Treatment outcomes and relative dose intensity of chemotherapy in patients with advanced Hodgkin lymphoma

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Abstract. The present retrospective study was undertaken to investigate the association of relative dose intensity (RDI) with the outcome of patients with advanced stage Hodgkin lymphoma (HL) receiving ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and escalated BEACOPP regimens (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). A total of 114 patients with HL treated between 2004 and 2013 were enrolled for evaluation. The association of variables with overall survival (OS) and progression-free survival (PFS) was analysed using univariate and multivariate Cox proportional hazards models. The median age of patients was 39 years, and the majority were male and had stage IV disease. A total of 54 patients received ABVD and 60 received BEACOPP chemotherapy with 24 and four deaths, respectively. Patients in the BEACOPP group were significantly younger with lower Charlson comorbidity index (CCI) and better performance status in comparison with the ABVD group, making the comparison of groups not possible. In the ABVD group, RDI was not significantly associated with OS (P=0.590) or PFS (P=0.354) in a multivariate model where age was controlled. The low number of events prevented this analysis in the BEACOPP group. The age of patients was strongly associated with both OS and PFS; all statistically significant predictors for OS and PFS from univariate analyses (chemotherapy regimen, CCI, RDI, performance status) lost their effect in multivariate analyses where age was controlled. Based on these observations, it was concluded that RDI was not associated with OS or PFS after age is controlled, neither in all patients combined nor in the ABVD group.

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Introduction

Hodgkin lymphoma (HL) is a unique lymphoid neoplasm characterized by malignant Reed-Sternberg cells in an inflammatory background (1). It has a distinctive bimodal age distribution with peaks around the second and sixth decade of life, but the incidence varies with the histological subtype and geography (2,3). Average annual observed number of new HL cases in Slovenia between 2004 and 2013 was 46.8 (4).

Staging is based on the Lugano classification, which is derived from the older Ann Arbour classification system (5). Afterwards, patients are assigned to one of the three categories-limited, intermediate and advanced stages, based on which the treatment is selected (6). Combination of chemo- and radiotherapy are the backbone of classical HL treatment, particularly in early stages, in late stages radiotherapy is reserved to consolidate partial remission. Early stages of HL, comprising limited and intermediate stages, are generally treated with ABVD chemotherapy regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) with involved-site radiation therapy. Advanced stages (stage IIB, III and IV) are usually treated with chemotherapy, and radiation therapy is used exclusively as consolidation for selected patients with partial remission (7-11). Chemotherapy regimens for advanced stage HL used extensively in Europe include escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and ABVD, along with BV-AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine) in recent years (12-14). Slovenian guidelines for treatment of malignant lymphomas propose treatment with ABVD for early stages of HL and ABVD or escalated BEACOPP for advanced stages HL.

Intensified first-line chemotherapeutic regimens (escalated BEACOPP) have been designed to overcome the risk of early chemo-resistance development. However, the treatment-related toxicity of intensive approaches is fairly high and is associated with complications that could delay the administration of further chemotherapeutic cycles or could lead to the cytostatic dose reductions (15). Relative dose intensity (RDI) represents the ratio of the amount of a drug actually administered to the patient in regard to the amount planned for a fixed time period (16,17). The purpose of calculating the RDI is to

evaluate whether or not the planned dose intensity of a chemotherapy treatment was actually achieved.

The aim of this retrospective study was to investigate the association of RDI with the outcome of HL patients with advanced stage disease therefore receiving ABVD and escalated BEACOPP regimen, representing all possible treatments for advanced stages according to Slovenian guidelines.

Materials and methods

Patients. We retrospectively reviewed medical records of histologically confirmed HL patients at the Institute of Oncology Ljubljana, Slovenia, between 2004 and 2013. We enrolled patients with advanced stage disease that were planned to receive either 8 cycles of ABVD or 4 cycles of escalated and 4 cycles of regular BEACOPP until 2011 and, from 2012 on, 6 cycles of escalated BEACOPP, because of modification of national guidelines. In line with this guidelines, ABVD was reserved for patients older than 60 years and for younger patients, who were unfit to receive escalated BEACOPP (patients with severe arterial hypertension, chronic obstructive pulmonary disease, and diabetes mellitus) or reluctant for aggressive chemotherapy (childcare, work during treatment).

