% were PET-positive (score 3, 4, or 5), with the majority of these patients scoring 3. The interpretation of PET negativity in this trial appears conservative, and a factor in this may be the lack of baseline FDG PET scan.

Results of the study are shown in Table 1. Patients that were PET negative who had no further treatment were three times more likely to develop progressive disease compared with patients who were PET-negative received radiation therapy (9.5% vs 3.8%).[10]

Table 1. Results of a Trial of PET-Directed Therapy for Early Stage Hodgkin Lymphoma[10]

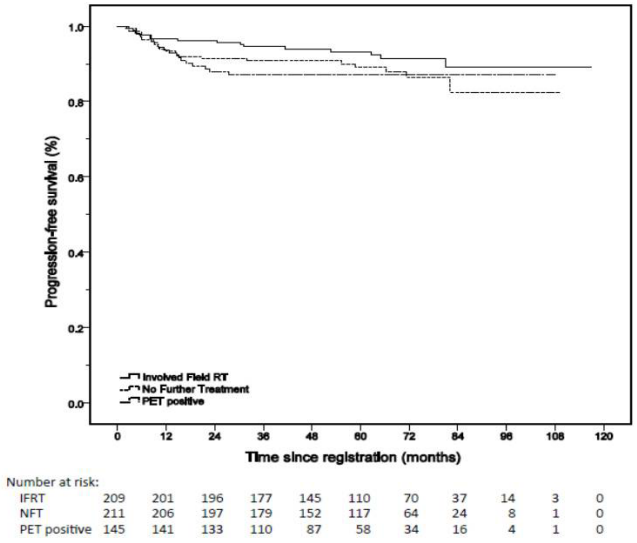
Events	PET-ve IFRT (%)	PET–ve NFT (%)	PET+ve (%)
Alive without PD	193 (92.3)	190 (90.0)	127 (87.6)
PD only	8 (3.8)	20 (9.5)	10 (6.9)
Died with PD	3 (1.4%)	2 (0.9%)	5 (3.4%)
Died without PD	5 (2.4%)	2 (0.9%)	3 (2.1%)
Total	209	211	145

Adapted from: Radford, et al.[10]

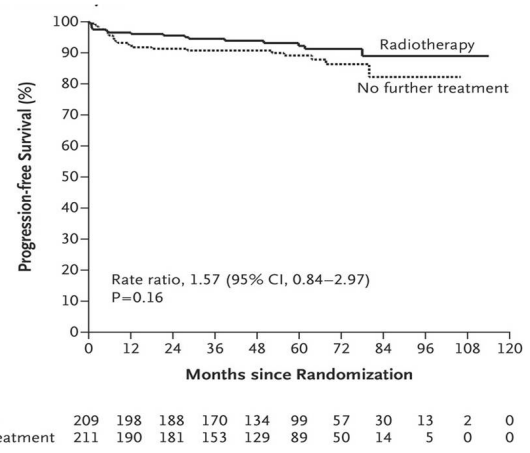
Based on the intention-to-treat analysis, the three curves were almost superimposable (Figure 5A). While there was an approximately 4% difference between the IFRT and the no further treatment group, the difference was not statistically significant.10 However, it is also important to appreciate the results of the per-protocol analysis in the interpretation and potential implementation of the trial results. There were 26 patients in the IFRT arm that did not receive radiotherapy. Five patients died in the radiotherapy arm before they actually received radiotherapy, with bleomycin toxicity being a recurrent theme. In the per-protocol analysis, the difference in favor of radiotherapy was highly statistically significant (*P*=.02) (Figure 5B).

Figure 5. Progression-free Survival in the Intention-to-Treat (A) and Per-protocol (B) Analyses of the RAPID Study[10]

A.



B.



Per protocol analysis in 392 PET-negative patients 3-year PFS 97.1% involved-field radiation therapy versus 90.8% no further treatment (*P*=.02).

