Impact of vincristine dose reduction on overall survival in patients with DLBCL

B.A. Zweers[1]-5617103

Dr. E. van Leeuwen-Segarceanu[2]
P.A. J. Kortleve[2]
Dr. M. Söhne[2]
Dr. A. de Vries Schultink[3]
Dr. M. van den Broek[3]

1 Utrecht University
2 Department of Hematology Sint Antoniusziekenhuis
3 Department of Clinical Pharmacy Sint Antoniusziekenhuis

January-April 2022

List of abbreviations

DLBCL = Diffuse large B-cell lymphoma

R-CHOP = Rituximab, Cyclophosphamide, Doxorubicin, Prednisone

LDH = Serum lactate dehydrogenase level

ECOG PS = Eastern Cooperative Oncology Group Performance Status,

IPI = International Prognostic Index

VIPN = Vincristine induced polyneuropathy

OS = Overall survival

PFS = Progression free survival

RDI = Relative dose intensity

IKNL = Netherlands cancer registry

GCB = Germinal center B-cell

HR = Hazard ratio

VSLI = Vincristine sulfate liposomal injection

Impact of vincristine dose reduction on overall survival in patients with DLBCL

B. A. Zweers

Abstract

Introduction The standard first-line treatment for diffuse large B-cel lymphoma (DLBCL), an aggressive non-hodgkin lymphoma, is the R-CHOP regimen: a combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. The most common adverse effect of this regime is neurotoxicity caused by vincristine. For this reason vincristine is frequently reduced or omitted from the therapy.

Methods In this retrospective cohort study medical records from patients with de novo DLBCL, diagnosed between 2015 and 2021, were reviewed. The objective was to investigate the effect of vincristine dose reduction on overall survival and progression free survival in DLBCL patients treated with R-CHOP. Patients were included if they had completed at least six courses of chemotherapy. Survival status was obtained through the personal records database.

Results In total 101 patients were included in our analysis. Vincristine was reduced or omitted in 49/101 patients. The overall survival of all patients was high, 88%. Vincristine reduction did not affect progression free survival or overall survival in our cohort. Relative dose intensity <85% produced a hazard ratio of 0.359 (95% confidence interval 0.097-1.325). In univariate analysis only age was associated with poorer survival.

Discussion Even though our study was potentially underpowered, we did not find a difference in progression free survival or in overall survival in DLBCL patients with and without reduction of vincristine from R-CHOP.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma which is the most common histological subtype among all non-Hogdkin's lymphoma's. (1–3)

The 5-year overall survival of patients diagnosed with DLBCL has increased to 50-60%, after introduction of the monoclonal antibody rituximab (R). (4,5) Known prognostic factors in DLBCL are age, Ann Arbor stage, number of extra nodal involvements, renal/adrenal involvement, elevated serum lactate dehydrogenase level (LDH) and Eastern Cooperative Oncology Group Performance Status (ECOG PS), summarized in the International Prognostic Index (IPI). (6–8) The standard first-line therapy for DLBCL consist of a combination of rituximab (R) with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Depending on stage of disease three till eight cycles of R-CHOP are administered. In case of primary testicular DLBCL, central nervous system (CNS) prophylaxis and contralateral radiotherapy is added to standard therapy. (9–14) Previous research shows that reduced relative dose intensity (RDI) of CHOP regimen is associated with poorer progression free survival (PFS) and overall survival (OS) in patients with DLBCL. (15–18) However, dose-limiting toxicities of the different chemotherapeutics in R-CHOP challenge clinical practice. For vincristine, a vinca-alkaloid, the dose-limiting complication is most often vincristine induced polyneuropathy (VIPN) which can be observed in 30-40% of DLBCL patients treated with R-CHOP regimens. (19–21) VIPN can range from mild sensory neuropathy, such as peripheral numbness or mild paresthesia, but can also cause more severe neuropathic pain or motor neuropathy interfering with daily activities and quality of life. (22,23) VIPN is dose intensity related and when vincristine is timely reduced or omitted from therapy neuropathic symptoms can be reversible. However, off-therapy worsening of VIPN is described in up to 30%. In advanced stage of VIPN, neuropathic damage is irreversible. (24,25) To date, there is no prophylaxis or treatment for neurotoxicity available, vincristine dose reduction or omission is the only intervention to ameliorate or prevent worsening of VIPN. (19,26,27) As previously described, RDI of CHOP regimens is associated with outcomes in DLBCL. However, limited evidence is available on the impact of vincristine dose reduction alone on overall survival. Recently, two large studies published a significant difference in OS between patients who were administered reduced dose of vincristine versus full dose of vincristine. (28,29) Whereas a third study did not find a difference in OS when patients with and without omitted vincristine were compared. (30)

The aim of this retrospective cohort study was to investigate the effect of vincristine relative dose intensity (RDI) on overall survival and progression free survival in de novo DLBCL patients treated with R-CHOP in routine clinical practice in the Sint Antoniusziekenhuis, the Netherlands.

Berber.a.zweers@gmail.com

Materials and Methods

Patients and data

Patients who were diagnosed with de novo DLBCL between January 2015 and August 2021 and treated with rituximab and either CHOP or mini-CHOP (reduced-dose CHOP) in the St. Antonius Hospital, the Netherlands, were reviewed retrospectively. Patients were identified through the Santeon Farmadatabase. Patients were included if they had completed at least six courses of R-CHOP, with or without radiation therapy, and were histologically confirmed as DLBCL. Patients with primary mediastinal and testicular DLBCL were also included in this analysis. Patients with transformed low-grade lymphoma, post-transplant lymphoproliferative disease and HIV positive patients were excluded. Patients were also excluded if they had received first line treatment regimens other than R-(mini)CHOP (e.g., R-CHOP + etoposide, radiation monotherapy). Or if they were enrolled in clinical trials receiving additional immunotherapy (e.g., HOVON 131/150).
Clinical data including age, gender, body surface area, ECOG PS, Ann Arbor stage, number of extra nodal involvements, and level of LDH were retrieved from electronic medical records. In addition to the presence of MYC, BCL-2 or BCL-6- gene rearrangements in the tumor tissue. The immunohistochemical expression of CD10, BCL-6 and MUM1 was used to classify the histological subtype Germinal Center B-Cell type (GCB) and non-GCB type DLBCL. (31) The ECOG Performance Scale is a measurement for level of physical functional ability ranging from 0 (normal) to 5 (dead). Severity of neurotoxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) from the national cancer institute. CTCAE ranges from 0 (no neuropathy) to 4 (paralysis).(32) Data extraction from medical records was performed manually by B.A. Zweers using RedCap version 12.0.19.

