



Current treatment and immunotherapy of Hodgkin's lymphoma

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The treatment of Hodgkin's lymphoma has changed significantly over the last decades, rendering this entity one of the most curable human cancers. To date, about 80% of patients achieve long-term disease-free survival. Current strategies in first-line treatment aim at further improving outcome and thereby preventing therapy-induced complications, such as infertility, cardiopulmonary toxicity, and secondary malignancies. Ongoing trials for patients in early stages are investigating lower radiation doses and smaller radiation fields and possible reductions in the doses or number of cycles of chemotherapy given. For patients in advanced stages, new drug combinations with higher dose density and intensity have been developed, and are currently being evaluated in clinical trials. Approaches for relapsed Hodgkin's lymphoma comprise salvage radiotherapy, salvage chemotherapy and high-dose chemotherapy followed by autologous stem cell transplantation. In recent years, the introduction of effective salvage high-dose therapy and a better understanding of prognostic factors have remarkably improved the management of relapsed Hodgkin's lymphoma. For multiple pretreated patients antibody-based agents that showed promising results in experimental models are being investigated in clinical trials. Radioimmunoconjugates and monoclonal antibodies have demonstrated some clinical efficacy. Here, we review new aspects in the treatment of primary and relapsed Hodgkin's lymphoma as well as recent immunotherapeutic approaches.

Key words: Hodgkin's disease, chemotherapy, early stage, advanced stage, relapsed, radiolabeled antibody, monoclonal antibody.

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At initial diagnosis, patients with Hodgkin's lymphoma are classified into risk groups according to the stage of the disease and the presence of risk factors such as B-symptoms, age, and an elevated erythrocyte sedimentation rate. The stage at diagnosis is usually determined according to the Cotswolds classification, the latest modified version of the Ann-Arbor classification that incorporates additional information on prognostic factors including the number and location of anatomical sites involved, bulky nodal disease, extranodal extension of disease, and subdiaphragmatic involvement.¹ Generally, patients in clinical stages I or II without risk factors are allocated to the early-stage favorable group, whereas those with risk factors are allocated to the early-stage unfavorable group. Patients with stage III or IV disease are assigned to the advanced-stage risk group. Besides stage and B-symptoms, most groups consider large tumor burden, including bulky disease >10 cm or a large mediastinal mass \geq one third of the thoracic diameter, as a relevant prognostic factor. However, there

are still small differences in the definition of risk factors used and the classification of certain subgroups of patients among the different study groups in Europe and the USA (Table 1).²

Early-stage favorable Hodgkin's lymphoma

The standard treatment modality for early-stage Hodgkin's lymphoma has long been considered, extended-field radiotherapy (EF-RT). The extended field strategy delivers radiation to all initially involved and adjacent lymph node regions, leading to large irradiation fields compared with involved-field radiotherapy (IF-RT), which is restricted to initially involved lymph node regions only. Together with the successful introduction of MOPP³ and ABVD⁴ chemotherapy for advanced stage disease in the 1980s, the paradigmatic shift from radiation alone to additional chemotherapy in early stages was accelerated by the realization of long-term toxicity and mortality related to large radiation fields and radiotherapy doses. Longer follow-up of patients who underwent EF-RT revealed severe late effects as competing causes of death, includ-

Table 1. Definitions of treatment groups according to the EORTC/GELA, GHSG, and NCIC/ ECOG.

Treatment Group	EORTC/GELA	GHSG	NCIC/ECOG
Early-stage favorable	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors	Standard risk group: favorable CS I-II (without risk factors)
Early-stage unfavorable (intermediate)	CS I-II with ≥ 1 risk factors (supradiaphragmatic)	CS I, CSIIA ≥ 1 risk factors; CS IIB with C/D but without A/B	Standard risk group: unfavorable CS I-II (at least one risk factor)
Advanced stage	CS III-IV	CS IIB with A/B; CS III-IV	High risk group: CS I or II with bulky disease; intraabdominal disease; CS III,IV
Risk factors (RF)	A large mediastinal mass B age ≥ 50 years C elevated ESR* D ≥ 4 involved regions	A large mediastinal mass B extranodal disease C elevated ESR* D ≥ 3 involved areas	A ≥ 40 years B not NPLHL or NS histology C ESR ≥ 50 mm/h D ≥ 4 involved nodal regions

GHSG: German Hodgkin Lymphoma Study Group; EORTC: European Organization for Research and Treatment of Cancer; GELA: Groupe d'Etude des Lymphomes de l'Adulte; ECOG: Eastern Cooperative Oncology Group; NCIC, National Cancer Institute of Canada* erythrocyte sedimentation rate (≥ 50 mm/h without or ≥ 30 mm/h with B-symptoms).

ing heart failure,⁵ pulmonary dysfunction,⁶ and secondary malignancies.⁷⁻⁹ Furthermore, though complete remission was generally achieved, there was a high risk of relapsing from first-line treatment when EF-RT alone was administered.¹⁰ Two different strategies were explored to prevent these relapses: either applying even more intensive radiotherapy or adding chemotherapy for early-favorable stages to control occult lesions.¹¹ The latter strategy produced better outcomes and at the same time enabled reduction of radiotherapy to the involved fields for this risk group.

Most centers and groups in Europe and the USA have now accepted combined modality treatment, consisting of two to four cycles of ABVD, followed by 30 Gy IF-RT as a standard of care for early favorable stage disease. Several randomized studies confirmed the superiority of combined modality treatment over radiotherapy alone. Other trials were conducted to investigate and reduce radiation fields and dose and, likewise, to decrease chemotherapy drug combinations and duration of treatment.

A selection of recent and ongoing trials is listed in Table 2. The Southwest Oncology Group (SWOG) demonstrated that patients treated with combined modality therapy, consisting of three cycles of doxorubicin and vinblastine followed by subtotal lymphoid irradiation, had a markedly superior outcome in terms

Table 2. Selected trials for early-stage favorable Hodgkin's lymphoma.