Before the initial treatment, physical and blood examination, echocardiography, chest X-ray, computed tomography or positron emission tomography-computed tomography, and bone marrow biopsy was conducted in all patients. In addition, performance status and the Charlson comorbidity index (CCI), which predicts the risk of mortality associated with a range comorbid conditions, were assessed as well (18).

ABVD regimen comprised of intravenous (IV) doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2 on days 1 and 15, every 28 days (13). Escalated BEACOPP regimen comprised of IV bleomycin 10 units/m^2 on day 8, etoposide 200 mg/m^2 on days 1 through 3, doxorubicin 35 mg/m^2 on day 1, cyclophosphamide 1,250 mg/m^2 on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) on day 8, and oral procarbazine 100 mg/m^2 on days 1 through 7 plus prednisone 40 mg/m^2 on days 1 through 14, every 21 days (12). Regular BEACOPP was designed in a similar manner, however the dose of etoposide was reduced to 100 mg/m^2, doxorubicin to 25 mg/m^2 and cyclophosphamide to 650 mg/m^2.

The study was approved by the Institutional Review Board at the Institute of Oncology Ljubljana (approval no. KSOPKR/72) and National Medical Ethics Committee of Republic of Slovenia (approval no. 0120-481/2017/5). Because of retrospective design of the study, informed consents were waived by the National Medical Ethics Committee of Republic of Slovenia.

Relative dose intensity calculation. According to the chemotherapy regimen, all patients were planned to receive the full doses of cytostatic drugs, however, treatment delays and/or dose reductions were found in most of them. RDI was calculated as described below.

We defined the RDI as the ratio of the drug dose administered in the actual time, over the planned dose in the planned time. Dose intensity (DI), which can be presented as the amount of a drug administered per time unit, is used to assess the intensity of chemotherapy. It is calculated as a dose of a drug per cycle (mg/m^2) divided by the number of weeks in a cycle (17). RDI of each drug is acquired as a fraction of actual DI and planned DI (according to full doses of drugs and total number of cycles-8 for ABVD and 6 or 8 for BEACOPP), whereas average RDI of chemotherapy regimen as a sum of RDI of each drug divided with the number of drugs in a regimen (4 for ABVD and 6 for BEACOPP). The purpose of calculating RDI of chemotherapy regimen is to evaluate if the planned DI was actually achieved.

Statistical analysis. Categorical variables were summarized with frequencies and percentages, numerical variables with medians, interquartile ranges (IQR) and ranges (due to the asymmetric shape of distributions). Patients' characteristics were compared between treatment groups by using chi-squared tests for categorical variables and Mann-Whitney U tests for numerical variables (Table I).

Overall survival (OS) and progression-free survival (PFS) probabilities were estimated from the end of treatment (as our aim was to investigate association with RDI which is known at the end of treatment) with Kaplan-Meier method (19), confidence intervals (CIs) were reported. To make comparison with other literature possible, 5- and 10-year OS from the start of treatment were additionally reported. The difference between OS from the start and end of treatment was small as there were no deaths or lost to follow-up during the treatment. Time to second malignancy was not analysed due to too few events. The association of variables with OS and PFS was analysed using univariate and multivariate Cox proportional hazards (CPH) models (20). The proportional hazards assumption was tested using Schoenfeld residuals, and it has not been violated for any of the variables in any of the models.

