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Combined modality treatment for early-stage Hodgkin's lymphoma: the GHSG experience

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The prognosis of patients has substantially improved over the last decades. Currently, approximately 80% of all patients remain disease free 5 years after treatment.[1] On the basis of clinical staging and risk factors as listed in Table 1 patients with Hodgkin lymphoma (HL) are usually classified into early favourable stages (CS 1-2 without risk factors), early-unfavorable stages (CS I-II with risk factors) or advanced stages. Here, we report on the experience of the GHSG and others in the treatment of early favourable and unfavourable HL.

Treatment-first line treatment

Early-stage favourable Hodgkin's lymphoma

Until recently, early-stage favourable Hodgkin's lymphoma was treated with extended-field radiatio (EF-RT). Due to the high incidence of relapse (25-30%) after EF-RT alone[2] and fatal long-term effects such as secondary malignancies, cardiac toxicity and pulmonary dysfunction, new treatment strategies were developed combining involved-field radiotherapy (IF-RT) with short-duration chemotherapy.

The most prominent, recently finished or ongoing international studies for early-stage favourable Hodgkin lymphoma are summarised in Table 2. The Southwest Oncology Group (SWOG) demonstrated that patients treated with combined modality treatment, consisting of three cycles of doxorubicin and vinblastine followed by subtotal lymphoid irradiation, had a significant better outcome in terms of freedom from treatment failure (FFTF) than those patients receiving subtotal lymphoid irradiation alone.[3] Studies from Milan and Stanford revealed that subtotal lymphoid irradiation can be effectively replaced by IF-RT after short-duration chemotherapy, such as ABVD (adriamycin, bleomycin, vinblastine, dacarbacine) or Stanford V (mechlorethamine, adriamycin, vinblastine, vincristine, bleomycin, etoposide, prednisone), without any change in progression-free and overall survival.[4,5] The EORTC and GELA could also demonstrate that combined modality treatment consisting of either six courses of EBVP (H7F trial) or three cycles of MOPP (mechlorethamine, vincristine, procarbacine, prednisone)/AVB (H8F trial) followed by IF-RT yields a significantly better event-free survival than subtotal nodal radiotherapy alone.[6,7] A combined modality approach was established in the HD7 trial by the GHSG. In this trial two cycles of ABVD plus extensive-field radiotherapy (EF-RT) were shown to be superior to EF-RT alone in terms of FFTF.[8] Thus two cycles of ABVD followed by 30 Gy IF radiotherapy is currently being regarded as standard of care by most groups.

Further improvement of treatment, with respect to the excellent long-term survival rates, seems difficult. Thus, strategies to reduce dose and toxicity of treatment while maintaining efficacy are being pursued. In the HD10 trial of the GHSG, a possible reduction of chemotherapy from four to two cycles of ABVD and/or IF-RT from 30 Gy to 20 Gy was evaluated. After a median observation time of two years, FFTF and overall survival rates were 96,6% and 98,5% without any significant differences between treatment arms.[9] A longer follow-up is needed to finally answer the questions of the best radiation dose, i.e. 20 or 30 Gy. The aim of the ongoing GHSG HD13 study for early stages is to omit the presumably less effective drugs, bleomycin and dacarbazine, from the ABVD regime. Patients are thus randomised between two cycles of ABVD, ABV, ABD or AV followed by 30 Gy IF-RT. Whether chemotherapy alone is sufficient to control disease, has yet to be determined and is a matter of ongoing trials.

Early-stage unfavourable disease

Similar to early-stage favourable HL, those patients with early-stage unfavourable disease generally receive combined modality treatment. However, best chemotherapy, optimal number of cycles and radiotherapy regime are not yet clearly defined and there is an ongoing desire to

Table 1. Definition of treatment groups according to the EORTC/GELA and GHSG.

Treatment Groups	*EORTC/GELA*	*GHSG*
Early-stage favourable	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors
Early-stage unfavourable (intermediate)	CS I-II with ≥1 risk factors (supradiaphragmatic)	CS I, CSIIA ≥1 risk factors; CS IIB with C/D but without A/B
Advanced stage	CS III-IV	CS IIB with A/B; 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

