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Chemotherapeutic intensity and survival differences in young patients with diffuse large B-cell lymphoma: a Swedish Lymphoma Registry study

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Summary

Young patients with diffuse large B-cell lymphoma (DLBCL) are variably treated with rituximab combined with (R-) cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP), CHOP-etoposide (CHOEP), and very intensive chemotherapy. Using the nationwide, population-based Swedish Lymphoma Registry, we investigated all 751 DLBCL patients ≤ 60 years without central nervous involvement, diagnosed in Sweden 2007-2012. Very intensive chemotherapy in Sweden included high-dose cytarabine in 100% of patients and high-dose methotrexate in 90%. Overall survival was estimated using multivariable Cox analysis. In age-adjusted international prognostic index (aaIPI) ≥ 2, 5-year overall survival was after R-CHOP 70%, R-CHOEP 76%, and R-very intensive chemotherapy 85% (P = 0·002); in aaIPI = 3, the corresponding estimates were 40%, 55%, and 92% (P = 0·014). There were large therapeutic differences between Sweden's six Healthcare Regions in aaIPI ≥ 2: three were "Moderate" (more R-CHOP) and three "Intensive" (more R-CHOEP and R-very intensive chemotherapy). In aaIPI ≥ 2, patients in Intensive Regions showed better overall survival (P < 0·00005), particularly those with aaIPI = 3 (5-year overall survival, 62% vs 30%; P < 0·00005). In aaIPI < 2, there were no Regional differences in therapy or survival. We conclude that in younger high-risk patients, survival appears superior after more intensive therapy than R-CHOP.

Keywords

Lymphoma, DLBCL, intensive chemotherapy, young, aaIPI

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a lethal but curable condition. Based on randomized trials, the most common therapy in DLBCL is rituximab combined with (R-) cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) (Coiffier *et al*, 2002; Habermann *et al*, 2006; Pfreundschuh *et al*, 2006).

In low-risk disease, age-adjusted international prognostic index (aaIPI) = 0 (1993), standard treatment with 6 cycles of R-CHOP-21 cure 93% of patients ≤ 60 years (Evens *et al*, 2015). In aaIPI > 0, there is no international consensus: R-CHOP and radiation to bulk is a common strategy in North America and parts of Europe. In aaIPI = 1, better survival has been demonstrated with the more intensive regimen rituximab-doxorubicin-cyclophosphamide-vindesine-bleomycin-prednisone (R-ACVBP) than R-CHOP-without-irradiation (Recher *et al*, 2011). In aaIPI ≥ 2, rituximab was combined with CHOP-etoposide (R-CHOEP), which is now common in Europe, but not in North America, where R-CHOP is given to most patients (Armitage, 2012; Schmitz *et al*, 2012). Recent Scandinavian registry studies suggest that R-CHOEP is preferable to R-CHOP in younger high-risk patients (Gang *et al*, 2012; Wasterlid *et al*, 2015). Extreme high-risk disease (aaIPI = 3) portends the highest mortality (Evens *et al*, 2015). Still, there is no strong evidence for more intensive regimens such as rituximab combined with hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone/high-dose-methotrexate-high-dose-cytarabine (R-hyper-CVAD/MA) or upfront autologous stem cell transplantation in high-risk disease (Oki *et al*, 2013; Stiff *et al*, 2013).

The background and hypothesis for this project was a concern shared between some haematologists/oncologists that different first-line regimens might cause survival differences among younger Swedish patients with high-risk disease.

Materials and methods

Swedish registries

The Swedish Cancer Registry and the Swedish Lymphoma Registry (SLR) have been described previously (Junlen *et al,* 2015).The coverage of the SLR (which includes all lymphomas in all adult patients) compared with the mandatory Swedish Cancer Registry (in which all Swedish cancer cases are registered) has been 95%-97% since its initiation in 2000, according to yearly reports; the SLR has been validated, showing a 95% agreement between the diagnosis reported to the SLR and the actual diagnosis in the local patient files (Junlen *et al,* 2015). For every resident in Sweden, date of death is centrally registered in the Causes of Death Registry, from which survival data was obtained.

