Treatment of Hodgkin lymphoma: the past, present, and future

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SUMMARY

Significant advances in the biology and treatment of Hodgkin lymphoma (HL) have been accomplished over the past decades. In a landmark study, DeVita and colleagues showed that half of patients with advanced-stage HL experienced long-term disease-free survival following treatment with a four-drug chemotherapy regimen. Subsequent reports and randomized clinical trials conducted over the past 40 years have defined prognostic categories and refined the treatment options for patients with early-stage and advanced-stage HL. New treatment concepts and regimens have continued to increase the cure rate of HL, while other analyses have documented the acute and long-term morbid and potentially fatal side effects of HL therapy. Increased knowledge of HL biology has been gained, in particular, much has been learnt about the genetic and phenotypic characteristics of malignant cells and the varied oncogenic signaling pathways involved in HL. Continued translational research is needed to improve the long-term survival and to lessen the toxicities associated with therapy. Furthermore, continued clinical-trial involvement by oncologists and patients is imperative to further advance the field of HL.

KEYWORDS: apoptosis, chemotherapy, clinical trials, involved-field radiotherapy

REVIEW CRITERIA

The PubMed and MEDLINE databases were searched for articles published until 1 August 2007. Only articles published in English were considered. The search terms used included "Hodgkin lymphoma" and "Hodgkin's disease" in association with other search terms: "chemotherapy" and "radiation" and "nodular lymphocyte predominant" and "ABVD", "BEACOPP" and "Stanford V" (combined with "growth factor", "treatment toxicity", "randomized", "early stage", "advanced stage", "elderly" and "secondary neoplasia"); "fluorodeoxyglucose-positron emission tomography," and "prognosis". When possible, primary sources have been quoted. Full articles were obtained and references were checked for additional material when appropriate.

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Received 12 July 2007 **Accepted** 3 January 2008 **Published online** 5 August 2008
www.nature.co/clinicalpractice
doi:10.1038/ncponc1186

INTRODUCTION

The majority of patients with Hodgkin lymphoma (HL) can be cured of their disease with contemporary treatment regimens. Major success in the treatment of HL was achieved by radiation therapy and by the development of multiagent polychemotherapy. In the 1960s, DeVita and colleagues pioneered the four-drug combination regimen comprising mustard, Oncovin (vincristine), procarbazine, and prednisone (MOPP) for the treatment of advanced-stage HL.[1] Over the past decades, newer chemotherapy regimens have been developed, leading to a multitude of large randomized clinical trials that have helped refine the treatment options for patients with newly diagnosed HL. In addition, increased insight has been gained into the acute and long-term toxicities of these therapies, and, in particular, how they relate to the incidence of secondary cancers and cardiopulmonary disease. More recently, significant progress has been made towards understanding the biology and translational science of HL.

TRANSLATIONAL SCIENCE OF HODGKIN LYMPHOMA

Significant knowledge of the genetic characteristics and transcriptional alterations of Hodgkin and Reed-Sternberg (H-RS) cells of classical HL (cHL) and lymphocytic and histiocytic (L&H) cells of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) has been gained, including information regarding transforming mechanisms and signaling pathways that contribute to the anti-apoptotic phenotype of H-RS and L&H cells.[2] The origin of the H-RS cells was established when single H-RS cells were analyzed for rearranged immunoglobulin (Ig) variable (VAR) region gene rearrangements. VAR gene rearrangements were found in nearly all cases of cHL, demonstrating that these cells are derived from B cells.[3,4]

Immunophenotypic studies indicated that H-RS cells lack expression of markers characteristic for B-lineage cells. Gene-expression profiling studies of HL cell lines showed global downregulation of

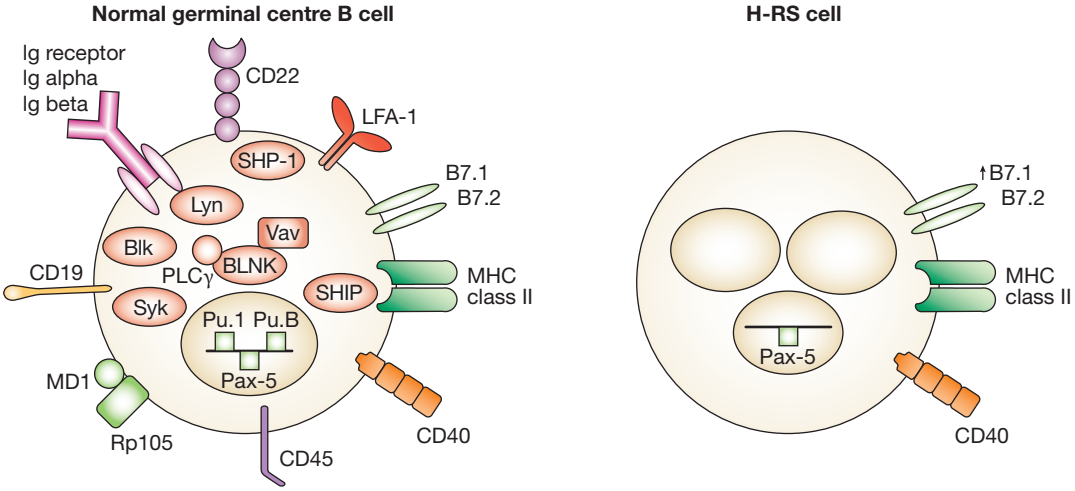

Figure 1 The lost B-cell identity of Hodgkin/Reed-Sternberg (H-RS) cells. A normal germinal center B-cell and H-RS are shown. H-RS are known to be derived from B-cells, although there is significant downregulation of the B-cell immunophenotype on H-RS cells. Varied B-cell transcription factors such as Pu.1 and Bob1 are downregulated and several typical B-cell surface receptors, in particular immunoglobulin, are missing, all contributing to the 'lost' identity of H-RS cells. Adapted with permission from Ralf Kuppers.