The main model for OS of ABVD patients was multivariate CPH model with variables RDI and age, allowing only linear effects (Table II). As a part of sensitivity analysis, RDI was included also nonlinearly (using restricted cubic splines with three knots). The association of RDI and age was evaluated with Pearson correlation coefficient. BEACOPP treatment group was not analysed due to too few events. The low number of events per variable prevented also analysis in all patients as groups significantly differed in age and RDI which would require too many variables in the model. As a part of exploratory analysis, the association of other variables with OS was additionally tested with and without age in the model (Table III). The sole purpose of the many models in Table III was to demonstrate the strong effect of age on OS (see section Results), and not to build a model (this would require more independent variables in one model and thus a much greater number of events). All analyses were repeated also for PFS, results were similar as for OS (see also Fig. S1, and Tables SI and SII).

$P<0.05$ was considered as statistically significant. All analyses were performed using R statistical software, version 3.6.3 (21).

Results

Patients' characteristics. Between May 2004 and December 2013, 114 patients received treatment for advanced HL and

Table I. Patients' characteristics.

Characteristic	All (n=114)	ABVD (n=54)	BEACOPP (n=60)	P-value
Median age, years (IQR)	39.2 (28.8-59.2)	59.8 (40.6-67.9)	32.9 (25.7-40.0)	<0.001[a]
Male gender, n (%)	66 (57.9)	31 (57.4)	35 (58.3)	0.920
Clinical stage IV, n (%)	68 (59.6)	33 (61.1)	35 (58.3)	0.763
Median CCI (IQR)	2 (2-4)	4 (2-6)	2 (2-2)	<0.001[a]
Median RDI, % (IQR)	91.0 (81.6-96.1)	82.3 (68.2-89.9)	95.9 (90.7-98.9)	<0.001[a]
Radiation therapy, n (%)	34 (29.8)	15 (27.8)	19 (31.7)	0.650
Median PS (IQR)	0 (0-1)	1 (0-2)	0 (0-0.2)	<0.001[a]
PS ≥2, n (%)	19 (16.7)	15 (27.8)	4 (6.7)	0.003[a]

IQR, interquartile range; CCI, Charlson comorbidity index; RDI, relative dose intensity; PS, performance status; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone. [a]P<0.05 BEACOPP vs. ABVD group.

Table II. Multivariate model for overall survival in ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) treatment group.

	ABVD group, multivariate model		
Variable	HR	95% CI for HR	P-value
RDI, %	1.01	[0.98, 1.04]	0.590
Age, years	1.07	[1.03, 1.11]	0.001[a]

RDI, relative dose intensity; HR, hazard ratio; CI, confidence interval. [a]P<0.05.

were enrolled for evaluation. Patients' and their disease characteristics are presented in Table I. The median age of patients was 39 years, majority of patients were males and had stage IV disease. Patients in the BEACOPP group were significantly younger, with less comorbidities, better performance status and they received a higher RDI (all *P<0.05, Table I).

There were 28 deaths (24.6%), 24 (44.4%) in ABVD and 4 (6.7%) in BEACOPP group. Relapse occurred in 15 (13.2%) patients, 12 (22.2%) in ABVD and 3 (5%) in BEACOPP group. Median follow-up time was 8.0 years. OS and PFS from the end of treatment are presented on the left panels of Figs. 1 and S1. Five-year OS was 84.2% [95% CI: (77.8, 91.2%)], 10-year OS 74.1% [95% CI: (66.0, 83.2%)], 5-year PFS 78.9% [95% CI: (71.8, 86.8%)], and 10-year PFS was 68.9% [95% CI: (60.3, 78.9%)]. Additionally, 5- and 10-year OS from the start of treatment was 87.7% [95% CI: (81.9, 94.0%)] and 73.7% [95% CI: (65.5, 83.0%)], respectively. There were only 7 (6.1%) secondary malignancies, 4 (7.4%) in ABVD and 3 (5%) in BEACOPP group, which prevented further analysis of this event.

Fifty-four patients received ABVD and 60 received BEACOPP chemotherapy. Median RDI in ABVD and BEACOPP group was 82.3 and 95.9%, respectively, in addition the interquartile range was narrower for the BEACOPP group (Table I). Eighty-one % of patients in ABVD group and 93% in BEACOPP group received all planned cycles of chemotherapy (Table IV). Approximately one third of patients received radiation therapy as consolidation.