Trial	Therapy regimen	# Pts.	Outcome	Ref.
SWOG #9133	A. 3 (dox.+vinbl.) + STLI (36-40 Gy)	165	94% (FFTF);98% (SV);	12
	B. STLI (36-40 Gy)	161	81% (FFTF); 96% (SV); [3 years]	
Milan 1990-97	A. 4 ABVD + STLI	65	97 % (FFP); 93% (SV)	13
	B. 4 ABVD + IF RT	68	97 % (FFP); 93% (SV); [5 years]	
Stanford V 8 weeks of Stanford V (CSI-IIA) + modified IF RT (30 Gy)		65	94.6% (FFP); 96.6% (SV) [16 months; estimated for 3 years]	14
EORTC/ GELA H7F	A. 6 EBVP+IF RT (36 Gy)	168	90 % (RFS); 98% (SV)	15
	B. STNI	165	81 % (RFS); 95% (SV); [5 years]	
EORTC/ GELA H8F	A. 3 MOPP/ABV+IF RT (36 Gy)	271	99 % (RFS); 99% (SV)	16
	B. STNI	272	80 % (RFS); 95% (SV); [4 years]	
EORTC/ GELA H9F	A. 6 EBVP+IF RT (36 Gy)	783	87 % (EFS); 98% (SV)	18
	B. 6 EBVP+IF RT (20 Gy)		84 % (EFS); 98% (SV); [4 years]	
	C. 6 EBVP		C closed because of high relapse rate;	
GHSG HD7	A. EF RT 30 Gy (40 Gy IF)	305	75% (FFTF); 94% (SV);	20
	B. 2 ABVD + EF RT 30 Gy (40 Gy IF)	312	91% (FFTF); 94% (SV); [5 years]	
GHSG HD10	A. 4 ABVD + IF RT (30Gy)	847	interim analysis [2 years]	21
	B. 4 ABVD + IF RT (20Gy)		all pts:	
	C. 2 ABVD + IF RT (30Gy)		96.6%(FFTF)	
	D. 2 ABVD + IF RT (20Gy)		98.5% (SV)	
GHSG HD13	A. 2 ABVD + IF RT (30Gy)		Ongoing trial	
	B. 2 ABV + IF RT (30Gy)			
	C. 2 AVD + IF RT (30Gy)			
	D. 2 AV + IF RT (30Gy)			

SWOG: Southwest Oncology Group; EORTC: European Organization for Research and Treatment of Cancer; GELA: Groupe d'Etude des Lymphomes de l'Adulte; GHSG: German Hodgkin Lymphoma Study Group; EF/IF-RT, extended/involved-field radiotherapy; STLI: subtotal lymphoid irradiation; STNI: subtotal nodal irradiation; FFTF: freedom from treatment failure; RFS: relapse-free survival; FFP, freedom from progression; EFS: event-free survival; SV: overall survival.

of freedom of treatment failure (FFTF) than those receiving subtotal lymphoid irradiation alone.¹² Studies from Milan and Stanford revealed that subtotal lymphoid irradiation can be effectively replaced by IF-RT after short duration chemotherapy, such as ABVD or Stanford-V (8 weeks), while maintaining progression-free and overall survival.^{13,14} The European Organization for Research and Treatment of Cancer (EORTC) and the Groupe d'Etude des Lymphomes de l'Adulte (GELA) demonstrated that combined modality treatment with either six courses of EBVP (H7F trial) or three of MOPP/ABV (H8F trial) followed by IF-RT yielded a significantly by better event-free survival than that achieved by subtotal nodal irradiation alone.^{15,16} The aim of the H9F trial was to evaluate a possible dose reduction of radiotherapy (36 Gy or 20 Gy or no radio-

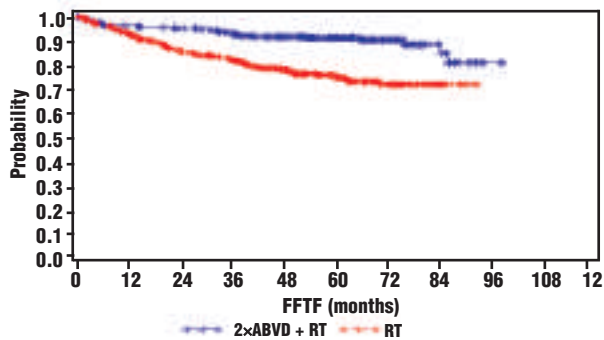


Figure 1. Results of the GHSG HD7 trial: freedom from treatment failure (FFTF) at 5 years: arm A (radiotherapy only) 75% and arm B (2xABVD+ radiotherapy) 91%.

therapy) after administering six cycles of EBVP. However, the arm without radiotherapy was closed prematurely due to a higher number of relapses than expected.^{17,18} Thus, the use of chemotherapy alone in early stages should still be regarded as experimental. A recent randomized trial on non-bulky, asymptomatic stage I-III Hodgkin's lymphoma failed to demonstrate any superiority of ABVD+radiotherapy over ABVD alone; however, the total number of patients was small and all patients received six cycles of ABVD, even those in clinical stage I or II without risk factors.¹⁹

A combined modality approach was also established in the HD7 trial by the German Hodgkin Study Group (GHSG). In this trial two cycles of ABVD plus EF-RT were shown to be superior to EF-RT alone in terms of FFTF (Figure 1). Overall survival was equal in both arms due to effective salvage treatment.²⁰ Further improvement of treatment, with respect to the excellent long-term survival rates, seems difficult. Thus, strategies to reduce drug dose and toxicity while maintaining efficacy are being pursued. In the subsequent HD10 trial of the GHSG, a possible reduction in chemotherapy from four to two cycles of ABVD and/or IF-RT from 30 to 20 Gy was evaluated. After a median observation time of two years, FFTF and overall survival rates were 96.6% and 98.5%. So far, no significant differences in FFTF or overall survival have been detected between recipients of four cycles of ABVD and those receiving two cycles of ABVD or between patients receiving different doses of radiotherapy (30Gy vs. 20Gy).²¹ The aim of the ongoing GHSG HD13 trial is to omit the presumably less effective drugs, bleomycin or dacarbazine, from the ABVD regimens. Patients are thus randomized between two cycles of ABVD, ABV, AVD or AV followed by 30 Gy IF-RT.

Patients with an initial diagnosis of nodular, lymphocyte-predominant Hodgkin's lymphoma (LPHL) in clinical stage IA without risk factors are usually not included in ongoing trials. On the basis of the very favorable prognosis of this subgroup, the EORTC and

the GHSG currently recommend treatment with 30 Gy IF-RT only. While being less toxic, this strategy seems to produce similar responses for LPHL stage IA patients as those achieved with combined modality treatment.²² Experimental approaches for these patients focus on the humanized monoclonal anti-CD20 antibody, rituximab, which has given impressive results in relapsed LPHL (*see below*) and will shortly be evaluated in a GHSG phase-II study in selected patients with stage IA LPHL patients.

