Received: 26 November 2019 | Revised: 4 February 2020 | Accepted: 12 March 2020

DOI: 10.1002/ajh.25789

RESEARCH ARTICLE

Outcome and determinants of failure to complete primary R-CHOP treatment for reasons other than non-response among patients with diffuse large B-cell lymphoma

Tove Wästerlid[1,2] | Sara Harrysson[1,2] | Therese M.-L. Andersson[3] | Sara Ekberg[1] | Gunilla Enblad[4] | Per-Ola Andersson[5,6] | Mats Jerkeman[7] | Sandra Eloranta[1] | Karin E. Smedby[1,2]

[1]Division of Clinical Epidemiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

[2]Department of Hematology, Karolinska University Hospital, Solna, Sweden

[3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4]Department of Oncology, Akademiska University Hospital, Uppsala, Sweden

[5]Department of Hematology, South Älvsborg Hospital, Borås, Sweden

[6]Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden

[7]Department of Oncology and Pathology, Institute of Clinical Sciences, Lund University, Lund, Sweden

Correspondence
Tove Wästerlid, Department of Medicine Solna, Karolinska Institutet, Division of Clinical Epidemiology, Karolinska University Hospital, SE-17176, Stockholm, Sweden.
Email: tove.wasterlid@ki.se

Funding information
This study was funded by the Swedish Cancer Society and through public-private real world evidence collaboration between Karolinska Institutet and Janssen Pharmaceuticals (contract: 5-63/2015)., Grant/Award Number: (contract: 5-63/2015); Karolinska Institutet and Janssen Pharmaceuticals, Grant/Award Number: 5–63/2015

Abstract

Patients with diffuse large B-cell lymphoma (DLBCL) who fail to complete planned treatment with R-CHOP due to toxicity are sparsely described. We investigated the extent of failure to complete treatment (six cycles or more, or three cycles + RT for patients with stage I disease) with R-CHOP for reasons unrelated to non-response, the determinants of such failure and the outcome among these patients. Three thousand one hundred and forty nine adult DLBCL patients who started primary treatment with R-CHOP were identified through the Swedish lymphoma register 2007-2014. Of these, 147 (5%) stopped prematurely after 1-3 cycles of R-CHOP for reasons unrelated to non-response, 168 (5%) after 4-5 cycles and 2639 patients (84%) completed planned treatment. Additionally, 195 (6%) patients did not complete treatment due to non-response or death before treatment end. In a multivariable logistic regression model, age > 75 years, poor performance status, extranodal disease and Charlson Comorbidity Index ≥1 were significantly associated with failure to complete planned R-CHOP treatment for other reasons than non-response. Non-completion of treatment strongly correlated with survival. Five-year overall survival for patients who received 1-3 cycles was 26% (95% CI: 19%-33%), 49% (95% CI: 41%-57%) for 4-5 cycles and 76% (74%-77%) for patients who completed treatment. Failure to complete planned R-CHOP treatment is an important clinical issue associated with inferior survival. Old age and poor performance status most strongly predict such failure. These results indicate a need for improved treatment tailoring for patients with certain baseline demographics to improve tolerability and chance for treatment completion.

1 | INTRODUCTION

Some patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) who start standard primary treatment with R-CHOP (rituximab- cyclophosphamide, doxorubicin, vincristine, prednisone) do not complete full treatment for reasons related to toxicity or other reasons unrelated to non-response. However, this group has seldom been formally studied.

That anthracycline-based immunochemotherapy is imperative in order to achieve cure for adult patients with diffuse large B-cell lymphoma (DLBCL) is well established.[1-4] The clinical trials that provide the evidence base for the current standard treatment with R-CHOP are all based on the administration of 6-8 cycles of chemotherapy.[1-3,5,6] Recently, a subanalysis of the GOYA-trial demonstrated no benefit of eight vs six cycles of chemotherapy,[7] which is also in accordance with a population-based real-world study, demonstrating comparable outcomes following use of six vs eight cycles of chemotherapy.[8] Further, the results of the FLYER-study were recently presented showing non-inferiority of four cycles of R-CHOP compared to six cycles of R-CHOP among low-risk patients (aaIPI 0 and non-bulky disease) aged ≤60 with DLBCL.[9] Thus, there is now sufficient evidence to claim that six cycles of R-CHOP, and even4four for a certain subgroup of low-risk patients, is the standard of care for patients with DLBCL. From prior trials we also know that the application of three cycles of R-CHOP followed by radiotherapy (RT) is a feasible alternative for patients with limited, stage I disease.[10]

However, the subgroup of patients who do not complete the full course of planned chemotherapy is not well described. In the clinical trials that provide the evidence base for the current standard treatment mentioned above, the proportion of patients who fail to complete all cycles of chemotherapy range from 7% to 21%.[1-5,11] For the majority of these trials, reasons for non-completion are not provided. However, in the studies that do report causes of non-completion, the group who stop treatment due to non-response appears to be small, 1%-3%, indicating that other reasons such as intolerance may be more common.[1-3] It is plausible to assume that the number of patients who do not complete treatment varies by clinical characteristics in the real-world setting with a higher proportion of elderly and non-selected patients, although rates of non-completion in this setting have seldom been reported.

We aimed to investigate the extent of failure to complete treatment with R-CHOP for other reasons than non-response (ie, premature stop due to intolerance/toxicity) in a real-world population-based setting, the determinants of such failure and finally the outcome of these patients.