Dose de-escalation for the escalated BEACOPP chemotherapy follows a predefined scheme, which is determined by the occurrence of toxic events in the previous cycles, such as leukopenia, thrombocytopenia and other toxicities (22). Treatment always begins at dose level 4, which is later reduced as necessary to level 1, before regular BEACOPP is used. In BEACOPP group, the majority of RDI reductions was a consequence of reduced cytostatic doses according to de-escalation protocol, whereas in ABVD it was mostly caused by non-protocol dose reductions and treatment delays.

Overall survival, PFS and their association with RDI. Overall survival and PFS were significantly better in the BEACOPP group compared to ABVD group (both *P<0.05, Figs. 1 and S1). However, direct comparison between the two groups is not reasonable, because the groups differed markedly, especially in terms of age and CCI. Median age in the ABVD group was 59.8 years, whereas it was only 32.9 years in the BEACOPP group. Furthermore, 27 patients in ABVD group were older than 60 years while none was in the BEACOPP group. Likewise, the median CCI was 4 in ABVD and 2 in BEACOPP group, respectively. Twenty-eight % of patients in ABVD group and only 2% in BEACOPP group had a CCI of more than 5, for which the estimated 10-year survival is 2% or lower (18).

The different patients' characteristics in treatment groups led to a separate analysis of the ABVD group. The low number of events prevented further analysis in the BEACOPP group. In ABVD group, RDI was not significantly associated with OS (P=0.590) or PFS (P=0.354) in a multivariate model where age was controlled (see Table II for OS and Table SI for PFS). As a part of sensitivity analysis, we included RDI in models for OS and PFS also nonlinearly, the effect of RDI remained non-significant (P=0.436 for OS, P=0.434 for PFS). This could be explained with a strong negative correlation between the RDI and age (Fig. 2). Pearson correlation coefficient was-0.61 for all patients and -0.45 for ABVD treatment group, indicating that patients with higher age received a lower RDI.

Table III. The demonstration of the effect of age on overall survival.

	All patients		ABVD group	
Variable	P-value in univariate model	P-value in model controlled for age	P-value in univariate model	P-value in model controlled for age
RDI	<0.001[a]	0.898	0.242	0.590
All cycles of CT[b]	0.064	0.979	0.418	0.868
Treatment	<0.001[a]	0.146	NA	NA
CCI	<0.001[a]	0.506	<0.001[a]	0.726
Clinical stage IV	0.649	0.364	0.617	0.190
Gender	0.733	0.105	0.957	0.275
PS ≥2	0.014[a]	0.340	0.224	0.420
Age	<0.001[a]	NA	<0.001[a]	NA

NA, not applicable; RDI, relative dose intensity; CCI, Charlson comorbidity index; PS, performance status; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine. [a]P<0.05; [b]Received all planned cycles of chemotherapy (yes/no).

