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ORIGINAL REPORT

Relapsed Hodgkin Lymphoma in Older Patients: A Comprehensive Analysis From the German Hodgkin Study Group

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ABSTRACT

Purpose
Progression or relapse of Hodgkin lymphoma (HL) is common among older patients. However, prognosis and effects of second-line treatment are thus far unknown.

Patients and Methods
We investigated second-line treatment and survival in older patients with progressive or relapsed HL. Patients treated within German Hodgkin Study Group first-line studies between 1993 and 2007 were screened for refractory disease or relapse (RR-HL). Patients with RR-HL age ≥ 60 years at first-line treatment were included in this analysis.

Results
We identified 105 patients (median age, 66 years); 28%, 31%, and 41% had progressive disease, early relapse, or late relapse, respectively. Second-line treatment strategies included intensified salvage regimens (22%), conventional polychemotherapy and/or salvage-radiotherapy with curative intent (42%), and palliative approaches (31%). Median overall survival (OS) for the entire cohort was 12 months; OS at 3 years was 31% (95% CI, 22% to 40%). A prognostic score with risk factors (RFs) of early relapse, clinical stage III/IV, and anemia identified patients with favorable and unfavorable prognosis (≤ one RF: 3-year OS, 59%; 95% CI, 44% to 74%; ≥ two RFs: 3-year OS, 9%; 95% CI, 1% to 18%). In low-risk patients, the impact of therapy on survival was significant in favor of the conventional polychemotherapy/salvage radiotherapy approach. In high-risk patients, OS was low overall and did not differ significantly among treatment strategies.

Conclusion
OS in older patients with RR-HL can be predicted using a simple prognostic score. Poor outcome in high-risk patients cannot be overcome by any of the applied treatment strategies. Our results might help to guide treatment decisions and evaluate new compounds in these patients.

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INTRODUCTION

Approximately one in four patients with first diagnosis of Hodgkin lymphoma (HL) is age ≥ 60 years.[1,2] Because of demographic changes, the proportion of older patients with HL will increase in the coming decades.[3] Despite dramatic advances in the treatment of younger patients with HL, prognosis for older patients with HL remains poor.[4,5] Compared with younger patients, older patients have more aggressive disease, more unfavorable prognostic features, and, most importantly, suffer from substantially increased toxicity of chemotherapy and radiotherapy (RT), frequently resulting in insufficient dose-intensity.[4,6-9] Consequently, refractory and progressive disease or relapse of HL (RR-HL) is common among older patients, and there are indications that RR-HL is the most common cause of death in this population.[6,10,11] In younger patients with RR-HL, intensified salvage chemotherapy followed by high-dose chemotherapy (HDCT) and autologous stem-cell transplantation (ASCT) is the generally accepted standard treatment, resulting in disease-free survival in approximately 50%; results depend on risk factors (RFs) such as disease stage and time from first diagnosis.[12-15] In contrast, there is no standard treatment for older patients with RR-HL. Thus far, the results of different approaches such as intensified

chemotherapy, conventional chemotherapy (poly-CT), salvage RT, or palliative treatment are largely unknown.

From the German Hodgkin Study Group (GHSG) database, we identified older patients with RR-HL after first-line treatment within GHSG trials conducted between 1993 and 2007. We updated information on second-line treatment, analyzed safety and efficacy of treatment strategies, and determined prognostic factors for survival in this population.

PATIENTS AND METHODS

Patients

We identified patients treated within GHSG trials between 1993 and 2007 with documented RR-HL and updated information on disease remission status, treatment of RR-HL, and survival of all patients age $\geq$ 60 years at random assignment in first-line trials (ie, older patients). Details on first-line trials and treatment at first diagnosis have been described previously[8,10,16-22] and are summarized in Appendix Table A1 (online only).

Study Objectives, Definition of End Points, and Statistical Methods

Progression (refractory HL) and relapse were defined as described previously[23]; any relapse $\geq$ 12 months after end of first-line therapy was considered late relapse. Disease stage at RR-HL was defined according to the GHSG risk stratification based on Ann Arbor stage and RFs, as described previously.[8]

The aim of this study was to investigate RR-HL in older patients and determine feasibility and efficacy of different treatment strategies in these patients. Primary end point was overall survival (OS), defined as time from diagnosis of RR-HL until death resulting from any cause, censored at the date of last information (including information obtained from population registries) and analyzed according to the Kaplan-Meier method. Prognostic value of various factors for OS was tested using univariate Cox regression analyses.

Second-line therapies were classified into three groups: one, intensified salvage regimens aiming at HDCT consolidation; two, conventional poly-CT and/or salvage RT; and three, palliative approaches including single-agent chemotherapy or best supportive care. To account for an expected imbalance of RFs within the three treatment groups, a comparison of treatment groups with regard to OS was performed, adjusting for the risk profile of patients in a multivariate Cox regression model.

Because of the retrospective nature of this analysis, information on the numerous univariately significant RFs was incomplete in individual patients. Accordingly, the sample size for a multivariate analysis was markedly reduced. We therefore decided not to develop a new prognostic score within this patient cohort, which would have represented only a subgroup of patients. Instead, we referred to the established four-level prognostic score for RR-HL developed by Josting et al.[23] This score is defined by presence of the following RFs: early relapse ($<$ 12 months from end of first-line treatment), clinical stage III or IV at relapse, and anemia (hemoglobin $<$ 10.5 g/dL in women and $<$ 12.0 g/dL in men). Patients were considered low or high risk if they presented with $\leq$ one or $>$ one of these risk factors, respectively.