2 | MATERIALS AND METHODS

The study population included adult patients diagnosed with DLBCL from January 1, 2007 to December 3, 2014 who started primary treatment with R-CHOP with the aim to receive 6-8 cycles, or three cycles + RT if stage I disease. Patients were identified through the Swedish Lymphoma Register (SLR), for which comprehensive data were available. The SLR was established in 2000 by the Swedish Lymphoma Group containing detailed clinical characteristics, and data regarding treatment and response since 2007.[12-14] Compared with the Swedish Cancer Register, to which all cancer diagnoses are registered by law, the coverage of the SLR is ~95% of all lymphoma cases diagnosed in Sweden.[15] In cases with missing data in the register regarding primary treatment and response, this was complemented from medical records. In cases where no formal interim evaluation was performed, medical records were checked to determine that the patients did not have stable or progressive disease. All lymphoma patients included were diagnosed according to the pathology guidelines specified by the WHO classification at the time of diagnosis.[16-18] Patients with primary central nervous system lymphoma were excluded. Patients who received other treatment than R-CHOP were excluded as were patients with an unknown number of administered cycles.

Full treatment was defined as completion of at least six cycles or three cycles and RT in the subset of patients with stage I disease (according to Swedish treatment guidelines). Dose reductions were allowed. In some analyses, patients who stopped treatment prematurely were stratified into two groups, 1-3 cycles and 4-5 cycles. Patients with stable or progressive disease at evaluation or relapse within 30 days of treatment end, who therefore did not complete R-CHOP, were separated from patients who did not complete treatment for other reasons than non-response in statistical analyses. Also, we used a conservative approach in defining the group classed as not completing treatment due to toxicity/other reasons than non-response, by not including patients who died within 30 days of treatment end (early death) in this group. This was done to avoid reverse causality for premature treatment stop, as cause of death was not available (even though it may have been due to toxicity). Among patients who completed treatment, patients who died within 30 days of treatment end (early death) were not included in the survival analysis, also to avoid reverse causality.

The cohort was linked to the Swedish Patient Register (coverage 85%-95%[19]) to collect information on comorbid disease during a period of 10 years prior to the diagnosis of DLBCL. We categorized comorbidity according to the Charlson Comorbidity Index (CCI), the most validated and extensively used tool to measure comorbidity among cancer patients.[20,21] Rheumatologic disease was disregarded if recorded during the year leading up to the diagnosis of DLBCL since such records could represent misclassified paramalignant symptoms of the yet undiagnosed lymphoma. The study was approved by the Regional Board of the Ethical Committee in Stockholm.

Multivariable logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CI) for the association between baseline clinical and demographic characteristics and failure to complete full R-CHOP treatment for other reasons than non-response or early death.

Overall survival by number of cycles was estimated using the Kaplan-Meier method in the entire cohort, and stratified by age

TABLE 1 Patient characteristics for all patients and stratified according to number of chemotherapy cycles received with patients who did not complete treatment due to non-response in a separate column

	Whole cohort (%)	1-5 cycles due to PD/SD/early death[b](%)	1-3 cycles for other reasons than non-response (%)	4-5 cycles, for other reasons than non-response (%)	Completed treatment (%)
N (%)	3149 (100)	195 (6)	147 (5)	168 (5)	2639 (84)
Median age, range	69, 18-94	75, 18-94	79, 31-93	77, 30-91	68, 18-94
Age at diagnosis					
≤ 55	493 (16)	15 (8)	6 (4)	15 (9)	457 (17)
56-65	675 (21)	26 (13)	9 (6)	20 (12)	620 (23)
66-75	1043 (33)	60 (31)	30 (20)	41 (24)	912 (35)
76-85	805 (26)	77 (39)	74 (50)	78 (46)	576 (22)
> 85	116 (4)	16 (8)	27 (18)	13 (8)	60 (2)
Missing	17 (1)	1 (1)	1 (1)	1 (1)	14 (1)
Sex					
Male	1770 (56)	118 (61)	74 (50)	89 (53)	1489 (56)
Female	1379 (44)	77 (39)	73 (50)	79 (47)	1150 (44)
Performance status					
0	1539 (49)	32 (16)	46 (31)	59 (35)	1402 (53)
1	1064 (34)	70 (36)	50 (34)	77 (46)	867 (33)
2	289 (9)	47 (24)	23 (16)	21 (13)	198 (7)
3	183 (6)	32 (16)	20 (14)	9 (5)	122 (5)
4	53 (2)	13 (7)	6 (4)	2 (1)	32 (1)
Missing	21 (1)	1 (1)	2 (1)	0 (0)	18 (1)
Ann Arbor stage					
I	673 (21)	24 (12)	26 (18)	38 (23)	585 (22)
II	818 (26)	42 (22)	34 (23)	53 (32)	689 (26)
III	597 (19)	33 (17)	26 (18)	20 (12)	518 (20)
IV	1005 (32)	89 (46)	54 (37)	54 (32)	808 (31)
Missing	56 (2)	7 (3)	7 (5)	3 (2)	39 (1)
LDH					
Normal	1314 (42)	37 (19)	55 (37)	91 (54)	1131 (43)
Elevated	1781 (56)	149 (76)	85 (58)	74 (44)	1473 (56)
Missing	54 (2)	9 (5)	7 (5)	3 (2)	35 (1)
Extranodal sites					
0	1704 (54)	81 (42)	70 (48)	70 (42)	1483 (56)
1	1014 (32)	71 (36)	49 (33)	65 (39)	829 (32)
> 1	431 (14)	43 (22)	28 (19)	33 (20)	327 (12)
IPI					
0-1	1019 (33)	18 (9)	29 (20)	60 (36)	914 (35)
2	819 (26)	37 (19)	37 (25)	36 (21)	709 (27)
3	724 (23)	65 (33)	28 (19)	36 (21)	595 (22)
4-5	450 (14)	61 (31)	37 (25)	29 (17)	323 (12)
Missing	137 (4)	16 (8)	16 (11)	7 (4)	98 (4)
Hb					
< 100	260 (8)	39 (20)	14 (10)	13 (8)	194 (7)
100-115	492 (16)	38 (19)	44 (30)	29 (17)	381 (15)
> 115	1760 (56)	85 (44)	67 (46)	94 (56)	1514 (57)
Missing	637 (20)	33 (17)	22 (15)	32 (19)	550 (21)