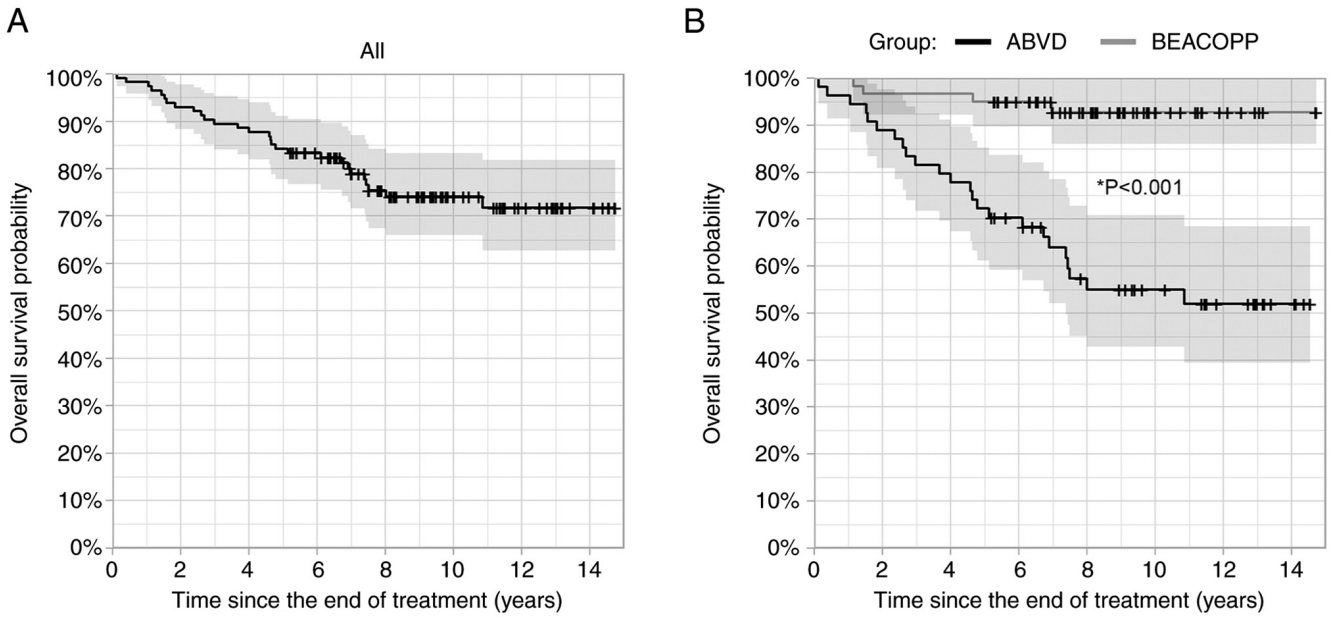

Figure 1. Overall survival of (A) all patients with Hodgkin lymphoma, and (B) for ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) treatment groups separately (Kaplan-Meier method). Shaded areas represent 95% confidence intervals, censoring times are marked with crosses. *P<0.05 BEACOPP vs. ABVD group (Cox proportional hazards model). ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.

Exploratory analysis showed that patients' age was strongly associated with both OS and PFS. To illustrate this, the association of other variables with OS (Table III) and PFS (Table SII, similar results) was additionally tested with and without age in the model. As a part of univariate model, the chemotherapy regimen, as well as CCI, RDI and performance status at least 2 were statistically significant predictors of OS (*P<0.05) in all patients combined. Noteworthy, none of these characteristics remained a statistically significant predictor in the multivariate model where age was controlled. In the ABVD group, only the CCI was a statistically significant predictor of OS (*P<0.05) in the univariate model. Similarly, CCI lost its effect in the multivariate analysis in the ABVD group, after age was controlled. Based on our observations, we can conclude that RDI is not associated with the OS or PFS after the age is controlled, neither in all patients combined nor in ABVD group.

Discussion

The ABVD and the BEACOPP represent the standard of care for patients with advanced HL (13,23). The aim of this study was to assess the association of RDI with the outcome of advanced HL patients, thus receiving either ABVD or BEACOPP regimen. Multiple works have reported an association between the RDI and survival prognosis, especially in

Table IV. Average RDI in ABVD and BEACOPP groups.

Planned treatment (number of cycles)	Actual treatment, number of cycles	Number of patients	Average RDI, %
8x ABVD	8x ABVD	44	81.2
	7.5x ABVD	3	78.7
	7x ABVD	3	73.6
	6x ABVD	3	55.6
	5.5x ABVD	1	52.7
4x eBEACOPP + 4x rBEACOPP	4x eBEACOPP + 4x rBEACOPP	42	94.3
	4x eBEACOPP + 3x rBEACOPP	1	87.5
6x eBEACOPP	6x eBEACOPP	14	96.8
	5x eBEACOPP + 1x rBEACOPP	1	85.4
	4x eBEACOPP + 2x rBEACOPP	1	83.9
	3x eBEACOPP + 3x rBEACOPP	1	76.5

RDI, relative dose intensity; eBEACOPP, escalated BEACOPP regimen; rBEACOPP, regular BEACOPP regimen; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.