Adapted from: Radford, et al.[10]

The EORTC H10 study had a similar design, but patients were divided into favorable and unfavorable arms.[11] Favorable patients were randomized to standard treatment consisting of 2 cycles of ABVD and then underwent a PET scan, followed by 3 cycles of ABVD and involved node radiotherapy of 30 Gy. This study employed small involved node radiotherapy volumes, which was a real step forward in reducing radiation normal tissue exposure in the use of combined modality treatment. For the experimental arm, PET-negative patients received two further cycles of ABVD, while PET-positive patients received 2 cycles of escalated BEACOPP followed by involved node radiotherapy. The results appear similar to the RAPID study (Table 2). The PFS was 100% in the standard arm compared with 95% the experimental arm. The independent data monitoring committee concluded that the study was unlikely to show non-inferiority for the experimental arm and the conclusion from the study was that combined modality treatment resulted in fewer early progressions in clinical stage 1 and 2 early HL. Long-term follow-up is needed.

increasingly toward personalized approaches and there is a group of patients who can be safely treated with chemotherapy alone; however, defining precisely who they are right now is very hard and remains the ongoing challenge. At the current time, the PET quality assurance does not appear up to the standard required to make universal decisions for all patients treated in the community. Therefore, for many patients, combined modality treatment should remain the standard of care, this is particularly true for older patients, those with cardiopulmonary comorbidity, and indeed all patients where the late toxicity associated with small involved-site radiotherapy is low or negligible and less than the risk of relapse with omitting radiotherapy. The decision becomes more controversial when younger female patients with mediastinal disease where the radiation field would involve radiation of the breast and the heart. For these patients the elimination of radiotherapy, despite the risk of progressive disease, may be a viable treatment option. Ultimately, the patient should be involved in that decision-making process.

Table 2. Results of the Favorable Risk Population from the GHSG HD10 Study[12]

H10F	Chemo	PET2	CT/RT	# Events	1-yr PFS
Standard	ABVDx2	+/-	INRT	1/188	100%
Experimental	ABVDx2	negative	ABVDx2	9/193	94.9%
		positive	BEACOPPesc x2 + INRT		

Adapted from: Andre, et al.[12]

The awaited results from the GHSG HD16 trial will also further inform the discussion. This study enrolled patients without clinical risk factors and starts with 2 cycles of ABVD followed by a PET scan. Patients in the standard arm receive 20 Gy of IFRT (regardless of PET findings). Patients in the experimental arm who are PET negative undergo no further treatment, while patients with PET-positive findings receive 20 Gy of IFRT. Results of this study are anticipated in late 2015 or perhaps 2016 pending the number of events.

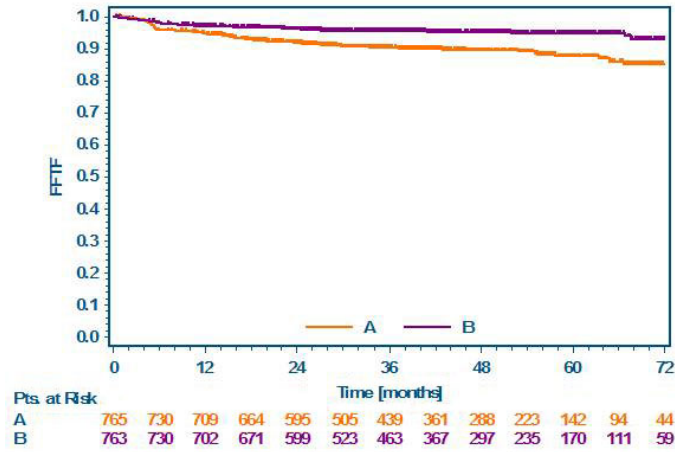
Summary of Treatment of Early-stage Disease

Early-stage disease is highly curable and the current focus of treatment should include both initial local control and life beyond the cure. Treatment is moving

Treatment of Early Stage Unfavorable Hodgkin Lymphoma

The GHSG HD11 study failed to show an advantage for any of the experimental arms. Importantly, in that study, it demonstrated an advantage for 30 Gy over 20 Gy, which has remained the standard moving forward in the HD14 study where 4 cycles of ABVD was compared with 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD (the 2+2 regimen). The HD14 study was a large study enrolling 1528 patients.[13] Escalated BEACOPP was associated with a 7.2% improvement in the freedom from treatment failure (P<.00001; Figure 6).

Figure 6. Freedom from Treatment Failure in the GHSG HD14 Study[13]



Adapted from: von Tresckow, et al.[13]

In the HD14 trial there was more acute toxicity associated with the BEACOPP, but no overall differences in treatment-related mortality and secondary malignancies, and the conclusion from the GHSG was that this intensified regimen with 2 cycles of BEACOPP escalated followed by 2 cycles of ABVD should be the new standard of care.

The 2+2 regimen forms the basis for the HD17 trial. The patients that are PET negative receive 30 Gy of IFRT or no further treatment. The patients that are PET positive receive either 30 Gy of IFRT or 30 Gy of involved-node radiation treatment. Results from this study are not anticipated until 2019.