TABLE 1 (Continued)

	Whole cohort (%)	1-5 cycles due to PD/SD/early death[b](%)	1-3 cycles for other reasons than non-response (%)	4-5 cycles, for other reasons than non-response (%)	Completed treatment (%)
Bulky disease					
Yes	567 (18)	52 (27)	29 (20)	20 (12)	466 (18)
No	2531 (80)	137 (70)	117 (80)	143 (85)	2134 (81)
Missing	51 (2)	6 (3)	1 (1)	5 (3)	39 (1)
Consolidative RT[a]					
Yes	330 (11)	26 (13)	35 (24)	25 (15)	244 (9)
No	2817 (89)	169 (87)	112 (76)	143 (85)	2393 (91)
Missing	2 (0)	0 (0)	0 (0)	0 (0)	2 (0)
CCI					
0	1805 (57)	85 (44)	52 (35)	66 (39)	1602 (61)
1	601 (19)	51 (26)	36 (24)	47 (28)	467 (18)
≥ 2	742 (24)	59 (30)	58 (39)	55 (33)	570 (21)
Missing	1 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Cycle interval					
14 days	1689 (54)	79 (41)	28 (19)	53 (32)	1529 (58)
21 days	1398 (44)	102 (52)	107 (73)	114 (68)	1075 (41)
Missing	62 (2)	14 (7)	12 (8)	1 (1)	35 (1)

Abbreviations: CCI, Charlson Comorbidity Index; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PD, progressive disease; RT, radiotherapy; SD, stable disease.

[a]Excluding patients with stage I disease, who were planned for R-CHOPx3 + RT.

[b]Death within 30 days from end of last treatment cycle.

65 years and younger, and over 65 years. Multivariable Cox regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for the association between failure to complete full R-CHOP treatment for other reasons than non-response and all-cause mortality. This was adjusted for sex, age, stage, performance status, lactate dehydrogenase (LDH), bulky disease and use of consolidative RT. In the regression analyses, a complete case approach to missing information was used. Start of follow-up in the Cox regression was defined as the date of treatment evaluation, (approximately 30 days after the date of last treatment cycle). And, the end of follow-up was the date of death, emigration, or end of follow-up (October 31, 2017), whichever occurred first. Thus, patients who did not complete planned R-CHOP due to progressive or stable disease at treatment evaluation, who died before treatment evaluation (within 30 days after the last treatment cycle, ie, early death), or completed treatment but had progressive or stable disease did not contribute to the survival analyses.

3 | RESULTS

From 2007 to 2014, 3149 adult patients with incident DLBCL were identified through the SLR and started primary treatment with R-CHOP with no missing data regarding number of cycles. Median age in the whole cohort was 69 years (range 18-94). Median follow-up time was: 4.5 years (range 0.003-10.5). There was a male predominance of 56% vs 44%.

Overall, 2639 patients (84%) completed their planned treatment (ie, at least six cycles or three cycles for patients with stage I disease and consolidative RT). Among patients who completed treatment, 2414 (92%) received six cycles, 36 (1%) 7 cycles and 131 (5%) eight cycles and 58 (2%) patients with stage I disease were managed with three cycles and consolidative RT. A total of 1398 (44%) patients received R-CHOP-21, 1689 (54%) received R-CHOP-14 and 2% had missing data regarding treatment interval.

A total of 315 (10%) patients did not complete treatment for other reasons than non-response or early death. Among these, 147 (5%) patients only received 1-3 cycles of R-CHOP and 168 (5%) stopped treatment prematurely after 4-5 cycles of treatment. In addition, 80 patients (3%) did not complete treatment due to progressive or stable disease at first evaluation or relapse within 30 days, 115 (4%) patients did not complete treatment due to early death (within 30 days after last treatment). In addition, 115 (4%) patients completed treatment but had progressive or stable disease at evaluation, 14 patients completed treatment but died before treatment evaluation and 10 patients completed treatment but relapsed within 30 days of treatment and never entered the survival analysis (n = 2815 patients left). In the logistic regression patients who did not complete treatment due to non-response or mortality were included as reference cases together with all patients who completed

treatment (n = 2954 reference cases). A flow chart of included patients is presented in Figure S1.