Early stage unfavorable (intermediate) Hodgkin's lymphoma

Patients with early-stage unfavorable (intermediate) Hodgkin's lymphoma generally qualify for combined modality treatment. However, the ideal chemotherapy and radiation regimens are not yet clearly defined and there is an ongoing desire to optimize therapy in this risk group. This is being attempted by reducing radiation doses and field sizes in a similar manner to that for early favorable stages. Several trials seem to indicate that the reduction of field size does not compromise the efficacy of treatment. A co-operative study comparing six cycles of MOPP sandwiched around 40 Gy of radiotherapy applied either to an involved or extended field, indicated no difference in terms of disease-free survival or overall survival.²³ Another trial from Italy comparing subtotal lymphoid irradiation with IF-RT after four cycles of ABVD in patients with early favorable (Table 2) and unfavorable stages reported a similar treatment outcome in both arms.¹³ In the H8U trial, the EORTC randomized patients between six cycles of MOPP/ABV+36 Gy IF-RT, four cycles of MOPP/ABV+36 Gy IF-RT, and four cycles of MOPP/ABV+subtotal lymphoid irradiation. There was no difference between the arms in terms of response rates, failure-free survival, or overall survival.²⁴ The largest trial investigating radiotherapy reduction was conducted by the GHSG: in the HD8 trial, patients were randomized to two alternating cycles of COPP/ABVD plus radiotherapy to either an extended field (arm A) or limited to involved fields (arm B). The final results at 5 years did not demonstrate significant differences between the two arms in terms of FFTF (Figure 2) and overall survival, however, more toxicity was reported in the patients who were treated with EF-RT (Table 3).²⁵ A NCIC/ECOG trial argues in favor of combined modality treatment over ABVD alone in unfavorable non-bulky stage IA/IIA Hodgkin's lymphoma.²⁶ Furthermore, a recent retrospective analysis supports the use of approximately 30 Gy IF-RT after a good response to ABVD,²⁷ a strategy that has been adopted in the ongoing GHSG and EORTC trials.

Efforts were also made to improve the efficacy of chemotherapy by altering drugs and schedules as well as the number of cycles. In the past, alternation or

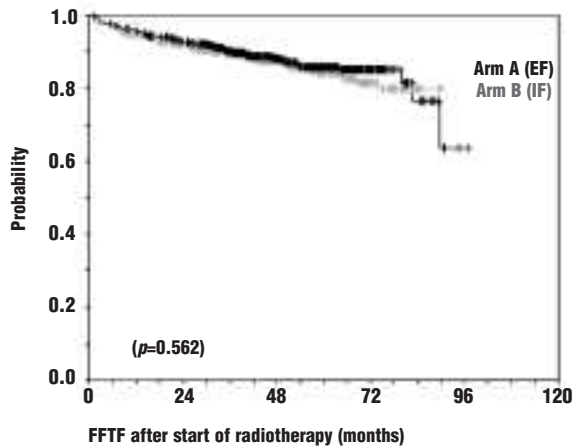


Figure 2. Results of the GHSG HD8 trial: freedom from treatment failure (FFT) trial at 5 years: arm A (2xCOOP/ABVD + extended-field RT) 86% and arm B (2xCOOP/ABVD + involved-field RT) 84%.

hybridization of MOPP-like regimens with ABVD did not produce better outcomes when compared with ABVD alone. Furthermore, studies in advanced stage Hodgkin's lymphoma indicated that ABVD alone is equally effective as and less myelotoxic than alternating MOPP/ABVD, and both are superior to MOPP alone.²⁸ Thus, a combined modality treatment consisting of four courses of ABVD followed by 30 Gy IF-RT is considered the standard treatment for patients with early-stage unfavorable Hodgkin's lymphoma. Despite the excellent initial remission rates obtained with ABVD and radiotherapy, approximately 15% of patients in early unfavorable stages relapse within 5 years and about another 5% suffer from primary progressive disease. These outcome rates are rather similar to those in patients in advanced stages, when treated with more intense regimens. Thus, study groups are currently evaluating different regimens for the early unfavorable group that were previously pioneered for the treatment of advanced stages (Table 3): in their ongoing intergroup trial #2496, the ECOG and SWOG are assessing whether the Stanford V regimen (12 weeks) is superior to six cycles of ABVD. In another approach, four cycles of ABVD and four cycles of BEACOPP-baseline were compared in by the EORTC-GELA (H9U trial) and by the GHSG (HD11 trial). In addition, two large trials analyzed whether four cycles of combined modality treatment are equally effective as six cycles (EORTC: H8U and H9U trial).

In the H9U trial, which was recently presented by the EORTC and GELA, patients were randomly assigned to six cycles of ABVD or four cycles of ABVD or four cycles of BEACOPP-baseline, followed by 30 Gy of IF-RT in all arms. After a median follow-up of 4 years, no significant difference was observed between the three different treatment arms with respect to event-free survival or overall survival.¹⁸ Interim results of the GHSG

Table 3. Selected trials for early-stage unfavorable Hodgkin's lymphoma.

Trial	Therapy regimen	# Pts.	Outcome	Ref.
EORTC/ GELA H8U	A. 6 MOPP/ABV+IF RT (36 Gy)	335	94% (RFS); 90% (SV)	24
	B. 4 MOPP/ABV+IF RT (36 Gy)	333	95% (RFS); 95% (SV)	
	C. 4 MOPP/ABV + STNI	327	96% (RFS); 93% (SV); [4 years]	
GHSG HD8	A. 2 COOP+ABVD + EF RT (30 Gy) + Bulk (10Gy)	532	86% (FFTF); 91% (SV)	25
	B. 2 COOP+ABVD + IF RT (30 Gy) + Bulk (10Gy)	532	84% (FFTF); 92% (SV); [5 years]	
SWOG/ ECOG #2496	A. 6 ABVD+IF RT (36 Gy) to bulk (>5 cm)		Ongoing trial	
	B. 12 weeks Stanford V+IF RT (36 Gy) to bulk (>5 cm)			
EORTC/ GELA H9U	A. 6 ABVD + IF RT	808	94 % (EFS); 96 % (SV)	18
	B. 4 ABVD + IF RT		89 % (EFS); 95 % (SV)	
	C. 4 BEACOPP bas.+ IF RT		91 % (EFS); 93 % (SV); [4 years]	
GHSG HD11	A. 4 ABVD+IF RT (30Gy)	1047	interim analysis [2 years]	29
	B. 4 ABVD+IF RT (20Gy)		all pts:	
	C. 4 BEACOPP bas.+IF RT (30Gy)		97.4% (FFTF)	
	D. 4 BEACOPP bas.+IF RT (20Gy)		89.9% (SV)	
GHSG HD14	A. 4 ABVD + IF RT (30Gy)		Ongoing trial	
	B. 2 BEACOPP esc. + 2 ABVD + IF RT (30Gy)			