Treatment

Patients were treated with R-CHOP regimens, including rituximab 375 mg/m^2 intravenous (i.v.) or a fixed dose of 1400 mg subcutaneous, cyclophosphamide 750mg/m2 i.v., doxorubicin 50mg/m^2 i.v., vincristine 1.4 mg/m^2 (maximum 2.0 mg) i.v. and prednisolone 100mg i.v. all given on day 1, and prednisolone 100mg orally on days 2 to 5. In some cases, for the first cycle a reversed-chop schedule was followed in which prednisone was given during a couple of days before day 1 of instead from day 2 to 5. R-CHOP therapy was on a 3-week cycle and treatment was completed after 6 or 8 cycles with or without radiation therapy. Patients aged above 80 years, or in frail condition were allocated to receive R-mini-CHOP which was administered according to the same schedule but with a reduced dose of vincristine (=1 mg fixed dose), doxorubicin (25 mg/m^2), cyclophosphamide (400mg/m^2) and prednisone (40 mg/m^2). The choices of treatment regimen, dose omission or reduction of all chemotherapeutic agents, and treatment schedule were adjusted by the attending physician. Data on the actual received dose was obtained from electronical medical records and was available for all patients.
Relative dose intensity (RDI) for vincristine, doxorubicin and cyclophosphamide was calculated using the following formula in accordance with Yamagushi et al. (33)

$$\frac{Actual\ delivered\ total\ dose\ chemotherapy\ \left(\frac{mg}{m2}\right)\ /\ Actual\ time\ to\ complete\ therapy}{Planned\ total\ dose\ chemotherapy\ \left(\frac{mg}{m2}\right)/\ Planned\ time\ to\ complete\ therapy}\ x\ 100\%$$

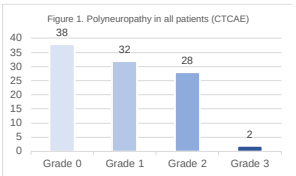
For example, if a patient received 2 mg vincristine from cycle 1 up to 3 and vincristine dose was reduced to 1 mg from cycle 4 up to 6 and no treatment delay had occurred RDI vincristine was calculated as 75%. For patients who were treated with mini-CHOP regime from start of therapy or from cycle 2, the mini-CHOP chemotherapy dose was regarded as the full planned total dose chemotherapy. In other cases, e.g., when a patient's regime was switched from full-dose CHOP to mini-CHOP from cycle 3 or later, this was regarded as a dose reduction for doxorubicin, vincristine, and cyclophosphamide.

Outcomes

Remission status was determined by end of treatment computed tomography (CT) or positron emission tomography (PET)-CT. Vital status was obtained through the personal records database on 31-01-2022. (34) OS was defined from date of diagnosis until death from any cause or censoring alive. PFS was defined as from date of diagnosis until disease progression, recurrence, or death, whatever came first, or last follow-up.

Statistical Analysis

For baseline characteristics the chi-square test was used to compare distribution of categorical variables in patients with and without vincristine reduction. The non-parametric Mann-Whitney U test was used for the IPI-score variable. Survival analysis was performed for OS and PFS using the Kaplan-Meijer method. Different RDI cut-offs values were compared using the log-rank test. RDI cut-off values of <85% and <50% for vincristine and doxorubicin, respectively were evaluated. (28,35) Univariate and multivariate analyses were performed using Cox proportional hazard regression to assess the effects of RDI vincristine and doxorubicin and prognostic variables from the IPI-score on OS. A p value of < 0.05 was considered statistically significant. A sensitivity analysis was performed including patients treated with R-mini-CHOP. All statistical analyses were conducted using IBM SPSS for Windows, Version 26.0 (2019)



Results

Study cohort and treatment regimen

A total of 148 patients diagnosed with primary DLBCL were treated with R-CHOP in the St. Antonius Hospital between January 2015 and August 2021. After screening 103 patients were eligible for inclusion, two moved away before end of treatment and were lost to follow-up. A total of 101 patients were included in this analysis. For full identification and exclusion process see appendix Figure 1. The mean age of the total population was 62 years, 51 patients were male, 4 had an ECOG PS of ≥2. Baseline characteristics of patients with and without dose reduction are shown in Table 1.

Vincristine tended to be more often reduced in female patients and patients with higher Ann Arbor stage (p=0.059, p=0.057).
All other clinical and tumor parameters were well balanced between patients with and without vincristine reduction. Vincristine dose was reduced in 49/101 patients. The reason for reduction was most commonly vincristine induced polyneuropathy (84%), other reasons were toxicity and toxicity related infections (12%), or constipation (4%). In 62% of all patients VIPN occurred at some point during therapy, percentage per grade are shown in figure 1. The main reason for treatment delay was (febrile) neutropenia. Some patients experiencing febrile neutropenia were treated with granulocyte colony-stimulation factor during the following cycles. Treatment delay varied from 3 days to 56 days. There was no difference observed in treatment delay between groups with or without vincristine reduction (x^2, p=0.114). Of 101 patients treated with R-CHOP, fourteen patients received R mini-CHOP from cycle 1 or 2 until end of treatment. Eight patients switched from R-CHOP to R-mini-CHOP during treatment. All patients treated (partially) with R mini-CHOP were aged > 70 years except for one who had pre-existent limited cardiac function. Doxorubicin was selectively reduced in three patients due to cardiotoxicity or transient liver dysfunction.

