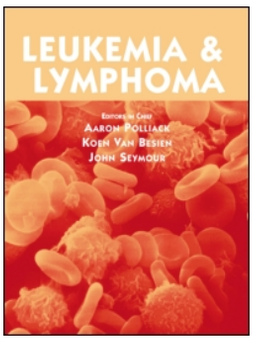

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Hodgkin lymphoma of the elderly patients: a retrospective multicenter analysis from the Polish Lymphoma Research Group*

Tomasz Wróbel[a], Przemysław Biecek[b], Justyna Rybka[a], Anna Szulgo[c], Natalia Sorbotten[c], Agnieszka Giza[d], Agata Tyczyńska[e], Elżbieta Nowara[f], Agnieszka Badora-Rybicka[f], Krzysztof Adamowicz[g], Waldemar Kulikowski[h], Renata Kroll-Balcerzak[i], Andrzej Balcerzak[i], Wojciech Spychałowicz[j], Ewa Kalinka-Warzocha[k], Beata Kumiega[l], Joanna Drozd-Sokołowska[m], Edyta Subocz[n], Agata Sałek[o], Maciej Machaczka[o], Jadwiga Hołojda[p], Joanna Pogrzeba[q], Olga Dobrzyńska[a], Ewa Chmielowska[c], Wojciech Jurczak[d], Wanda Knopińska-Posłuszny[h], Krzysztof Leśniewski-Kmak[e,r] and Jan Maciej Zaucha[e,s]

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ABSTRACT

We retrospectively analyzed long-term disease outcome of 350 elderly Hodgkin Lymphoma (eHL) patients treated with ABVD/ABVD-like regimen enrolled in the PLRG-R9 study between 2001 and 2013 in Poland. Complete remission was reported for 73% of early (ES) and 61% advanced stage (AS) patients. Nine (10%) ES and 56 (20%) AS patients have died. With the median follow-up of 36 (1–190) months, 3-year EFS and OS was 0.74 (95%CI: 0.63–0.85) and 0.90 (95%CI: 0.82–0.98) for ES; 0.51 (95%CI: 0.44–0.57), and 0.81 (95%CI: 0.75–0.86) for AS patients, respectively. For ES patients, Cox regression revealed ECOG <2 and age >70 as predictive for inferior OS and EFS. For AS patients, the most predictive for OS was the presence of cardiovascular disorders (CVD) ($p = .00044$), while for EFS four factors were significantly associated with a poor outcome: ECOG< 2, age >70 years, CVD and extranodal disease. In conclusion, CVD significantly impacts outcomes of ABVD-treated advanced eHL patients.

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Hodgkin lymphoma; elderly patients; ABVD treatment

Introduction

The outcome of Hodgkin Lymphoma (HL) in the adults is generally considered good. However, HL in the elderly (eHL), occurring in 20–25% of the whole HL population [1,2], the survival rate is disproportionally reduced, with the 5-year overall survival (OS) ranging between 40 and 70%, depending on the stage of the disease [3,4].

The reasons for the poor prognosis of the eHL patients are not clear: they might be related to the biology of the disease and/or to the patients themselves. Old age is an independent negative risk factor in HL [1,3,5,6]. In the elderly patients, HL is more often diagnosed in the advanced stage, has a more aggressive clinical course [1,3,5,6] and its outcome is worsened by comorbidities [1,2,7]. The latter along with a poor tolerance of cytostatic therapy contribute to the treatment-related mortality and limit treatment intensity [6,8].

A definite standard of care is still unsettled in eHL. Previous studies indicated that patients treated with anthracycline-based chemotherapy with relative dose intensity (RDI) >65% had a superior outcome compared to the same treatment with <65% RDI and to MOPP (mechlorethamine, vincristine, procarbazine,

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*Preliminary data from this study have been presented at the 52nd conference of the American Society of Hematology in San Francisco, December 2014.