Patients and Healthcare Regions

From the SLR, we included all patients ≤ 60 years diagnosed from 2007 through 2012 with DLBCL, except those with CNS involvement. Patients were not excluded because of other malignancies or other diseases. All patients were observed from date of diagnosis until death, emigration or end of follow-up (October, 2014). From the SLR, we obtained information on first-line therapy and clinical factors. Anthracycline-containing first-line regimens were divided into three orders of intensity as shown below. We also compared the Swedish

Healthcare Regions. Sweden is divided into six geographical Healthcare Regions, each with a distinct healthcare system and a population between 0·9 and 2·3 million people. Every patient is exclusively treated within the Region of residence, and selection or transfer of patients between Regions does not exist. Patients do not move between Regions for therapy, because in every Region there is full expertise to give all components of anti-lymphoma therapy, including intensive chemotherapy, irradiation and autologous and allogeneic stem-cell transplantation. This study was approved by the Ethics Committee, Stockholm, Sweden.

Statistical analysis

Independent variables' relations with one another were investigated using the χ^2 (between categorical variables), Wilcoxon (between categorical and ordered/continuous variables), and Spearman (between ordered/continuous variables) tests. Overall survival was calculated from the date of diagnosis to the date of death. Patients were censored at last follow-up. Univariable analysis for overall survival was conducted using Kaplan-Meier curves and the log-rank test (Mantel, 1966). Factors significant in univariable analysis competed in multivariable analysis, using forward stepwise Cox regression; the proportional hazards assumption was checked with graphs based on Schoenfeld residuals (Cox, 1972). All P values are two-tailed and calculated using Stata 14.1 (StataCorp, College Station, TX, USA). $P < 0{\cdot}05$ was considered significant.

Therapy guidelines in Sweden 2007-2012

With the first national guidelines, published in May 2006, R-chemotherapy was made a national standard with the following recommendations: aaIPI = 0, 6 cycles of R-CHOP-21

(alternatively for stage IA, 3 R-CHOP-21 + 30 Gy local irradiation); aaIPI = 1, 6 R-CHOP-14 or 8 R-CHOP-21; aaIPI ≥ 2, 6 R-CHOEP-14 (in ≤ 65 years) and 6 R-CHOP-14 (in > 65). Some Healthcare Regions retained a tradition, outside of the guidelines, of using even more intensive regimens, here termed R-very intensive chemotherapy, such as R-hyper-CVAD/MA or additional high-dose cytarabine/methotrexate courses after R-CHO(E)P, for younger patients with high-risk disease. In the first revision of the national guidelines, published in January 2007, the only change was in aaIPI ≥ 2 where 6 R-CHOP-14 was inserted as the primary option for all ages, based on a discussion whether rituximab might nullify the benefit of CHOEP over CHOP (Pfreundschuh *et al*, 2004). Some disagreed, why 6 R-CHOEP-14 was retained as an alternative for patients ≤ 65. In all guidelines of the study period, CNS prophylaxis was recommended for patients with involvement of the testis or those with elevated lactate dehydrogenase (LDH) and >1 extranodal site. The guidelines specified CNS prophylaxis with intrathecal methotrexate injections with each cycle of R-CHO(E)P or high-dose cytarabine and high-dose methotrexate (as extra cycles added to R-CHO(E)P or as part of hyper-CVAD/MA or R-B-NHL-BFM 04 (Holte *et al*, 2011; Lisfeld *et al*, 2013)). The national guidelines remained unchanged throughout the study period. In the 2014 revision, 6 R-CHOEP-14 became, again, the only recommendation for all patients ≤ 65 years with aaIPI ≥ 2.