Standardized mortality ratios (SMRs) were calculated by dividing the observed number of deaths by the expected number of deaths, obtained using reference data from German death registries (years 2008 to 2010), adjusted for age and sex. CIs for SMRs were determined using χ^2 distribution.

Demographics and disease characteristics were summarized using descriptive statistics; exact CIs were used when appropriate. Statistical analyses were performed using SAS software (version 9.3 for Microsoft Windows; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

RR-HL was documented in 843 patients, of whom 115 were older patients. Ten of the 115 older patients had received extended-field RT only without chemotherapy as first-line treatment and were therefore analyzed separately (results listed in Appendix Table A2, online only), resulting in 105 evaluable patients; 38% of these had not completed first-line treatment as planned, mostly because of toxicity or progressive lymphoma.

At diagnosis of RR-HL, median age in the older group was 66 years; there were slightly more men, and mixed cellularity was the predominant histologic subtype. More than half of the patients had progression or early relapse (28% and 31%, respectively), and the majority had clinically advanced stage disease at progression/relapse. Prognostic score according to Josting et al[23] could be calculated for 86 patients (82%; in 15, one of the three factors was missing, but risk group was clearly definable by the two nonmissing factors) and was $\leq$ 1 in 50% and $>$ 1 in 50%. Patient and disease characteristics are summarized in Table 1.

Second-Line Treatment

In the first group, 23 patients (22%) received intensified salvage regimens such as DHAP (dexamethasone, high-dose cytarabine, and cisplatin), mini-BEAM (carmustine, etoposide, cytarabine, and melphalan), or others as reinduction therapy before consolidating HDCT and ASCT. However, HDCT and ASCT were finally conducted in only a minority (five of 23) of the patients in this group. In the second group, 44 patients (42%) received conventional poly-CT such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or comparable first-line regimens and/or salvage RT, defined as RT with curative intent. In the third group, 33 patients (31%) were treated with palliative approaches only. The remaining five patients could not be classified into one of the three groups, because detailed information on second-line treatment was not available. Details on treatment approaches to RR-HL in the older patients are listed in Table 2. Details on second-line treatment are listed in Appendix Table A3 (online only).

With regard to treatment modality, the majority of patients (58%) received CT only; 11% were treated with RT only, and 13% received both CT and RT; 15% of patients did not receive any CT or RT; information on treatment modality was not available in 3% of patients.

Of 101 patients with available information, 38 (36%) responded to second-line treatment with complete response (CR) or unconfirmed CR (CRu). Rates differed between treatment groups, with 30%, 59%, and 12% of CRs/CRus occurring after treatment with intensified salvage regimens, poly-CT and/or salvage RT, and palliative treatment approaches, respectively.

Survival and Causes of Death

With a median observation time of 72 months after diagnosis of RR-HL, 86% of all evaluable patients had died at the time of data collection. Most frequent causes of death were progressive HL (59%), treatment toxicity (9%), and secondary malignancies (6%). The lowest proportion of deaths resulting from progressive HL was observed in the subgroup treated with conventional poly-CT and/or salvage RT.

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	All Evaluable Patients (N = 105)		Second-Line Treatment: Intensified Treatment (n = 23)		Second-Line Treatment: Poly-CT/Salvage RT (n = 44)		Second-Line Treatment: Palliative Approaches (n = 33)	
	No.	%	No.	%	No.	%	No.	%
Age at first diagnosis, years								
Median	66		63		67		67	
Range	60-75		60-73		60-74		61-75	
Age at RR-HL, years								
Median	68		65		69		68	
Range	61-77		61-77		61-77		62-77	
Sex								
Male	56	53	15	65	24	55	13	39
Female	49	47	8	35	20	46	20	61
First diagnosis								
Histologic subtype								
Mixed cellularity	35 of 81	43	7 of 18	39	19 of 34	56	8 of 26	31
Nodular sclerosis	33 of 81	41	9 of 18	50	13 of 34	38	11 of 26	42
Lymphocyte rich	1 of 81	1					1 of 26	4
Lymphocyte predominant	3 of 81	4	1 of 18	6			2 of 26	8
Other/not classified	9 of 81	11	1 of 18	6	2 of 34	6	4 of 26	15
Clinical stage								
I-II	46	44	8	35	26	59	9	27
III-IV	59	56	15	65	18	41	24	73
B symptoms	56	53	13	57	21	48	18	55
GHSG stage								
Early	44	42	7	30	26	59	8	24
Advanced	61	58	16	70	18	41	25	76
RR-HL diagnosis								
Clinical stage								
I-II	50 of 96	52	9 of 22	41	27 of 43	63	11 of 26	42
III-IV	46 of 96	48	13 of 22	59	16 of 43	37	15 of 26	58
B symptoms	29 of 76	38	6 of 19	32	13 of 36	36	9 of 18	50
Type of event								
Refractory HL (PD)	29	28	10	44	6	14	11	33
Early relapse	33	31	8	35	13	30	11	33
Late relapse	43	41	5	22	25	57	11	33
Anemia	32 of 72	44	10 of 17	59	12 of 36	33	9 of 17	53
Prognostic score								
≤ 1	43 of 86	50	5 of 19	26	28 of 40	70	8 of 23	35
> 1	43 of 86	50	14 of 19	74	12 of 40	30	15 of 23	65

NOTE. Five patients could not be allocated to one of three treatment groups.
Abbreviations: GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; PD, progressive disease; poly-CT, polychemotherapy; RR, relapsed/refractory Hodgkin lymphoma; RT, radiotherapy.