the B-cell phenotype in H-RS cells.[5] The downregulation of several B-cell-specific transcription factors (i.e. Oct-2, Bob1, and Pu.1) have been described,[6,7] and this probably contributes to the lost B-cell phenotype of H-RS cells as well as the downregulation of Ig expression (Figure 1). Tumor cells of NLPHL and L&H cells showed an immunophenotype indicating B-cell origin. L&H cells express the general B-cell markers CD20 and CD79a, while expression of the B-cell–specific transcription factors Pax-5, Oct-2, and Bob-1, and Ig is also found.[8] The germinal center B-cell origin had also been confirmed through single-cell microdissection of L&H cells, which found clonal and somatically mutated VAR Ig rearrangements.[4,9,10]

Several transcriptional signaling pathways involved in the anti-apoptotic phenotype of H-RS and L&H cells have been identified. The major inhibitory molecules that prevent downstream caspase 3 activation in H-RS cells are c-FLICE inhibitory protein (c-FLIP)[11,12] and X-linked inhibitor of apoptosis proteins (XIAP),[13] which block the extrinsic and intrinsic apoptotic pathways, respectively. The involvement of these pathways in the pathogenesis of HL indicates that they could be useful potential targets for the treatment of this disease. Many other factors, including multiple cytokine and chemokine interactions, as well as the HL tumor microenvironment,[14] are also involved in the pathogenesis of HL and have been reviewed elsewhere in detail.[2]

EARLY-STAGE DISEASE

Defining early-stage HL: favorable versus unfavorable (intermediate) disease

In Europe, the German Hodgkin Lymphoma Study Group (GHSG) defines clinical stage I–II patients as unfavorable (intermediate) if they present with any of the following four factors: large mediastinal mass (LMM), extranodal disease, elevated erythrocyte sedimentation rate (≥50 without or ≥30 with B symptoms), and/or ≥3 involved nodal regions.[15,16] The European Organisation for Research and Treatment of Cancer (EORTC) criteria differs substituting age ≥50 years in place of the extranodal disease criterion and specifying ≥4 involved regions rather than ≥3, as in the GHSG.[17]

The National Cancer Institute of Canada (NCIC) and the Eastern Cooperative Oncology Group (ECOG) subdivided early-stage HL into risk categories, with 'low risk' being NLPHL and nodular sclerosis histology, age <40 years, erythrocyte sedimentation rate (ESR) <50, and ≤3 disease regions and 'high risk', all other cases with stage I–II disease, except those with bulky disease >10 cm, which are assigned advanced-stage disease.[18] In the GHSG, all stage III and IV patients plus stage IIB patients with LMM or E-lesions (extralymphatic extension of the disease) are included in the 'advanced-stage' group. Certain other trial groups include stage I–II patients with B symptoms and/or bulk >10 cm in the "advanced-stage" prognostic group.

Table 1 Favorable early-stage I–II Hodgkin lymphoma: recent randomized studies.

Trial[a]	Treatment regimens	Number of patients	Outcome	
EORTC H8F[20]		543	5-year RFS	5-year OS
	3 MOPP/ABV + IFRT (36 Gy)		99%	99%
	STLI		80%	95%
			P <0.0001	*P* <0.0186
EORTC H9F[21]		783	4-year EFS	4-year OS
	6 EBVP + IFRT (36 Gy)		88%	98%
	6 EBVP + IFRT (20 Gy)		85%	100%
	6 EBVP (no RT)		69%	98%
			P <0.001	*P* = 0.241
			'No RT' arm closed because of elevated relapse rate	
GHSG HD10[22]	2 ABVD + IFRT (30 Gy)	1,370	Median follow-up 53 months, no survival differences between patients given different number of ABVD cycles or radiation dose (FFTF 91–92% OS 96–97%)	
	2 ABVD + IFRT (20 Gy)			
	4 ABVD + IFRT (30 Gy)			
	4 ABVD + IFRT (20 Gy)			
NCI-C/ECOG[18]		123	5-year EFS	5-year OS
	ABVD 4–6 cycles		87%	97%
	STLI		88%	100%
			P = NS	*P* = NS
GHSG HD13	2 ABVD + 30 Gy IFRT	Ongoing	AV and ABV arm closed September 2006 because of elevated relapse rate	
	2 ABV + 30 Gy IFRT			
	2 AVD + 30 Gy IFRT			
	2 AV + 30 Gy IFRT			

[a]See text for definitions of favorable early stage category. Minimum HL favorable early stage study size 120 patients. Abbreviations: ABVD, doxorubicin, vinblastine, bleomycin, dacarbazine; EBVP, epirubicin, bleomycin, vinblastine, prednisone; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; FFP, freedom from progression; FFTF, freedom from treatment failure; GHSG, German Hodgkin Study Group; Gy, gray; IFRT, involved-field radiation therapy; NCI-C, National Cancer Institute of Canada; NS, not significant; OS, overall survival; RT, radiotherapy; STLI, subtotal nodal irradiation.

Combined-modality treatment of favorable early-stage disease

In most centers or trial groups, patients with stage I–II disease, 'early-stage disease', are treated with combined-modality strategies that comprise both chemotherapy and radiotherapy.[19] Many of the ongoing and recently completed studies of early-stage disease[15–18,20–27] were developed to examine regimens designed to reduce the long-term morbid and potentially fatal side effects of treatment, in particular the development of secondary tumors[28–32] and cardiovascular toxicity,[33–36] without increasing the rate of relapse from HL. These studies evaluated the outcomes of reductions in radiation dose or field size, and tried to determine the optimum chemotherapy regimen, the optimum number of chemotherapy cycles, and the optimum volume and dose of radiation when given in combination with chemotherapy.

Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) is the standard regimen for patients with clinical stage I–II HL. Most centers and groups in the US and in Europe have studied combined-modality treatment, comprising moderate chemotherapy (typically 3–4 cycles of ABVD) and a reduced radiotherapy field of involved-field radiotherapy (IFRT) at a dosage of 20–30 Gy, in early stage, favorable HL (Table 1).[15,17,18,20–22,26] The GHSG HD10 trial was a phase III 2×2 factorial design trial (4 arms) among 1,370 patients with early-stage favorable disease who were randomized to 2 or 4 cycles of ABVD and then IFRT at either 20 Gy or 30 Gy.[22] At a median follow-up of 53 months, there was no difference in the rates of freedom from treatment failure (FFTF) or overall survival (OS) between the two ABVD arms or between the different radiotherapy arms. Continued follow up is important to confirm these preliminary findings, as several of the aforementioned clinical trials examining early-stage disease have been reported only in abstract form.[20–25]

Combined-modality treatment of intermediate early-stage disease

It is generally accepted that patients with intermediate (unfavorable) early-stage HL (I and II with risk factors) are candidates for combined

Table 2 Intermediate early-stage I-II Hodgkin lymphoma: randomized chemotherapy studies.

Trial[a,b]	Treatment regimens	Number of patients	Outcome	
EORTC H6U[114]	3 MOPP + Mantle + 3 MOPP 3 ABVD + Mantle + 3 ABVD	316	10-year FFS 77% 88% $P<0.0001$	10-year OS 87% 87% $P=0.52$
EORTC H7U[17]	6 EBVP + IFRT (36 Gy) 6 MOPP/ABV + IFRT	316	6-year EFS 68% 88% $P<0.001$	6-year OS 79% 87% $P=0.0175$
GHSG HD11[25]	4 ABVD + IFRT (30 Gy) 4 ABVD + IFRT (20 Gy) 4 BEACOPP-baseline + IFRT (30 Gy) 4 BEACOPP-baseline + IFRT (20 Gy)	1,422	Median follow-up 30 months: no differences between ABVD and BEACOPP (FFS 89% and 91%, respectively), or between 20 Gy and 30 Gy IFRT (FFS 91% and 93%, respectively)	
EORTC/GELA H8U[24]	6 MOPP/ABV + IFRT (36 Gy) 4 MOPP/ABV + IFRT (36 Gy) 4 MOPP/ABV + STLI	995	4-year RFS 94% 95% 96% $P=$NS	4-year OS 90% 95% 93% $P=$NS
NCI-C/ECOG[18]	ABVD 4-6 cycles ABVD 2 cycles + STLI	276	5-year EFS 88% 92% $P=0.09$	5-year OS 95% 92% $P=$NS
EORTC H9U[23]	6 ABVD + IFRT (30 Gy) 4 ABVD + IFRT (30 Gy) 4 BEACOPP-baseline + IFRT (30 Gy)	808	4-year EFS 91% 87% 90% $P=$NS	4-year OS 95% 94% 93% $P=$NS
GHSG HD14	4 ABVD + IFRT (30 Gy) 2 BEACOPP-escalated + 2 ABVD + IFRT (30 Gy)	Ongoing	Open	

[a]See text for definitions of intermediate early stage category. [b]Minimum study size 250 patients. Abbreviations: ABVD, doxorubicin, vinblastine, bleomycin, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin (adriamycin), cyclophosphamide, vincristine, procarbazine and prednisone; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; FFS, failure-free survival; FFTF, freedom from treatment failure; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; Gy, gray; IFRT, involved-field radiation therapy; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; NCI-C, National Cancer Institute of Canada; NS, not significant; OS, overall survival; RFS, relapse free survival; STLI, subtotal nodal irradiation.

chemotherapy and radiotherapy.[16–18,23–25] The prognostic impact of a single risk factor, the number of chemotherapy cycles, the dosage of radiation, and whether chemotherapy can be used alone (i.e., no radiation) are subjects of ongoing studies and continuing debates (Table 2). ABVD has been the standard chemotherapy regimen used in combination with IFRT for intermediate early-stage HL. The EORTC H7U study randomized patients to six cycles of epirubicin, bleomycin, vinblastine and prednisone (EBVP) or six cycles of MOPP/ABV, with all patients receiving IFRT. EBVP produced inferior outcomes with a significantly lower 10-year event-free survival (EFS) and OS.[17]

The GHSG HD11 trial in a 2×2 factorial design randomized 1,422 patients to either four cycles of ABVD or four cycles of baseline-BEACOPP (bleomycin, etoposide, doxorubicin (adriamycin), cyclophosphamide, vincristine, procarbazine, prednisone) and IFRT at a dose of either 20 Gy or 30 Gy. After a median observation time of 30 months, there was no difference in failure-free survival (FFS) between the chemotherapy arms or IFRT doses, with 97% OS for all patients.[25] The EORTC H8U study randomized 995 patients to four cycles of MOPP/ABV with subtotal nodal irradiation (STLI), or four cycles of MOPP/ABV with 36 Gy IFRT, or six cycles of MOPP/ABV with 36 Gy. Neither relapse-free survival (94–96%) nor OS (90–93%) differed among the three groups.[24] Another trial randomized patients to four cycles of ABVD, or six cycles of ABVD, or four cycles of baseline-BEACOPP; all patients received 36–40 Gy IFRT. As reported in an abstract, at a median follow-up of 57 months, there were no differences in EFS or OS between the three regimens.[23]

Chemotherapy alone for early-stage HL

Chemotherapy alone represents a treatment option for early-stage HL, especially among patients for whom the risk of acute and/or long-term radiotherapy toxicity is deemed unacceptable.[18,21,24,27,37] A study from India randomized 179 patients in complete remission (CR) following six cycles of ABVD to IFRT or no radiotherapy.[37] The trial included a heterogeneous patient population (stages I–IV; 53% with stage I/II): >80% of the population had mixed cellularity or NLPHL histology, and half of the patients were aged over 15 years. No differences in EFS or OS were detected among the different groups of patients with stage I–II disease. The 8-year EFS of patients treated with chemotherapy alone was 94%, compared with 97% in those who also received IFRT ($P=0.29$), while OS was 98% in the chemotherapy-alone group compared with 100% in the group who received combined modality treatment ($P=0.26$). A multivariate subgroup analysis of all patients showed superior EFS with IFRT in those patients with B-symptoms, bulky disease, age <15 years, and advanced-stage disease. Surprisingly, radiotherapy provided a greater EFS benefit among patients without mediastinal involvement. For OS, the IFRT arm was superior in the patient subgroups with B symptoms, stage III–IV disease, and patients aged <15 years, but not for patients with bulky disease.