We investigated the given regimens' association with survival. To reduce the selection bias that is inherent in retrospective analyses of different therapeutic algorithms, we also compared treatment differences in the healthcare Regions and investigated whether these Regional policy differences correlated with survival in all patients within the Regions (regardless of actual treatment given). The intensity of therapy in each Region was estimated using a simple

algorithm in which each Region's percentage of R-CHOEP was multiplied by 1 and of R-very intensive chemotherapy by 1·5.

Results

Between 2007 and 2012, the SLR registered 751 patients ≤ 60 years with a new diagnosis of DLBCL and no CNS involvement. Clinical characteristics are presented in Table I. Median follow-up was 4·9 years. Factors to calculate the aaIPI (lactate dehydrogenase level, WHO performance status, and Ann Arbor stage) were available for 736 patients (98%). There were no differences in survival between 2007-2009 and 2010-2012 (P = 0·81). In multivariable competition between clinical characteristics, age, aaIPI, bulky disease, and male sex were independent risk factors for poor survival (aaIPI-constituting variables were excluded). Extranodal sites ≥ 2 was not an independent variable and therefore not included in subsequent models. Overall survival at five years in all 751 patients ≤ 60 years diagnosed with DLBCL in Sweden 2007-2012 was 81% (95% confidence interval [CI], 78%-84%). Survival by age categories is shown in Figure 1A. Patients aged 18-40 years had a 5-year overall survival of 90% (95% CI, 83%-94%), those aged 41-50 82% (95% CI, 76%-87%), and 51-60 78% (95% CI, 73%-82%).

Treatment intensity with standard, etoposide-added, and very intensive regimens: R-CHOP, R-CHOEP, and R-very intensive chemotherapy

There were registry reports on primary therapy in 623 patients (83%). Identical prognosis in patients treated with R-CHOP-14 and R-CHOP-21 has already been demonstrated (Cunningham *et al*, 2011; Wasterlid *et al*, 2015). R-CHOP(-14/-21) was considered the

reference treatment in this report (n = 464). Of patients treated with R-CHOP, 91% received at least six cycles. However, to discern policy differences at initial treatment, we always considered the intended initial therapy reported to the SLR as the relevant one. In the same vein, patients who were treated with reduced doses from the first cycle are not counted into the R-CHOP group.

There were 51 patients treated with R-CHOEP(-14 or -21) and no further chemotherapy. They constitute an intermediate intensity group, where 92% received at least six cycles.

The R-very intensive chemotherapy group (n = 108) comprised patients treated with 1. R-CHO(E)P followed by high-dose cytarabine and/or high-dose methotrexate (n = 80), 2. R-hyper-CVAD/MA or R-B-NHL-BFM 04 (n = 17), or 3. R-anthracycline-based chemotherapy followed by primary carmustine-etoposide-cytarabine-melphalan/cyclophosphamide (BEAM/BEAC) and autologous stem cell transplantation (n = 11). Of these patients, 95% received at least six cycles.

Non-anthracycline-based regimens followed by autologous SCT (for example, because of previous anthracyclines in breast cancer therapy) are counted as salvage, not as R-very intensive chemotherapy. There were 25 patients who received salvage (n = 7), palliative/reduced/none (n = 15), or unspecified (n = 3) therapies, without any differences between healthcare Regions (P = 0·72); those variants were not further analyzed. Primary irradiation was given to 11% of the patients, without differences between Regions (P = 0·43) and no impact on overall survival (P = 0·78).