Patients who failed to complete planned cycles of R-CHOP, for other reasons than non-response, more often presented with high-risk disease characteristics at diagnosis. Median age for patients who stopped at 1-3 or 4-5 cycles was 79 and 77 years respectively, compared to 68 years in the group who completed treatment (Table 1). Patients who stopped treatment after 1-3 cycles or 4-5 cycles more often presented with stage IV disease (37% vs 32% vs 31%) and performance status (PS) score ≥ 2 (34% vs 19% vs 13%) compared with patients who completed treatment. Thus, the proportion of patients with a high-risk IPI score was higher among patients who only received 1-3 cycles or 4-5 cycles (25% and 17% with high-risk IPI compared to 12% in the cohort of patients who completed treatment). Among patients who discontinued treatment for other reasons than non-response, 70% were managed with R-CHOP-21. Overall, 16% of patients managed with R-CHOP-21 discontinued treatment due to other reasons than non-response, compared to 5% among patients treated with R-CHOP-14. As expected, patients who did not complete treatment due to stable or progressive disease or early death also had a worse prognostic setting (Table 1).

Patients who did not complete treatment received consolidative RT (ie, not including patients with stage I disease planned to receive three cycles followed by RT) to a larger extent. Among patients who stopped treatment after 1-3 and 4-5 cycles for other reasons than non-response, 24% and 15% of patients received consolidative radiotherapy compared to 9% among patients who completed treatment. Survival analysis stratified by number of cycles and RT were not performed due to inherent risk of immortal time bias.

The proportion of patients who did not complete planned treatment for other reasons than non-response increased with age. Among patients aged ≤55 years, 4% of patients did not complete treatment for reasons unrelated to non-response, compared to 4%, 7%, 19% and 34% among patients aged 56-65, 66-75, 76-85 and 86 or above, respectively.

Using logistic regression, age, poor performance status (PS≥1 compared to PS 0), elevated LDH, hemoglobin levels 100-115 (compared to >115), extranodal disease and CCI ≥1 (compared to CCI 0) were significantly associated with failure to complete planned R-CHOP in univariable analysis. Also, administration of R-CHOP in 21 day intervals (compared to 14 days) was associated with failure to complete full R-CHOP treatment. In a multivariable logistic regression model, age > 75 years, poor performance status, CCI ≥1, extranodal disease and chemotherapy administration in 21 day intervals remained significantly associated with an increased risk of failure to complete full chemotherapy (Figure 1). The largest impact was seen among patients aged 85 or above, where the odds of not receiving planned chemotherapy was six times higher compared to patients aged 66-75. Neither sex, stage, elevated LDH, bulky disease nor hemoglobin level had predictive value for whether full chemotherapy could be administered in the multivariable model.

For patients who stopped treatment after 1-3 cycles for other reasons than non-response, the majority never underwent formal interim evaluation (45% missing evaluation), although it was determined based on available medical record data that they did not have stable or progressive disease. Still, 34% (n = 50) achieved complete remission (CR) in this group, and 20% (n = 30) partial remission (PR). Corresponding rates for patients who stopped treatment after 4-5 cycles were 75% CR and 15% PR, compared to 83% CR and 11% PR among patients who completed treatment. The number of patients with missing formal response evaluation was smaller among patients who received 4-5 cycles or completed treatment, 9% and 2% respectively.

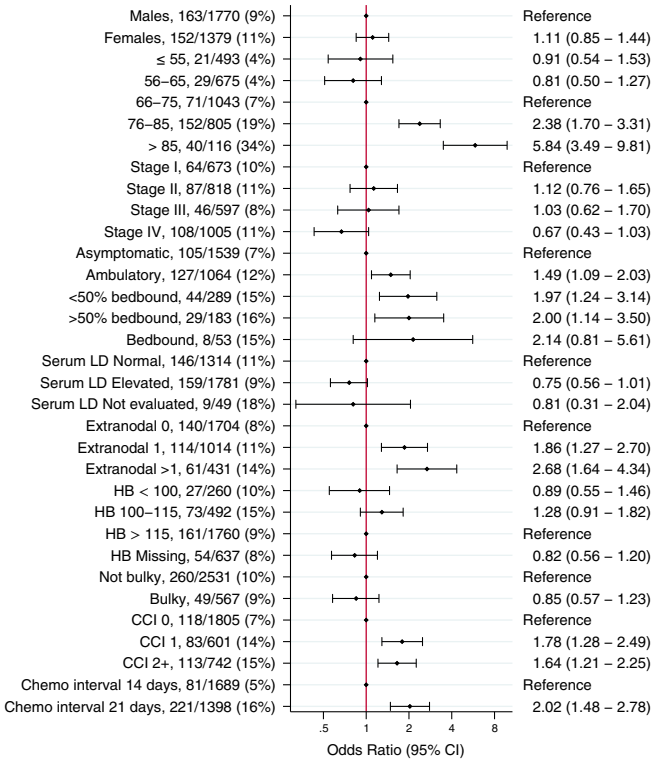

FIGURE 1 Odds ratios (OR) with 95% confidence intervals (CI) for associations between clinical characteristics and failure to complete R-CHOP for other reasons than non-response or early death, along with number and proportion of patients in each category. Patients who completed treatment or stopped treatment due to non-response or early death are included in the reference group [Color figure can be viewed at wileyonlinelibrary.com]