Treatment-related mortality was highest in the subgroup receiving intensified regimens (Table 3).

Median OS for all evaluable patients was 12 months (95% CI, 8 to 19 months; Figs 1A to 1D). The SMR in comparison with a reference population with similar distributions of age and sex was 20.9 (95% CI, 16.8 to 25.7).

Prognostic Factors for OS

In univariate Cox regression analyses of candidate prognostic factors, several significant factors for OS were identified, including time from first-line therapy ($P < .001$), anemia ($P < .001$), advanced stage at initial diagnosis ($P < .01$), and clinical stage III/IV at diagnosis of RR-HL ($P = .03$). Nonsignificant factors included sex, incomplete first-line therapy, comorbidity, age at relapse, study generation, and first-line treatment (ABVD-like *v* BEACOPP-like). Detailed results on univariate Cox regression analyses are listed in Table 4.

Importantly, all single factors included in the four-level prognostic score by Josting et al,[23] as well as the score itself (dichotomized as low and high risk), had a significant impact on OS (Figs 1A to 1D). Median OS was 45 (95% CI, 27 to 59 months) and 9 months (95% CI, 6 to 12 months) and SMR was 9.3 (95% CI, 6.3 to 13.4) and 48.8 (95% CI, 35.2 to 66.0) in the low- and high-risk groups, respectively.

Impact of Treatment Approach and Prognostic Score on OS

Median OS was 10 (95% CI, 6 to 14), 41 (95% CI, 25 to 48), and 7 months (95% CI, 4 to 9 months) for patients receiving intensified salvage regimens, poly-CT and/or salvage RT, and palliative treatment

Table 2. Second-Line Treatment Modality and Strategy

Treatment	All Evaluable Patients (N = 105) No.	%
Treatment modality		
CT	61	58
RT	11	11
CT and RT	14	13
No CT or RT	16	15
Unknown	3	3
Treatment strategy		
Intensified treatment		
Total	23	22
DHAP/IVE/ICE	13	
Dexa-BEAM	5	
DHAP + BEAM + PBSCT	5	
Poly-CT/salvage RT		
Total	44	42
Poly-CT		
COPP-ABVD	11	
BEACOPP	10	
Other regimens	13	
Salvage RT	10	
Palliative approaches		
Total	33	31
Gemcitabine	8	
Other mono-CT	7	
Palliative RT	2	
Best supportive care	16	
Unknown	5	5

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEAM, carmustine, etoposide, cytarabine, and melphalan; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CT, chemotherapy; dexa-BEAM, dexamethasone, carmustine, etoposide, cytarabine, and melphalan; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; IVE, ifosfamide, vinorelbin, and etoposide; poly-CT, polychemotherapy; RT, radiotherapy.

Table 3. Survival and Causes of Death in All Patients and According to Treatment Strategy

Cause of Death	All Patients (N = 105) No.	%	Second-Line Treatment: Intensified Treatment (n = 23) No.	%	Poly-CT/ Salvage RT (n = 44) No.	%	Palliative Approaches (n = 33) No.	%
HL	62	59	16	70	18	41	25	76
Acute toxicity	9	9	3	13	3	7	3	9
Secondary malignancy	6	6			2	5	3	9
Infection/sepsis	2	2			2	5		
Cardiovascular	1	1			1	2		
Other reasons	6	6	1	4	4	9	1	3
Unclear	3	3	2	9	1	2		
Total deaths	90	86	22	96	31	71	32	97

Abbreviations: HL, Hodgkin lymphoma; poly-CT, polychemotherapy; RT, radiotherapy.

approaches, respectively. However, frequency of most of the identified RFs differed significantly among the three treatment groups; patients who received either intensified or palliative approaches had more advanced disease and unfavorable risk profiles compared with patients receiving poly-CT and/or salvage RT (Table 1). Regarding prognostic score, 30% of patients receiving poly-CT and/or salvage RT were considered high risk, whereas this was the case for 74% and 65% of patients receiving intensified or palliative treatment, respectively.

To distinguish between effects of treatment and risk profile, we performed a multivariate analysis, including both the Josting et al[23] score groups (high *v* low risk) and second-line treatment groups (intensive reinduction and palliative treatment *v* poly-CT and/or salvage RT). In this model (including 82 patients with sufficient documentation), both risk group and treatment group had significant impact on OS, with hazard ratios of 3.17 (95% CI, 1.75 to 5.75; $P < .001$), 2.51 (95% CI, 1.27 to 4.98, $P = .008$), and 3.25 (95% CI, 1.69 to 6.27; $P < .001$) for high-risk patients, patients treated with intensified regimens, and patients treated with palliative approaches, respectively. Thus, superiority of the poly-CT and/or salvage RT approach could be established even with adjustment for the risk profile of patients.

