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Impact of intended and relative dose intensity of R-CHOP in a large, consecutive cohort of elderly DLBCL patients treated with curative intent: no difference in cumulative incidence of relapse comparing patients by age

Toby A. Eyre (1), Nicolas Martinez-Calle (2), Catherine Hildyard (3), David W. Eyre (4, 5), Hannah Plaschkes (6), John Griffith (7), Julia Wolf (7), Paul Fields (8), Arief Gunawan (8), Rebecca Oliver (9), Faouzi Djebbari (10), Stephen Booth (11), Andrew McMillan (2), Christopher P. Fox (2), Mark J Bishton (2) Graham P. Collins (1), Chris S.R. Hatton (1)

*Author responsible for correspondence. Toby A. Eyre, Department of Haematology, Cancer and Haematology Centre, Oxford University Hospitals NHS Trust, OX3 7LE. Email: toby.eyre@ouh.nhs.uk

1. Department of Haematology, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, OX3 7LE
2. Department of Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, UK.
3. Department of Haematology, Milton Keynes Hospital, MK6 5LD
4. Nuffield Department of Medicine, University of Oxford, Oxford, UK.
5. Big Data Institute, University of Oxford, Oxford, UK.
6. Oxford University Medical School, Oxford OX1 2JD
7. Department of Haematology, Great Western Hospital, Swindon, SN3 6BB
8. Department of Haematology, Guys and St Thomas' Hospitals NHS Foundation Trust, London, SE1 7EH
9. Department of Haematology University Hospitals Bristol NHS Foundation Trust, Bristol, BS2 8HW
10. Department of Cancer Pharmacy, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, OX3 7LE
11. Department of Haematology, Royal Berkshire Hospital NHS Foundation Trust, Reading, RG1 5LE

Abstract 250 words max (249 words)

Background. The increasing incidence of DLBCL in aging populations places a significant burden on healthcare systems. Co-morbidity, frailty, and reduced organ and physiological reserve contribute to treatment-related complications. The optimal dose intensity of R-CHOP to optimise outcome across different ages with variable frailty and comorbidity burden is unclear. *Objectives and Methods.* We examined the influence of intended (IDI) and relative (RDI) dose intensity of the combination of cyclophosphamide and doxorubicin, age and co-morbidity on outcomes for DLBCL patients ≥ 70 years in a representative, consecutive cohort across 8 UK centres (2009-2018). We determined predictors of survival using multivariable Cox regression, and predictors of recurrence before death using competing risks regression. *Results.* PFS and OS were significantly inferior in patients ≥ 80 versus 70-79 years ($p < 0.001$). In contrast, 2-year cumulative relapse incidence, when accounting for non-relapse mortality as a competing risk, was no different between 70-79 versus ≥ 80 years ($p = 0.27$) or

comorbidity status (CIRS-G:0-6 vs >6) ($p=0.27$). In 70-79 years, patients with an IDI $\geq 80\%$ had a significantly improved PFS and OS ($p<0.001$) compared to IDI $<80\%$. Conversely, in patients ≥ 80 years, there was no difference in PFS ($p=0.88$) or OS ($p=0.75$) according to IDI $<80\%$ versus $\geq 80\%$. On multivariable analysis, when comparing by age, there was a significantly higher cumulative relapse rate for patients aged 70-79 years with an IDI $<80\%$ (vs. $>80\%$) ($p=0.04$) but not for patients ≥ 80 years comparing IDI ($p=0.32$). Conclusion 'R-mini-CHOP' provides adequate lymphoma-specific disease control and represents a reasonable treatment option in elderly patients ≥ 80 years aiming for cure.