The overall 2- and 5-year OS rates were 83% (95% CI: 82%-85%) and 72% (95% CI: 70%-73%), respectively. Number of received R-CHOP cycles strongly correlated with survival (Figure 2A). For patients who stopped treatment after 1-3 cycles, 5-year OS was 26% (95% CI: 19%-33%). The corresponding rates for patients who stopped after 4-5 cycles and patients who completed treatment were 49% (95% CI: 41%-57%) and 76% (74%-77%), respectively. Among patients 65 years of age or younger, 5-year OS varied from 51% (95% CI: 24%-74%), following 1-3 cycles, to 79% (95% CI:60%-89%) following 4-5 cycles, and 87% (95% CI: 85%-89%) for patients who completed treatment. Among patients older than 65 years, the corresponding rates were 23% (95% CI: 16%-31%), 41% (95% CI: 32%-50%) and 68% (95% CI: 65%-70%), respectively (Figure 2B,C).

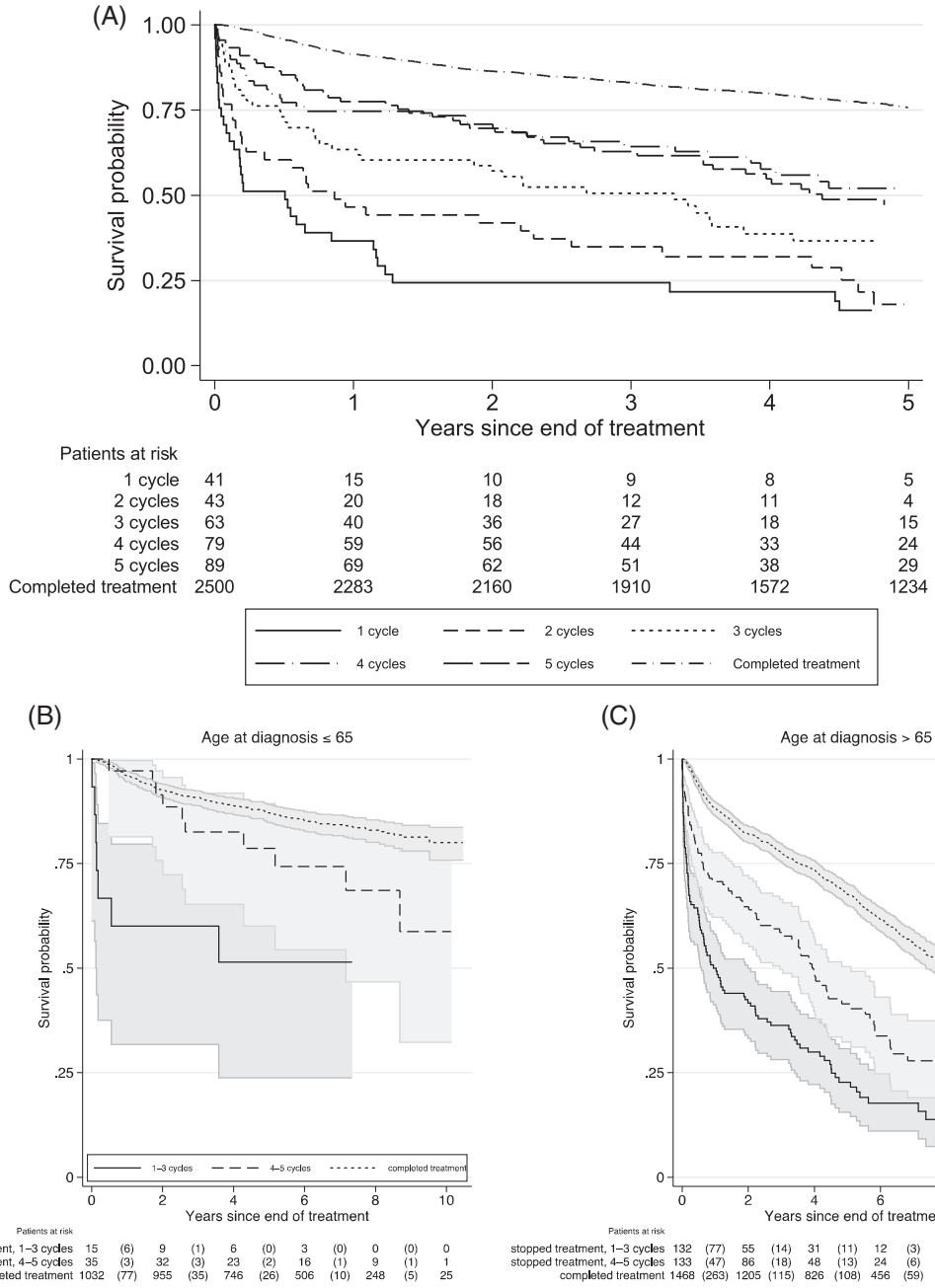

FIGURE 2 A, Kaplan Meier curve depicting overall survival stratified according to number of R-CHOP cycles received among patients who completed treatment and those who failed to complete for other reasons than non-response or early death (within 30 days after end of last treatment cycle). 5-year OS rates for patients who received 1, 2, 3, 4, 5 or completed treatment were: 16% (95% CI: 7%-29%), 18% (95% CI: 7%-33%), 37% (95% CI: 24%-49%), 52% (95% CI: 40%-63%), 47% (95% CI: 36%-58%) and 76% (95% CI: 74%-77%), respectively. Overall log rank *P*-value: <.000. B and C, Kaplan Meier curve depicting overall survival with 95% CI according to number of R-CHOP cycles received among patients who completed treatment and those who failed to complete for other reasons than non-response or early death (within 30 days after end of last treatment cycle) stratified into 4-5 cycles or 1-3 cycles, among patients 65 years or younger (B) versus older than 65 years at diagnosis (C). Overall log rank *P*-value: <.000