SWOG, Southwest Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Lymphoma Study Group; ECOG, Eastern Cooperative Oncology Group; EF/IF-RT, extended/involved-field radiotherapy; STNI, subtotal nodal irradiation; FFTF, freedom from treatment failure; RFS, relapse free survival; EFS, event-free survival; SV, overall survival.

HD11 trial at two years demonstrated an FFTF of 89.9% and an overall survival of 97.4% for all patients. At that interim point there was also no difference with respect to outcome, either between the ABVD and BEACOPP arms or between the 30 Gy and 20 Gy IF-RT.²⁹ Although it should be taken into account that these are relatively early data, there is, nevertheless, no evidence for changing treatment from four to six cycles of ABVD or for recommending four cycles of BEACOPP-baseline in this group of patients. However, the low FFTF in this risk group led the GHSG to a further intensification of treatment. In the ongoing HD14 trial for early-unfavorable stage Hodgkin's lymphoma the BEACOPP-escalated regimen was introduced into the experimental arm.³⁰ Patients are currently being randomized to 2xBEACOPP-escalated + 2xABVD or 4xABVD followed by 30 Gy IF-RT.

Advanced stage Hodgkin's lymphoma

MOPP was successfully used for many years for advanced-stage disease, producing long-term remission rates of nearly 50%.^{31,3} This regimen was then replaced by ABVD, since large multicenter trials proved the superiority of ABVD and alternating MOPP/ABVD over MOPP alone.^{32,33} Hybrid regimens such as MOPP/ABV were demonstrated to be only equally effective as alternating MOPP/ABVD and even rapidly alternating multidrug regimens such as COPP/ABV/IMEP did not result in better outcome.^{30,31} However, more acute toxicity and a higher incidence of leukemia were reported after the MOPP/ABV hybrid than after ABVD.³² Thus far, ABVD is regarded as the standard regimen against which all new combinations have to be tested in the future. However, a long-term follow-up report of 123 patients who were previously treated with ABVD for advanced Hodgkin's lymphoma revealed a failure-free survival of only 47% and an overall survival of 59% after 14.1 years. These poor long-term results may also be partially due to the fact that radiotherapy was not administered.

Different study groups tried to improve these rates by developing new regimens with additional drugs and by increasing dose intensity and dose density with the support of colony-stimulating factors and modern antibiotics. These new approaches include multidrug regimens such as Stanford V, MEC, VAPEC-B, ChIVPP/EVA and BEACOPP.^{37-39,30} Stanford V seemed to be a promising strategy in a single center; however, a randomized comparison with MEC and ABVD showed that stanford was clearly inferior.³⁸ The conflicting results may be partially explained by the use of less radiotherapy in the randomized setting. The GHSG HD9 trial compared COPP/ABVD, BEACOPP-baseline and BEACOPP-escalated. Results from 1195 randomized patients after 5 years demonstrated a clear superiority of the escalated BEACOPP over the BEACOPP-baseline and COPP/ABVD.³⁰ The follow-up data at 7 years reinforced these results: with a median follow-up of 82 months, the FFTF and overall survival rates were 67% and 79% in the COPP/ABVD group, 75% and 84% in the BEACOPP baseline group and 85% and 90% in the BEACOPP-escalated group ($p < 0.001$ and $p = 0.004$) (Figure 3).⁴⁰ The subsequent GHSG HD12 trial aimed at de-escalating chemotherapy and radiotherapy by comparing eight courses of BEACOPP-escalated with four courses of escalated and four courses of baseline BEACOPP, with or without consolidating radiation to initial bulky and residual disease. In the latest interim analysis of HD12 at a median follow-up of 30 months, the FFTF was 88% and overall survival 94% for the whole cohort. So far, there has been no significant difference between the different arms.⁴⁰ In the ongoing HD15 trial, patients are randomized between

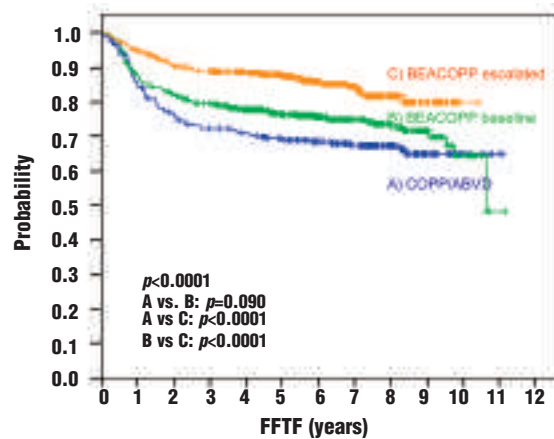


Figure 3. Follow-up results of the GHSG HD9 trial: freedom from treatment failure (FFTF) at 7 years: arm A (COPP/ABVD) 67%, arm B (BEACOPP-baseline) 75%, and arm C (BEACOPP-escalated) 85%.

eight courses of BEACOPP-escalated, six courses of BEACOPP-escalated, or eight courses of BEACOPP-14, which is a time-intensified variant of BEACOPP-baseline. Additional radiotherapy is only applied to residual lesions >2.5 cm positive by positron emission tomography (PET). The question of whether escalated BEACOPP is superior to ABVD alone in a randomized setting is currently being evaluated in an intergroup trial initiated by the EORTC (#20012).¹⁷ Here, eight cycles of ABVD are being compared with four cycles of BEACOPP-escalated plus four of BEACOPP baseline.