Treatment of Advanced Stage Hodgkin Lymphoma

The ongoing debate regarding the optimal treatment approach using ABVD or BEACOPP, for patients with advanced disease continues. The key question is whether the more toxic BEACOPP is required for all patients, given that patients with good to intermediate risk, treated with ABVD achieve good results for freedom from progression and OS (Table 3) while experiencing reduced toxicity and preservation of fertility.

Table 3. Patient Outcomes with ABVD in Current Era

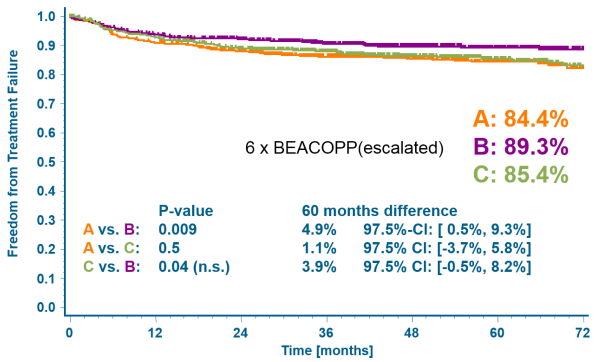
IPS Score	% 5y FFP	Current	% 5y OS	Current
0	84	83	89	98
1	77	84	90	97
2	67	80	81	92
3	60	77	78	91
4	51	73	61	87
>4	42	71	56	73

It becomes an even more difficult debate with patients who present with an International Prognostic Score (IPS) sore of 4 and the 5-year overall, where overall survival is only 73% and there is clearly room for improvement. One might argue that you should treat with ABVD and if relapse occurs the patient can be salvaged with transplantation. A study that directly compared 8 cycles of ABVD to 8 cycles of BEACOPP (4 cycles escalated followed by 4 cycles of standard BEACOPP) revealed that the BEACOPP regimen was superior to the ABVD with regard to freedom from progression.[14] However, no significant difference in OS was reported.

The GSHG HD15 study compared 3 BEACOPP regimens: 8 cycles of escalated BEACOPP; 6 cycles of escalated BEACOPP; or 8 cycles of BEACOPP.[15] After the initial treatment, the patients were restaged. Patients with a persistent mass after chemotherapy measuring 2.5 cm or larger and positive on PET scan received additional radiotherapy with 30 Gy. The results showed that 6 cycles of escalated BEACOPP was superior to 8 cycles of escalated BEACOPP, with regard to freedom from treatment failure and overall survival (Figure 7).

Figure 7. Freedom from Treatment Failure (A) and Overall Survival (B) in the GHSG HD15 Study[15]

A.



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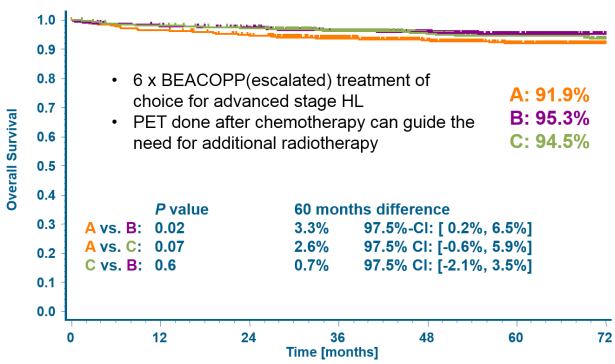


Adapted from: Engert, et al.[15]

Two potential strategies for reducing late events while maintaining high cure rates in patients with advanced stage disease are:

1. FDG-PET response adjusted therapy
2. Replacing "older" more toxic drugs with "new" more effective and less toxic drugs

Role of FDG-PET Response Adjusted Therapy in the Treatment of Advanced Hodgkin Lymphoma

Over the past several years, FDG-PET has been repeatedly identified as a powerful prognostic marker in HL. Gallamini and colleagues[16] have reported on a sequential series of unfavorable and advanced HL evaluated with PET after 2 cycles of ABVD in Denmark and Italy. Of 195 lower risk patients, just 25 (13%) were PET positive, whereas 25 of 65 (38%) with intermediate/high risk were PET positive. Some key points from this study are that the majority (75%) of patients enrolled had low IPS score, which should be taken into consideration when interpreting this data to larger populations of advanced-stage patients. Secondly, although patients with PET positivity had poorer outcomes, it should be noted that fewer patients with an IPS score of 0 to 2 were PET positive compared with patients with IPS scores of 3 to 7 (13% vs 38%, respectively).