Table 1. Baseline characteristics

	Vincristine reduced dose N= 49, (%)	**Vincristine full dose N= 52, (%)**	***P* Value**
Gender			
Male	20 (41)	31 (60)	0.059[a]
Female	29 (59)	21 (40)	
Age,y			
Mean age (SD)	62,7 (15,5)	61,6 (17,3)	0.726[a]
>60	31 (63)	30 (58)	0.567[a]
ECOG PS			
2 - 4	3 (6)	1 (2)	0.279[a]
LDH			
>Upper normal limit	30 (61)	32 (62)	0.975[a]
Stage Ann Arbor			
III-IV	30 (61)	22 (42)	0.057[a]
Extranodal involvements			
≥ 2	11 (22)	22 (21)	0.875[a]
Kidney/adrenal	4 (8)	4 (8)	0.930[a]
IPI score			0.171[b]
0	4 (8)	5 (10)	
1	10 (20)	16 (31)	
2	18 (37)	19 (37)	
3	9 (18)	6 (11)	
4	8 (16)	6 (11)	
5	0	0	
Myc-rearrangement			
Myc- mutation	2 (4)	3 (6)	0.887[a]
Double hit	2 (4)	3 (6)	0.887[a]
Unknown	15 (31)	7 (13)	
Tumor Type			
GCB	20 (41)	28 (54)	0.209[a]
Non-GCB	25 (51)	23 (44)	
Unknown	4 (8)	1 (2)	

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; LDH= lactate dehydrogenase; IPI = international prognostic index (0-1 low risk, 2-3 intermediate risk, 4-5 high risk); GCB = germinal center Bcell-like.
[a]= X^2
[b]= Mann-Whitney *U* test

Figure 2. Kaplan-Meijer curve of overall survival (OS) for patients sorted by relative dose intensity (RDI) of vincristine

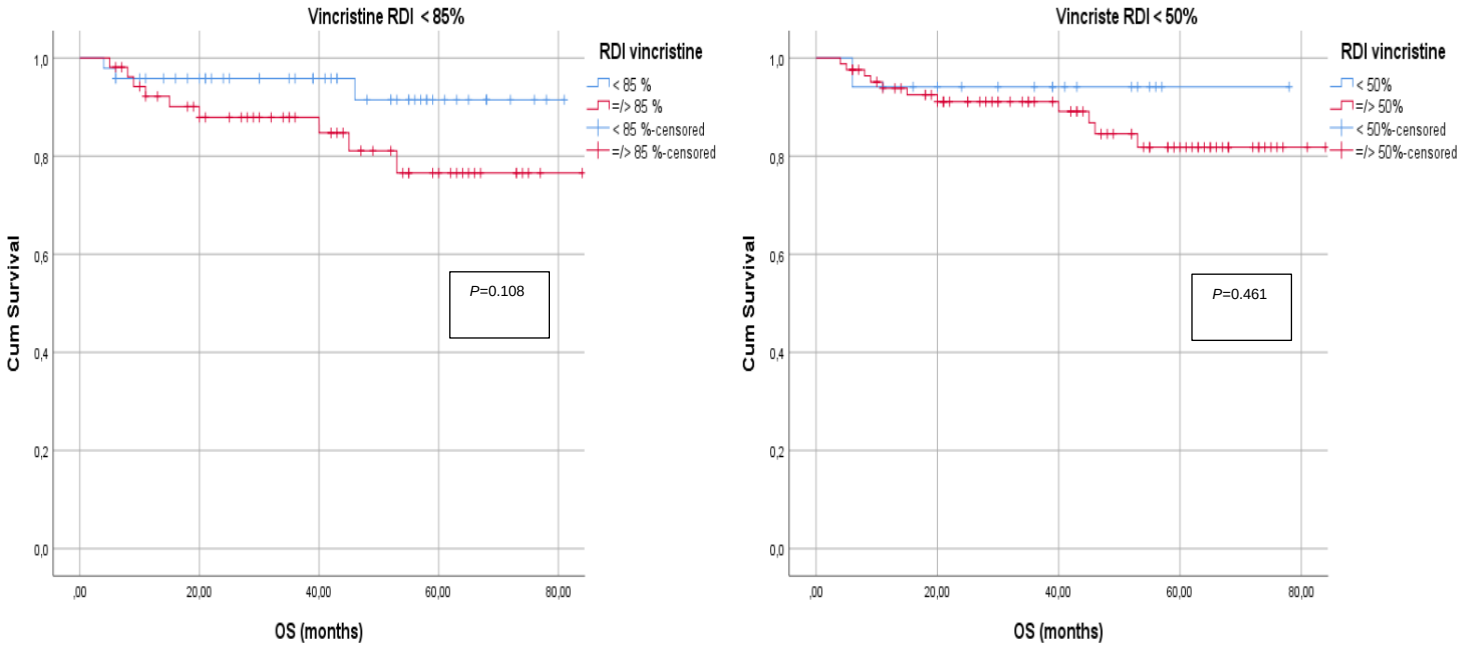
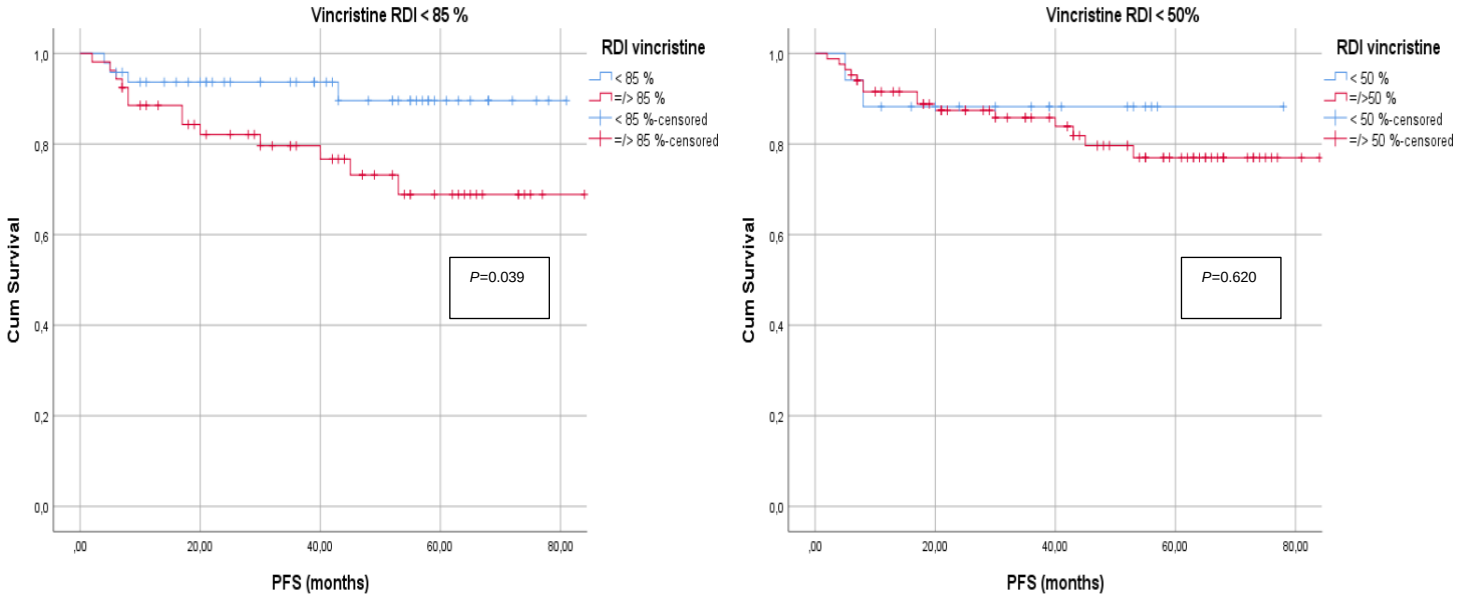