To assess the interaction of risk group and treatment strategy, OS of the different treatment groups was compared within the subgroups of high- and low-risk patients (Figs 1C and 1D). Within the low-risk subgroup, OS was significantly better in those who received poly-CT and/or salvage RT compared with those who received either intensified or palliative treatment ($P < .001$); median OS was 61 versus 6 and 9 months, and SMR was 5.6 versus 63.8 and 26.5, respectively. In the high-risk subgroup, median OS was short overall, and no difference between the treatment groups could be detected.

Characteristics of Survivors

Fifteen of the analyzed patients were alive at the time of data collection, which was 13 to 79 months after their first progression/relapse of HL. Only one of these patients had a prognostic score > 1, and all except two had suffered late relapse. The majority of the surviving patients had early-stage disease at first diagnosis as well as at RR-HL and had been treated with conventional poly-CT and/or salvage RT; only one patient each received palliative or intensified second-line treatment. All survivors achieved an objective response after second-line treatment (14 CRs/CRus, one partial response); no other relapses were documented for any of these patients. Detailed information on survivors is listed in Appendix Table A4 (online only).

DISCUSSION

Despite advances in the treatment of HL, management of older patients remains a clinical challenge. This is especially true for patients with RR- HL. We therefore analyzed the GHSG database for characteristics, treatment, and survival of older patients with RR-HL. The key findings of this first, to our knowledge, comprehensive analysis in this group of patients are as follows: First, older patients with RR-HL have a median OS of only 12 months and > 20-fold risk of death compared with a German reference population with comparable distributions of sex and age. Second, OS can be predicted by a simple score[23] using early relapse, clinical stage III or IV at relapse, and anemia as RFs, dividing the cohort into high- and low-risk groups with