prednisone) [9]. Since 2002, it was known that the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen, recommended for younger patients [10], is not optimal for the elderly due to excessive toxicity [11]. Different chemotherapy regimens have been proposed aimed at generating an effective treatment with acceptable toxicity [7,12,13]. Despite encouraging results, especially for the Italian regimen VEPEMB (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, and bleomycin) [7], none of them became a recommended standard. In routine practice, ABVD has remained widely used for eHL [3,10]. Even in the prospective SHIELD study, by the decision of treating physicians, 20% of patients were given ABVD instead of the recommended VEPEMB [6]. Moreover, in the ESMO guideline, ABVD remains the standard regimen for the elderly but fit patients [10]. The recent randomized comparison of standard ABVD to VEPEMB showed better PFS and OS for ABVD, although the differences were not statistically significant [14]. The selection of patients eligible for ABVD is not simple due to the scarcity of data on treatment outcomes and complications in eHL patients. To address this question, we analyzed a large cohort of eHL patients treated in Poland between 2001 and 2013

Methods

Our analysis included 385 patients (aged >50) treated for classical HL at 13 hematology/oncology centers; Patients' records were anonymized. Cardiovascular disorders (CVD) were defined as the documented history of arterial hypertension, coronary artery disease, cardiac arrhythmias or heart failure. Treatment response assessment was performed according to the International Harmonization Project criteria [15]. The study was registered at the Polish Lymphoma Research Group (PLRG) as PLRG-R9 in 2014. Most of the required data were available for 350/385 cases. Since the commonly accepted definition of eHL patients is >60 years, the results were reported separately for younger (50–60) and older than 60 years old.

Statistical analysis

Differences between categorical values were tested with the chi-squared test and Fisher's exact test, while differences between continuous variables with the Wilcoxon test. OS was defined as the time from diagnosis until death from any cause or censoring in patients still alive at the time of the last follow-up. Event-free survival (EFS) was calculated from the date of diagnosis to: the first disease progression, death from any cause, a start of palliative treatment or treatment discontinuation for any reason. The impact of age on EFS and OS was assessed using log-rank test for trend. Univariate and multivariate models for EFS and OS survival were fitted with the Cox proportional hazards regression model [16]. Assumptions of the Cox model were verified with the test for proportional hazards [17]. p Values $<.05$ for double-sided hypothesis were considered statistically significant. All analyses were performed with R statistical software, version 3.3.0 [R2016].

Results

Patient characteristics

The median follow-up for all patients was 36 (1–215) months. The median age of the patients was 59 (range: 50–93) years; 201 (57%) were less and 149 (43%) more than 60. Within the eHL group 23% were between 61 and 70 and 20% > 70. There were more males 56% than females 44%; however, only in the younger group (Table 1).

The most predominant histological subtype was nodular sclerosis (51%), followed by mixed cellularity (36%) with a significantly higher prevalence of mixed cellularity over nodular sclerosis ($p = .019$) in older patients (Table 1). More patients, 264 (75%), were diagnosed in the advanced than in the early, 86 (25%), stages with an even distribution in younger and older group. No difference in stage and International Prognostic Score (IPS) class breakdown or incidence of low albumin, B symptoms, and extra-nodal disease was observed between the two age cohorts. However, remarkably, older patients had more frequently a poorer performance status (PS), with a score >2 according to ECOG score ($p = .003$), and suffered from more comorbidity ($p < .0001$), with particular emphasis to CVD.

Treatment

Treatment was ABVD ± Radiotherapy (RT) in most patients (85%), with the same frequency in both age groups; BEACOPP escalated was offered to young patients in most cases 18/21, while CHOP/PVAG regimen mainly to elderly patients (0/9). Eight patients with one site involved were treated with RT. The median number of ABVD cycles in the early-stage and advanced stage patients were 4 and 6, respectively. Twelve patients: two early and 10 advanced stage patients were offered only palliative treatment, (Table 1). The median age of those patients was 70

Table 1. Clinical characteristics of patients among different age groups.