In a multivariable Cox regression analysis including number of chemotherapy cycles, sex, age, stage, PS, bulky disease, elevated LDH, radiotherapy and comorbidity, the overall mortality rate for patients who stopped treatment after 1-3 cycles was 3.3 times higher (95% CI: 2.6-4.1, *P* < .000) than that of patients who completed treatment. The mortality for patients who stopped treatment after 4-5 cycles of treatment was nearly 2-fold compared to patients who completed treatment (HR:1.9, 95% CI: 1.5-2.3, *P* < .000) (Table 2).

The FLYER-study demonstrated that among low-risk patients with aaIPI 0, non-bulky disease aged 60 years or younger, treatment with four cycles of R-CHOP was non-inferior to six cycles of R-CHOP. Therefore, we performed a subgroup analysis of patients aged

TABLE 2 Multivariable analysis presenting hazard ratios (HR) with 95% confidence intervals (CI) for the association of premature treatment stop on outcome, with HR also presented for the adjusting variables sex, age, stage, performance status, elevated LDH, bulky disease, radiotherapy and comorbidity, with patients who stopped treatment due to non-response or early death excluded

	HR	95% CI	*P*-value
Number of cycles			
Completed	1.00 (Reference)	NA	
4-5	1.9	1.5-2.3	<.000
1-3	3.3	2.6-4.1	<.000
Sex			
Female	0.74	0.65-0.85	<.000
Age category			
66-75	1.00 (Reference)	NA	
< 56	0.29	0.21-0.40	<.000
56-65	0.66	0.53-0.81	<.000
76-85	1.7	1.5-2.0	<.000
> 85	2.6	2.0-3.5	<.000
Ann Arbor stage			
I	1.00 (Reference)	NA	
II	1.0	0.8-1.2	.7
III	1.3	1.0-1.6	.03
IV	1.4	1.1-1.7	.004
Performance status score			
0	1.00 (Reference)	NA	
1	1.4	1.2-1.7	<.000
2	1.6	1.2-2.0	<.000
3	1.5	1.1-2.0	.009
4	3.0	1.9-4.7	<.000
LDH			
Normal	1.00 (Reference)	NA	
Elevated	1.3	1.1-1.5	.002
Missing	1.1	0.7-1.8	.6
Bulky disease			
Yes	1.04	0.9-1.2	.7
Radiotherapy			
Yes	0.8	0.6-1.0	.04
CCI			
0	1.00 (Reference)	NA	
1	1.4	1.2-1.7	<.000
≥ 2	1.6	1.3-1.8	<.000

Abbreviations: CCI, Charlson Comorbidity Index; LDH, lactate dehydrogenase; NA = not applicable.

60 years or younger with aaIPI 0 and non-bulky disease in our cohort. In this population-based study, only 234 (7%) patients fulfilled these criteria. Overall, the 5-year OS in this group was 95% (95% CI: 92%-98%). In this group, 218 (93%) completed treatment and only 15 (7%) did not complete treatment for other reasons than non-response or early death, and one patient did not complete treatment due to non-response. Due to these small cohorts, further analyses were not feasible.

4 | DISCUSSION

In this large population-based cohort we demonstrate that 10% of patients diagnosed with DLBCL intended for standard treatment with R-CHOP failed to complete planned treatment for reasons unrelated to non-response. Additionally, 6% stopped treatment prematurely due to stable/progressive disease or early death. Advanced age and poor performance status most strongly predicted failure to complete planned treatment for other reasons than non-response, with 19% and 34% of patients aged 75-85 and >85 years not completing planned treatment, respectively. Further, we show that failure to complete treatment is associated with inferior survival.

The group of DLBCL patients who do not complete planned treatment have not previously been described in detail. A minority of clinical trials provide reasons for why treatment was not completed. In the GELA-study that compared R-CHOP-14 to R-CHOP-21 among patients with DLBCL aged 60-80, 21% of patients withdrew from the study during treatment.[3] Among those who did not complete treatment, 8% stopped treatment due to toxic effects, 6% died, 2% had treatment failure and 5% stopped for other reasons. However, characteristics were not provided for these patients, precluding assessment of risk factors for non-completion. In the pivotal R-CHOP vs CHOP studies by Coiffier et al and Habermann et al (both including patients aged 60 and above) approximately 20% did not receive full treatment, including due to non-response or death.[1,5] In a Danish population-based study, 18.6% of patients received 3-5 cycles, although also including patients with stage I disease managed with 3 cycles + RT. Similarly, in 690 consecutive British patients aged ≥70 treated with R-CHOP, only 71% of patients completed at least six cycles of R-CHOP.[22] In a Portuguese multicenter study including 378 patients aged 60 or above, 23% did not complete planned treatment.[23] Thus, the risk of non-completion is a frequent clinical issue which has, as demonstrated in this study, a major impact on outcome.