The NCI-C/ECOG HD6 trial evaluated 399 HL patients with early stage I–II disease, excluding patients with LMM or bulky disease (>10 cm).[18] Favorable patients were randomized to STLI or 4–6cycles of ABVD (two cycles beyond CR) without radiotherapy, while unfavorable patients were randomized to two cycles of ABVD with STLI or 4–6 total cycles of ABVD alone. With both prognostic groups combined, freedom from progression (FFP) and EFS were superior in patients who received radiation (5-year FFP, 93% versus 87%; $P=0.006$, and EFS, 88% versus 86%; $P=0.06$), while OS was similar (94% and 96%; $P=0.40$). Differences were less apparent when the early-stage subgroups were examined separately (Tables 1 and 2).

The EORTC-GELA H9F trial randomly allocated 783 patients to six cycles of EBVP with 20 Gy IFRT, six cycles of EBVP with 36 Gy IFRT, or six cycles of EBVP without radiation.[21] The arm without radiation was stopped early owing to a high relapse rate. Although, as shown previously with the EORTC H7U data, it is apparent that the EBVP regimen is inferior to ABVD. At a median follow-up of 33 months, there were no differences in OS between the two radiation dosing groups with OS being 98% in all arms (Table 1). Straus and colleagues reported a single institution trial of 152 patients that compared six cycles of ABVD alone with six cycles ABVD and 36 Gy IFRT among patients with stages I–II or IIIA HL.[27] There were no differences in FFS or OS between the treatment groups; however, the sample size of the trial might have limited the ability to detect a small difference.

Recent/ongoing early-stage trial data

The GHSG HD13 was initiated as a 4-arm phase III trial and randomized patients with favorable, early-stage disease to two cycles each of ABVD, AVD, ABV or AV with all arms followed by 30 Gy IFRT. In preliminary analysis, the two non-dacarbazine containing arms, ABV and AV, were closed prematurely because of increased relapse rates. Accrual continues to the ABVD and AVD arms. It seems that dacarbazine is an important therapeutic agent in the treatment of early-stage HL. For early-stage intermediate HL, the GHSG HD14 trial is comparing two courses of intensified BEACOPP followed by two cycles of ABVD with four cycles of ABVD, with patients in both arms receiving 30 Gy IFRT.

Studies by the EORTC and a UK trial examining early-stage HL have incorporated [18F]fluorodeoxyglucose- PET response-adapted therapy into their designs. The ongoing UK trial treats all patients with early-stage disease with three ABVD cycles, followed by PET restaging. PET-negative patients are randomized to 30 Gy IFRT or no radiation, while PET-positive patients receive a fourth ABVD cycle followed by IFRT. The recently initiated EORTC/GELA H10 Intergroup trial is comparing 'standard therapy' to PET-based response-adapted therapy (i.e. PET after two cycles ABVD) for favorable and intermediate group patients with early-stage HL.

ADVANCED-STAGE DISEASE

Initial chemotherapy studies

DeVita and colleagues showed that more than 80% of patients with advanced HL achieved remission and approximately 50% were alive at 5 years following MOPP combination chemotherapy.[1] Other trials studying MOPP showed long-term FFP rates of 36–52% and OS of 50–64%.[1,38,39] Several MOPP variants have been studied including substitution of vinblastine for oncovin (MVPP), which produced comparable remission and OS to MOPP.[40,41] In a randomized trial, the British

National Lymphoma Investigation substituted mustard with chlorambucil (leukeran; LOPP) and compared this regimen with MOPP.[42] The LOPP regimen was less toxic but no significant survival differences were seen. The UK trial also substituted chlorambucil for mustard, developing the chlorambucil, vinblastine, procarbazine, and prednisone regimen (ChlVPP);[43] this regimen seemed comparable to MOPP, although a randomized trial was not performed. In a randomized study, the ECOG compared a carmustine-containing regimen and cyclophosphamide, vinblastine, procarbazine and prednisone (BCVPP) with MOPP.[44] At 5 years, patients who received BCVPP had a significantly higher FFP (50% versus 33%) and OS (83% versus 75%) than patients who received MOPP. In 1975, Bonadonna and colleagues developed the ABVD regimen[45] as a noncross-resistant regimen for patients who had relapsed following MOPP. The Milan group subsequently compared three cycles of MOPP and three cycles ABVD preceding and following extended-field radiotherapy. The results of this study are shown in Table 3.[46]

Hybrid regimens

Investigators in Vancouver[47] and Milan[48] designed two hybrid regimens of MOPP and ABVD. There was no significant difference in OS between the hybrid regimens; however, the hybrid regimens were associated with higher hematologic and nonhematologic toxicities. The Milan group randomized patients to MOPP/ABVD alternating monthly and alternating one-half cycles of MOPP and ABVD.[48] No survival differences were detected among these hybrid regimens, with 67–69% of patients without progression and 72–74% alive at 10 years. The Cancer and Leukemia Group B (CALGB) investigated sequential MOPP-ABV and a MOPP/ABV hybrid in patients with newly diagnosed and first relapsed advanced-stage HL.[49] FFS and OS were significantly better with the hybrid regimen. The EORTC compared two courses of MOPP alternating with two courses of ABVD to a total of eight cycles with MOPP.[50] MOPP/ABVD was associated with significantly higher FFP than MOPP: 60% versus 43%, respectively. The randomized phase III trials showed that ABVD alone was as equally effective as MOPP/ABVD and MOPP-ABV hybrid but less toxic, and all regimens were more effective than MOPP alone (Table 3).[51,52] In addition, ABVD caused less acute toxicity, such as sterility, and few or no secondary acute leukemia/myelodysplastic syndrome (AML/MDS). At present, ABVD is the internationally accepted standard regimen against which all experimental combinations should be tested.