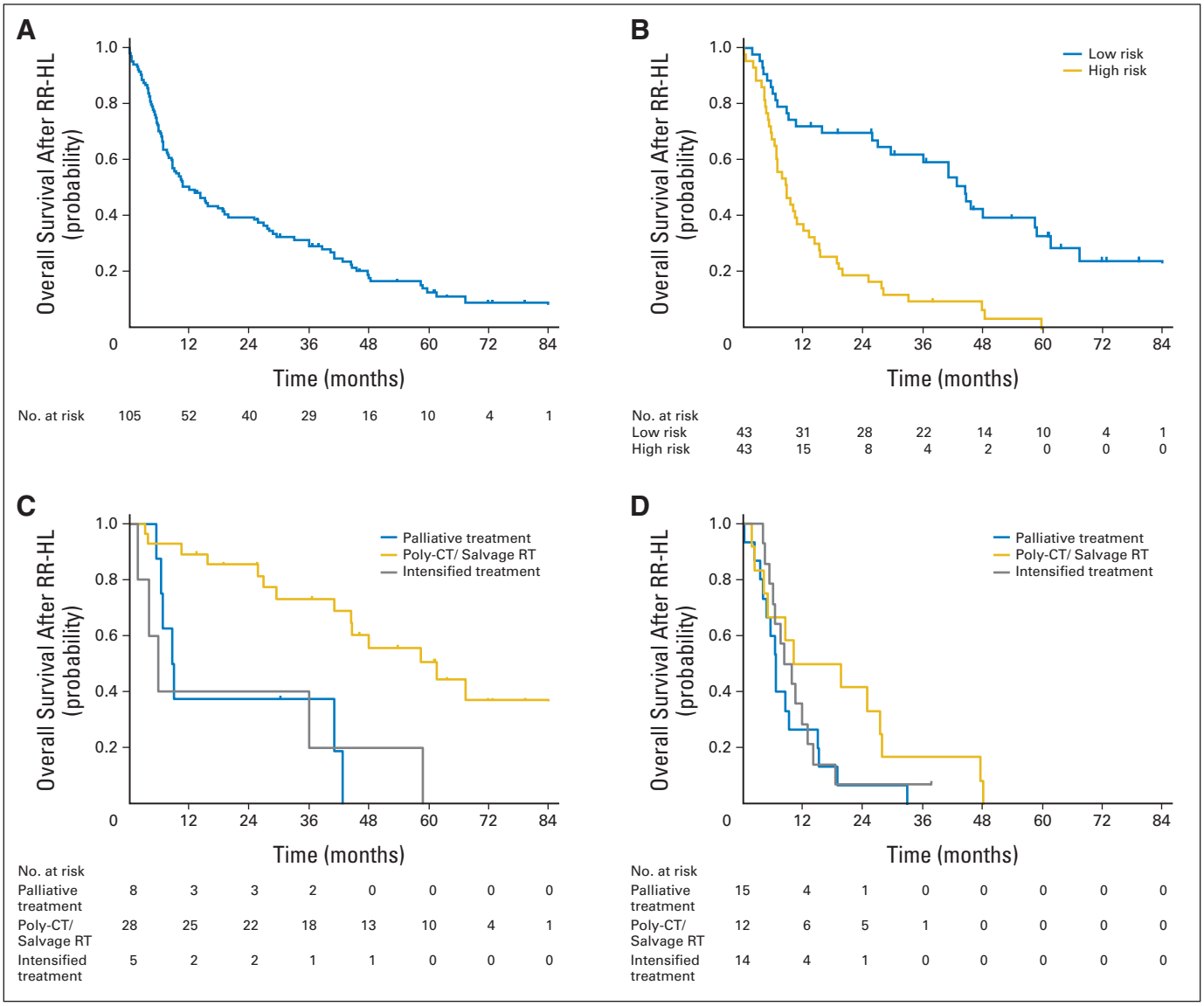

Fig 1. Kaplan-Meier plots of overall survival (OS) in (A) all evaluable patients (median OS, 12 months; 95% CI, 8 to 19 months; 3-year OS, 31%; 95% CI, 22% to 40%), (B) all evaluable patients according to risk group (high-risk patients: 3-year OS, 11%; 95% CI, 1% to 22%; low-risk patients: 3-year OS, 57%; 95% CI, 40% to 73%), (C) low-risk patients according to treatment (intensified treatment: 3-year OS, 20%; 95% CI, 0% to 55%; polychemotherapy [poly-CT]/salvage radiotherapy [RT]: 3-year OS, 71%; 95% CI, 53% to 89%; could not be estimated for patients receiving palliative treatment), and (D) high-risk patients according to treatment. RR-HL, relapsed/refractory Hodgkin lymphoma.

median OS of 9 and 45 months, respectively. Third, in low-risk patients (score ≤ 1), conventional poly-CT and/or salvage RT as second-line treatment results in significantly longer survival compared with intensified and palliative approaches. In high-risk patients, survival does not differ significantly among the three treatment groups. In our analysis, neither high- nor low-risk patients benefitted from intensified treatment aimed at HDCT and ASCT.

A large number of trials and retrospective analyses have been performed in younger patients with RR-HL.[12-15] However, no trial or large systematic analysis of RR-HL in older patients has been published thus far. We found poor survival in this cohort of patients to be the result not only of progressive HL but of excessive treatment-related mortality as well, which was high in all three treatment groups. Even palliative chemotherapy led to 9% deaths resulting from toxicity, reflecting relevant toxicity in this patient cohort not deemed eligible for poly-CT with curative intent. Our findings are even more surprising because we analyzed only patients enrolled onto first-line trials of the GHSG. This group likely represents a selection of relatively non-frail older patients. Therefore, the toxicity observed in our study is likely to be underestimated and would be higher in a nonselected population of older patients with RR-HL.

Although median OS was short in our analysis, individual survival varied substantially. The prognostic factors of time to relapse, tumor burden, and anemia previously established for younger patients with relapsed disease proved to be valuable in older patients as well.[23] Patients with $\leq$ one of these factors (low risk) could achieve long-term survival, particularly those treated with conventional poly-CT and/or RT. We observed the best outcome with this

Table 4. Univariate Cox Regression Analyses of Candidate Prognostic Factors for OS

Factor	No. of Nonmissing Observations	HR	95% CI	*P*
Age at random assignment, years	105	1.02	0.97 to 1.07	.5
Male sex	105	1.09	0.72 to 1.65	.7
Initial diagnosis				
Advanced stage*	105	1.83	1.19 to 2.83	.006
Clinical stage III/IV	105	1.91	1.24 to 2.93	.003
B symptoms	105	1.55	1.02 to 2.36	.04
Histologic subtype (MC *v* other)	81	0.46	0.28 to 0.77	.003
First-line therapy				
Study generation†	88	NA	NA	.2
Type of first-line therapy (BEACOPP-like *v* ABVD-like)	105	1.44	0.95 to 2.19	.09
Incomplete first-line therapy	105	1.07	0.69 to 1.64	.8
RR-HL diagnosis				
Age at RR-HL diagnosis, years	105	0.99	0.94 to 1.03	.5
Comorbidity	105	0.73	0.47 to 1.11	.1
Karnofsky status	44	0.96	0.93 to 0.98	.002
Anemia‡§	72	2.83	1.66 to 4.83	< .001
Time from first-line therapy, months	105	0.97	0.96 to 0.99	< .001
Early relapse‡‖	105	2.80	1.77 to 4.42	< .001
Clinical stage III/IV‡	96	1.66	1.06 to 2.61	.03
B symptoms	76	1.95	1.17 to 3.25	.01
Extranodal disease	76	1.92	1.12 to 3.29	.02
≥ Three nodal areas	74	1.80	1.04 to 3.11	.04
Elevated ESR	67	1.49	0.86 to 2.57	.2
High risk¶	86	3.64	2.17 to 6.11	< .001

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HR, hazard ratio; MC, mixed cellularity; NA, not applicable; OS, overall survival; RR, relapsed/refractory Hodgkin lymphoma.

*According to GHSG definition.

†1993 to 1998 versus 1998 to 2003 versus trials for older patients from 2004 to 2007; early favorable-stage patients excluded because they were not included in any trials for older patients.

‡Factor included in prognostic score.

§Hemoglobin < 10.5 g/dL in women or < 12.0 g/dL in men.

‖< 12 months from end of first-line treatment.