Patients characteristics	Age 50–60 (Y)	Age >60 (O)	*p*
No (%)	201 (57%)	149 (43%)	
Age median	54	70	
Range	50–60	61–93	
Sex F/M	79/122	74/75	.053
%	39/61	50/50	
Early-stage I-IIA (%)	53 (26%)	33 (22%)	.362
I	17 (32%)	11 (33%)	
IIA	36 (68%)	22 (67%)	
Advanced stage IIB-IV	148 (74%)	116(78%)	
IIB	33 (23%)	21 (18%)	
III	60 (40%)	62 (53%)	
IV	55 (37%)	33 (28%)	
B symptoms yes (%)	123 (83%)	90 (78%)	
HL subtype (%)			.019
NS	128 (64%)	76 (51%)	
MC	47 (23%)	54 (36%)	
LR	11 (5.5%)	13 (9%)	
LD	3 (1.5%)	3 (2%)	
NC	12 (6%)	3 (2%)	
IPS			.075
0–3/4–7/unknown	62/52/34	63/27/26	
%	42%/35%/23%	54%/23%/22%	
Albumin <39g/l (%)	56%	57%	.67
Extrandoal disease: Yes (%)	25 (12.5%)	18 (12%)	.91
ECOG			.003
0–1/2–4/unknown	135/23/43	76/45/28	
%	67%/11.5%/21.5%	51%/30%/19%	
Comorbidities (%)	80 (40%)	98 (66%)	<.00001
Cardiovascular system (%)	45 (22.5%)	74 (50%)	<.00001
Treatment: early (%)			
RT alone	3 (6%)	5 (15%)	
ABVD ± RT	47 (89%)	25 (76%)	
CHOP ± RT	0	1 (3%)	
BEACOPP	3 (6%)	0	
Palliative	0	2 (6%)	
Treatment: advanced (%)			
ABVD-/ABVD-like ± RT	125 (85%)	100 (86%)	
MOPP			
CHOP/PVAG	0	8 (7%)	
BEACOPP	18 (12%)	3 (3%)	
Palliative	5 (3%)	5 (4%)	

NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; NS: nodular sclerosis; MC: mixed cellularity; LR: lymphocyte rich; LD: lymphocyte depletion; IPS: International Prognostic Score; ECOG: performance scale of Eastern Cooperative Oncology Group

Table 2. Treatment and treatment response and EFS events.

	Age 50–60 (Y)	Age >60 (O)	*p*
Early stages	53	33	
Completed treatment Yes	53	28	.004
(%)	(100%)	(85%)	
CR	44 (83%)	19 (58%)	.01[a]
PR	8 (15%)	10 (30%)	
NR	0	0	
NA	1 (2%)	4 (12%)	
Progression/relapse documented	12 (23%)	5 (18%)	.72
Death	3 (6%)	6 (18%)	.08
Early death (<6 month)	1	2	
Death cause			
HL	2	4	
Toxicity	1	1	
Other	0	1	
EFS@3 years	0.80	0.56	.04
95%CI	0.68–0.93	0.34–0.77	
OS@3 years	0.93	0.73	.02
95%CI	0.84–1.0	0.52–0.96	
Advanced stages	148	116	
Completed treatment	126	80	.002
(%)	(85%)	(69%)	
CR (%)	92 (62%)	70 (60%)	.86
PR	27 (18%)	25 (22%)	
NR	20 (14%)	13 (11%)	
NA	9 (6%)	8 (7%)	
Progression/relapse documented	53 (36%)	27(24%)	.03
Death	26 (18%)	27 (23%)	.009
Early death (<6 month)	8 (5%)	18 (16%)	
Death cause			
HL (%)	18 (12%)	17 (15%)	
Toxicity (%)	4 (3%)	7 (6%)	
Other (%)	4 (3%)	3 (2%0	
EFS@3 years	0.53	0.48	.13
95%CI	0.45–0.62	0.37–0.59	
OS@3 years	0.83	0.76	.033
95%CI	0.76–0.89	0.66–0.85	
ABVD treated patients			
EFS@3 years	0.51	0.54	NS
95%CI	0.42–0.61	0.43–0.66	
OS@3 years	0.82	0.80	NS
95%CI	0.74–0.89	0.71–0.90	

CR: complete remission; PR: partial remission; NR: no response; NA: not assessed; NS: not significant.
[a]Frequency of CR vs. no CR.

(52–93) years old, 5 patients were in the younger and 7 patients were in the older group. The reasons of treatment declining in the younger group were poor PS and the presence of significant comorbidities, whereas in the older group: age by itself (age >76 years) in five patients and the presence of comorbidities with poor PS (ECOG =3) in one patient, as well as one case of lack of compliance.