Role of Less Toxic Agents Therapy in the Treatment of Advanced Hodgkin Lymphoma

Brentuximab vedotin, or SGN 35, is an antibody drug conjugate that combines an anti-CD30 antibody with a cytotoxic chemotherapy agent (monomethyl auristatin E [MMAE]). CD30 is expressed on HL cells and upon binding to CD30 brentuximab vedotin is internalized and trafficked to the lysosome where the MMAE is released. MMAE then disrupts the microtubule network, leading to cell cycle arrest and apoptosis.

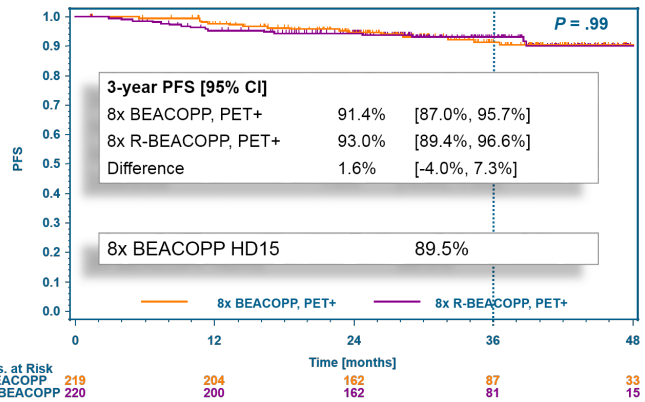
Current international standard approaches for improving treatment of advanced HL appear to be moving in the same direction. Results from the recent E2496 study, which investigated the effectiveness of ABVD in patients with advanced disease showed a 3-year PFS of 71% with the 29% failure rate.[17] While results from the GHSG HD15 study, which investigated 6 cycles of BEACOPP, had an excellent PFS of 91%, however, toxicity remained a challenge with this regimen. Both of these chemotherapeutic regimens have room to improve in either increasing efficacy or decreasing toxicity. One of the remaining unanswered questions is whether FDG PET can be used to guide treatment, and can we improve efficacy or safety by incorporating brentuximab into the treatment paradigm?

Figure 8. **Summary of Studies of Advanced HL PET-adapted Therapy**

UK RATHL	ABVD. Escalation to esc B if PET+
	PET- randomized to ABVD vs AVD
GHSG: HD18	PET+ randomized to R-esc B vs B esc
	PET- randomized to 4 vs 8 B esc
Italian	Escalation to ASCT if PET+
US Intergroup	ABVD. Escalation to esc B if PET+
CALGB (I-IIX)	ABVD. Escalation to esc B if PET+. No RT
E2410 (I-IIX)	ABVD. Escalation to esc B if PET+, INRT

PET-adapted therapy is extremely well studied, and the results from numerous ongoing studies will address this question (Figure 8). Interim results from the GHSG HD18 study are available. GHSG HD18 compared several BEACOPP-based treatment regimens. All patients received 2 cycles of escalated BEACOPP followed by PET analysis. Patients with PET-positive lesions received either a further 6 cycles of escalated BEACOPP plus rituximab or 6 cycles of escalated BEACOPP alone. Patients with PET-negative lesions received either an additional 2 or 6 cycles of escalated BEACOPP. Results for PET-positive patients showed no difference between the escalated BEACOPP and escalated BEACOPP plus rituximab treatment groups for 3-year PFS (Figure 9).[18] The authors concluded therefore that interim PET does not define a high-risk cohort.

Figure 9. **Interim Progression-free Survival from the GHSG HD18 Study[18]**



Adapted from: Gallamini, et al.[18]

In terms of improving outcome with the drug brentuximab vedotin, it is possible to combine brentuximab with AVD but not ABVD, as this combination is associated with significant pulmonary toxicities, primarily due to the inclusion of bleomycin. Based on results from initial studies, AVD with brentuximab vedotin looks to be a highly effective regimen. This has prompted the initiation of a large randomized study called ECHELON-1. ECHELON-1 is a phase 3 trial comparing brentuximab vedotin in combination with AVD versus standard ABVD as frontline therapy for patients with advanced HL. The study is currently recruiting and results are anticipated in 2020.