¶According to prognostic score by Josting et al[23] (> one risk factor).

treatment approach compared with both intensified treatment and palliative approaches. This held true despite considerable toxicity observed with poly-CT with curative intent in this cohort. Therefore, the main challenge remains not only identifying patients who are likely to respond to this treatment (ie, the low-risk patients in our study) but also assessing patients for frailty and vulnerability.[24] Several risk scores predicting treatment-related toxicity have been developed.[25,26] However, these tools have not been validated in older patients with HL thus far, and further research is needed to evaluate vulnerability or frailty scores before they can be used to guide individual treatment decisions.[9,24]

In contrast to the low-risk patients in our study, patients with ≥ one RF (high risk) had poor OS regardless of treatment strategy. Even intensified treatment aimed at HDCT was not able to overcome poor prognosis in this group of patients. This result challenges the use of intensive salvage regimens in older patients even if they are deemed eligible for a more aggressive treatment approach. Obviously, this conclusion is not in line with the results of HDCT as standard treatment for younger patients with RR-HL.[12-15] Use of HDCT in relapsed HL is based on two randomized trials showing superiority of intensified treatment with HDCT and ASCT over conventional salvage therapy.[12,13] However, both studies excluded older patients; the British National Lymphoma Investigation (BNLI) trial included patients age ≤ 40 years,[13] and the GHSG HDR1 trial did not include patients age > 60 years.[12]

Nonetheless, our results should be interpreted with caution because only five of the 23 patients treated with intensified salvage regimens aimed at HDCT finally completed HDCT and ASCT. Therapy was not concluded in the remaining 18 of 23 patients, mainly because of HL progression or intolerable toxicity, even though these patients were relatively young and deemed eligible for HDCT. Because this was a retrospective analysis, we cannot exclude inappropriate allocation to the HDCT approach. In contrast to our findings, a recent analysis of 15 older patients who underwent HDCT and ASCT for RR-HL in a single institution reported favorable results.[27] Importantly, only patients who had completed HDCT and ASCT were included in this retrospective analysis, and the authors therefore suspected influence of referral bias.[27] Our analysis was devoid of this bias, and we did not observe a relevant benefit from intensified treatment for any risk group. Therefore, our results might more closely reflect the actual efficacy of this aggressive treatment strategy in older patients with RR-HL. However, before finally judging the value of HDCT in this patient cohort, our results should be validated in patient cohorts from other cooperative groups.

One important limitation is the retrospective nature of this analysis resulting in heterogeneity of patients with regard to patient characteristics and choice of salvage therapy. In addition, only a limited number of patients had complete data on all RFs identified in the univariate analysis. Taken together, this prevented us from establishing a specific risk score for older patients with RR-HL. However, the established score for RR-HL published by Josting et al[23] proved to be valuable in older patients as well.

In summary, older patients with RR-HL have poor outcome that can be predicted using a simple prognostic score. For low-risk patients, conventional poly-CT and/or RT are valuable treatment options with limited toxicity and potential for long-term survival. In high-risk patients, none of the treatment strategies, including aggressive reinduction and HDCT, were able to overcome the poor prognosis. Novel targeted drugs as brentuximab vedotin[28] should also be evaluated in older high-risk patients with RR-HL and patients who cannot tolerate conventional cytotoxic treatment. Unfortunately, even the recently licensed novel drug brentuximab vedotin has only been investigated in patients after ASCT[29]; thus, the results are not applicable to the majority of older patients with RR-HL, and evidence is based only on the thus far uncontrolled findings.[28,30]

In conclusion, our results might help in planning studies for novel agents and developing new treatment strategies in older patients with RR-HL. Moreover, the risk score might also be used in clinical routines to support patients and physicians during a shared decision-making process in life-threatening situations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are

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Collection and assembly of data: All authors
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Appendix

Table A1. Trials and Treatment at First Diagnosis

Trial	Years	Treatment Protocols	Age Limit (years)	Qualified Patients Included	Qualified Patients Age ≥ 60 Years Included	Identified Older Patients With RR-HL	Reference
GHSG early favorable stages							
HD7	1993-1998	Arm A: 30-Gy EFRT/40-Gy IFRT; arm B: 2ABVD + 30-Gy EFRT/40-Gy IFRT	16 to 75	627	63	12	Engert et al[19]
HD10	1998-2003	Arm A: 4ABVD + 30-Gy IFRT; arm B: 4ABVD + 20-Gy IFRT; arm C: 2ABVD + 30-Gy IFRT; arm D: 2ABVD + 20-Gy IFRT	16 to 75	1,190	139	15	Engert et al[21]
GHSG early unfavorable stages							
HD8	1993-1998	Arm A: 2COPP/ABVD + 30-Gy EFRT; arm B: 2COPP/ABVD + 30-Gy IFRT	16 to 75	1,064	98	11	Engert et al[18]
HD11	1998-2003	Arm A: 4ABVD + 30-Gy IFRT; arm B: 4ABVD + 20-Gy IFRT; arm C: 4BEACOPP baseline + 30-Gy IFRT; arm D: 4BEACOPP baseline + 20-Gy IFRT	16 to 75	1395	101	12	Eich et al[17]
GHSG advanced stages							
HD9	1993-1998	Arm A: 4COPP/ABVD ± RT; arm B: 8BEACOPP baseline ± RT; arm C: 8BEACOPP escalated ± RT	16 to 65	1,196	64	14	Engert et al[20]
HD12	1998-2003	Arm A: 8BEACOPP escalated + 30-Gy RT on bulk and residual lesions; arm B: 8BEACOPP escalated; arm C: 4BEACOPP escalated + 4BEACOPP baseline + 30-Gy RT on bulk and residual lesions; arm D: 4BEACOPP escalated + 4BEACOPP baseline	16 to 65	1,574	100	9	Borchmann et al[16]
GHSG trials for older patients							
HD9 elderly	1993-1998	Arm A: 4COPP/ABVD ± RT; arm B: 8BEACOPP baseline ± RT	66 to 75	72	72	16	Ballova et al[10]
BACOPP	2004-2005	6-8BACOPP ± RT	60 to 75	60	60	12	Halbsguth et al[22]
PVAG	2004-2007	6-8PVAG ± RT	60 to 75	57	57	14	Böll et al[8]