Other chemotherapy regimens

Stanford V, a seven-drug regimen, was developed as a short-duration, reduced-toxicity program. This regimen comprises doxorubicin, vinblastine, mechlorethamine, bleomycin, vincristine, etoposide, and prednisone. Stanford V is given weekly over 12 weeks and consolidative radiotherapy is applied to tumors ≥5 cm.[53] In an Italian multicenter phase III trial, 334 patients were randomized to ABVD, Stanford V, or MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine).[54] The dose intensities varied slightly between the regimens with ABVD at 83%, Stanford V at 81%, and MOPPEBVCAD at 73%. Of note, radiotherapy was administered to fewer patients allocated to Stanford V (66%) than was the case in the original Stanford program (>90%). The 5-year FFS and progression-free survival (PFS) rates achieved with Stanford V were inferior to those achieved with ABVD and MOPPEBVCAD, while ABVD produced better OS than Stanford V ($P<0.04$). The North American Intergroup phase III trial, which randomly allocated patients to either Stanford V or ABVD, has completed accrual and the follow-up of patient events continues.

In a UK randomized trial, the abbreviated 11-week chemotherapy program, VAPEC-B (vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin), was compared with the hybrid ChlVPP/EVA (etoposide, vincristine, and doxorubicin) regimen, with radiation applied to all patients with initial bulk or residual disease.[55] The study was stopped after 26 months owing to a threefold increase in the rate of progression after VAPEC-B. The UK trial subsequently randomized 807 patients over 42 months to ABVD or two multidrug regimens (MDRs), ChlVPP alternating with PABIOE (prednisolone, doxorubicin, bleomycin, vincristine, and etoposide) or ChlVPP/EVA. The 3-year EFS and OS rates at a median follow-up of 52 months were similar for ABVD and the MDRs (Table 3). Of note, EFS and OS for patients aged greater than 45 years were significantly better with ABVD that with the MDRs.

Regimens increasing dose intensity and dose density

In 1992, the GHSG designed the BEACOPP regimen, which comprised similar drugs to the

Table 3 Advanced-stage Hodgkin lymphoma: ABVD and BEACOPP randomized trials.

Trial	Treatment regimens	Number of patients	Outcome	
Milan[46]		232	7-year EFS	7-year OS
	ABVD 6 cycles + STLI		81%	77%
	MOPP 6 cycles + STLI		63%	68%
			$P<0.002$	$P<0.03$
CALGB[51]		361	5-year FFS	5-year OS
	ABVD 6–8 cycles		61%	73%
	MOPP 6–8 cycles		50%	66%
	MOPP/ABVD 12 cycles		65%	75%
			$P=0.03$	$P=$NS
CALGB[52]		856	5-year FFS	5-year OS
	ABVD 8–10 cycles		63%	82%
	MOPP-ABV 8–10 cycles		66%	81%
			$P=$NS	$P=$NS
GHSG HD9[56]		1,201	5-year FFTF	5-year OS
	COPP/ABVD × 8 cycles + IFRT[a]		69%	83%
	BEACOPP-baseline × 8 cycles + IFRT[a]		76%	88%
	BEACOPP-escalated × 8 cycles + IFRT[a]		87%	91%
			$P<0.002$	$P<0.002$
United Kingdom[79]		807	3-year EFS	3-year OS
	ABVD 6 cycles + 30–35 Gy[a]		75%	90%
	MDR (ChlVPP/PABIOE or		75%	88%
	ChlVPP/EVA) 6 cycles + 30–35 Gy[a]		$P=$NS	$P=$NS
Italy[54]		355	5-year PFS	5-year OS
	ABVD × 6 cycles + IFRT (to 62% of pts)[a]		85%	90%
	MOPPEBVCAD × 6 cycles + IFRT (to 66%)[a]		94%	89%
	Stanford V × 3 cycles + IFRT (to 47%)[a]		73%	82%
			$P<0.01$	$P<0.04$
GHSG HD12[63]		1,502	4-year FFTF	4-year OS
	BEACOPP-escalated × 8 cycles		86%	88%
	BEACOPP × 4 escalated and 4 baseline cycles		91%	91%
	BEACOPP + 30 Gy IFRT		91%	95%
	BEACOPP without RT		88%	95%
			$P=$NS	$P=$NS
EORTC 20012	For patients IPS 4–7 only: ABVD × 8 cycles BEACOPP × 4 escalated and 4 baseline cycles	Approx. 250 (ongoing)	Open—targeted sample size 550	
GHSG HD15	BEACOPP-escalated × 8 cycles +/– 30 Gy IFRT[a] BEACOPP-escalated × 6 cycles +/– 30 Gy IFRT[a] BEACOPP-14 × 8 cycles +/– 30 Gy IFRT[a]	1,500	All patients: FFTF 86% and OS 95% at median follow-up of 21 months	

[a]Radiation delivered to sites of initial bulk disease or partial remission after chemotherapy. For GHSG HD15, radiation was given only to patients with disease >2.5 cm following chemotherapy that was PET positive. Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin (adriamycin), cyclophosphamide, vincristine, procarbazine, prednisone; CALGB, Cancer and Leukemia Group B; ChlVPP/PABIOE chlorambucil, vinblastine, procarbazine, prednisone/prednisolone, doxorubicin, bleomycin, vincristine, etoposide; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; EFS, event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; EVA, etoposide, vincristine, and doxorubicin; FFS, failure-free survival; FFTF, freedom-from-treatment failure; GHSG, German Hodgkin Study Group; IFRT, involved-field radiation therapy; IPS, international prognostic score; MDR, multidrug regimen; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; MOPP-ABV, mechlorethamine, vincristine, procarbazine, prednisone-doxorubicin, bleomycin, vinblastine; MOPPEBVCAD, mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine; NS, not significant; OS, overall survival; PFS, progression-free survival; STLI, subtotal nodal irradiation.