Figures: 1-2

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Supplementary Figures: S1-S3

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy. The cure rate is 50-90% depending on age, fitness, disease biology and therapy [1]. The increasing incidence of DLBCL in an aging population places a significant burden on healthcare systems [2]. Ensuring that elderly patients with DLBCL receive treatment that maximises the chance of cure whilst minimising toxicity is important [2]. Standard therapy is derived from landmark randomised trials which almost completely exclude ($<1\%$) patients ≥ 80 years [3–6]. As such, prospective evidence in patients ≥ 80 years is limited to two phase II trials. These trials show that patients ≥ 80 years receiving attenuated or 'mini' CHOP (25mg/m² doxorubicin; 400mg/m² cyclophosphamide, 1mg vincristine) with an anti-CD20 monoclonal antibody can induce a sustained remission in 50-60% [7,8]. These studies support the use of modified anthracycline-based therapy in patients ≥ 80 years.

Co-morbidity, frailty, vulnerability to infection, reduced organ and physiological reserve and impaired performance status contribute to treatment-related complications. A Swedish DLBCL registry (including $n=2038 \geq 70$ years), which analysed patients across all ages receiving curative and non-curative regimens, showed a clear association between Charlson Comorbidity Index (CCI), worse performance status, lower probability of receiving curative therapy and higher all-cause and lymphoma-specific mortality[9]. Patients with co-morbidity (CCI ≥ 1) who received curative treatment had a reduced overall survival (OS) due to other-cause death but had a similar lymphoma-specific death rate compared to patients with no comorbidity (CCI=0).

In light of these data, there remains an open question as to what dose intensity of rituximab plus CHOP (R-CHOP) is necessary in different ages with variable frailty and comorbidity burden in order to optimise outcome. To date, no randomised trials comparing cyclophosphamide and doxorubicin dose(s) in elderly DLBCL patients have been performed. Several small studies have documented that retaining relative dose

intensity (RDI) improves outcomes [10–13]. However, dose reductions in these studies may be heterogeneous, for example planned lower doses from the outset, may have a different outcome compared to reduced dose intensity during treatment following toxicity or a poor response. Therefore, we [14] and others [15] have previously analysed the impact of planned dose reductions at treatment initiation, i.e. intended dose intensity (IDI), in relatively small series. Although IDI reduction can result in a reduced overall RDI, these *may* be associated with less toxicity and an overall improved or equivalent outcome in elderly patients. Both series demonstrated that full dose R-CHOP compared to attenuated R-CHOP did *not* improve outcome in patients ≥ 80 years and may worsen survival due to enhanced toxicity.

In addition, a recent Danish registry analysis included 557 R-CHOP-treated patients >75 years where IDI information was available [16]. IDI $<80\%$ (defined by either cyclophosphamide or doxorubicin $<80\%$ in cycle 1) when compared to $\geq 80\%$ was associated with a similar OS in patients 80–85 years, suggesting R-CHOP could be reasonably attenuated in patients >80 years. However, these conclusions were limited by the lack of an integrated RDI analysis, the method of IDI calculation, the relatively large number of unknown causes of death, and the consequent lack of assessment of the cumulative risk of relapse.

Our study aimed to examine the influence of IDI and RDI of the combined average dosage of cyclophosphamide and doxorubicin, age and co-morbidity on outcomes for elderly DLBCL patients by assessing in the survival and toxicity outcomes in a representative, consecutive cohort aged ≥ 70 years receiving R-CHOP.

Methodology

Data on 690 consecutive patients were retrospectively collected across eight UK centres from 2009–2018. All patients had untreated *de novo* DLBCL or untreated transformed indolent B-cell non-Hodgkin lymphoma (iNHL). Leg-type DLBCL, post transplantation lymphoproliferative disease, HIV infection, central nervous system (CNS) involvement, or previously treated transformed iNHL were excluded. All patients received 1–8 cycles of R-CHOP at a minimum interval of 21 days with curative intent. Patients must have completed R-CHOP and received ≥ 1 cycle (including patients that stop early due to toxicity/progression) to be included.

Patient notes were systematically reviewed. Detailed baseline disease and patient characteristics collected included gender, age, ECOG PS (Eastern Cooperative Oncology Group performance status), B symptoms, international prognostic index (IPI) components, composite or preceding iNHL, bulk (defined $\geq 10\text{cm}$), haemoglobin, albumin, CIRS-G (Cumulative Illness Rating Scale for Geriatrics) score, and CIRS-G severity ratio (absolute CIRS-G value divided by the number of contributory categories).