Survival according to the aaIPI is shown in Figure 1B. Patients with zero risk factors according to the aaIPI had a 5-year overall survival of 94% (95% confidence interval [CI], 89%-97%); those with 1, 87% (95% CI, 81%-91%); 2, 78% (95% CI, 71%-82%); 3, 48% (95% CI, 36%-59%); ≥ 2, 71% (95% CI, 66%-76%).

aaIPI ≥ 2 (n = 338)

R-CHOP was given to 60%, R-CHOEP to 13%, and R-very intensive chemotherapy to 27%. There was a survival benefit from regimens more intensive than R-CHOP which was independent in multivariable analysis (P = 0·0004; Table II). Increasing chemotherapeutic intensity from R-CHOP to R-CHOEP to R-very intensive chemotherapy correlated with improved survival (Figure 2A; multivariable P = 0·002 [Table II]). Overall survival at five years in aaIPI ≥ 2 was for patients treated with R-CHOP 70% (95% CI, 62%-76%), with R-CHOEP 76% (95% CI, 58%-87%), with R-very intensive chemotherapy 85% (95% CI, 73%-92%). Patients who received R-CHOP were older (median 53 years, versus 49 for R-CHOEP and 52 for R-very intensive chemotherapy) but otherwise there were no differences in the distribution of clinical factors between regimens (Table III).

Because only patients who initially responded to R-CHO(E)P would have completed six courses before proceeding to high-dose cytarabine/high-dose methotrexate or BEAM/BEAC, there was a selection of early responders in the very intensive category. The selection of responders after six cycles also gave an immortality bias during the first 70 to 120 days after diagnosis. We therefore repeated the above multivariate analysis in the subset of patients who had completed at least six courses of first-line therapy and with overall survival counted from

200 days after diagnosis (prior deaths were disregarded), showing again that R-very intensive chemotherapy was independent (HR = 0·44; P = 0·036; n = 239).

In extreme high-risk cases (aaIPI = 3; n = 72), the improvement in overall survival with more intensive regimens was even more apparent, particularly for R-very intensive chemotherapy (Figure 2B). In multivariable analysis, increasing intensity correlated with better overall survival (P = 0·014); the hazard ratio (HR) for R-CHOEP was 0·36 (95% CI, 0.13-0.99) and for R-very intensive chemotherapy 0·08 (95% CI, 0.01-0.63). Overall survival at five years in aaIPI = 3 was for R-CHOP 40% (95% CI, 22%-56%), R-CHOEP 55% (23%-78%), R-very intensive chemotherapy 92% (95% CI, 54%-99%).

Regional differences

To validate the correlations between treatment intensity and overall survival in aaIPI ≥ 2 (and to minimize selection bias), we also investigated Regional treatment differences. We wanted to see if Regional traditions of more or less intensive regimens would have an impact on overall survival (assuming equal distributions of co-morbidity between the Regions). The Regional use of R-CHOP, R-CHOEP, and R-very intensive chemotherapy in aaIPI ≥ 2 is shown in Table IV. For statistical considerations, the Regions were grouped into two categories: Regions 1, 2, and 3 comprised “Moderate” Regions and Regions 4, 5, and 6 “Intensive Regions”. The total use of R-CHOEP/R-very intensive chemotherapy in the Moderate Regions was 30% (R-CHOEP, 8%; R-very intensive chemotherapy, 22%) and in the Intensive Regions 52% (R-CHOEP, 18%; R-very intensive chemotherapy, 34%), a significant difference (P = 0·001). The subsequent Regional survival analysis naturally includes more patients than the above survival analysis of anthracycline-based regimens,

because here all patients are investigated, regardless of given therapy, including those treated with palliative or salvage regimens. A comparison with respect to overall survival showed that patients with aaIPI ≥ 2 treated in Intensive Regions lived longer (Figure 2C; multivariable P < 0·00005 [Table II]). Overall survival at five years in aaIPI ≥ 2 was in Moderate Regions 67% (95% CI, 59%-74%) compared with 75% (95% CI, 67%-81%) in Intensive Regions. The Regional survival difference was especially marked in aaIPI = 3 (Figure 2D; multivariable P < 0·00005); HR for Intensive Regions was 0.17 (95% CI, 0.08-0.37). Five-year overall survival was 30% (95% CI, 15%-47%) in Moderate and 62% (95% CI, 45%-74%) in Intensive Regions.