COPP/ABVD regimen but included etoposide instead of vinblastine and dacarbazine. The GHSG designed the HD9 trial, which compared COPP/ABVD, standard-BEACOPP and escalated-BEACOPP in 1,201 patients with advanced-stage HL.[56] Radiotherapy was prescribed for bulky disease at diagnosis (30 Gy) or for residual disease (40 Gy) after eight cycles of chemotherapy; about two thirds of patients received consolidative radiotherapy. FFTF was significantly higher in the escalated-BEACOPP arm than in the COPP/ABVD arm (Table 3).[56] The OS difference between COPP/ABVD and escalated-BEACOPP was also significant ($P<0.002$). Escalated BEACOPP was associated with greater hematological toxicity including a higher number of platelet and red blood cell

transfusions. Second malignancies, including AML were reported; 9, 4 and 1 AML/MDS were reported for the BEACOPP-escalated, BEACOPP-baseline, COPP/ABVD regimens, respectively. The total rate of secondary neoplasias was highest in the COPP/ABVD arm with 4.2% compared with 3.4% in the BEACOPP-escalated arm.

Their experiences with the high efficacy but also increased toxicity of the escalated-BEACOPP principal (given in 21-day intervals) led the GHSG to consider a BEACOPP variant, in which the drug dosage and duration of treatment, determined according to the effective dose model of Hasenclever,[56] would accomplish the same efficacy, but with a reduced toxicity, especially with regard to the rate of AML/MDS. The result was the construction of a time-intensified baseline-BEACOPP regimen given in 14-day intervals with granulocyte-colony stimulating factors support for advanced HL (BEACOPP-14). In a multicenter pilot study including 32 centers, the GHSG tested the feasibility, toxicity, and efficacy pf this regimen in 99 patients with stage IIB and LMM/extranodal disease (23%) or advanced-stage disease (77%).[57] At a median 34-month follow-up, the estimated FFTF was 90% and the OS was 97%. Hematotoxicity was moderate, with 75% experiencing WHO grade 3 or 4 leukopenia, 23% thrombocytopenia and 65% anemia. The GHSG HD15 trial, which randomized 1,500 patients to eight cycles of escalated-BEACOPP, six cycles of escalated-BEACOPP or eight cycles of BEACOPP-14 and included a second randomization within each arm to either additional epoetin or not, has recently completed accrual.

Role of radiotherapy in advanced-stage Hodgkin lymphoma

A number of phase III trials investigated the role of consolidative radiotherapy after primary chemotherapy; the vast majority has shown no EFS or OS advantage associated with radiotherapy.[37,58–62] The GHSG compared the efficacy of low-dose (20 Gy) IFRT with two cycles of further chemotherapy consolidation in 288 patients in CR after initial chemotherapy with COPP/ABVD.[59] There was no significant difference in FFP or OS rates between the two treatment arms. In the GHSG HD12 trial, 1,661 patients were randomized to eight cycles of intensified-BEACOPP or four cycles each of escalated-BEACOPP/baseline-BEACOPP, with a second randomization for initial bulky and/or residual disease to IFRT or no radiotherapy.[63] Reported in abstract form, the overall FFTF was 86% and OS was 92%, with a toxicity similar to that described in the HD9 trial, after a median observation time of 4 years.[63] There was no difference between the two chemotherapy regimens or between the IFRT arm and the no radiotherapy arm with regard to outcome. (Table 3).

In the EORTC 20884 trial, patients with advanced-stage HL achieving CR after 6–8 cycles of a MOPP-ABV hybrid were randomly assigned to receive either IFRT or no further treatment.[58,61] Those with a PR after six cycles were treated with IFRT. Of 739 initial patients, 333 patients with a CR were randomized, and 227 patients with a PR received IFRT. The 8-year EFS and OS rates were 77% and 85%, respectively, for patients without radiotherapy and 73% and 78% in the group assigned to IFRT. The 8-year EFS and OS were 76% and 84%, respectively, for patients with a PR who received IFRT. Furthermore, a meta-analysis showed that combined-modality therapy in advanced-stage HL prevented progression and/or relapse but had no effect on OS and was associated with an increased incidence of secondary malignancies.[64]

SPECIFIC HODGKIN LYMPHOMA TOPICS

PET to predict outcome in HL

So far, the most important prognostic tool in advanced-stage HL has been the International Prognostic Score. An international research effort led by Hasenclever and Diehl[65] involving more than 5,000 patients identified seven adverse prognostic factors for advanced HL. PET has become a standard imaging modality complementing CT scans in the management of HL.[66,67] In advanced-stage HL, treatment intensification could benefit the proportion of patients who respond poorly to therapy or who relapse. The optimum timing and selection of patients for treatment intensification is crucial. Several early studies examining mixed populations of patients with non-Hodgkin's lymphoma or HL showed that early PET is a strong indicator of survival.[66–68]

Hutchings and colleagues reported a prospective study of PET after two cycles of ABVD (PET-2) followed by continued ABVD treatment for 77 patients with HL: 79% had negative PET-2, while 21% had positive PET-2.[69] An early PET response was significantly predictive of survival; the 2-year PFS for PET-2 negative patients was 96% compared with 0% for PET-2 positive patients. In addition, there was no appreciable difference between the prognostic value of PET after two cycles compared with four cycles of chemotherapy

or at the end of therapy. Gallamini and colleagues reported on the prognostic importance of 'early PET' after two of six planned chemotherapy cycles (ABVD in 96%) among 108 patients with advanced-stage HL.[70] The 2-year PFS rate for patients with a negative PET-2 compared with a positive PET-2 were 96% and 6%, respectively ($P<0.01$). Zinzani and colleagues also reported results for PET-2 among 40 patients newly diagnosed with advanced-stage HL who were treated with six ABVD cycles.[71] Among the PET-2 negative group, no relapses were seen at 1 year following the end of treatment, while all PET-positive patients relapsed or had primary refractory disease. Early PET assessment has also been studied with BEACOPP chemotherapy. Dann and colleagues studied early PET in two different HL risk groups following two cycles of BEACOPP.[72] Early positive PET was used to decrease or intensify therapy based on PET-2 outcome. Recently published data from an Italian/Danish multicenter study show that PET-2 has prognostic value independent of risk stratification by the International Prognostic Score.[73]