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BACOPP, bleomycin, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; EFRT, extended-field radiation therapy; GHSG, German Hodgkin Study Group; IFRT, involved-field radiation therapy; PVAG, prednisone, vinblastine, doxorubicin, and gemcitabine; RR-HL, relapsed/refractory Hodgkin lymphoma; RT, radiotherapy.

Table A2. Patients With RT Only As First-Line Treatment

Age at First Diagnosis (years)	Age at RR-HL Diagnosis (years)	Sex	Type of Event	Risk Group	Second-Line Treatment	Further Treatment	Cause of Death	OS (months)
66	66	Male	Progression	Low	20-Gy IFRT	COPP/ABVD	Acute toxicity	37
60	65	Male	Late relapse	Low	BEACOPP baseline		Acute toxicity	5
62	62	Male	Early relapse	High	CyMEP		Acute toxicity	6
65	69	Male	Late relapse	High	COPP/ABVD		Cardiovascular	5
65	65	Female	Progression	High	COPP/ABVD		Cardiovascular	31
65	66	Female	Early relapse	Low	COPP/ABVD		Acute toxicity	7
64	65	Male	Early relapse	High	BEACOPP	Gemcitabine, 40-Gy RT, CEP	HL	56
60	67	Male	Late relapse	Low	ABVD		Alive	45
75	78	Female	Late relapse	Low	CHOP		HL	1
74	75	Male	Late relapse	High	COPP/ABVD		Respiratory	8

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEP, lomustine, etoposide, and prednimustine; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CyMEP, cyclophosphamide, methotrexate, etoposide, prednisone; HL, Hodgkin lymphoma; IFRT, involved-field radiation therapy; OS, overall survival; RR-HL, relapsed/refractory Hodgkin lymphoma; RT, radiotherapy.

Table A3. Details on Second-Line Treatment

CT	RT
Treatment group unknown	
None	No information on dose
Yes (unknown)	None
Unknown	None
Unknown	None
Unknown	None
Intensified treatment	
Dexa-BEAM 1×	Palliative
Dexa-BEAM 2×	Mediastinum 20 Gy
Dexa-BEAM 2×	None
DHAP	None
DHAP	None
DHAP 4×	None
DHAP 2×	None
DHAP 2×	None
DHAP 2×	None
DHAP 2×	None
DHAP 2× + BEAM + autoPBSCT	None
DHAP 2× + BEAM + autoPBSCT	None
DHAP 2× + 4× GemVap	None
DHAP 2× + HD + BEAM + PBSCT	None
DHAP 2×, HD CTX, HD MTX + Vcr	Extended RT
DHAP 4×	None
DHAP 4× + high-dose-BEAM + aPBCT	None
DHAP 6×	None
Dexa-BEAM 2×	None
Dexa-BEAM 1×	None
HD MTX, VP 16, BEAM + PBSCT, DHAP	None
ICE rituximab 1×	None
IVE	None
Poly-CT/salvage RT	
ABVD 1× + BEACOPP 3×	None
COPP 3× + BEACOPP 5×	None
ABVD 3×, COPP 3×	40 Gy
COPP 4×	None
BEACOPP escalated 4×	30-Gy IFRT
BEACOPP 6× (fifth/sixth cycle 75%)	None
Gemcitabine + dexa 9× + CEVD 2×	Infradiaphragmatic 50 Gy
ABVD-IMEP/BEACOPP 3×	None
ABVD/COPP 1×	None
ABVD 3×	None
ABVD 4×	Iliac and inguinal 33.8 Gy
ABVD 4×	30-Gy IFRT
ABVD 4×	None
ABVD 6×	None
ABVD 6×	None
ABVD 2× + etoposide/prednisone 2× + PHAD + navelbine	None
BACOPP 4×	40 Gy
BEACOPP 6×	None
BEACOPP 6×	None
BEACOPP 8×	None
BEACOPP 3×	None
BEACOPP escalated 1×	None
CEP 1×	None
CEP 4×	None
CEP 8×	None
CEVD 2×	None
CEVD 4×	None
CEVD 4×	None
CEVD 4×	None

(continued on following page)

Table A3. Details on Second-Line Treatment (continued)