Further intensification of first-line treatment in high-risk patients by directly administering high-dose chemotherapy and autologous stem cell transplantation after four instead of eight cycles of ABVD did not improve outcome compared with conventional treatment.⁴¹ BEACOPP chemotherapy is generally associated with greater hematologic toxicity, sterility, and secondary leukemia when compared with ABVD. Nevertheless, cardiotoxicity and pulmonary side-effects are similar with both regimens, especially when combined with radiotherapy. A combination of gemcitabine and bleomycin in a BEACOPP variant (BAG-COPP) resulted in severe pulmonary toxicity and should be avoided.⁴²

The role of consolidating radiotherapy after effective chemotherapy in the treatment of patients with advanced Hodgkin's lymphoma is still subject to clinical research. A meta-analysis comparing combined modality approaches and chemotherapy alone reported equal tumor control and even better overall survival in patients treated with chemotherapy alone.⁴³ Therefore, randomized trials are currently evaluating the impact of radiotherapy after effective chemotherapy for advanced Hodgkin's lymphoma. A study conducted by the EORTC indicated that consolidating IF-RT did

not result in better outcome in patients who had already achieved a complete remission after six to eight cycles of MOPP/ABV, although it may be beneficial to patients with partial remissions.⁴⁴ Longer follow-up of the recently terminated GHSG HD12 trial and the ongoing HD15 trial may help to define the role of radiotherapy for residual disease. In ongoing studies, PET scanning is not only utilized as a tool to analyze tumor activity in residual masses after chemotherapy, as in the GHSG HD15 trial. There are some data suggesting that early PET scans during chemotherapy may identify responders and non-responders and thus have a potential role in directing early treatment modifications.^{45,46}

Elderly patients with Hodgkin's lymphoma

Although there is great variety in the health and physical conditions of elderly patients with Hodgkin's lymphoma, the age at diagnosis remains an unfavorable risk factor, particularly in patients with advanced stages of disease. Most groups consider patients *elderly* if they are aged 60 years or older. Factors such as more aggressive disease, more frequent diagnosis of advanced stage, comorbidity, poor tolerance of treatment, failure to maintain dose intensity, shorter survival after relapse and death due to other causes contribute to the poorer outcome of elderly patients. A retrospective analysis of GHSG trials showed that elderly patients have a poorer risk profile, more treatment-associated toxicity, receive a lower dose-intensity and have higher mortality as major factors for poorer outcome.⁴⁷ In the HD9-elderly trial of the GHSG, patients between 66 and 75 years old with advanced stage Hodgkin's lymphoma were treated with either COPP/ABVD or BEACOPP-baseline. Tumor control appeared to be better with the BEACOPP regimen, but toxicity was higher, resulting in no differences in FF2F or overall survival.⁴⁸ In phase I/II trials of the GHSG two new regimens are currently being evaluated for elderly patients: PVAG (prednisone, vinblastine, doxorubicin and gemcitabine) and BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone).

Relapsed and refractory Hodgkin's lymphoma

The majority of patients with Hodgkin's lymphoma nowadays achieve complete remission after first-line treatment. However, patients relapsing after a first complete remission still have a chance of being cured with adequate salvage treatment. Patients with relapsed or refractory Hodgkin's lymphoma have various treatment options depending on the first-line therapy. Conventional chemotherapy is the treatment of choice for patients who relapse after initial radiotherapy. In contrast, options for those who relapse after prior chemotherapy include salvage

radiotherapy for localized relapse in previously non-irradiated areas, salvage chemotherapy, or high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (SCT). Other options, such as allogeneic SCT and experimental strategies, are being evaluated for multiply pretreated patients. Most study groups categorize failures into three subgroups depending on the duration of remission after first-line treatment: early and late relapses of Hodgkin's lymphoma and primary, progressive Hodgkin's lymphoma.

Salvage radiotherapy and salvage polychemotherapy

Salvage radiotherapy alone offers an effective treatment option for a selected subset of patients with relapsed Hodgkin's lymphoma. This applies to patients with localized relapses in previously non-irradiated areas. In a retrospective analysis from the GHSG database including 624 patients with relapsed or refractory Hodgkin's lymphoma, 100 were eligible to receive salvage with radiotherapy alone: the 5-year freedom from second failure (FF2F) and overall survival rates were 28% and 51%, respectively. Prognostic factors for overall survival were B-symptoms, stage at relapse, performance status and duration of first remission in limited stage relapses.⁴⁹

Conventional chemotherapy is the treatment of choice for patients who relapse after initial radiotherapy for early-stage disease. The survival of these patients is at least equal to that of patients with advanced stage disease initially treated with chemotherapy.⁵⁰ The best treatment for recurrent Hodgkin's lymphoma after primary chemotherapy is high-dose chemotherapy. A number of conventional salvage protocols have been developed during the last decade. However, long-term follow-up data are scarce since most of the patients achieving complete or partial remission immediately proceeded to HDCT plus autologous SCT. Overall response rates to salvage therapy were high, being 60-80%, but only 20-35% of the patients achieved a complete remission. Patients relapsing after more than two cycles of polychemotherapy should be treated with HDCT at relapse. The best treatment for those relapsing after two cycles of treatment plus IF-RT remains to be defined.

HDCT followed by autologous SCT

Younger patients relapsing after initial chemotherapy are usually treated with HDCT and peripheral blood SCT. This strategy has been shown to produce long-term disease-free survival in 30-65% selected patients with refractory or relapsed Hodgkin's lymphoma.^{51,52} The reduction in the percentage of early transplant-related mortality to less than 5% has led to a widespread acceptance of this treatment strategy. Thus far, two randomized trials have demonstrated the superior-

ity of HDCT followed by autologous SCT over conventional chemotherapy. The British National Lymphoma Investigation (BNLI) reported that patients with relapsed or refractory Hodgkin's lymphoma receiving high-dose BEAM with autologous SCT fared significantly better than those treated with conventional dose mini-BEAM, resulting in a 3-year event-free survival of 53% versus 10%.⁵³ In the HD-R1-trial of the GHSG, chemosensitive patients relapsing after initial chemotherapy were randomized between four cycles of Dexamethasone-BEAM and two cycles of Dexamethasone-BEAM followed by BEAM and autologous SCT. The final results of this trial demonstrated a higher FF2F in the transplanted group than in the group receiving conventional salvage-chemotherapy (55% vs. 34%).⁵⁴ Even in the subgroup of patients with late relapse the FF2F was significantly better (75% and 44%). The FF2F for patients with early relapse was 41% and 12%, respectively. The overall survival did not differ significantly between the two treatment arms. This might be due, at least in part, to the fact that many patients relapsing after conventional salvage-therapy received autologous SCT upon subsequent relapse. The follow-up data after 7 years confirm these results.⁵⁵ The success of HDCT followed by peripheral blood SCT does not only depend on obvious factors such as tumor burden or chemosensitivity. A prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma also identified the time to relapse, the clinical stage at relapse and the presence of anemia as independent risk factors.⁵⁶