Clinical factors were evenly distributed in the Moderate and the Intensive Regions, with the exception of there being more patients with WHO performance status ≥ 2 in the Intensive Regions (Table III).

The Regions were also analyzed in three orders of intensity: Regions 1+2 vs 3+4 vs 5+6, showing independently better survival with increasing Regional treatment intensity in aaIPI ≥ 2 (Table II) and in aaIPI = 3 (multivariable P = 0·0001).

Finally, multivariable analyses of therapeutic and Regional intensity together showed that both factors were independent predictors for overall survival in aaIPI ≥ 2 (Table II).

aaIPI < 2 (n = 398)

R-CHOP was used in 86% of these patients, R-CHOEP in 5%, and R-very intensive chemotherapy in 9%. R-CHOP and R-CHOEP had similar, excellent, survival, while R-very

intensive chemotherapy correlated with inferior outcome (Table II, Figure 2E). There were no differences in the Regional use of R-CHOP, R-CHOEP, or R-very intensive chemotherapy (P = 0·76), nor in survival between Regions (P = 0·39). Furthermore, in aaIPI < 2 there were no survival differences (P = 0·70) between Moderate and Intensive Regions (as defined by the Regional therapeutic differences in aaIPI ≥ 2).

CNS prophylaxis

In total, CNS prophylaxis was given to 22% of patients treated with anthracyclines in first line (only high-dose cytarabine/methotrexate, 7%; only intrathecal prophylaxis, 6%; both, 9%). Intensive Regions (as defined in aaIPI ≥ 2) used more CNS prophylaxis (P = 0·009). CNS prophylaxis correlated with better overall survival in aaIPI ≥ 2 (multivariable P = 0·013) but not in aaIPI < 2 (P = 0·55). In aaIPI ≥ 2, CNS prophylaxis was associated with better survival both in patients with indication for prophylaxis according to guidelines (n = 76; multivariable P = 0·049) and in those without indication (n = 207; P = 0·019). Furthermore, in aaIPI ≥ 2, prophylaxis with high-dose cytarabine/methotrexate, when excluding patients given intrathecal therapy, was associated with longer overall survival (multivariable P = 0·031), but not prophylaxis with intrathecal therapy, when excluding high-dose cytarabine/methotrexate (P = 0·94). In aaIPI < 2, five patients received CNS prophylaxis out of eight in whom it was indicated; these small numbers prohibited further analysis.

Discussion

In this large, nationwide, population-based study we show that R-CHOP is inferior to more intensive regimens in younger patients with high-risk DLBCL.

In patients ≤ 60 years and aaIPI ≥ 2 (particularly aaIPI = 3), R-CHOEP and, even more so, R-very intensive therapy correlated with superior survival compared with R-CHOP. In the analysis of actually given treatments, it appeared that R-CHOEP was better than R-CHOP and R-very intensive chemotherapy was better than R-CHOEP. R-very intensive chemotherapy mostly includes R-CHO(E)P plus high-dose cytarabine/methotrexate. The remaining R-very intensive chemotherapy patients also received high-dose cytarabine but in even more intensive regimens (R-hyper-CVAD, R-B-NHL-BFM 04, and BEAM/BEAC).