Dose Intensity Calculation

The IDI decision was often documented following multidisciplinary discussion or by treating physicians. However, in the absence of such documentation, as the data were collected retrospectively from chemotherapy prescribing databases, the IDI was defined as the average dose of doxorubicin and

cyclophosphamide received in cycle 1. The total cumulative dose of both cyclophosphamide and doxorubicin across all cycles received (RDI) was calculated in each case, and a correction factor was used to account for the total number of days delay within the full treatment course. For example, if across 6 cycles of full dose R-CHOP a total of 25 days delay occurred, a correction factor of number of expected days for R-CHOP course divided by the actual cumulative number of days for R-CHOP course i.e. $(21 \times 6) / ((21 \times 6) + 25) = 0.83$ was included. On occasions when treatment was stopped prematurely due to toxicity or death, RDI was the average delivered dose as a proportion of the expected dose censored at that time point. For example, if a patient died of neutropenic sepsis after 3 cycles of R-CHOP given on time at 50% dosage with the intention to receive 6 cycles; the IDI was calculated as 50% and the RDI as 50% i.e. the RDI was not divided by the non-administered cycles 4-6 in this case. This is to avoid the bias of poor outcomes due to treatment-related mortality being associated with falsely low or 'diluted' RDI as a result of non-administered cycles.

The ratio of RDI divided by IDI was calculated to provide an indicator as to what extent the intended regime was followed throughout the treatment course. Values <1 represented RDI reductions from the IDI and values >1 represented RDI increases from the IDI. We analysed IDI and the RDI/IDI ratio as predictors of outcome in our analysis. G-CSF was regularly given as per local practice. In patients ≥ 70 years of age, vincristine dose was not separately analysed as the majority of patients ≥ 70 years within our study had a 1 mg dose cap per cycle. Standard full dose R-CHOP consisted of 375 mg/m^2 rituximab, 50 mg/m^2 doxorubicin, 750 mg/m^2 cyclophosphamide, typically 1mg vincristine on day 1 and 40 mg/m^2 prednisolone on days 1–5.

Causes of death

Causes of death were obtained following detailed medical review of the patients electronic and/or paper notes. For patients discharged from secondary care follow up, the cause of death was obtained from their community physician and date of death obtained from searches on the NHS national database. For the few patients whose date of death was known but cause of death was unobtainable, the cause was classified as unknown but the patients were included within the survival analysis.

Statistical analysis

Progression-free survival (PFS) was calculated as the time from DLBCL diagnosis to relapse, disease progression, death, or censored at the last follow-up. Overall survival (OS) was calculated from DLBCL diagnosis to death or censored at the last follow-up. Cumulative incidence of relapse, treating death without progression as a competing risk, was calculated from DLBCL diagnosis to disease relapse or progression or censored at the last follow-up. For the PFS and relapse analyses, in the few ($n=8$) patients that died with an unconfirmed remission status, the cases were censored at the date last known to be both alive and progression free. This only affected the PFS and relapse analysis and not the OS analysis as the date of death in these cases were known. Cox regression was used to determine univariable and multivariable predictors of PFS and OS. Similarly, competing risks survival regression was used for to determine predictors of relapse before death. A competing risks approach was used to avoid over-estimating relapse rates given the relatively high

proportion of patients who die without experiencing a relapse [17]. In addition, a cox regression analysis for the risk of relapse was also performed. All factors that were considered to potentially directly relate to relapse, PFS and OS were included in the multivariable model. Fractional polynomials were used to allow for nonlinear effects of continuous variables. The proportional hazard assumption was tested using log-log plots and by comparison of Kaplan-Meier observed survival curves and Cox predicted curves. In a pre-specified analysis plan and to be consistent with published literature, IDI was analysed as a categorical variable (full dose, i.e. $\geq 80\%$ of weight-based dose and attenuated, i.e. $< 80\%$), as most patients received either 100% or approximately 50% of full dose. As understanding the impact of dose attenuation in patients ≥ 80 years was the principal aim of the study, age was analysed as a categorical variable 70-79 years and ≥ 80 years. Additional interactions between age, IDI and other predictors were investigated, and retained in the final model if the Wald p-value for the interaction term was < 0.01 . All statistical analyses were performed with Stata version 15.1 (Stata Corp., College Station, TX). All authors had full access to the data in the study and the corresponding author had final responsibility for the decision to submit the manuscript for publication. The study received service evaluation approval at each of the participating sites and as such formal ethical approval was not required.