Outcome

Early-stage patients

Three early-stage patients out of 84 (4%), all in the older group failed to complete initial chemotherapy (all ABVD) due to toxicity. Together with two other patients not qualified for any treatment, 5/86 (6%) early patients, all in the older group did not start/complete any chemotherapy (Table 2). Complete response (CR) was documented in 63/84 (75%) patients, significantly more often in the younger than in the older group. Progression or relapse was documented in 17 (20%) early patients with a similar frequency in the younger and the older group. Nine patients died: six of HL, two of toxicity after completion of the treatment and one of unrelated causes. The 3-year EFS and OS was 0.74 (95%CI: 0.63–0.85) and 0.90 (95%CI: 0.82–0.98), respectively.

Advanced stage patients

In the advanced patients, 48/254 (19%) did not complete chemotherapy due to toxicity; more often ($p = .001$) in the older group: 31/111 (28%) compared to 17/143 (12%) in the younger group. Four patients: two in the younger group and two in the older group,

died from treatment related-toxicity: three of them were receiving ABVD one PVAG. Together with 10 patients qualified only for palliative care, 58/264 (22%) advanced patients, all in the older group, have not started/completed any chemotherapy. CR was achieved in 162/254 (64%) treated patients. Progression was documented in 80 (31%) patients with advanced stages. Fifty-three patients died: 35 from HL, 11 from treatment-related toxicity, and 7 from other causes. The median EFS time was 39 months, the median OS was not reached. The 3-year EFS and OS was 0.51 (95%CI: 0.44–0.57) and 0.81 (95%CI: 0.75–0.86), respectively.

Univariate and multivariate analysis of overall survival and event free survival

The test for proportional hazards showed that the assumptions of Cox model were met ($p = .21$).

Early-stage patients

In the early-stage patients, a univariate Cox model identified only two factors as significant: age >70 years and poor PS (ECOG <2), which were predictive for inferior OS and EFS, (Table 3). Both variables are correlated and in the multivariate model, only one of them is selected as conditionally important. For EFS, the effect of age is more pronounced (HR= 5.06; 95%CI: 1.81–14.09; $p = .005$), while for OS, the ECOG is more significant (HR =4.71; 95%CI: 0.86–5.45; $p = .079$). The negative impact of age on OS and EFS in patients with early stages is shown in Figure 1: there was no statistically significant difference in OS and EFS between 50–60 and 61–70 years old groups, whereas the oldest patients (>70) had statistically significant inferior OS than patients 50–60 ($p = .008$) and EFS compared to both groups of younger patients with p values .001 for 50–60 and .009 for group 60–70. The log-rank test for trend showed statistically significant ($p = .0001$) decreasing OS and EFS with increasing age.

Advanced stages

In the advanced group, a univariate Cox model identified the following variables as significant: for OS: age >70 years, presence of any comorbidity, presence of CVD, HL subtype (MC + LD vs. others), presence of bulky disease, whereas for EFS: age >70 years, poor PS (ECOG <2), presence of any comorbidity, presence of CVD, HL subtype (MC + LD vs. others) and the presence of extranodal disease (Table 4). In the multivariate model, significant predictors for inferior OS remained the presence of CVD (most important) (HR =2.76; 95%CI: 1.57–4.87; $p = .00044$) whereas the HR for age >70 was 1.73 (95%CI: 0.94–3.19; $p = .079$); for EFS: poor performance status (ECOG <2) (HR =1.68; 95%CI: 1.05–1.59, $p = .014$), age >70 years (HR =1.42; 95%CI:1.0–2.49, $p = .05$), the presence of CVD (HR =1.43; 95%CI: 0.96–2.11, $p = .078$;) and the presence of extranodal disease (HR =1.68; 95%CI:1.04–2.71, $p = .033$). The variable 'any comorbidity' was correlated with 'the presence of CVD' and was not significant if 'presence of CVD' was in the model.

The impact of cardiovascular disorders on OS and EFS in patients with advanced HL

The negative impact of concomitant CVD on OS and EFS was observed in patients with advanced disease younger than 70 years old and was similar in patients aged 50–60 and 61–70 years old, (Figure 2). The difference in the probability of OS and EFS between patients with and without CVD were statistically significant with $p = .00023$ and $p = .014$, respectively, Figure 2.

Discussion

We included in the study patients aged more than 50 since the second peak of HL incidence starts at age of 50, with an average value of about 7.5 new cases per 100,000 resulting in about 450 (20% of all) new cases annually [18,19]. However, two important prognostic factors such as ECOG performance status and

Table 3. Patients at the early stages – clinical and disease characteristics with univariate analysis.