Figure 3. Kaplan-Meijer curve of progression free survival (PFS) for patients sorted by relative dose intensity (RDI) of vincristine



RDI and treatment outcomes

The mean observation time was 3.6 years for the patients that survived. Of all patients, 89% achieved complete remission, 6% had partial response and 5% had progressive disease after first line of therapy. Patients with vincristine reduction had similar overall response with complete remission in 92%, partial response in 6%, and progressive disease in 2%. At the time of data cut-off 12 deaths had occurred in the total population. For all patients OS was 88.2%, PFS was 83.2%. Mean RDI of vincristine was 78%. Patients with reduced vincristine RDI had similar OS compared with patients who received full dose of vincristine. OS curves of vincristine RDI <85% and RDI <50% are shown in Figure 2. In univariate analysis, only age was significantly associated with OS with hazard ratio (HR) of 1.115 (95% CI, 1.039-1.197). Other predictors from the IPI-score such as LDH level, ECOG PS, Ann Arbor stage, number of extra nodal involvements, did not reach statistical significance in univariate model. OS did not differ for the small number of patients with double hit lymphoma in our cohort compared with those without MYC-rearrangements. Reduced RDI of either vincristine or doxorubicin was not significantly associated with OS in univariate analysis. In multivariate Cox regression when RDI of vincristine was

inserted alternately with one other predictor, vincristine relative dose intensity also did not reach statistical significance as predictor for OS, HR 1.024 (0.990-1.060). When inserted with RDI vincristine in multivariate analysis, age with HR 1.114 (1.039-1.194); and ECOG PS with HR 15.173 (1.306-176.32) were significantly associated with poorer OS. Results of univariate and multivariate analysis are shown in Table 2.

Patients with vincristine RDI < 85% of vincristine tended to have better PFS than patients with vincristine RDI> 85% (p=0.039). PFS curves are shown in figure 3. Univariate analysis for PFS, demonstrated that the association between vincristine RDI < 85% and higher PFS did not prevail with HR of 0.328 (0.107-1.005, p=0.051). Multivariate analysis with RDI vincristine and RDI doxorubicin produced HR 1.018 (0.992-1.045, p=0.1018) and HR 1.047 (0.953-1.151, p=0.339), respectively.

R-mini-CHOP

A sensitivity analysis was performed for the effect of treatment regimen on OS. Patients who were treated with R-mini-CHOP regimen from the start or from the second cycle were compared with patients who were switched to R-mini-CHOP later in treatment or received regular R-CHOP regimen trough all cycles. Patients treated with R-mini-CHOP had significantly worse OS than patients treated with regular R-CHOP. Kaplan-Meijer curves for OS are shown in figure 4. In univariate analysis R-mini-CHOP regimen produced HR of 11.1 (95% CI 3.470-35.707, p<0.001). When treatment regimen and age were assessed together in multivariate analysis, both predictors did not reach statistical significance with HR 4.1 (0.928-18.162, p=0.063) and HR 1.066 (0.989-1.149, p=0.097), respectively. When only patients allocated to regular R-CHOP were analyzed, vincristine RDI was also not associated with OS.