Two remodeled BEACOPP regimens that integrate brentuximab vedotin have been considered (Figure 10). Bleomycin has been removed from the new regimen to reduced pulmonary toxicity (BrECAPP). In addition, another regimen under investigation excludes procarbazine and prednisone to reduce the impact on fertility and replaces it with dacarbazine and dexamethasone (BrECADD).

Figure 10. **Remodeling Escalated BEACOPP with Brentuximab Vedotin**

Drug	Day	6x BEACOPP	6x BrECADD	6x BrECAPP
Bleomycin	8	10		
Etoposide	1-3	200	150	200
Adriamycin	1	35	40	35
Cyclophosphamide	2	1250	1250	1250
Vincristine	8	1.4		
Brentuximab vedotin	1		1.8	1.8
Procarbazine	1-7	100		100
Prednisone	1-14	40		40
Dacarbazine	2-3		250	
Dexamethasone	1-4		40	

The GHSG HD21 study will compare the efficacy (non-inferiority for PFS, OS, tumor response) and tolerability (infertility, hypogonadism, therapy adherence, and quality of life) of escalated BEACOPP with BrECADD. Patients will receive 2 cycles of either escalated BEACOPP or BrECADD followed by PET analysis. Patients will subsequently receive 4 cycles of the initial chemotherapeutic regimen.

Summary of the Treatment of Advanced Hodgkin Lymphoma

Hodgkin lymphoma is one of the most curable cancers, but we have significant challenges with the remaining front-line therapy. Challenges include the treatment of elderly patients, what to do in the primary refractory patient, and for all patients reducing late toxicity. Combined modality treatment in early stage disease is moving toward personalized therapy, and based on both risks and response, it is clear that as the years evolve, the one size fits all mentality for combined modality treatment no longer applies. For advanced-stage disease, proponents of ABVD will continue to focus attention on improving progression-free survival by escalating treatment — using FDG-PET to inform treatment. Proponents of BEACOPP will shift focus to reducing toxicity, primarily by incorporating brentuximab vedotin and eliminating agents with excessive toxicity. For advanced disease, FDG-PET is likely to guide treatment with the goal of de-escalating treatment. As always, the only way to make real progress is to perform international trials that are of high quality and to put our patients into trial so we get the answers to improve treatment outcomes in a timely manner.

RELAPSED/REFRACTORY HODGKIN LYMPHOMA: CHANGING TREATMENT PARADIGMS?

Peter Borchmann, MD

Relapsed/refractory HL is quite different from treatment-naïve HL. Evidence is readily available to answer questions in treatment-naïve HL; however, this evidence in relapsed/refractory HL is still lacking.

At present, appropriate treatment for relapsed/refractory patients includes:

1. Second-line treatment in transplant-eligible patients
2. Third-line treatment after failure of high-dose chemotherapy

Second-line Treatment in Transplant-eligible Patients

Autologous Stem Cell Transplantation for Relapsed/Refractory Hodgkin Lymphoma

Currently, the standard of care is 2 cycles of induction followed by high-dose chemotherapy and consolidation with autologous stem-cell transplant (ASCT). This is based on the results of two small studies reported in the 1990s.[19,20] Both studies reported similar results of a 3-year PFS of approximately 50%, which was significantly superior to conventional chemotherapy. No differences in OS were noted, however, the studies had small sample sizes. Since the 1990s, significant improvements in the treatment of HL have occurred and it raises the question of whether the data from these earlier studies are still applicable in today's clinical practice?

More recent data, although still a decade old, from the European Bone Marrow Transplant Registry show a 5-year PFS of 49%. Importantly, one must remember that these are registry data and therefore represent a highly selected patient population.

At present, the only unbiased prospective data available come from the study by Viviani and colleagues.[14] Patients (n = 166) received ABVD, 45 (27%) of which required salvage therapy that could be completed in 30 (67%) patients. CR at the end of salvage therapy was achieved in 23 (51%) patients and 15 (33%) patients remained in CR at a median follow-up of 62 months. Thus, these data, suggest that the standard of care achieves a cure in approximately 30% of patients. Importantly, this would only apply to transplant-eligible patients and therefore, many of our elderly patients would not be considered candidates for this standard of care.

Two questions remain — which patients do we treat with standard of care and which patients do we consider to be high-risk?

Defining the High-risk Relapsed/Refractory HL Patient

Numerous factors have been described to identify high-risk patients (Table 4).[21-23]

The different scores are based on the most important factors: early relapse, (relapsing within the first year after first-line therapy), refractory disease, and tumor burden (higher risk with higher disease tumor burden). The level of risk cannot be determined before treatment commences. Patients with good responses will achieve good outcomes, while a patient who fails to respond will have a poor outcome.