These data support the concept of early risk assessment using PET imaging in the study of newly diagnosed HL. However, several issues regarding PET response-adapted therapy need to be considered, including consistent definitions of PET-negativity versus positivity and strategy of trial design with appropriate control arms. The GHSG HD18 trial, examining advanced HL, is using early PET following 2 cycles of escalated-BEACOPP, while trials being conducted in Europe and the US are examining PET-response-adapted treatment following initial ABVD therapy.

Dose intensity and ABVD

A high dose intensity of MOPP-based therapy (i.e. full chemotherapy doses and no treatment delays) is associated with significant improvements in overall and disease-free survival.[74,75] The GHSG showed that the overall degree of hematologic toxicity was an independent predictor of survival in HL; severe leukopenia during treatment was associated with superior OS.[76] Among the 4,626 patients studied, severe leukopenia was more frequent in women, yet women had a similar infection rate and an improved FFTF compared with men. Furthermore, severe leukopenia during chemotherapy in both men and women was associated with improved FFTF by multivariate analysis ($P<0.001$).

The importance of ABVD dose intensity in determining remission and survival is not defined. Landgren and colleagues reported that OS was significantly improved in elderly patients who received a greater than 65% dose intensity of ABVD.[77] Myelosuppression, especially neutropenia, is common during ABVD treatment.[27,54,78,79] Treatment strategies include either dose reduction or treatment delay, and/or use of G-CSF to maintain dose intensity, although data to support this recommendation (i.e. G-CSF with ABVD) are lacking.[80,81] Three retrospective analyses have reported that ABVD can be safely administered at a very high dose intensity.[82–84] Furthermore, it has been shown that ABVD can be administered in full doses safely and effectively and without delay (>99% dose intensity) and without G-CSF, irrespective of the treatment-day granulocyte count.[85] This treatment strategy needs to be tested further and confirmed in prospective multicenter trials.

Prognosis and treatment of NLPHL

The aforementioned recommendations of combined-modality therapy for early-stage HL might not apply to patients with the NLPHL subtype in favorable stage IA who do not have risk factors. These patients can be treated by lymph-node excision followed by a 'wait and see' strategy or with 20–30 Gy IFRT alone.[86,87] The GHSG showed CR rates of 98% after extended-field radiotherapy, 100% after IFRT, and 95% after combined-modality treatment.[86] Furthermore, FFTF at 24 months was 100%, 92%, and 97%, respectively, while OS for patients in all three treatment arms was 99%.

NLPHL at all stages has been regarded as an entity with a more indolent course, characterized by more frequent late recurrences than cHL.[86,87] A comprehensive analysis of 394 cases of NLPHL (among a total patients population of 8,298 patients), showed that patients with NLPHL or cHL had similar overall relapse rates (7.9% versus 8.1%), but that patients with NLPHL had significantly fewer 'early' relapses (0.76% versus 3.2%; $P=0.02$).[88] At a median observation of 41–48 months, the FFTFs for NLPHL and cHL were 88% and 82%, respectively ($P=0.0093$), and the rates of OS were 96% and 92% ($P=0.016$). Of note, a slightly increased rate of secondary non-Hodgkin's lymphoma, typically diffuse large B-cell lymphoma, was seen with NLPHL compared with cHL.

Currently, it is recommended that newly diagnosed NLPHL at any stage is treated with regimens similar to those used for cHL. Rituximab

has shown encouraging activity as a single-agent in relapsed CD20+ NLPHL with remission rates of 86–100% reported in two studies, although remissions were typically not durable.[89,90] Rituximab should be studied in combination with induction chemotherapy and/or radiotherapy in NLPHL.

Hodgkin lymphoma in the elderly

In population-based studies, the proportion of patients with HL who are older than 60 years of age ranges between 20% and 40%.[77,91] The proportion of elderly patients participating in prospective trials, however, is considerably lower.[92] Treatment for all stages in the elderly should be given with curative intent, although careful monitoring for treatment-related toxicity during therapy is warranted (i.e. frequent cardiac and pulmonary testing). The BEACOPP regimen is too toxic for patients over the age of 60.[93] ABVD may be given to select patients,[77] although bleomycin and/or adriamycin toxicity might be prohibitive. Support with hematopoietic growth factors should be considered, although attention should be given to the potential accentuation of bleomycin-associated lung toxicity with concurrent use of G-CSF.[94]

The majority of data regarding the treatment of elderly patients with HL stems from retrospective analyses. Treatment often needs to be individualized for patients with impairment of the lungs, liver, heart, and/or kidneys. Single drugs that cause organ-specific toxicities, such as bleomycin (pulmonary), may need to be omitted from the chemotherapy regimen, replaced, or modified in dose. There is retrospective data that indicates bleomycin might not be needed to maintain efficacy of ABVD treatment, although this finding needs to be confirmed in a randomized study.[94,95] In addition, alternative regimens such as BCVPP and ChlVPP are active and associated with less toxicity and, as such, may be considered for elderly patients with HL, although inclusion of anthracycline therapy may be important.[96] Kolstad and colleagues recently reported encouraging results with the use of CHOP chemotherapy for HL patients over 60 years of age (median age 71 years); the 3-year rates of PFS and OS were 72% and 67%, respectively, for patients with advanced-stage disease. Furthermore, the corresponding 3-year PFS and OS rates for patients with early-stage disease were 82% and 91%.[97] Other international studies examining specific regimens for the elderly are ongoing, such as the SHIELD project, which is examining VEPEMB chemotherapy in a phase II clinical trial.[98] Further clinical trials enrolling elderly patients with HL are needed.