	EFS			OS		
Prognostic factor	HR	*p*	95%CI	HR	*p*	95%CI
Age ≥70 vs. < 70 years old	6.19	<.001	2.57–14.94	8.46	.003	2.06–34.69
Sex (male vs. female)	0.87	.73	0.38–1.96	0.51	.32	0.14–1.91
HL subtype (MC + LD vs. all others)	1.78	.18	0.77–4.08	2.65	.15	0.7–9.95
Presence of bulky disease	1.25	.68	0.43–3.69	0.65	.69	0.08–5.24
ECOG (≥ 2 vs. < 2)	3.43	.017	1.12–3.07	6.83	.025	1.13–6.05
Any comorbidity (any vs. none)	1.57	.28	0.69–3.6	1.2	.78	0.32–4.48
Cardiovascular disorder (any vs. none)	0.69	.43	0.27–1.74	0.62	.56	0.13–3.01
Albumin (< 39g/L vs. ≥39g/L	2.85	.06	0.95–8.03	1.63	.59	0.1–3.66

HL: Hodgkin lymphoma; MC: mixed cellularity subtype of HL; LD: lymphocyte depletion subtype of HL; ECOG: Eastern Cooperative Oncology Group performance status; EFS: event free survival; OS: overall survival; HR: hazard ratio; 95%CI: confidence intervals.

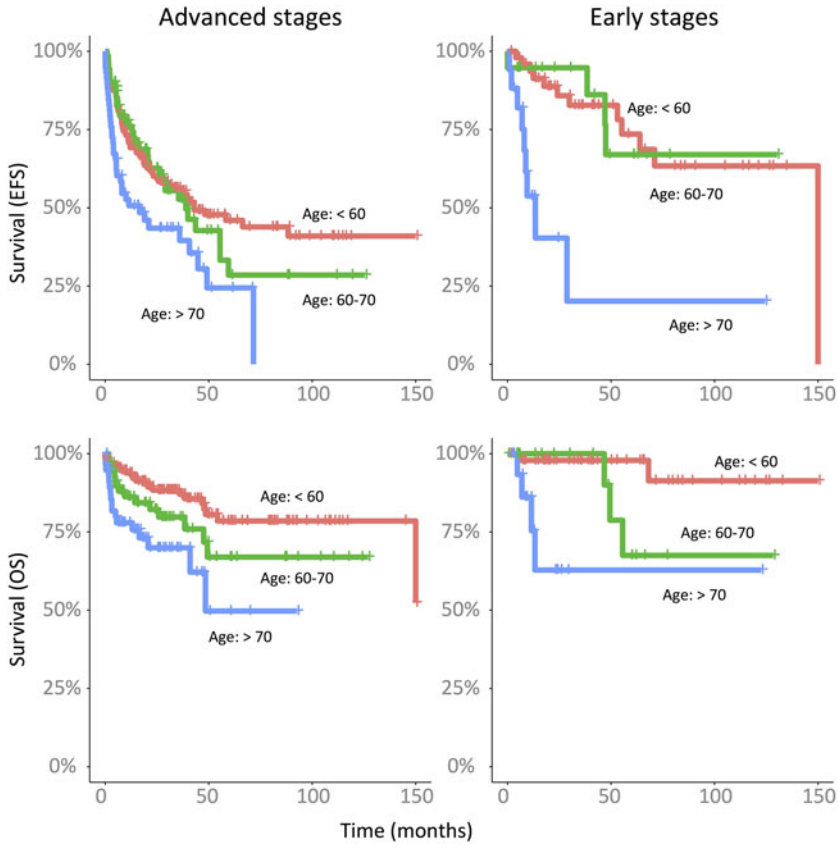

Figure 1. Overall survival and event free survival in the advanced and early-stage patients divided in three age groups: 50–60, 61–70, and >70 years old. Logrank test for trend showed statistically significant (p=.0001) decreasing OS and EFS with increasing age for both groups of patients.

Table 4. Patients at the advanced stages – clinical and disease characteristics with univariate analysis.