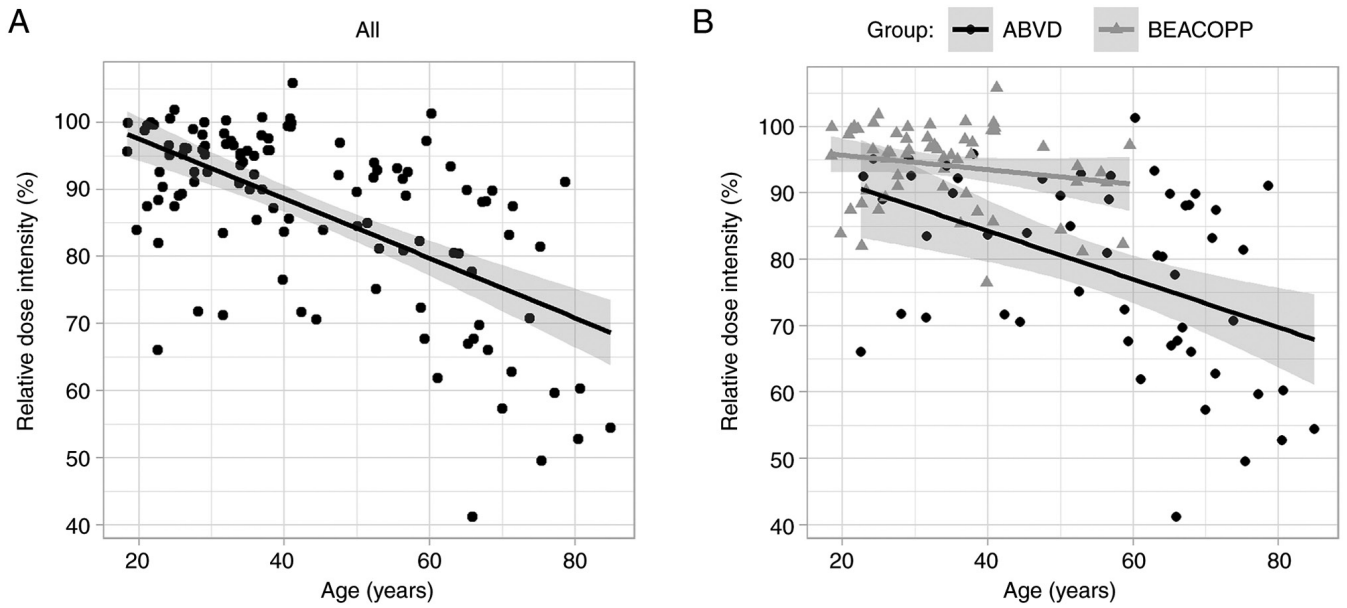

Figure 2. Correlation between relative dose intensity and age (A) for all patients with Hodgkin lymphoma, and (B) for ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) treatment groups separately. Shaded areas represent 95% confidence intervals around regression lines. ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.

breast cancer and aggressive lymphoma (17,24-26). However, only a few studies have addressed this issue in HL.

The results of present analysis indicate that there is no evidence that a higher RDI results in better prognosis of HL patients. These findings are in concordance with the key study published on this topic on 380 patients by Owadally *et al*, who also found no clear evidence that DI influences the outcome (27). However, in the study of Owadally *et al* the DI was measured only in first two cycles of ABVD chemotherapy, whereas in our study the RDI was measured throughout the whole treatment with either ABVD or BEACOPP, the treatments lasting from 6 to 8 cycles. It is worth noting that it is especially hard to maintain high DI in the last cycles of treatment, particularly on account of accumulated toxicities and complications from previous cycles. The median RDI in the study of Owadally *et al* was 89% with the lower and upper quartiles of 79 and 97%, respectively, whereas we found a median RDI of 82.3% and the lower and upper quartiles of 68.2 and 89.9% for the ABVD group, respectively. Patients included by Owadally *et al* were younger, with a median age of 36 years, having both early and advanced stages of HL, while our patients in the ABVD group were characterized with advanced stage disease and a median age of 59.8 years. Therefore, the calculation of RDI for all 8 cycles of ABVD, the older age of patients and the advanced stage HL in all patients might explain the difference in lower RDI achieved in our study.