CT	RT
CH LVPP	None
COPP 2×	None
COPP-ABVD 2×	Mantle field RT
COPP-ABVD 2×	Palliative
Gemcitabine	60-Gy IFRT
Gemcitabine	36-44 Gy on residual lesions
None	40-Gy IFRT
R-COP 6×	None
None	40-Gy IFRT
None	40-Gy IFRT
None	Mediastinum
None	Cervical + epipharynx 32 Gy
None	36-Gy IFRT
None	Inverted Y
None	cerv./supraclav. 30 Gy
Palliative approaches	
Bendamustin	None
Bleomycin + vincristine	None
Dexa	None
Gemcitabine	None
Gemcitabine + caelyx	None
Gemcitabine + dexa	None
Gemcitabine + prednisone	None
Gemcitabine	None
Gemcitabine/dexa	None
Gemcitabine/dexa	None
Gemcitabine/ribomustin/navelbine 4×	None
Vinblastine, CVP, ixoten	None
Vinblastine/prednisolone	None
Vinblastine	None
Vinorelbine	No information on dose
None	
None	
None	RT spine
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	None
None	Palliative

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEAM, carmustine, etoposide, cytarabine, and melphalan; CEP, lomustine, etoposide, and prednimustine; CEVD, lomustine, etoposide, vindesine, and dexamethasone; CH, cyclophosphamide, doxorubicine; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CT, chemotherapy; CTX, dexa, dexamethasone; CVP, cyclophosphamide, vincristin, prednisone; dexa-BEAM, dexamethasone, carmustine, etoposide, cytarabine, and melphalan; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; GemVap, gemcitabine, asparaginase, prednisone; HD, high dose; ICE, ifosfamide, carboplatin, and etoposide; IFRT, involved-field radiation therapy; IVE, ifosfamide, vinorelbin, and etoposide; LVPP, chlorambucil, vinblastin, procarbacine, prednisone; MTX, methotrexate; PBSCT, peripheral blood stem-cell transplantation; PHAD, cisplatinum, high-dose Ara-C, dexamethasone; poly-CT, polychemotherapy; R-COP, rituximab, cyclophosphamide, vincristin, prednisone; RT, radiotherapy; VP, etoposide.

Table A4. Details on Survivors

Age at First Diagnosis (years)	Age at RR-HL Diagnosis (years)	Sex	Initial Stage	First-Line Study/ Treatment Arm	Type of Event	Stage at RR-HL	Risk Group	Second-Line Treatment	Second-Line Treatment Outcome	OS (months)
Intensified treatment										
65	66	Male	IIIA (advanced)	PVAG	Progression	IVA (advanced)	High	DHAP 4×	CR	38
Poly-CT/salvage RT										
70	75	Female	IA (early favorable)	HD10/B	Late relapse	IIIA (advanced)	Low	CEVD 4×	CRu	54
71	73	Male	IA (early favorable)	HD10/C	Late relapse	IA (early unfavorable)	Low	BEACOPP 6× (fifth/ sixth cycle 75%)	CRu	79
68	75	Female	IIA (early favorable)	HD10/D	Late relapse	IIA (early fav)	Low	ABVD 4× + 30-Gy IFRT	CRu	13
62	64	Female	IIIB (advanced)	HD9/B	Early relapse	IA (early favorable)	Low	Mediastinal RT	CR	73
63	69	Female	IIA (early favorable)	HD7/B	Late relapse	IIA (early favorable)	Low	BEACOPP 6×	CR	64
61	69	Male	IIB (early unfavorable)	HD8/B	Late relapse	IIA (early favorable)	Low	ABVD 4× + iliacal/ inguinal 33.8 Gy	CR	26
72	75	Female	IVB (advanced)	HD9/A	Late relapse	IIB (early unfavorable)	Low	ABVD 3×	CR	61
60	61	Male	IVB (advanced)	HD12/A	Progression	II (early unfavorable)	Low	Gemcitabine + 60-Gy IFRT	CRu	79
73	75	Male	IIA (early favorable)	HD10/A	Late relapse	IIIA (advanced)	Low	BEACOPP escalated 1×	CR	72
71	74	Male	IA (early favorable)	HD10/A	Late relapse	IV (advanced)	Low	COPP 4×	CRu	46
60	63	Female	IA (early favorable)	HD10/C	Late relapse	IA (early favorable)	Low	BEACOPP escalated 4× + 30-Gy IFRT	CR	61
64	66	Male	IIA (early unfavorable)	BACOPP	Late relapse	IA (early favorable)	Low	40-Gy IFRT	CRu	19
74	76	Male	IIIB (advanced)	PVAG	Late relapse	IIIA (advanced)	Low	ABVD 6×	PR	37
Palliative approaches										
63	64	Female	IIB (advanced)	PVAG	Late relapse	IB (early favorable)	Low	Gemcitabine + prednisone	CRu	30

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BACOPP, bleomycin, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEVD, lomustine, etoposide, vindesine, and dexamethasone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete response; CRu, unconfirmed complete response; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; IFRT, involved-field radiation therapy; OS, overall survival; poly-CT, polychemotherapy; PR, partial response; PVAG, prednisone, vinblastine, doxorubicin, and gemcitabine; RR-HL, relapsed/refractory Hodgkin lymphoma; RT, radiotherapy.