Figure 4. Kaplan-Meijer curve of OS for patients treated with R-CHOP vs R-mini-CHOP regimen

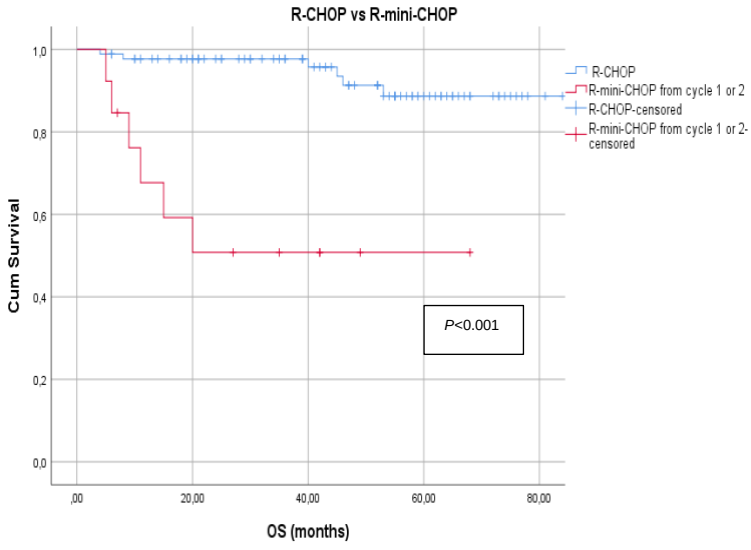


Table 2. Univariate and multivariate analysis for factors involved overall survival.

	n, (%)	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P Value	HR (95% CI)	P Value
Age >60	61 (60)	7.67 (0.991-59.491)	0.051		
Age continue		1.115 (1.039-1.197)	**0.003**	1.114 (1.039-1.194)	**0.003**
LDH > upper normal limit	62 (61)	1.304 (0.392-4.333)	0.665		
ECOG PS 2-4	4 (4)	5.007 (0.611-41.035)	0.133	15.173 (1.306-176.328)	**0.030**
Ann Arbor stage III-IV	52 (51)	1.909 (0.575-6.346)	0.291		
IPI score > 2	29 (29)	2.554 (0.823-7.922)	0.105	2.777 (0.892-8.652)	0.078
Extranodal involvements ≥ 2	22 (22)	1.127 (0.313-4.282)	0.827		
Double hit lymphoma	5 (5)	1.736 (0.217-13.887)	0.603		
Vincristine RDI <85%	48 (48)	0.359 (0.097-1.325)	0.359		
Vincristine RDI <50%	17 (17)	0.471 (0.061-3.655)	0.472		
Doxorubicin RDI <85 %	13 (13)	0.041 (0.000-102.252	0.423		
Vincristine RDI continuous		1.023 (0.991-1.056)	0.156	1.024 (0.990-1.060)	0.170
Doxorubicin RDI continuous		1.031 (0.949-1.122)	0.460	1.015 (0.933-1.105)	0.724

Cox proportional hazard regression analysis.
Abbreviations: HR = Hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; IPI = international prognostic index (0-1 low risk, 2-3 intermediate risk, 4-5 high risk); GCB = germinal center Bcell-like; RDI = relative dose intensity,

Discussion

In this retrospective study the relation between relative dose intensity of vincristine and overall survival was investigated. In our cohort consisting of 101 de novo DLBCL patients, there was no significant difference found in OS between patients who had received high relative dose intensity versus low relative dose intensity of vincristine. When treatment delay was disregarded and only the actual received dose of chemotherapy was considered, there was also no association found between relative received dose of vincristine and OS. Surprisingly, patients with RDI vincristine < 85% tended to have higher PFS than patients with RDI vincristine > 85%. This could be explained by the fact that in PFS death also counted as an event, and in our study population most patients that had died had a vincristine RDI >85%. In univariate and multivariate analysis this association did not prevail.

Patients who were treated with R-mini-CHOP had significantly worse OS than patients treated with regular R-CHOP in this cohort. However, since R-mini-CHOP regimen is administered only in patients with advanced age, frail condition or in patients with comorbidity, this difference in OS between patients treated with mini-CHOP and regular CHOP can not only be attributed to the treatment regimen. In previously conducted research similar outcomes were found for reduced CHOP-regimens. A large systematic review by Bataillard et al, considering 5188 patients, concluded that R-mini-CHOP regimen is associated with inferior survival in DLBCL patients aged < 80 years, but lower intended or relative dose intensity is not associated with poorer outcome in the elderly above 80 years. (36, 37) To our knowledge, four retrospective studies have investigated the effect of vincristine reduction alone on OS. The first study to investigate this effect was conducted by Utsu et. al, in which low RDI of Vincristine was associated with significant lower OS (74% vs 96%) even when high RDI's of doxorubicin and cyclophosphamide was maintained.(35) A second study by Marshall et al, consisting of 576 DLBCL patients, also found an association between lower RDI of vincristine and impaired 4-year overall survival (70% vs. 82%). In multivariate analysis this association only prevailed for the subgroup who had received very low RDI vincristine (<25%). A third study by Hatzl et. al analyzed two

cohorts, one cohort consisting of patients with and without reduced dose of vincristine (n=382) and a second cohort (n=605) in which vincristine was substituted with vinorelbine when VIPN occurred. Within the first cohort reduced dose of vincristine was associated with impaired 5-year OS (61% vs 73%). In the second cohort patients receiving substituted vinorelbine reported improvement of neuropathy symptoms and had better 5-year OS (75% vs. 70%). However, in the fourth study by Mörth et. al in which 541 DLBCL patients with were analyzed, no association between vincristine RDI and overall survival was found. (30)

The findings of the present study should be seen in light of its strengths and limitations. First, to enable accurate calculations of RDI's of chemotherapeutic agents, patients were only considered eligible when they had completed at least six cycles of R-(mini)-CHOP. This led to a smaller sample size and introduced inclusion bias, since patients who had died before end of treatment were excluded from our report. This is however in line with methodology of previous studies covering the same topic.