We also made use of a natural experiment induced by Regionally divergent therapeutic traditions and showed that survival for younger high-risk patients were better in Regions where intensive regimens were more common. This was particularly pronounced in aaIPI = 3. Adverse risk factors were not less frequent in the Intensive Regions, and was thus not the cause for the survival differences. Likewise, it does not appear that socioeconomic differences are the underlying factor, because between the Regions there were tiny differences in median income, tertiary education, and life expectancy (people in Regions 1+2, with the most inferior outcome in aaIPI ≥ 2, were actually somewhat better off with respect to affluence, education, and life expectancy than Regions with better outcome; data not shown) (2015). The absence of Regional survival differences in aaIPI < 2 also argues against socioeconomic causes. In the final multivariable analysis, R-CHOEP/R-very intensive chemotherapy and the Regions 3+4/5+6 were independently associated with better overall survival. This finding strengthens an interpretation that R-CHOEP and R-very intensive chemotherapy are preferable to R-CHOP in aaIPI ≥ 2, but it also suggests that some of the Regional survival differences are due to other factors than first-line chemotherapy regimens. It could be such things as different management of complications or lymphoma relapses; this is mere speculation because the

SLR does not include data on complications or second-line therapy. There has been no Regional selection of patients and every Region has a tertiary lymphoma centre; clinical characteristics were not more favorable in Intensive Regions than in Moderate Regions. Male sex correlated with inferior prognosis, here also in patients ≤ 60 years. This gender effect has previously been more apparent in older patients (Muller *et al*, 2012; Pfreundschuh *et al*, 2014). We emphasize that our findings were independent in multivariate analysis adjusted for all prognostic clinical factors (gender, age, aaIPI and bulky disease).

Our results agree with previous reports that outcome appears better after R-CHOEP than R-CHOP in aaIPI ≥ 2 (Gang *et al*, 2012; Wasterlid *et al*, 2015). Furthermore, and particularly in aaIPI = 3, in our material there was also a benefit with further intensifying therapy by adding high-dose cytarabine/methotrexate or autologous stem cell transplantation, or with other very intensive regimens (which also included high-dose cytarabine/methotrexate). All patients in the high-intensity group thus received high-dose cytarabine and 90% received high-dose methotrexate. Indeed, high-dose cytarabine/methotrexate was in itself associated with better OS in all patients with aaIPI ≥ 2, not just in those with indication for CNS prophylaxis. It might be that cytarabine and methotrexate in high doses protect from all kinds of relapse, and they do constitute a different way of dose intensification than the R-MegaCHOEP regimen, which, using the same drugs as R-CHOEP-14 but in higher doses, did not improve outcome compared with R-CHOEP-14 in young patients with aaIPI ≥ 2 (Schmitz *et al*, 2012).

The limitations of our study should be noted, and in the absence of randomized trials with high-dose cytarabine/methotrexate, our retrospective data have to be cautiously interpreted. The main strengths of our population-based study are the lack of bias in the Regional analysis and its large size, albeit such a large, nationwide material makes impossible a central

pathology review for biological factors such as double hit and cell-of-origin (Rosenwald *et al*, 2002; Sarkozy *et al*, 2015). However, patients in this material with, for example, double-hit lymphoma would more likely have been treated with intensive chemotherapy and selection bias would therefore have worked against very intensive chemotherapy in the survival analysis. This is a likely explanation for the inferior survival seen in low risk (aaIPI < 2) patients treated with very intensive chemotherapy: more intensive chemotherapy has probably been chosen for patients with clinical low-risk but biologic high-risk disease. Still, in the absence of information on biologic adverse prognostic markers, R-CHO(E)P appears to be the best option in aaIPI < 2. There were no Regional differences in therapy or survival in aaIPI < 2. Another potential concern is that 84% of those treated with R-very intensive chemotherapy received dose-intensification after the completion of R-CHO(E)P, which gives bias (because these patients had completed six courses with some form of response to be eligible for dose-intensification). We addressed this problem in two ways. First, we showed that R-very intensive chemotherapy was independent in multivariable analysis of exclusively early responders (patients who had received at least six cycles in primary therapy) and with survival calculated from 200 days after diagnosis (to nullify immortality bias). Second, the Regional differences in therapeutic intensity and in survival cannot come from bias. The Swedish source population is more or less identical in all Regions and there are no geographical differences in clinical characteristics. The patient's residence decides treatment paradigm. The Regional analysis is thus in effect a geographic randomization. The Regional analysis is therefore unaffected by such factors as response to therapy and co-morbidity. These validated and reliable registry data also feature long-term (and virtually none lost to) follow-up.