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

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

Trial	*Therapy regimen*	*# Pts.*	*Outcome*	*References*
SWOG #9133	A. 3 (dox.+vinbl.) + STLI (36-40 Gy) B. STLI (36-40 Gy)	165 161	94% (FFTF);98% (SV); 81% (FFTF); 96% (SV); [3 years]	Press *et al.*, 2001
Milan 1990-97	A. 4 ABVD + STLI B. 4 ABVD + IF RT	65 68	97 % (FFP); 93% (SV) 97 % (FFP); 93% (SV); [5 years]	Bonadonna *et al.*, 2004
Stanford V (CSI-IIA)	8 weeks of Stanford V + modified IF RT (30 Gy)	65	94.6% (FFP); 96.6% (SV) [16 months; estimated for 3 years]	Horning et al., 1999
EORTC/ GELA H7F	A. 6 EBVP + IF RT (36 Gy) B. STNI	168 165	90 % (RFS); 98% (SV) 81 % (RFS); 95% (SV); [5 years]	Carde et al., 1997
EORTC/ GELA H8F	A. 3 MOPP/ABV + IF RT (36 Gy) B. STNI	271 272	99 % (RFS); 99% (SV) 80 % (RFS); 95% (SV); [4 years]	Hagenbeek et al., 2000
EORTC/ GELA H9F	A. 6 EBVP + IF RT (36 Gy) B. 6 EBVP + IF RT (20 Gy) C. 6 EBVP	783	87 % (EFS); 98% (SV) 84 % (EFS); 98% (SV); [4 years] C closed because of high relapse rate;	Nordijk et al., 2005
GHSG HD7	A. EF RT 30 Gy (40 Gy IF) B. 2 ABVD + EF RT 30 Gy (40 Gy IF)	305 312	75% (FFTF); 94% (SV); 91% (FFTF); 94% (SV); [5 years]	Sieber et al., 2002
GHSG HD10	A. 4 ABVD + IF RT (30Gy) B. 4 ABVD + IF RT (20Gy) C. 2 ABVD + IF RT (30Gy) D. 2 ABVD + IF RT (20Gy)	847	interim analysis [2 years] all pts: 96.6%(FFTF) 98.5% (SV)	Diehl et al., 2005
GHSG HD13	A. 2 ABVD + IF RT (30Gy) B. 2 ABV + IF RT (30Gy) C. 2 AVD + IF RT (30Gy) D. 2 AV + IF RT (30Gy)		Ongoing trial	

Abbreviations: 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 of treatment failure; RFS, relapse free survival; FFP, freedom from progression; EFS, event-free suvival; SV, overall survival.

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

Trial	*Therapy regimen*	*# Pts.*	*Outcome*	*Ref.*
EORTC/	A.6 MOPP/ABV + IF RT (36 Gy)	335	94% (RFS); 90% (SV)	Ferme et al., 2000
GELA H8U	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 COPP+ABVD + EF RT (30 Gy) + Bulk (10Gy)	532	86% (FFTF); 91% (SV)	Engert et al., 2003
	B. 2 COPP+ABVD + IF RT (30 Gy) + Bulk (10Gy)	532	84% (FFTF); 92% (SV); [5 years]	
SWOG/ 6	A. 6 ABVD + IF RT (36 Gy) to bulk		Ongoing trial	
ECOG #249	(>5 cm)			
	B. 12 weeks Stanford V + IF RT (36 Gy) to bulk (>5 cm)			
EORTC/	A. 6 ABVD + IF RT	808	94 % (EFS); 96 % (SV)	Nordijk et al., 2005
GELA H9U	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]	Klimm et al., 2005
	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)			

Abbreviations: 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 suvival; SV, overall survival.

optimise therapy in this risk group.

Several trials have shown that the reduction of field size to IF radiotherapy does not compromise the efficacy of treatment: a cooperative study comparing six cycles of MOPP sandwiched around 40 Gy of radiotherapy applied either in IF or EF, indicated no difference in terms of disease-free survival or OS.[10] In their H8U trial, the EORTC randomised 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 + STLI. There was no difference between the arms in terms of response rates, failure-free survival or overall survival.[11] The largest trial investigating radiotherapy reduction was conducted by the GHSG: in the HD8 trial, patients were randomised to two alternating cycles of COPP (cyclophosphamide, vincristine, procarbacine, prednisone)/ABVD followed by 30 Gy radiotherapy in either EF (arm A) or IF (arm B) technique. Final results at five years did not disclose significant differences between the two arms in terms of FFTF and overall survival; however, more toxicity was reported in the patients who were treated with EF-RT[12] (Table 3).

Efforts have also been made to improve the efficacy of chemotherapy by altering drugs and schedules as well as the number of cycles. Alternation or hybridisation of a MOPP-like regimen with ABVD did not produce better outcomes when compared with ABVD alone.[13]

Despite the excellent initial remission rates obtained with ABVD and radiotherapy, approximately 15% of patients in early unfavourable stage relapse within five years and about another 5% have primary progressive disease. Because of these disappointing outcome rates more intensive chemotherapy regimes, which were originally developed for the treatment of advanced stages, have been evaluated for the treatment of early unfavourable stage (Table 3): in their ongoing intergroup trial #2496, the ECOG and SWOG assess whether the Stanford V regimen (12 weeks) is superior to six cycles of ABVD. In another approach, the HD11 trial (GHSG) and the H9U trial (EORTC-GELA) compared four cycles of ABVD and four cycles of BEACOPP-baseline (bleomycin, etoposide, adriamycin, cyclophosphamide, vinristine, procarbazine, prednisone). The resently presented H9U trial additionally

analysed wether six cycles of ABVD are more affective than four cycles of ABVD. After a median follow-up of four years no significant difference was observed between treatment arms of the H9U trial.[14] Interim analysis of the GHSG HD11 trial at two years did not show any significant difference between ABVD and BEACOPP baseline.[15] The GHSG decided to evaluate further treatment intensification in the ongoing HD 14 trial. Patients are currently being randomised to two cycles of BEACOPP-escalated plus two cycles of ABVD or four cycles of ABVD followed by 30 Gy IF-RT.

A combined modality treatment consisting of four courses of ABVD followed by 30 Gy IF-RT remains standard treatment for patients with early-stage unfavourable HL until a more efficient chemotherapy regimen is established.

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