Results

Baseline characteristics

690 patients received R-CHOP with curative intent; 51% were male and 49% were female. Baseline characteristics are outlined in Table 1 and divide patients by age and IDI. Median follow-up was 2.8 years (range 0.4-8.9). The median number of cycles of R-CHOP was 6 (range 1-9) with 71% (493/690) completing 6 cycles (Figure S1). The number of patients with an IDI $< 80\%$ with an early cessation of treatment was higher 112/356 (31%) vs those with an IDI $\geq 80\%$, 66/334 (20%) ($p < 0.001$). Of 452 patients aged 70-79 years, 299 (66%) had an IDI $\geq 80\%$ and 153 (34%) had an IDI $< 80\%$. Of 238 patients ≥ 80 years, 35 (15%) had an IDI $\geq 80\%$ and 203 (85%) had an IDI $< 80\%$. In patients aged 70-79 years, compared to an IDI $\geq 80\%$, patients with an IDI $< 80\%$ were more likely to have a higher ECOG PS, 2-4, (57% vs 28%; $p < 0.001$), a higher IPI, 3-5, (75% vs 63%; $p = 0.02$), lower haemoglobin (≤ 12.5 g/dl: 71% vs 54%; $p = 0.001$), lower albumin (≤ 36 g/L: 59% vs 47%; $p = 0.01$) and higher CIRS-G (> 6 : 43% vs 27%; $p = 0.001$). Patients ≥ 80 years receiving IDI $\geq 80\%$, compared to IDI $< 80\%$, had better ECOG PS (0-1: 74% vs 52%; $p = 0.02$), higher haemoglobin (> 12.5 g/dl: 54% vs 37%; $p = 0.07$), and a lower CIRS-G (> 6 : 23% vs 40%; $p = 0.06$).

Most patients aged 70-79 years had a combined doxorubicin and cyclophosphamide IDI of close to 100% in contrast to patients aged ≥ 80 years, who more typically had an IDI of 50%. When the RDI/IDI ratio was assessed according to age, 70-79 years versus ≥ 80 years, most patients retain an IDI/RDI close to 1, with a small number reducing from the intended dose, IDI/RDI < 0.8 (43/452, 10% and 23/238, 10% respectively) or increasing dose > 1.2 (45, 10% and 18, 8%). Patients of all ages with an IDI c.100% rarely increase RDI, whilst those starting with an IDI of approximately 50% increase or decrease RDI in approximately equal amounts (Figure S1).

Survival analysis

Across all patients, the median PFS was 5.1 years (95% confidence interval (CI) 4.1-6.4) with a 2-year PFS 67% (95% CI 63-70%). The median OS was 4.8 years (95% CI 4.2-6.4) with a 2-year OS 69% (95% CI 65-73%) (Figure 1A-B). The median PFS is marginally longer than the OS due to the 8 cases censored for PFS as last known follow up who later died with an unconfirmed relapse status. Figure 1C shows the cumulative relapse incidence, treating death without relapse as a competing risk. The incidence of relapse before death at 1 year was 19% (95% CI 16-22%) and 22% (95% CI 19-26%) at 2 years.

When analysed by age (70-79 vs ≥ 80 years): 2-year PFS was 71% (95% CI 66-75%) vs 60% (95% CI 52-66%) (log-rank $p=0.003$) and 2-year OS was 74% (95% CI 69-78%) vs 59% (95% CI 52-66%) ($p<0.001$) (Figure 1D-E). In contrast, the 2-year cumulative relapse incidence, when accounting for death as a competing risk, was no different between 70-79 vs. ≥ 80 years (univariable subhazard ratio, SHR, 1.20 (95% 0.87-1.67) $p=0.27$) (Figure 1F). This suggests that in patients ≥ 80 years the inferior survival in terms of PFS and OS are primarily driven by non-relapse mortality; due to a combination of causes including treatment toxicity and unrelated causes of death.