The fact that we include adult patients of all ages, might partly explain why the rate of 10% of patients who failed to complete R-CHOP for other reasons than non-response in our study, is lower than that from the clinical trials and population-based studies referenced above, that included a larger proportion of older patients. Further, the 10% of patients with premature treatment stop for other reasons than non-response or early death reported in this study is a conservative estimation as the patients who died before treatment evaluation (likely due to a combination of toxicity and frailty due to the disease) were not included in this count, in order to minimize the risk of reverse causality for non-completion of treatment. When excluding patients who stopped treatment due to death or non-response in the GELA-trial (patients aged 60-80 years), the proportion of non-completing patients was 13%, similar to the proportion of non-completion due to non-response seen in our study. The corresponding

fraction for non-completion excluding death and non-response in the similar, but including patients aged >18, study by Cunningham et al is 9%.[2] The corresponding figure in the MiNT-study, restricted to patients aged 60 or below, was 7%.[6] The difference between non-completion proportions in these clinical trials, that include different age groups, and the higher numbers of non-completion in population-based studies restricted to an older DLBCL cohort, is in line with our study where the risk of non-completion clearly increases with age.

It would be advantageous to be able to identify patients at risk of not completing planned treatment at treatment initiation, in order to be able to modify treatment accordingly to optimize the chance for treatment completion, and thus hopefully improve patient outcome. In this study, patients who did not complete planned cycles of R-CHOP presented with an inferior prognostic setting at diagnosis, with advanced age, poor PS scores and a slightly larger proportion of patients with elevated LDH, extranodal disease and stage IV disease, thus primarily representing an older, frail population of DLBCL patients with advanced disease. This is in line with results from a recent study assessing the use of comprehensive geriatric assessment for DLBCL patients where 20% of patients deemed frail ended treatment prematurely, compared to only 9% among patients classed as fit.[24] Old age, poor performance status, presence of comorbidity and extranodal disease all increased the odds of not completing treatment. This indicates that for patients with these demographics, special considerations should be taken before initiating treatment, to optimize chance for completion.

Discussions regarding optimal treatment for frail patients are ongoing. As demonstrated in the current study, it is important to ensure tolerability of treatment to increase the chance for patients to complete treatment. Thus, an important part in improving outcomes for frail patients may lie in thorough pre-treatment assessment to identify if full standard treatment is feasible or if alternative treatment options, such as initial dose reductions, may in fact be more beneficial by enabling frail patient to actually tolerate, and thus complete treatment. This is in accordance with studies which indicate that well-judged dose reductions are associated with similar outcomes as patients administered full treatment among elderly patients. Previous studies have shown that pre-planned dose reductions are not associated with inferior outcome among comorbid patients aged >80, and non-inferior for patients aged >85.[25,26] Also, the use of pre-phase treatment has been shown to improve treatment tolerability among older patients, and may constitute an important addition to treatment in this group.[27] Unfortunately, data regarding pre-phase treatment was not available and its impact on treatment completion was therefore not possible to evaluate in this series. Further, results in this study high-light the need for novel, more tolerable treatment options for all, put particularly elderly and frail DLBCL patients. The association between 21-day cycle administration with failure to complete planned R-CHOP seen in our study, is likely due to residual confounding by indication. And, the cohort managed with R-CHOP-21 had a poorer prognostic setting at diagnosis compared to patients selected for treatment with R-CHOP-14.

Recently, results from the FLYER study were presented. Here, non-inferiority of four cycles, compared to six, of R-CHOP was demonstrated for low-risk patients aged ≤60 with aaIPI 0 and non-bulky disease.[9] Thus, for the first time it has been shown that full treatment with 6-8 cycles of R-CHOP is not always necessary. The group of patients who fulfilled inclusion criteria for the FLYER-study in this population-based study was very small (7%). This, in combination with the observational and retrospective nature of our study, precluded us from validating their results in the current population-based setting. Nonetheless, although non-completion of treatment was clearly associated with significantly inferior survival, it is noteworthy that there is still a small proportion of non-completing patients in this study who survive long-term. This is even after having received only 1-3 or 4-5 cycles of R-CHOP, although these data need to be interpreted in the light of the fact that patients who died within 30 days of treatment end were not included in the survival analysis. Nonetheless, this indicates that also fewer cycles of R-CHOP may in some cases be able to incur long-term remission, although we lack data regarding additional treatment these patients may have received, apart from radiotherapy. Whether consolidative RT may improve survival among non-completing patients cannot be evaluated in the current study due to the inherent risk of immortal time bias.

This study uses real-world data including the whole DLBCL population in Sweden who started R-CHOP during the studied time period. The availability of data from a recent medical chart review has further minimized the amount of missing data related to treatment response in this study. This represents strengths of our study as a large proportion of patients studied in the current series would have been precluded from inclusion in clinical trials. There are also limitations. Firstly, we lack data regarding dose reductions. It is likely that a proportion of patients, particularly aged >80 years will have received dose-reduced regimens such as R-mini-CHOP. That this data is not available precludes us from deducing mechanistic associations between effect of potential dose reductions on efficacy and tolerability, potentially enabling completion of treatment to a higher extent particularly among elderly/frail patients. However, the probable use of dose-reduced regimens for elderly patients in this study would likely have permitted completion of treatment in a larger proportion of elderly patients, wherefore the lack of data regarding dose reductions does not limit our conclusions. Also, we lack detailed data regarding reasons for premature treatment stop, but with non-response and death excluded it is likely that toxicity is the main reason for why treatment was stopped prematurely in this series.