Table 4. Risk Factors for First Relapse[21-23]

Author	n	Factor	Outcome
Brice, et al. 1997	214	– Time to relapse (≤12 m vs > 12 m) – Stage III or IV at relapse – Relapse within previously irradiated sites	0 RF: 4-yr OS 93% 1 RF: 4-yr OS 59% 2 RF: 4-yr OS 43%
Josting, et al. 2002	422	– Time to relapse (≤12 m vs > 12 m) – Stage III or IV at relapse – Anemia at relapse	0/1 RF: FF2F 45% 2 RF: 32% 3 RF: 18%
Moskowitz, et al. 2001	65	– B symptoms – Extranodal disease – CR < 12 mo	0/1 RF: EFS 83% 2 RF: 27% 3 RF: 10%
		– Chemosensitivity	Very adverse factor in many analyses

Improving the Outcome of High-risk Patients

Several different strategies exist that may improve outcomes in high-risk patients. They primarily focus on treatment intensification.

Treatment strategies that focus on intensification:

1. Tandem transplantation
2. PET response adapted: second, non-cross resistant salvage regimen for non-CR patients before ASCT
3. Brentuximab vedotin consolidation/maintenance after ASCT

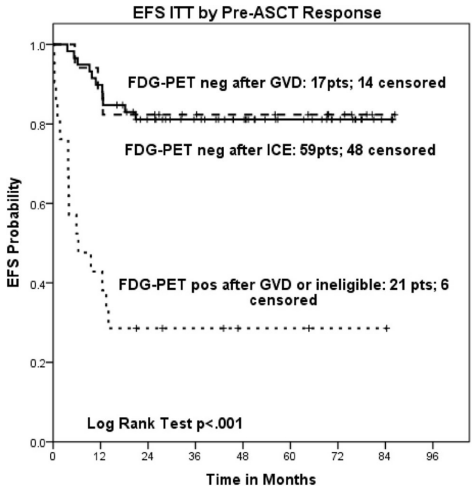
Role of Tandem Autologous Stem Cell Transplantation in the Treatment of High-risk Relapsed/Refractory Patients

A prospective multicenter trial evaluated a risk-adapted salvage treatment with single or tandem ASCT for 245 HL patients who experienced treatment failure with first-line therapy.[24] Among poor-risk patients, 70% received tandem ASCT. According to the intention-to-treat analysis, the 5-year freedom from second failure and OS estimates were 46% and 57%, respectively, for the poor-risk group. The authors concluded that for poor-risk patients, tandem ASCT may be beneficial for patients with poor prognostic features.

Role of Second-line Salvage in the Treatment of High-risk Relapsed/Refractory Patients

A phase 2 study examined whether pre-salvage therapy prognostic factors and post-salvage therapy FDG-PET response in a risk-adapted approach resulted in improved PFS after high-dose radio-chemotherapy (HDT) and ASCT.[25] The first salvage therapy used was 2 cycles of ifosfamide, carboplatin, and etoposide (ICE) in a standard or augmented dose (ICE/aICE), followed by restaging FDG-PET scan. Patients with a negative scan received a transplant. FDG-PET positive patients received 4 biweekly doses of gemcitabine, vinorelbine, and liposomal doxorubicin (GVD). Patients without evidence of disease progression proceeded to HDT/ASCT; those with progressive disease were considered study failures. At a median follow-up of 51 months, event-free survival (EFS) analyzed by intention-to-treat as well as for transplanted patients was 70% and 79%, respectively (Figure 11). Patients transplanted with negative FDG-PET, pre-HDT/ASCT after 1 or 2 salvage therapies, had an EFS of >80%, versus 28.6% for patients with a positive scan (P<.001). The results from this study suggest that the goal of salvage therapy in patients with HL should be a negative FDG-PET scan before HDT/ASCT.