Considering all patients, irrespective of age, those with an IDI $<80\%$ had an inferior PFS ($p<0.001$), OS ($p<0.001$) and an increased the univariable cumulative relapse incidence ($p=0.03$) (Figure S2A-C). However, analysing survival according to age and IDI, in patients aged 70-79 years, those with an IDI $\geq 80\%$ versus $<80\%$ had higher PFS and OS (both $p<0.001$). Conversely, in patients ≥ 80 years, there was no difference in PFS ($p=0.88$) or OS ($p=0.75$) according to IDI $<80\%$ compared to $\geq 80\%$ (Figure 2A-D).

Univariable analysis

Baseline parameters that were statistically significant univariable predictors of PFS, OS and relapse before death (Tables S1-3) included male gender, ECOG PS, raised LDH, stage, >1 extranodal site, low albumin, low haemoglobin and B symptoms. Disease-specific parameters, namely raised LDH, bulk, stage, >1 extranodal site, and B symptoms all had a consistently higher SHR for relapse compared to PFS and OS analysis. IDI/RDI ratio was not predictive of relapse or either survival outcome. All measured dose intensity parameters (measured as continuous variables; doxorubicin IDI, cyclophosphamide IDI and combined IDI) were each univariable predictors of PFS and OS. Patients who start treatment as an inpatient (for any reason), are admitted for infection during R-CHOP, or spend longer ($>15\%$ of time) as an inpatient during cycle 1-2 (all causes) have a worse outcome in terms of PFS, OS and relapse before death.

Age (continuous variable and 70-79 vs ≥ 80 y) and comorbidity (CIRS-G 0-6 vs. >6) were both strongly associated with a worse PFS and OS ($p<0.001$), but neither were associated with a higher relapse incidence (continuous: $p=0.30$, categorical: $p=0.27$, CIRS-G >6 : $p=0.27$) (Table S1-3; Figure S3), suggesting that age and co-morbidity primarily impact all-cause mortality as opposed to relapse risk and subsequent lymphoma-specific mortality.

Multivariable analysis (MVA)

Adjusting for all other factors considered, when cumulative incidence of relapse before death was analysed by IDI and age categories (using 70-79 years / IDI $\geq 80\%$ as the comparator), the SHRs for patients 70-79 years with IDI $< 80\%$ were 1.61 (95% CI 1.02-2.53; $p=0.04$), for patients ≥ 80 years with IDI $\geq 80\%$ 2.16 (1.05-4.43; $p=0.04$) and with IDI $< 80\%$ 1.48 (0.96-2.97; $p=0.08$) (Table 2). When compared within age categories, there was a significantly higher cumulative relapse rate for patients aged 70-79 years with an IDI $< 80\%$ (vs. $> 80\%$) ($p=0.04$) but not for patients aged ≥ 80 years comparing IDI ($p=0.32$) (Figure 2E, Table 2). Similar results were obtained if a standard Cox model for relapse was fitted treating death as an uninformative censoring event ($p=0.02$ and $p=0.25$ respectively) On MVA, when compared to IDI $\geq 80\%$ in age 70-79 years, all other 3 age/IDI categories had inferior PFS and OS (Table S4-5, all $p \leq 0.004$). However, considering only patients ≥ 80 years, there was no evidence in the MVA for a significant difference in PFS and OS with reductions in IDI ($p=0.47$ and $p=0.58$ respectively).