	EFS			OS		
Prognostic factor	HR	p	95%CI	HR	p	95%CI
Age ≥70 vs. < 70 years old	1.83	.0021	1.25–2.69	2.53	.002	1.4–4.55
Sex (male vs. female)	1.03	.88	0.73–1.44	1.16	.5	0.67–2
HL subtype (MC + LD vs. all others)	1.4	.065	0.98–2.01	0.59	.063	0.97–2.95
B-symptoms (Yes vs. No)	1.37	.18	0.87–2.16	1.64	.22	0.74–3.64
Presence of bulky disease	0.74	.21	0.46–1.19	0.33	.034	0.12–0.92
Extranodal disease (Yes vs. No)	1.78	.0089	1.15–2.73	1.73	.11	0.89–3.37
ECOG (≥ 2 vs. < 2)	1.84	.0033	1.23–2.77	1.61	.14	0.92–1.74
Any comorbidity (any vs. none)	1.47	.025	1.05–2.07	2.81	.00047	1.57–5.01
Cardiovascular disorder (any vs. none)	1.77	.0014	1.25–2.51	3.22	.000027	1.87–5.56
Albumin (<39g/L vs. ≥39g/L	1.09	.7	0.68–1.73	0.83	.63	0.38–1.79

HL: Hodgkin lymphoma; MC: mixed cellularity subtype of HL; LD: lymphocyte depletion subtype of HL; ECOG: Eastern Cooperative Oncology Group performance status; EFS: event free survival; OS: overall survival; HR: hazard ratio; 95%CI: confidence intervals.

comorbidity showed a skewed incidence in patients aged less and more than 60, confirming that the generally accepted cutoff of 60 years is still valid [2,20]. In particular, comorbidity is of paramount importance, as in Poland, the median life expectancy is approximately 7 years shorter than in western countries mostly due to the high incidence of CVD that are the leading causes of death [21]. The clinical characteristics of our elderly patients fit the picture of the eHL patients reported so far [4,6,7,20,22,23]. Most of the patients presented with advanced disease and B symptoms. With increasing age, more patients with the MC subtype (although NS remained the main histology subtype), more patients with inferior ECOG and comorbidities, especially CVD were recorded. The absence of male prevalence reported by others might

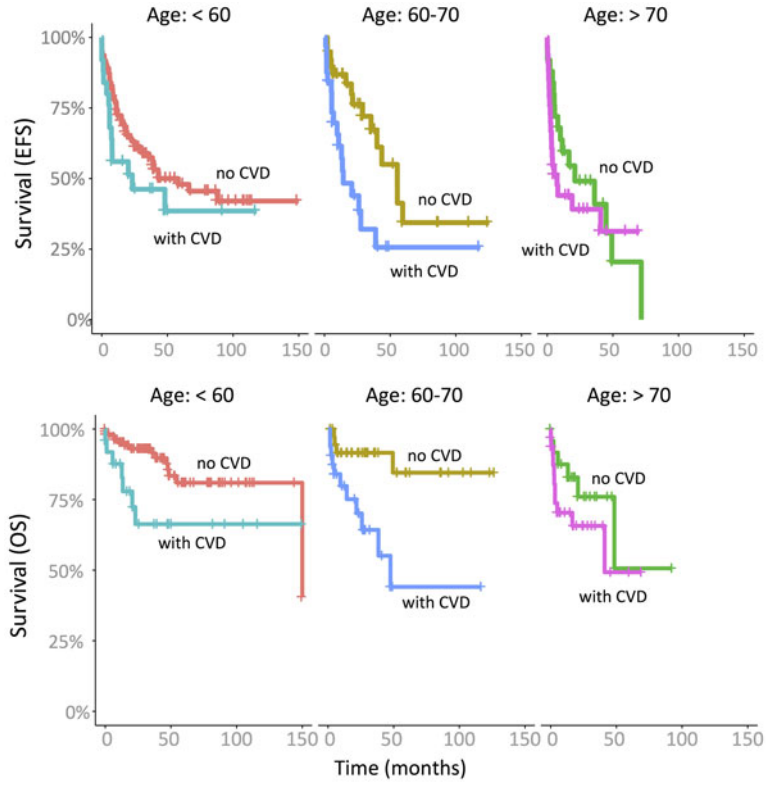

Figure 2. Cardiovascular disorders have a negative impact on overall survival, and to a lesser extent on event free survival in patients younger than 70 years old.

be related to a higher percentage of women within population greater than 60 years old in Poland [19].