Second, to prevent overestimation of the effect of vincristine RDI if the R-mini-CHOP regime was planned from the first or second treatment cycle, the mini-CHOP regime was regarded as the full planned chemotherapy dose. In previously conducted research this was addressed in a similar way. (28) Third, overall survival rate in our cohort was high, 88%. On forehand, sample size was calculated based on results of previous studies and minimal needed sample size was predicted between 82 and 487 patients. The overall survival rate in our cohort was higher than in previous studies in which overall survival rate ranged between 67.3%(29), 76.5%(35) and 81% (28). The mean follow-up time of our cohort was 3.6 years, in the previous studies mentioned this ranged from 2.5 – 10 years. Strict inclusion criteria were used to create a representative study population for our research question. Unfortunately, these strict inclusion criteria in combination with low event rate, led to an underpowered study sample.

The fourth limitation is the retrospective design of this study. However, since 2015 chemotherapy administration is registered in electronical patients records and data on actual received dose of vincristine, doxorubicin, cyclophosphamide, and rituximab is reliable. Because cyclophosphamide was only reduced paired with doxorubicin, we decided to correct in multivariate analysis only for doxorubicin RDI. For self-administered oral prednisone, only prescriptions were available in medical records. Therefore, actual prednisone administration could not be verified. To our knowledge, only one patient did not take the prescribed prednisone during treatment. We did not include RDI of prednisone in our statistical model. Our sample size and event rate were too small to perform sub analyses on cause of death.

The main reason for vincristine reduction is VIPN. (26,36) Different approaches for delivering high dose of anti-tumor vinca-alkaloid with acceptable toxicity are currently investigated. For example, vinorelbine as a substitute for vincristine showed promising results in Hatzl et. al. (29) And in animal models vincristine sulfate liposomal injection (VSLI) resulted in higher maximum tolerated dose and anti-tumor property than regular vincristine. (38) In a phase-2 study in young patients with acute lymphatic leukemia, high delivered dose VSLI had comparable toxicity compared with vincristine. (39) And in a phase 2 study regarding aggressive non-Hodgkin lymphoma's and DLBCL, substitution of vincristine by high dose VSLI in R-CHOP resulted in slightly better OS with similar toxicity. (40) However, the number of participants in these 2 studies was small and the reduction of VIPN is arguable. The results of a large, randomized phase 3 trial on VSLI in elderly patients with DLBCL (NCT01478542) are expected in 2024.

Conclusion

In our cohort we did not observe a relationship between relative dose intensity of vincristine and overall survival in DLBCL patients. Considering recent literature, were reduced dose of vincristine was to some extent associated with worse outcome, our study was potentially underpowered.

Declarations

The study was approved by the local review board of st. Antonius Ziekenhuis Nieuwegein, the Netherlands. The authors declare no conflicts of interest.