To our knowledge, this is the first study to analyze the group of DLBCL patients who do not complete planned treatment with R-CHOP for other reasons than non-response. We demonstrate that non-completion of treatment for other reasons than non-response is an important clinical issue, concerning 10% of all adult patients. Age > 75 years and poor performance status were the most important factors to predict failure to complete planned treatment. Further, we show that failure to complete planned treatment with R-CHOP is strongly associated with adverse outcome. These findings indicate a need for improved treatment tailoring with pre-planned dose reductions and/or novel more tolerable therapeutic options, for patients with certain base-line characteristic. To better ascertain which clinical and biological characteristics this may be, further studies are needed.

ACKNOWLEDGMENTS

This study was funded by the Swedish Cancer Society and through public-private real world evidence collaboration between Karolinska Institutet and Janssen Pharmaceuticals (contract: 5–63/2015).

ORCID

Tove Wästerlid https://orcid.org/0000-0002-4281-0349
Sara Ekberg https://orcid.org/0000-0002-7063-467X
Sandra Eloranta https://orcid.org/0000-0001-5806-0573

REFERENCES

1. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235-242.
2. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*. 2013;381:1817-1826.
3. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol*. 2013;14:525-533.
4. Pfreundschuh M, Kuhnt E, Trumper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011;12:1013-1022.
5. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol*. 2006;24:3121-3127.
6. Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2006;7:379-391.
7. Sehn HL et al. No added benefit of eight versus six cycles of CHOP when combined with rituximab in previously untreated diffuse large B-cell lymphoma patients: results from the International Phase III GOYA study. Presented at: The ASH 60th Annual Meeting and Exposition; December 2018; San Diego, CA.
8. Wasterlid T, Biccler JL, Brown PN, et al. Six cycles of R-CHOP-21 are not inferior to eight cycles for treatment of diffuse large B-cell lymphoma: a Nordic Lymphoma Group Population-based Study. *Ann Oncol*. 2018;29:1882-1883.
9. Poeschel V, Held G, Ziepert M, et al. Excellent outcome of young patients (18-60 years) with favourable-prognosis diffuse large B-cell lymphoma (DLBCL) treated with 4 cycles CHOP plus 6 applications of rituximab: results of the 592 patients of the Flyer Trial of the Dshnhl/GLA. *Blood*. 2018;132:781-781.
10. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol*. 2008;26:2258-2263.
11. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol*. 2008;9:105-116.
12. Glimelius I, Ekberg S, Jerkeman M, et al. Long-term survival in young and middle-aged Hodgkin lymphoma patients in Sweden 1992-2009-trends in cure proportions by clinical characteristics. *Am J Hematol*. 2015;90:1128-1134.
13. Ellin F, Landstrom J, Jerkeman M, et al. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood*. 2014;124:1570-1577.
14. Wästerlid T, Brown PN, Hagberg O, et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic Lymphoma Group. *Ann Oncol*. 2013;24:1879-1886.
15. Jerkeman M. *Swedish Lymphoma Registry 2000-2012*. Lund, Sweden: Regional Cancer Center South; 2014.
16. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
17. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology*. 2019;2009(1):523-531. https://doi.org/10.1182/asheducation-2009.1.523.
18. Jaffe HN, Steain H, Vardiman JW, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001.
19. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.
20. de Groot V, Beckerman H, Lankhorst GJ, et al. How to measure comorbidity. a critical review of available methods. *J Clin Epidemiol*. 2003;56:221-229.
21. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendationsdagger. *Ann Oncol*. 2015;26:288-300.
22. Eyre TA, Martinez-Calle N, Hildyard C, et al. Impact of intended and relative dose intensity of R-CHOP in a large, consecutive cohort of elderly diffuse large B-cell lymphoma patients treated with curative intent: no difference in cumulative incidence of relapse comparing patients by age. *J Intern Med*. 2019;285:681-692.
23. Alvarez R, Esteves S, Chacim S, et al. What determines therapeutic choices for elderly patients with DLBCL? Clinical findings of a multicenter study in Portugal. *Clin Lymphoma Myeloma Leuk*. 2014;14:370-379.
24. Ong DM, Ashby M, Grigg A, et al. Comprehensive geriatric assessment is useful in an elderly Australian population with diffuse large B-cell lymphoma receiving rituximab-chemotherapy combinations. *Br J Haematol*. 2019;187:73-81.
25. Eyre TA, Salisbury R, Eyre DW, et al. Results of a large retrospective analysis of the effect of intended dose intensity of R-CHOP on outcome in a cohort of consecutive, unselected elderly patients with de novo diffuse large B cell lymphoma. *Br J Haematol*. 2016;173:487-491.
26. Juul MB, Jensen PH, Engberg H, et al. Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: A Danish population-based cohort study. *Eur J Cancer*. 2018;99:86-96.
27. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood*. 2004;104:634-641.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Wästerlid T, Harrysson S, Andersson TM-L, et al. Outcome and determinants of failure to complete primary R-CHOP treatment for reasons other than non-response among patients with diffuse large B-cell lymphoma. *Am J Hematol*. 2020;95:740–748. https://doi.org/10.1002/ajh.25789