Figure 11. Event-free Survival in High-risk FDG-PET-positive Patients[25]



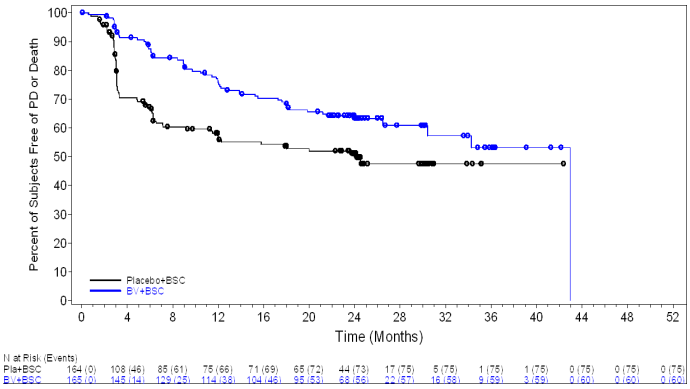
Adapted from: Moskowitz, et al.[25]

The results from this study suggest that a reasonable approach is to try another salvage regimen in PET-positive patients before proceeding to BEAM (BCNU, etoposide, Ara-C, melphalan) as it may be possible to rescue the patient. In contrast, if patients do not respond to the second salvage, then the prognosis is very poor. Since the study is not randomized, it remains unclear if this an appropriate strategy for the entire group of relapsed HL patients.

Role of Maintenance Therapy After Autologous Stem Cell Transplantation

The ATHERA trial was a randomized, double-blind, phase 3 trial that investigated whether brentuximab vedotin improved PFS when given as early consolidation after ASCT.[26] Patients with unfavorable-risk relapsed/refractory HL who had undergone ASCT were randomly assigned to receive 16 cycles of 1.8 mg/kg brentuximab vedotin or placebo intravenously every 3 weeks, starting 30 to 45 days after transplantation. PFS was significantly longer in patients in the brentuximab vedotin group compared with those in the placebo group (hazard ratio [HR] 0.57, 95% CI 0.40–0.81; P=.0013; Figure 12).

Figure 12. Progression-free Survival in Patients Receiving Brentuximab Vedotin as Maintenance Therapy after Autologous Stem Cell Transplantation[26]



Adapted from: Moskowitz, et al.[26]

The PFS was 24 months versus 42 months for placebo compared with brentuximab vedotin, with most of the benefit gained within the first 6 to 8 months. Afterwards, the curves are almost parallel, but very early on there is a huge difference. The relapse rate in the placebo group is high, suggesting that maintenance therapy with brentuximab vedotin may eradicate residual disease. The benefits seen in PFS did not translate into an OS benefit as the study was not sufficiently powered for this particular endpoint. Additionally, 85% of the placebo patients subsequently received brentuximab vedotin. Subgroup analyses showed that all patients regardless of age, number of prior therapies, FDG-PET findings pre-ASCT, presence of extranodal disease or B symptoms, HL status after frontline therapy, or response to salvage therapy gained benefit from maintenance therapy with brentuximab vedotin.

Adverse events in the study were consistent with what has been previously described in the literature. Peripheral sensory neuropathy was one of the most common adverse events, occurring in 56% of patients in the brentuximab vedotin group compared with 16% of the placebo group.[26] Importantly, 85% of patients who developed neuropathy recovered. While this adverse event may appear to be dramatic, the toxicity with brentuximab vedotin remains much lower than that expected with a second high-dose chemotherapy or second salvage regimen. Another important consideration is the long-lasting neutropenia that occurred in the placebo group. The neutropenia was considered to be severe because 23% of patients in the placebo group developed upper respiratory tract and/or severe infections. The authors of the study concluded that early consolidation with brentuximab vedotin after ASCT improved PFS; and therefore, provides a therapeutic option for patients undergoing ASCT.

Summary of Second-line Treatment in Transplant-eligible Patients

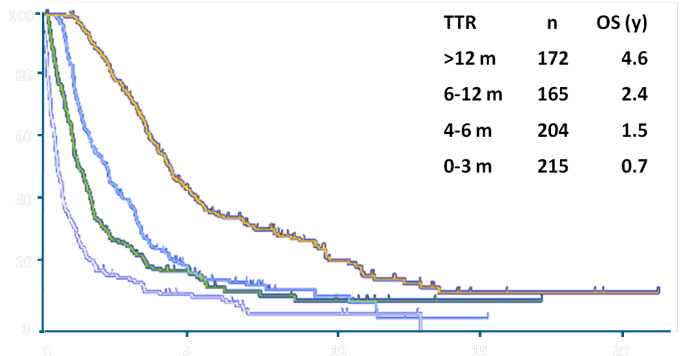
All strategies aim at treatment intensification, but have different pros and cons.