The reduction of tumor volume prior to HDCT followed by autologous SCT is an important variable affecting outcome in relapsed and refractory Hodgkin's lymphoma. A brief tumor-reducing program with two cycles of DHAP given at short intervals supported by granulocyte colony-stimulating factor was shown to be both effective and well-tolerated in patients with relapsed and refractory disease.⁵⁷ Therefore, this regimen was chosen for the HD-R2 study instead of previously used regimens, such as Dexamethasone-BEAM, which were associated with severe treatment-related toxicity and mortality before the dose reduction of etoposide.⁵⁴ Furthermore, the DHAP regimen can be used to collect stem cells successfully in more than 90% of patients with Hodgkin's lymphoma.⁵⁸

The strategy of sequential HDCT follows the Norton-Simon hypothesis: after initial cytoreduction, a few non-cross-resistant agents are given at short intervals. The transplantation of peripheral blood stem cells and the use of growth factors allow the application of the most effective drugs at the highest possible doses at short intervals of one to three weeks. The Cologne high-dose, sequential, chemotherapy trial conducted by the GHSG evaluated the feasibility and efficacy of

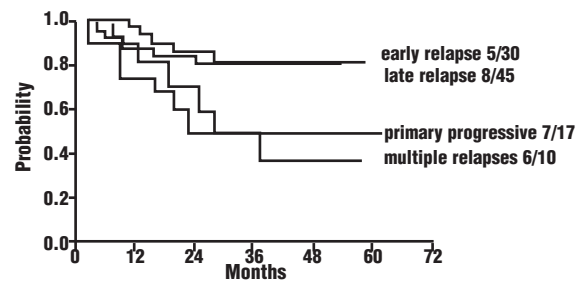


Figure 4. Cologne high-dose sequential trial of the GHSG: overall survival according to the duration of first remission at 30 months: for patients with early relapse 81%, with late relapse 81%; with progressive disease 48%, and with multiple relapses 48%.

this novel approach including a high-dose sequential chemotherapy program and a final myeloablative course in 102 patients with relapsed or refractory Hodgkin's lymphoma. Treatment consisted of two cycles of DHAP (dexamethasone, ara-C, cisplatin) followed by a sequential high-dose chemotherapy with cyclophosphamide, methotrexate plus vincristine, and etoposide. The final myeloablative course of BEAM was followed by peripheral blood SCT. With a median follow-up of 30 months, FF2F and overall survival rates were 59% and 78% respectively, for all patients. FF2F and overall survival rates for patients with early relapse were 62% and 81%, for those with late relapse 65% and 81%; for those with progressive disease 41% and 48%, and for those with multiple relapses 39% and 48%, respectively (Figure 4). In multivariate analysis response after DHAP and duration of first remission were prognostic factors for FF2F and overall survival.⁵⁹ Based on the promising results of this study, the GHSG started a prospective European intergroup trial together with the EORTC, the GELCAB and the EBMT (HD-R2). The rationale of this trial, which is still open, is to compare the effectiveness of two courses of DHAP followed by BEAM with the intensified sequential strategy in a randomized setting. Patients with histologically confirmed early or late relapsed Hodgkin's lymphoma, and patients in second relapse with no prior HDCT are included.⁶⁰

Primary progressive and refractory Hodgkin's lymphoma

For patients with primary progressive disease during induction treatment or within 3 months after the end of first-line therapy, conventional salvage chemotherapy has given disappointing results in the vast majority of patients. No response at all or only a very short response to salvage treatment resulted in a very poor 8-year overall survival of between 0% and 8%.^{61,62} To determine prognostic factors and treatment outcome of patients with primary progressive Hodgkin's lym-

phoma, the GHSG retrospectively analyzed 206 patients with progressive disease. The 5-year FF2F and overall survival for all patients were 17% and 26%, whereas the corresponding figures for patients treated with HDCT were 31% and 43%, respectively. The low percentage of only 33% of patients who received HDCT was due to rapidly fatal disease or life-threatening severe toxicity after salvage therapy. Other reasons for not proceeding to HDCT were an insufficient stem cell harvest, poor performance status and older age. In multivariate analysis low Karnofsky performance score at the time of progression, age above 50 years, and failure to attain a temporary remission on first-line treatment were significant adverse prognostic factors for overall survival.⁶³

The effectiveness of HDCT and autologous SCT for patients with biopsy-proven primary refractory Hodgkin's lymphoma was shown by the Memorial Sloan Kettering Cancer Center in New York in a study of 75 consecutive patients who were treated with HDCT and autologous SCT. At a median follow-up of 10 years for surviving patients, the event-free survival, progression-free survival, and overall survival rates were 45%, 49% and 48%, respectively. Chemosensitivity to standard-dose second-line chemotherapy was predictive of a better survival.⁶⁴

Allogeneic stem cell transplantation

Allogeneic SCT cannot yet be considered an alternative standard treatment in patients with relapsed Hodgkin's lymphoma. So far, the advantages of a potential graft-versus-lymphoma effect have been offset by a very high transplant-related mortality of more than 50%. Furthermore, donor availability and age constraints have limited a broader application of allogeneic SCT in patients with Hodgkin's lymphoma. As shown by a recently published matched-pair analysis, transplant-related mortality might be significantly reduced by employing reduced-intensity conditioning.⁶⁵ Allogeneic SCT following reduced-intensity conditioning might thus become an appropriate strategy in selected subgroups of young poor-risk patients, e.g. for those in whom autologous transplantation failed, patients with primary refractory disease, or for patients with early relapse and further risk factors.⁶⁶ However to date, the number of patients treated is small, and further clinical studies and information are required in order to define clear indications for this strategy.