Causes of Death

Overall, there were 255 deaths (Table S6). 105 deaths occurred in 238 patients ≥ 80 years and were as follows: systemic progressive disease (PD) ($n=48$), CNS +/- concurrent systemic PD ($n=5$), secondary malignancies ($n=6$), infection ($n=19$), vascular event ($n=10$), not known ($n=10$) and other ($n=8$). 150 deaths occurred in 452 patients 70-79 years and were as follows: systemic PD ($n=68$), CNS +/- concurrent systemic PD ($n=13$), secondary malignancies ($n=11$), infection ($n=35$), vascular event ($n=4$), not known ($n=8$) and other ($n=11$). Of specific interest, 20 patients ≥ 80 years with an IDI $\geq 80\%$ died of the following causes: infection ($n=4$), systemic PD ($n=11$), cerebral vascular accident leading to stopping R-CHOP post C1 (subsequent PD) ($n=1$), unknown ($n=2$), and dementia ($n=1$).

Admissions

Across a total of 3681 cycles, there were 798 admissions. The primary initial cause for admission was documented. The mean number of admissions per treatment cycle was 0.27 per cycle, i.e. 27%. The mean number cycles in patients 70-79 years with an IDI $\geq 80\%$ was 5.6, compared to 5.2 with an IDI $< 80\%$ ($p=0.01$), and in patients ≥ 80 years, 4.9 and 5.1 respectively ($p=0.47$). 58% of all patients were admitted ≥ 1 time during treatment. The median number of admissions was 1 (range 0-9). The most common reasons were febrile neutropenia ($n=179$) and non-neutropenic infection ($n=140$) (Table S7). 29% were admitted for ≥ 1 infective episode. 32% started cycle 1 as an inpatient, either due to elective admission or to initiate therapy after the initial presentation had resulted in admission. The mean number of admissions per cycle in patients 70-79 years with an IDI $\geq 80\%$ was 22%, compared to 29% with an IDI $< 80\%$ ($p=0.07$), and in patients ≥ 80 years, 35% and 31% respectively ($p=0.61$).

Discussion

To our knowledge, this is the largest series that has systematically analysed RDI, IDI and co-morbidities in consecutive unselected elderly DLBCL patients. Taken together, the following key conclusions can be made.

Firstly, considering patients 70-79 years and controlling for multiple baseline factors, IDI $\geq 80\%$ is associated with reduced relapse risk and improved PFS and OS. Secondly, patients ≥ 80 years receiving R-mini-CHOP (IDI $< 80\%$) had similar OS, PFS and relapse before death to those ≥ 80 years receiving full dose R-CHOP. Thirdly, given the decisions made about IDI, the RDI/IDI ratio does not influence survival or relapse risk. Fourthly, R-mini-CHOP in patients ≥ 80 years results in prolonged PFS in $\sim 50\%$, with $\sim 30\%$ having a disease relapse, and $\sim 20\%$ dying of other causes.

Although previously published data sets [9,12,16] have analysed each of these factors in relative isolation, this is the first substantial analysis combining these variables. Consistent with recent literature [16], there is no clear benefit to PFS, OS or relapse risk in increasing dose intensity beyond 80% (IDI $\geq 80\%$) in patients ≥ 80 years. This sample was relatively under-powered to detect a difference in adverse events in those ≥ 80 years receiving full dose R-CHOP, e.g. cycle number completed or admissions per cycle. However, the failure to show improved outcomes with full or near full dose R-CHOP suggests this is probably less well tolerated in patients ≥ 80 years despite these selected patients having a favourable baseline status and that it does not provide enhanced disease control.

IDI is a predictor of outcome across the whole cohort demonstrating the broad importance of dose intensity in terms of providing adequate DLBCL control. Patients 70-79 years with IDI $< 80\%$ were less robust (higher ECOG PS and CIRS-G) which is likely to have limited IDI and RDI. This is likely to have impacted their lymphoma-specific survival in addition to all-cause mortality.