TREATMENT TOXICITY IN HL

The most common acute side effect caused by chemotherapy for HL is myelosuppression with associated cytopenias, which contribute to an increased risk of infection. Pulmonary toxicity can be caused by bleomycin and/or radiotherapy. The incidence of bleomycin-associated lung toxicity in the literature is variable, although rates as high as 46% have been reported.[82,99] Risk factors for bleomycin-associated lung toxicity include older age, cumulative bleomycin dose, renal insufficiency, pulmonary radiation, underlying lung disease, and history of tobacco use.[82,99] Case reports[100,101] and preclinical data[83,102] have suggested that G-CSF increases the incidence of bleomycin-associated lung toxicity. A recent report showed a significantly increased incidence of bleomycin-associated lung toxicity when G-CSF was used during bleomycin-containing chemotherapy for HL (26% versus 9% without G-CSF, $P=0.014$) with an associated mortality rate of 24%.[94]

The most common serious long-term toxicities associated with HL therapy include: secondary cancers such as MDS/AML and solid tumors,[28–32] gonadal dysfunction including sterility,[84,103] hypothyroidism, typically related to radiotherapy,[104] and cardiovascular disease including increased rates of ischemic heart disease and stroke.[33–36] The 20–25 year cumulative actuarial risk (adjusting for background incidence) of secondary cancers among patients with HL is 24–28%, with the highest overall risk seen 15–20 years after treatment.[28,30,32] The strongest predisposing factor is radiation,[38,41,43] although some secondary cancers are seen after chemotherapy alone.[29] The most common second malignancy is breast cancer, although the rates for many other tumors including lung and gastrointestinal are also significantly increased.[28–30,32] Furthermore, the risk of secondary cancer is significant for all patient ages, and the risks have not declined over time: the rate of second tumors during the 1960s and 1970s is similar to that seen during the 1980s and 1990s.[38,41] It should be noted that much of the data regarding long-term radiation-related side effects are derived from patient groups treated with older radiotherapy methods and more-extensive treatment fields than those used today. The potential diminution of long-term toxicity with contemporary radiation techniques is not known.

NOVEL TREATMENT AGENTS

Multiple novel therapeutic options are being explored in HL including antibody therapy and small-molecule inhibitors. Anti-CD30 antibodies currently being studied include the fully humanized antibodies MDX-060 and MDX-1401 (Medarex, Princeton, NJ) and the chimeric antibody SGN-35 (Seattle Genetics, Bothell, WA). Rituximab has activity in NLPHL[86,87] and is also being studied in cHL with the concept of depleting surrounding/infiltrating normal B-cells.[105] Other targeted treatments include the anti–IL-13 antibody CAT-354 (Cambridge Antibody Technology, Cambridge, UK), the anti-CD40 antibody CHIR-12, (Chiron Oncology, Emeryville, CA),[12] the anti-RANKL antibody AMG162 (Amgen, Thousand Oaks, CA), and proapoptotic TRAIL using anti–TRAIL-R1 antibodies (Human Genome Sciences. Rockville, MD).

Modulation of intracellular pathways important for H-RS and L&H cells are being investigated, including novel compounds that target the Iκ-Kinase-IκB-NFκB cascade.[106–108] The proteasome inhibitor, bortezomib has limited activity as a single-agent in relapsed/refractory HL,[109] but the potential synergistic activity of combination regimens that include bortezomib should be explored.[110,111] Histone deacetylase inhibitors are being investigated in part because they interfere with activation of NFκB and mediate apoptosis through cFLIP inhibition, induction of p21, and production of reactive oxygen species;[112] while XIAP is being targeted with antisense oligonucleotides. Finally, cellular strategies directed against EBV-encoded proteins are being tested, as are therapeutics that target the varied pathways downstream of LMP2a, including mTOR, Ras, and Akt.[113]

CONCLUSIONS

Many advances have been made in the treatment of HL, and more than 70–80% of all patients diagnosed with HL are cured of their disease. Continued clinical and translational research is warranted, in order to improve the survival of patients with HL as well as to lessen the toxicities associated with HL-related therapy. Ongoing and planned studies are using the principles of response-adapted (e.g. early PET) and/or risk-adapted therapy (e.g. genotypic analysis) to tailor treatments to individual patients. In order to continue to advance the field of HL treatment, it is critical that international collaborative efforts continue and that oncologists offer all patients with HL the opportunity to participate in clinical trials.

KEY POINTS

- Preclinical translational studies have demonstrated that the Reed-Sternberg cells of classical Hodgkin lymphoma (HL) and the lymphocytic and histiocytic cells of nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) are derived from B-cell origins and that several anti-apoptotic signaling pathways are involved in the survival of these malignant cells
- Patients with stage I–II, (i.e. 'early stage') HL should usually be treated with combined-modality therapy comprising chemotherapy (ABVD) followed by involved-field radiotherapy
- Chemotherapy alone is a treatment option for early-stage HL, especially where the risks of acute and/or long-term radiotherapy are deemed unacceptable
- At present, ABVD is the internationally accepted standard regimen for advanced-stage HL, and is the regimen against which all experimental combinations should be tested; other chemotherapy programs such as Stanford V, and the more-intensive regimen, BEACOPP, represent treatment options for HL and data from randomized trials continues to be analyzed
- Acute treatment-related toxicities (i.e. bleomycin-associated lung toxicity) and chronic treatment-related toxicities (secondary cancers, cardiovascular disease) should be considered when therapy choices are made, especially when treating HL in elderly patients
- For advancement in the outcome of HL, it is imperative that international collaborative efforts continue and that oncologists offer all patients with HL the opportunity to participate in clinical trials

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Competing interests
The authors declared no competing interests.

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