Similar conclusions were also drawn by Raida *et al* (28). Likewise, they found no influence of primary chemotherapy DI on the probability of complete remission, disease relapse, event-free survival and OS. They included 194 heterogeneous patients with predominantly early HL (63.4%), who had the median age of 28 years and have received diverse chemotherapeutic regimes, including ABVD, BEACOPP, and Stanford V among others. In the study of Raida *et al*, the median RDI was not reported, however 76.3% of patients received a RDI of 90% or more, which is considerably higher than 51.8% of patients with the RDI of 90% or more achieved in our study for both chemotherapy groups combined. Again, the reason for the difference in the attained RDI is most likely due to the significantly older patient population and more intensive chemotherapy regimens in our study. As shown in Results, because of a strong negative correlation between the RDI and age, we can assume that patients with higher age achieve a lower RDI.

Landgren *et al* evaluated the effect of RDI on prognosis of 88 elderly (>60 years) HL patients, though the final study cohort consisted of 59 patients only (29). Unlike our study and previous two studies, Landgren *et al* reported a significantly better OS in patients with the RDI >65% compared to those with the RDI ≤65%, despite the relatively low number of enrolled patients. It is worth noting that RDI was not controlled for age in a multivariate model, which might explain the association with OS. Similar to the report of Owadally *et al* the calculated RDI values were based on the initial two cycles of chemotherapy only. Patients included by Landgren *et al* had various stages of HL, the majority (69.3%) of them being advanced stage, they also received five different chemotherapy protocols. We agree with Raida *et al* that the RDI of ≤65% suggested by Landgren *et al* may be considered as a significant violation of primary chemotherapy protocol, and is as such not appropriate to arbitrary divide the patients with good or bad prognosis.

Our study has several limitations that merit consideration. The major limitation is the modest sample size and the difference in patients' characteristics between the ABVD and BEACOPP groups. The ABVD group was considerably older and had more comorbidities, therefore we cannot compare the two groups directly. Moreover, too few events prevented the analysis of RDI in BEACOPP group. Additionally, the RDI analyses performed in our study were retrospective in design, therefore only hypotheses about possible association can be formulated.

The available evidence suggests that small dose reductions or short delays between chemotherapy cycles, which still result in a decreased RDI, may not affect overall outcomes of HL patients, most likely due to a relatively good prognosis and chemosensitivity of this disease. To our knowledge, this is the first study to evaluate the impact of RDI throughout whole treatment in patients with advanced HL treated exclusively with ABVD or BEACOPP chemotherapy. The lack of association between the RDI and response to treatment is in concordance with the current literature. However, in order to fully elucidate the relationship between the RDI and response, a prospective trial with a larger number of patients would be required.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SR contributed to the conception of the study. SR and BJN confirm the authenticity of all the raw data. SR, BJN and SN designed the study and analysed the clinical data. NRG performed statistical analysis. All authors contributed to the acquisition, analysis or interpretation of data for this article and drafts of the article. All authors participated in writing the manuscript and approved the final version of it. All authors were involved in revising the paper critically for intellectual content and gave final approval for the submission of the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board at the Institute of Oncology Ljubljana (approval number KSOPKR/72) and National Medical Ethics Committee of Republic of Slovenia (approval number 0120-481/2017/5). Because of retrospective design of the study, informed consents were waived by the National Medical Ethics Committee of Republic of Slovenia.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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