When OS, PFS, and cumulative relapse risk were analysed by CIRS-G score, the PFS and OS were significantly worse in patients with a higher score. In contrast, comorbidity was associated with a lower relapse risk before death as comorbid patients were more likely to die of other causes. These findings are consistent with recent Swedish registry data analysing CCI as a co-morbidity index [9]. Together, our data suggests that increasing age and co-morbidity impacts non-lymphoma specific mortality but not lymphoma-specific mortality. As such, when managing patients with co-morbidity and increasing age (particularly ≥ 80 years), there remains a careful balance to be struck when deciding on dose intensity. Our data suggest that this balance is best retained by an IDI (and subsequent RDI as it is relatively uncommon to alter IDI) of approximately 50% in patients ≥ 80 years i.e. R-mini-CHOP. This conclusion is consistent with previously published data [14] and recent ESMO guidelines for managing elderly DLBCL [18].

A strength of our data lies in its consecutive, unselected nature of a representative population with a single regimen and as such this is directly applicable to daily practice. Many of these patients would not have been eligible for clinical trials due to, for example, poor PS (ECOG PS 2-4 40%) and/or co-morbidities (CIRS-G > 6 34%) and therefore these findings are only available from this type of analysis. In comparison to recent population-based analysis [16], our results present minimal missing data, especially in relation to the causes of death and progression events, which has enabled detailed analysis of the cumulative relapse risk.

Weaknesses of our study include its retrospective non-randomised nature, with the inherent possibility of unmeasured confounding factors and the potential for medical chart misinterpretation. We did not collect data on patients with DLBCL who were not eligible for anthracycline-based curative treatment. We therefore cannot say what proportion of patients overall received treatment with curative intent, and accept that a proportion of patients aged >80 years may not have been deemed eligible for R-CHOP. However the aim of the study was to focus on patients suitable for an anthracycline-based, curative treatment schedule. Despite analysing a large cohort, we studied only a relatively small number of patients ≥ 80 years receiving an IDI $>80\%$. As such, the power to detect significant differences in outcomes and adverse events compared to $\leq 80\%$ IDI has the potential to be limited. Our findings should be interpreted in this light. It is also possible that the relatively limited follow up of 2.8 years may have affected the interpretation of the number of relapses seen in a small proportion of patients. There was a lack of prospective documentation of certain baseline characteristics such as ECOG PS and disease stage, we did not collect data regarding pre-phase treatment or the specific timings of each admission within each treatment course. It is not possible to be certain of the physician's dose intensity intention as this is infrequently specifically documented, and as such the first dose given was considered an adequate and reliable surrogate. Although this methodology is consistent with the published literature in relation to IDI calculation, it is open to bias. We pragmatically decided to analyse only the individual and combined dose intensity of cyclophosphamide and doxorubicin as key components of the R-CHOP regimen. In an ideal setting, dose intensity analysis of all 5 components of the regimen would be collected, but in the authors experience, it is uncommon to dose attenuate rituximab, vincristine and steroids. Recent published data has suggest that unlike doxorubicin and cyclophosphamide, vincristine dose intensity has shown minimal effects on survival of disease-free survival or OS in elderly patients with DLBCL [19,20].

In conclusion, we present a comprehensive analysis of the relative importance of age, co-morbidity and doxorubicin and cyclophosphamide dose intensity on the outcome of 690 consecutive, unselected R-CHOP-treated DLBCL patients ≥ 70 years. IDI $\geq 80\%$ in patients ≥ 80 years resulted in no improvement in PFS, OS or reduction in relapse. Although OS and PFS are significantly inferior in patients ≥ 80 years, this difference is driven primarily by non-relapse mortality including unrelated deaths. We show no clear benefit in reducing relapse risk by increasing IDI to $\geq 80\%$ in patients ≥ 80 years compared to other patients of the same age receiving IDI $<80\%$. Together this suggests 'R-mini-CHOP' dosing provides adequate lymphoma-specific disease control and represents a reasonable treatment option in elderly patients ≥ 80 years aiming for a curative approach.

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Author contributions

TE, DE, GC and CSH designed the study; TE, NMC, CH, HP, JG, JW, AM, CF, MB, RO, PF, FD, SB and AG collected the majority of the data. DE performed the statistical analysis. TE wrote the manuscript, which all authors critically reviewed. GC, TE, AM, CF, MB, GC and CH managed many patients in the study.

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