Immunotherapy in Hodgkin's lymphoma

Radioimmunotherapy. Radiolabeled antibodies have been studied both for imaging and treatment of lymphoma. Most radiolabeled antibodies for therapeutic use consist of a specific antibody labeled with iodine-131 (¹³¹I) or yttrium-90 (⁹⁰Y). These radionuclides must

have energetic particulate radiation, such as α - or β -emitters, to focus the radiation dose to defined areas. A substantial advantage of radiolabeled antibodies is their ability to kill tumor cells adjacent to cells to which the radioimmunoconjugate is bound (the cross-fire effect). Currently, both, non-myeloablative and myeloablative strategies involving radiolabeled antibodies are being pursued. Since Hodgkin's lymphoma is very sensitive to radiotherapy, radioimmunotherapeutic approaches using polyclonal antiferritin antibodies labeled with ¹³¹I or ⁹⁰Y and monoclonal the anti-CD30 Ki-4 labeled with ¹³¹I have been studied.

Low-dose radioimmunotherapy using polyclonal ferritin-directed antibodies. Ferritin is a tumor-associated protein which was described in Hodgkin's lymphoma and other tumors. In a first trial 38 patients with Hodgkin's lymphoma received ¹³¹I-labeled polyclonal ferritin-directed antibodies delivering an activity of 50 mCi. There was 40% tumor regression.⁶⁷ Side effects were related to bone marrow toxicity with grade 4 thrombocytopenia in 10% and grade 4 neutropenia in 5%. In another trial the use of fractionated (2x0.25 mCi/kg) or unfractionated (0.3-0.5 mCi/kg) ⁹⁰Y-labeled antiferritin antibodies was evaluated.⁶⁸ Side effects were flu-like symptoms 2-3 days after treatment in half of the patients. The most significant toxicity was thrombocytopenia. In summary, fractionation did not provide any decrease in hematologic toxicity. Tumor response was dose-related and varied from 22% to 86%. Out of a total of 90 patients treated,¹⁵ achieved complete remission and 29 partial remission with a median duration of 6 months.

Low-dose radioimmunotherapy using an anti-CD30 monoclonal antibody. Twenty-two patients with relapsed or refractory CD30-positive Hodgkin's lymphoma were treated with ¹³¹I-labeled Ki-4.⁶⁹ Imaging demonstrated localization of involved areas measuring 5 cm in diameter or more in four patients and 2.5 cm in one patient. The patients received total body doses of 0.035 Gy to 0.99 Gy. Acute toxicity was mild with grade I fatigue in 19 of the 22 patients. Seven patients experienced grade IV hematotoxicity 4-8 weeks after treatment. The best predictors of hematotoxicity were erythrocyte, sedimentation rate and Karnofsky index reflecting advanced disease. There was one complete response, five partial responses and 3 minor responses.

High-dose radioimmunotherapy using polyclonal ferritin-directed antibodies. Vriesendorp and colleagues performed a phase I/II study with ⁹⁰Y-labeled polyclonal antiferritin immunoglobulins and autologous bone marrow transplantation for patients with refractory Hodgkin's lymphoma.⁷⁰ Nineteen patients received

Table 4. Clinical trials with different immunoconjugates in Hodgkin's lymphoma.

Group	Antigen	Construct	Application (Dose, MTD)	Toxicity	Immune response	Response	Reference
A							
RAb	anti-ferritin	¹³¹ I-antiferritin	bolus i.v.30mCi day 1 bolus i.v. 20mCi day 5	myelosuppression	ND	1/37 CR 14/37 PR	67
RAb	anti-ferritin	⁹⁰ Y-antiferritin	bolus i.v. 20-50mCi day 1 ±ABMT	myelosuppression	none	9/29 CR 9/29 PR	70
RAb	anti-ferritin	⁹⁰ Y-antiferritin	bolus i.v. 20-50mCi day 1 CX + ABMT	myelosuppression	ND	1/12 CR 3/12 PR	72
RAb	anti-ferritin	⁹⁰ Y-antiferritin	bolus i.v. 20-50mCi day 1	myelosuppression, mild fever and fatigue	none	10/39 CR 10/39 PR	71
RAb	anti-ferritin	⁹⁰ Y-antiferritin	bolus i.v. 0.3-0.5mCi/kg day 1 or 2×0.25mCi/kg day 1 + 8	myelosuppression, mild fever and fatigue	ND	15/90 CR 29/90 PR	68
RAb	CD30	¹³¹ I-Ki-4	bolus i.v. 20-100mCi day 1	myelosuppression, fever, fatigue	18% HAMA	1/22 CR 5/22 PR	69
B							
MAb	CD20	Rituximab (LPHL)	4×1 bolus infusion/w (given dose: 375 mg/m ²)	rhinitis, fever, chills, nausea	none	8/14 CR 4/14 PR	76
MAb	CD20	Rituximab (LPHL)	4×1 bolus infusion/w (given dose: 375 mg/m ²)	no grade 3 or 4 toxicities	ND	10/22 CR 12/22 PR	77
MAb	CD20	Rituximab (cHL)	6×1 bolus infusion/w (given dose: 375 mg/m ²)	ND	ND	1/15 CR 2/15 PR	78
MAb	CD30	SGN-30	6×1 bolus infusion/w (given dose: 2-12 mg/kg) 6 x 1 bolus infusion/w (given dose: 6 mg/kg)	fatigue	ND	None of 21 None of 12	74
MAb	CD30	MDX060	4×1 bolus infusion/w (given dose: 0.1-15 mg/kg)	2 grade 3 toxicities (elevated liver transaminase, pneumonia)	ND	1/40 CR 2/40 PR	75

ABMT: autologous bone marrow transplantation; MAb, monoclonal antibody; IT: immunotoxin; rIT: recombinant immunotoxin; Bi-MAb: bispecific antibody; RAb: radiolabeled antibody; i.v., intravenous; CR, complete remission; PR, partial remission; MR, minor response; VLS, vascular-leak-syndrome; HAMA: human anti-mouse-antibodies; HARA: human anti-ricin-antibodies; anti-DT-A: anti-diphtheria toxin-antibodies; anti-DAB-A: anti-DAB-antibodies; anti-IL-2-A: anti-interleukin-2-antibodies; ND: not done.