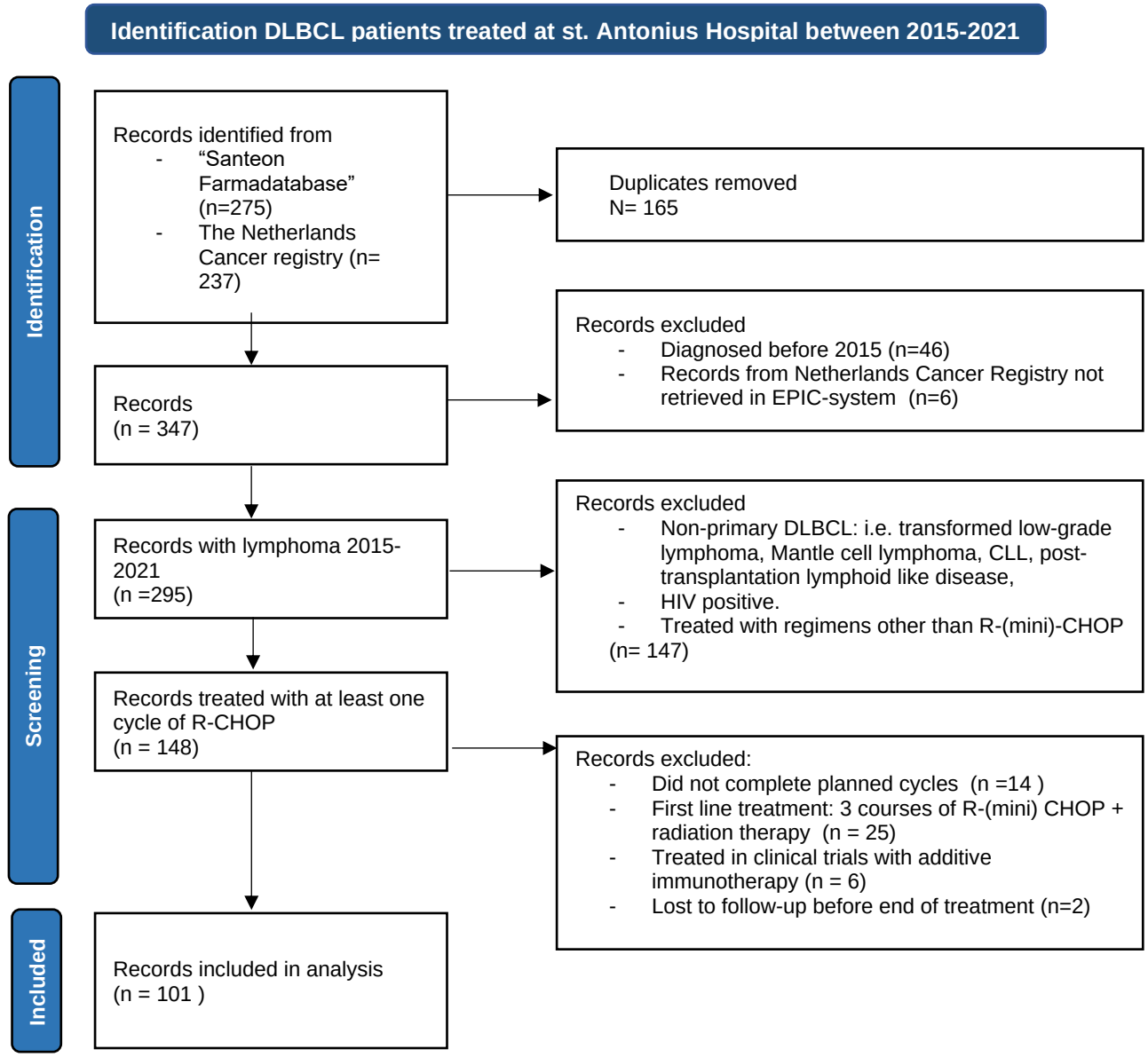
References

1. Non-Hodgkin's Lymphoma | Harrison's Principles of Internal Medicine, 20e | AccessMedicine | McGraw Hill Medical [Internet]. [cited 2022 Feb 10]. Available from: https://accessmedicine-mhmedical-com.proxy.library.uu.nl/content.aspx?sectionid=192018038&bookid=2129#247827892
2. Borowitz et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Swerdlow SH, editor. Vol. 2, WHO Press, Geneva. 2008. 176–8, 171-5,168-70, 150–1 p.
3. Caron A. Jacobson; Dan L. Longo. Non-Hodgkin's Lymphoma | Harrison's Principles of Internal Medicine, 20e | AccessMedicine | McGraw Hill Medical [Internet]. 2018 [cited 2022 Feb 10]. Available from: https://accessmedicine-mhmedical-com.proxy.library.uu.nl/content.aspx?sectionid=192018038&bookid=2129#247827892
4. Nederlandse Kankerregistratie, IKNL [Internet]. [cited 2022 Feb 10]. Available from: https://iknl.nl/kankersoorten/hemato-oncologie/nkr-cijfers/dlbcl
5. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. American Journal of Hematology [Internet]. 2019 May 1 [cited 2022 Feb 10];94(5):604–16. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25460
6. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood [Internet]. 2007 Mar 1 [cited 2022 Feb 10];109(5):1857–61. Available from: https://pubmed.ncbi.nlm.nih.gov/17105812/
7. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. J Clin Oncol [Internet]. 2016 Sep 10 [cited 2022 Feb 10];34(26):3150–6. Available from: https://pubmed.ncbi.nlm.nih.gov/27382100/
8. Oken MM, Creech RH, Davis TE. Toxicology and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology: Cancer Clinical Trials [Internet]. 1982 [cited 2022 Feb 11];5(6):649–55. Available from: https://ecog-acrin.org/resources/ecog-performance-status/
9. Pfreundschuh M, Trümper L, Österborg A, Pettengell R, Trneny M, Imrie K, 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. The Lancet Oncology. 2006 May 1;7(5):379–91.
10. Coiffier B, Thieblemont C, van den Neste E, Lepeu G, Plantier I, Castaigne S, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010 Sep 23;116(12):2040–5.
11. Hovon richtlijn- Diffuus grootcellig B-cel lymfoom [Internet]. 2018. [cited 2022 Feb 10]. Available from: https://hovon.nl/_asset/_public/TreatmentGuidelines/Treatme