The main endpoint of the study was to examine the effect of an older age in the clinical practice of HL treatment in the real daily life. ABVD chemotherapy was the most frequently chosen with the intention to cure. Other regimens such as CHOP [24] or PVAG or even BEACOPP were tested occasionally outside the general practice. ABVD treatment was well tolerated in early-stage eHL: 85% completed the planned treatment. However, some older patients were offered only RT, which may explain the worse CR rate (58%) in this group compared to younger patients. Two early deaths happened in patients receiving four cycles of ABVD, which points to the recent observation reported by the German Hodgkin Study Group of a high risk of severe toxicity of bleomycin in older HL patients receiving more than two cycles of ABVD [25]. The CR rate in advanced patients, who completed treatment (≈60%) was similar to other reports [4,6] and was not different between younger (<60) and older patients. However, age clearly affected tolerance of ABVD (in most cases six cycles): 85% of younger patients completed the planned treatment compared to 69% of patients older than 60 years with significantly higher (5% vs.16%) early death rate. Most (61%) of the early deaths in older group happened in patients older than 70 years old. Unfortunately, we were unable to assess accurately the incidence of bleomycin-induced toxicity (some patients died outside treating centers) but most likely, it was underestimated especially for patients dying during ABVD treatment. A safe omission of bleomycin in patients with negative interim PET reported by RATHL study [26] and recently confirmed with a longer follow-up [27] should be especially appealing for elderly patients treated with ABVD. However, this should be prospectively tested since patients older than 60 years old accounted for only 8.7% of patients in the RATHL study.

Age affected OS significantly. In the early-stage patients, the 3-year OS decreased from 0.95 in younger to 0.73 in older (>60) ($p = .02$) patients and was inferior to that (being in the range 0.79–0.95) reported by the other studies [6,7,28]. One study used CHOP 2–4 cycles with RT [28] whereas the two other studies [6,7] used the VEPEMB regimen that is considered less toxic compared to ABVD. Our results are at the lower limit of the 95%CI of 5-years OS estimate (0.73) of the elderly early-stage patients treated with ABVD and RT by the GHSG in HD10 and HD11 trials [23], which again points to the differences between patients treated in and outside clinical trials. In the

advanced stage patients, increasing age also decreased OS significantly ($p = .03$), and was comparable to other studies reporting OS in the range of 0.42 to 0.71 [6,7,12,13,24,28,29].

To better assess the outcome, we used EFS instead of PFS to include patients who were offered only a palliative care and to compensate for early censoring that we considered as a clinically relevant event. This probably explains the worse 3-years EFS (0.56) in the older (>60) compared to 0.8 in the younger group that is similar to the PFS reported by other studies in eHL being in the range of 0.74–0.82 [6,7,23,28]. In contrast, in the advanced stage patients' age did not affect EFS significantly. In fact, EFS of older patients treated only with ABVD was comparable to younger patients (0.51 vs. 0.54) and very similar to PFS of 0.58 reported by Proctor et al. for patients treated with VEPEMB [6] and to 0.56 reported by Evans et al. for patients treated with ABVD in the modern era [4]. This observation suggests that the biology of HL outweighs a better initial toleration of ABVD treatment by younger (50–60) advanced eHL patients.

The negative impact of age is multifactorial. It affects the biology of HL which is reflected by the specific clinical characteristics of elderly HL patients with increasing adverse features such as B symptoms and presence of extranodal disease [30]. It also impairs the toleration of treatment which was the worst in patients >70 years. Fewer patients are able to complete the planned treatment especially in patients with advanced disease. Identification of CVD as independent risk factor for on poor outcomes in advanced patients is a clinically relevant finding and it probably reflects a more toxic effect of anthracycline in this patient subset, as reported in patients with diffuse large B cell lymphoma treated with R-CHOP [31].

In conclusion, our observations might be helpful in proper selection of elderly patients eligible for ABVD program. For early-stage patients with good PS and younger than 70 years a standard ABVD treatment (up to four cycles) seems an acceptable approach. For advanced-stage eHL <70 years and without CVD, ABVD could be still proposed with routine interim PET response assessment to identify patients eligible for safe bleomycin omission. Other patients should be offered either less toxic programs (such as VEPEMB [14]) or be encouraged to participate in clinical trials with novel agents such as brentuximab vedotin (BV) [32]. The preliminary results of combination BV and dacarbazine (CR rate 62% with median PFS 17.9 months) is very promising for a population of frail elderly patients [33].

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