doses ranging from 20-50 mCi followed by transplantation with an overall response rate of 65%. Sixteen patients with bone marrow involvement or unsuccessful marrow harvest were treated with a reduced activity protocol (20 mCi) and had an overall response rate of 58%. In general, responses were better in patients with smaller tumor burden (< 30 cm³) than in those with large tumor masses (>500 cm³). When the overall response rate were compared, 20 mCi ⁹⁰Y-labeled anti-ferritin was as effective as 40 mCi, while myelosuppression was reduced with the lower activity. An update of this trial including 39 patients evaluable for response reported ten complete responses and ten partial responses: nine of the complete responses occurred in patients who had received more than one cycle of treatment.⁷¹ Another trial evaluated the feasibility of combining radio-immunotherapy with high-dose chemotherapy followed by autologous bone marrow transplantation.⁷² Twelve patients received 20 to 30 mCi ⁹⁰Y-labeled antiferritin and high-dose cyclophos-

phamide, carmustine, and etoposide with bone marrow reinfusion. Four patients died early of a transplant-related cause (infections, bleeding and diffuse alveolar damage). Of the remaining eight patients, one achieved a complete response and three had partial responses. A summary is given in Table 4A.

Monoclonal antibodies

Since large amounts of CD30 are expressed on H-RS cells of classical Hodgkin's lymphoma, CD30 is the most interesting antigen for immunotherapy in this disease. Apart from diverse interactions between CD30 and anti-CD30 monoclonal antibodies, targeting this receptor with human antibodies might recruit effector mechanisms including complement-dependent and antibody-dependent cytotoxicity. Currently, clinical investigations are focusing on two anti-CD30 monoclonal antibodies, the humanized SGN-30 monoclonal antibody and the fully human 5F11 monoclonal antibody (Table 4B). SGN-30, a chimeric anti-CD30

monoclonal antibody, has demonstrated antitumor activity in preclinical models of Hodgkin's lymphoma and anaplastic large cell lymphoma. In a first phase I single-dose trial this monoclonal antibody showed minimal toxicity associated with doses of 1-15 mg/kg and antitumor activity was seen in 2/13 patients.⁷³ In a phase I/II dose-escalation study of six weekly i.v. infusions of SGN-30 at doses of 2 to 12 mg/kg per cohort, 24 patients were enrolled. The monoclonal antibody was very well tolerated. Drug-related adverse events have been typically mild and consistent with monoclonal antibody administration.⁷⁴ Of the 21 patients with Hodgkin's lymphoma accrued in the phase I study, four patients had stable disease. Fifteen patients with Hodgkin's lymphoma have been enrolled in a phase II multi-dose study using six weekly i.v. infusions of 6 mg/kg of SGN-30. Of twelve evaluable patients only six disease stabilizations were reported.

MDX-060 is a fully human IgG1κ monoclonal antibody that recognizes CD30 and mediates killing of Hodgkin's lymphoma and anaplastic large cell lymphoma cell lines *in vitro* and in xenograft tumor models. In a phase I/II open-label, dose-escalation study of MDX-060 in patients with relapsed or refractory Hodgkin's lymphoma, anaplastic large cell lymphoma, or other CD30⁺ lymphomas, MDX-060 was administered intravenously at doses of 0.1 to 10 mg/kg weekly for 4 weeks without any dose-limiting toxicities occurring. There were two drug-related serious adverse events (grade 3 rise in liver transaminases, and grade 3 pneumonia/grade 4 acute respiratory distress syndrome). In the currently ongoing phase II trial, larger cohorts are receiving MDX-060 at 10 or 15 mg/kg.⁷⁵ To date, 48 patients, including 40 with Hodgkin's lymphoma, have been treated without significant infusion-related reactions. Objective clinical responses have been observed in three patients with Hodgkin's lymphoma (one complete, two partial). These preliminary results indicate that MDX-060 is well tolerated and has clinical activity.

The anti-CD20 antibody rituximab has demonstrated clinical efficacy in LPHL in which H-RS cells express B-cell antigens such as CD20. In a multicenter phase II trial, 11 patients with refractory Hodgkin's lymphoma with CD20⁺ histology were treated with a standard dose of rituximab (4×375 mg/m², weekly).⁷⁶ Nine patients achieved a complete remission and two patients a partial remission. Ten patients are still in remission with a median response duration of 14+ months (5-19 months). Similar results were seen in another trial involving 22 evaluable patients with recurrent LPHL, among whom there was an overall response rate of 100%.⁷⁷ Rituximab is a less successful

treatment for classical Hodgkin's lymphoma,⁷⁸ which is not surprising taking into account the CD20 expression which is present in only a small proportion of the patients. Twenty-two patients with relapsed Hodgkin's lymphoma receiving 6×375 mg/m² rituximab were evaluable for response. Five of these 22 patients had some kind of response lasting for a median of 7.8 months. Responses occurred irrespective of the CD20 expression on H-RS cells indicating a transient decrease of the lymph nodes due to elimination of CD20-positive B cells.

Clinical trials with radiolabeled antibodies and monoclonal antibody are summarized in Table 4. Despite several monoclonal antibody-based constructs having been investigated in Hodgkin's lymphoma, none has advanced into phase III trials. Radiolabeled antibodies seem to be the most promising immunoconjugates because of the encouraging clinical responses. Since radiolabeled antibodies can be associated with significant hematotoxicity, future treatment strategies should investigate the use of such antibodies combined with autologous SCT in patients with relapsed or refractory Hodgkin's lymphoma.

Native anti-CD30 monoclonal antibodies demonstrated some activity in relapsed Hodgkin's lymphoma patients in phase-I trials. Ongoing clinical studies will show whether naked monoclonal antibodies can have an impact on the treatment of Hodgkin's lymphoma. Rituximab is extremely effective but can only be applied to the limited subgroup of Hodgkin's lymphoma patients with LPHL.

Conclusions

The treatment of choice for patients with early-stage favorable Hodgkin's lymphoma consists of two to four cycles of ABVD, followed by 30 Gy IF-RT. The recommendation for early-stage unfavorable (intermediate) disease includes four to six cycles of ABVD, followed by 30 Gy IF-RT. In contrast, the significance of additional radiotherapy in patients with advanced stage Hodgkin's lymphoma is questionable and six to eight cycles of BEACOPP-escalated are favored. Single HDCT followed by autologous SCT is recommended for patients with Hodgkin's lymphoma in first relapse.

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