ntGuidelines_Lymphoma/DLBCL-HOVON-website-augustus-2018-clean.pdf
12. Vitolo U, Chiappella A, Ferreri AJM, Martelli M, Baldi I, Balzarotti M, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. J Clin Oncol [Internet]. 2011 Jul 10 [cited 2022 Feb 10];29(20):2766–72. Available from: https://pubmed.ncbi.nlm.nih.gov/21646602/
13. Cunningham D, Hawkes EA, Jack A, Qian W, Smith P, Mouncey P, 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 [Internet]. 2013 [cited 2022 Feb 10];381(9880):1817–26. Available from: https://pubmed.ncbi.nlm.nih.gov/23615461/
14. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. American Journal of Hematology [Internet]. 2019 May 1 [cited 2022 Mar 26];94(5):604–16. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/ajh.25460
15. Yamaguchi H, Hirakawa T, Inokuchi K. Importance of Relative Dose Intensity in Chemotherapy for Diffuse Large B-Cell Lymphoma. 〔J Clin Exp Hematopathol. 2011;51(1):1–5.
16. Długosz-Danecka M, Szmit S, Ogórka T, Skotnicki AB, Jurczak W. The average relative dose intensity of R-CHOP is an independent factor determining favorable overall survival in diffuse large B-cell lymphoma patients. Cancer Medicine. 2019 Mar 1;8(3):1103–9.
17. Epelbaum R, Haim N, Ben-Shahar M, Ron Y, Cohen Y. Dose-intensity analysis for CHOP chemotherapy in diffuse aggressive large cell lymphoma. Isr J Med Sci. 24(9–10):533–8.
18. Hirakawa T, Yamaguchi H, Yokose N, Gomi S, Inokuchi K, Dan K. Importance of maintaining the relative dose intensity of CHOP-like regimens combined with rituximab in patients with diffuse large B-cell lymphoma. Annals of Hematology. 2010 Sep;89(9):897–904.
19. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. Journal of the Peripheral Nervous System [Internet]. 2008 Mar 1 [cited 2022 Feb 10];13(1):27–46. Available from: https://onlinelibrary-wiley-com.proxy.library.uu.nl/doi/full/10.1111/j.1529-8027.2008.00156.x
20. Verstappen CCP, Koeppen S, Heimans JJ, Huijgens PC, Scheulen ME, Strumberg D, et al. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology. 2005 Mar 22;64(6):1076–7.
21. Burgess J, Ferdousi M, Gosal D, Boon C, Matsumoto K, Marshall A, et al. Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment. Oncol Ther [Internet]. 2021 Dec 1 [cited 2022 Apr 6];9(2):385–450. Available from: https://pubmed.ncbi.nlm.nih.gov/34655433/
22. Legha SS. Vincristine Neurotoxicity. Medical Toxicology 1986 1:6 [Internet]. 2012 Nov 27 [cited 2022 Feb 23];1(6):421–7. Available from: https://link.springer.com/article/10.1007/BF03259853
23. Gidding CEM, Kellie SJ, Kamps WA, de Graaf SSN. Vincristine revisited. Critical Reviews in Oncology/Hematology. 1999 Feb 1;29(3):267–87.
24. Postma TJ, Benard BA, Huijgens PC, Ossenkoppele GJ, Heimans JJ. Long-term effects of vincristine on the peripheral nervous system. J Neurooncol [Internet]. 1993 Jan [cited 2022 Apr 7];15(1):23–7. Available from: https://pubmed.ncbi.nlm.nih.gov/8384253/
25. Verstappen CCP, Koeppen S, Heimans JJ, Huijgens PC, Scheulen ME, Strumberg D, et al. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. Neurology. 2005 Mar 22;64(6):1076–7.
26. Li G zhou, Hu Y hui, Li D yi, Zhang Y, Guo H li, Li Y man, et al. Vincristine-induced peripheral neuropathy: A mini-review. NeuroToxicology. 2020 Dec 1;81:161–71.
27. Koeppen S, Verstappen CCP, Körte R, Scheulen ME, Strumberg D, Postma TJ, et al. Lack of neuroprotection by an ACTH (4-9) analogue. A randomized trial in patients treated with vincristine for Hodgkin's or non-Hodgkin's lymphoma. Journal of Cancer Research and Clinical Oncology [Internet]. 2004 Mar 16 [cited 2022 Feb 23];130(3):153–60. Available from: https://link.springer.com/article/10.1007/s00432-003-0524-9
28. Marshall S, Nishimura N, Inoue N, Yamauchi H, Tsuyama N, Takeuchi K, et al. Impact of Omission/Reduction of Vincristine From R-CHOP in Treatment of DLBCL. Clin Lymphoma Myeloma Leuk [Internet]. 2021 Mar 1 [cited 2022 Feb 10];21(3):162–9. Available from: https://pubmed.ncbi.nlm.nih.gov/33483276/
29. Hatzl S, Posch F, Rezai A, Gornicec M, Beham-Schmid C, Magnes T, et al. Vinorelbine as substitute for vincristine in patients with diffuse large B cell lymphoma and vincristine-induced neuropathy. Supportive Care in Cancer. 2021 Sep 1;29(9):5197–207.
30. Mörth C, Valachis A, Sabaa AA, Molin D, Flogegård M, Enblad G. Does the omission of vincristine in patients with diffuse large B cell lymphoma affect treatment outcome? Ann Hematol [Internet]. 2018 Nov 1 [cited 2022 Feb 10];97(11):2129–35. Available from: https://pubmed.ncbi.nlm.nih.gov/30091025/
31. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood [Internet]. 2004 Jan 1 [cited 2022 Feb 23];103(1):275–82. Available from: https://pubmed.ncbi.nlm.nih.gov/14504078/
32. Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP [Internet]. [cited 2022 Feb 23]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
33. Yamaguchi H, Hirakawa T, Inokuchi K. Importance of Relative Dose Intensity in Chemotherapy for Diffuse Large B-Cell Lymphoma. Journal of Clinical and Experimental Hematopathology. 2011;51(1):1–5.
34. Personal Records Database (BRP) | Personal data | Government.nl [Internet]. [cited 2022 Mar 26]. Available from: https://www.government.nl/topics/personal-data/personal-records-database-brp
35. Utsu Y, Takaishi K, Inagaki S, Arai H, Yuasa H, Masuda S, et al. Influence of dose reduction of vincristine in R-CHOP on outcomes of diffuse large B cell lymphoma. Annals of Hematology. 2016 Jan 1;95(1):41–7.
36. Bataillard EJ, Cheah CY, Maurer MJ, Khurana A, Eyre TA, El-Galaly TC. Impact of R-CHOP dose intensity on survival outcomes in diffuse large B-cell lymphoma: a systematic review. Blood Adv [Internet]. 2021 May 11 [cited 2022 Apr 3];5(9):2426–37. Available from: https://pubmed.ncbi.nlm.nih.gov/33961018/
37. Juul MB, Jensen PH, Engberg H, Wehberg S, Dessau-Arp A, Haziri D, 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 [Internet]. 2018 Aug 1 [cited 2022 Apr 3];99:86–96. Available from: https://pubmed.ncbi.nlm.nih.gov/29935491/
38. Silverman JA, Deitcher SR. Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. Cancer Chemother Pharmacol [Internet]. 2013 Mar [cited 2022 Apr 4];71(3):555–64. Available from: https://pubmed.ncbi.nlm.nih.gov/23212117/
39. Schiller GJ, Damon LE, Coutre SE, Hsu P, Bhat G, Douer D. High-Dose Vincristine Sulfate Liposome Injection, for Advanced, Relapsed, or Refractory Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia in an Adolescent and Young Adult Subgroup of a Phase 2 Clinical Trial. J Adolesc Young Adult Oncol [Internet]. 2018 Oct 1 [cited 2022 Apr 4];7(5):546–52. Available from: https://pubmed.ncbi.nlm.nih.gov/30239252/
40. Hagemeister F, Rodriguez MA, Deitcher SR, Younes A, Fayad L, Goy A, et al. Long term results of a phase 2 study of vincristine sulfate liposome injection (Marqibo®) substituted for non-liposomal vincristine in cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab for patients with untreated aggressive non-Hodgkin lymphomas. British Journal of Haematology [Internet]. 2013 Sep 1 [cited 2022 Apr 4];162(5):631–8. Available from: https://onlinelibrary-wiley-com.proxy.library.uu.nl/doi/full/10.1111/bjh.12446.

Appendix

Appendix figure 1. Flow-chart of inclusion progress



EPIC-system= electronic medical records system, DLBCL= diffuse large B-cell lymphoma, CLL= chronic lymphatic leukemia, HIV= humane immunodeficiencies virus,