1. Tandem transplantation: phase 2 data only, long follow-up, restricted to young patients (<45 years)
2. PET response adapted: phase 2 only, no standard treatment arm to judge on the PET-guided approach, especially chance for PET positive patients not proceeding to transplant might be missed
3. Brentuximab vedotin: phase 3 data, proven PFS benefit, long treatment duration and likelihood of peripheral neuropathy must be taken into consideration

Third-line Treatment After Failure of High-dose Chemotherapy

In transplant-eligible patients who fail second-line therapy, the treatment paradigm shifts to palliative care. An analysis of 800 patients from Europe and the United States showed that three-quarters of patients relapsed within the first year after high-dose chemotherapy, and if they did so, the overall survival curve was poor (Figure 13).[27]

Figure 13. Overall Survival After Relapse After Autologous Stem Cell Transplantation[27]

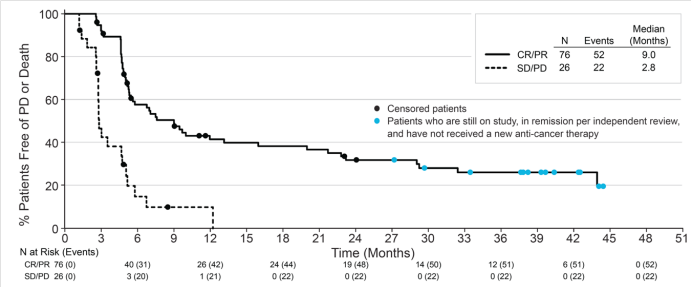


Adapted from: Arai, et al.[27]

Brentuximab Vedotin as Third-line Therapy for Relapsed/Refractory Hodgkin Lymphoma

In a phase 2 study, brentuximab vedotin was shown to be effective in relapsed/refractory patients as a third-line treatment option with an overall response rate of 75% and a CR rate of 34%.[28] The adverse event profile included neutropenia, thrombocytopenia, and grade 3 neuropathy; however, the event rates were lower than polychemotherapy. The CRs translated into long-lasting remissions (Figure 14).[29] Although patients achieved a CR, they eventually relapsed, and few patients were cured by this intervention.

Figure 14. Progression-free Survival by Best Clinical Response Per Central Independent Review[29]



Adapted from: Gopal, et al.[29]

Harnessing the Immune System as Third-line Therapy for Relapsed/Refractory HL

The PD-1 pathway serves as an immune checkpoint to dampen immune responses. The tumor microenvironment in classical HL overexpresses the PD-1 ligands, resulting in a successful mechanism of tumor immune escape. Blocking PD-1 interactions with its ligands is therefore a promising treatment approach, particularly as genetic alterations result in PD-L1 and PD-L2 copy gain and thus overexpression of PD-1 ligands. Nivolumab and pembrolizumab are monoclonal antibodies that target the PD-1 pathway.

Two recent clinical trials targeting PD-1/PD-1-ligand interactions have been reported. In a clinical trial utilizing nivolumab, 23 patients with relapsed or refractory HL were treated every 2 weeks with 3 mg/kg of the antibody.[30] The majority of these patients had previously received an autologous stem cell transplant, and most had received previous brentuximab vedotin. Nivolumab was associated with an overall response rate of 87%. Nivolumab was well tolerated with no drug-related AEs or fatal events. Thrombocytopenia (Grade 3) in a patient treated with 6 prior therapies and pancreatitis (Grade 3) were the only AEs leading to study termination. Other Grade 3 AEs included lymphopenia, gastrointestinal inflammation, and post-ASCT pneumonitis, colitis, and stomatitis.[30]

In a second trial utilizing the anti-PD-1 monoclonal antibody pembrolizumab, an overall response rate of 53% in heavily pretreated patients was reported. Several clinical trials investigating nivolumab and pembrolizumab are currently underway.

Summary of Treatment of Relapsed/Refractory Hodgkin Lymphoma

For the first time in quite some time, the treatment paradigm is changing for patients with relapsed/refractory HL. Results from recent clinical trials have challenged the dogma that high-dose chemotherapy followed by ASCT is the standard of care for these patients. The availability of new therapies that target specific pathways integral to HL has allowed treatment paradigms to be modified to increase efficacy while reducing toxicity. Maintenance of consolidation after high-dose chemotherapy with brentuximab vedotin is a new concept in the treatment of HL. It is feasible and well tolerated. In the third-line for failures of high-dose chemotherapy, we have a completely new treatment option, the anti-PD-1 antibodies. While the data are very preliminary, these agents show great promise and may potentially become an important treatment option for the very difficult to treat patients.

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