We conclude that patients ≤ 60 years and with aaIPI ≥ 2 should be given therapy more intensive and more effective than R-CHOP.

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Conflicts of interest

The authors have no conflict of interest.

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Figure legends.

Figure 1. Overall survival of patients ≤ 60 years diagnosed 2007-2012 with diffuse large B-cell lymphoma in Sweden.

Kaplan-Meier graphs by (A) age groups (in years), (B) age-adjusted international prognostic index (aaIPI).

Figure 2. Overall survival by therapy and Regions.

Kaplen-Meier graphs by (A) first-line anthracycline-containing regimen in aaIPI ≥ 2, (B) first-line anthracycline-containing regimen in aaIPI = 3, (C) Regional treatment intensity in aaIPI ≥ 2, (D) Regional treatment intensity in aaIPI = 3, (E) first-line anthracycline-containing regimen in aaIPI < 2. P values from the log-rank test. Abbreviations: R-CHOP, rituximab combined with cyclophosphamide-doxorubicin-vincristine-prednisone; R-CHOEP, rituximab combined with CHOP-etoposide; R-VIC, rituximab combined with very intensive chemotherapy.

Table I. Clinical characteristics of patients ≤ 60 years old in Sweden 2007-2012.

Characteristic		N	%	HR (95% CI)	P
Gender					0·089
	Female	307	40·9	1	
	Male	444	59·1	1·36 (0·96-1·92)	
Age, years					0·015
	18-40	139	18·5	1	
	41-50	216	28·8	1·80 (0·98-3·33)	
	51-60	396	52·7	2·26 (1·28-3·97)	
LDH					< 0·00005
	Normal	282	38·1	1	
	Elevated	459	61·9	4·29 (2·64-6·97)	
WHO performance status					< 0·00005
	0-1	658	87·7	1	
	≥ 2	92	12·3	4·67 (3·26-6·68)	
Ann Arbor stage					< 0·00005
	I-II	324	43·4	1	
	III-IV	422	56·6	2·79 (1·87-4·16)	
Age-adjusted IPI					< 0·00005
	0	184	25·0	1	
	1	214	29·1	2·65 (1·24-5·65)	
	2	266	36·1	4·99 (2·48-10·05)	
	3	72	9·8	17·60 (8·52-36·36)	
Extranodal sites					0·0002
	0-1	654	87·1	1	
	≥ 2	97	12·9	1·96 (1·29-2·96)	
Bulky disease					< 0·00005
	No	597	80·2	1	
	Yes	147	19·8	2·48 (1·75-3·53)	

Abbreviations: HR, hazard ratio (with respect to overall survival in univariable analysis); CI, confidence interval; LDH, lactate dehydrogenase; WHO, World Health Organization; IPI, international prognostic index.

Table II. Multivariable models with respect to overall survival.

Model	Factor	HR	95% CI	P
Regimens in aaIPI ≥ 2 (N = 265)	Regimen			0·0004
	R-CHOP	1		
	R-CHOEP or R-VIC	0·37	0·21-0·64	
Ordered regimens in aaIPI ≥ 2 (N = 265)	Regimen			0·002
	R-CHOP	1		
	R-CHOEP	0·49	0·23-1·01	
	R-VIC	0·31	0·15-0·61	
Regional differences in treatment intensity in aaIPI ≥ 2 (N = 333)	Region			<0·00005
	Moderate Regions (1+2+3)	1		
	Intensive Regions (4+5+6)	0·39	0·25-0·60	
Ordered Regional differences in treatment intensity in aaIPI ≥ 2 (N = 333)	Region			0·0001
	Regions 1+2	1		
	Regions 3+4	0·58	0·31-1·08	
	Regions 5+6	0·35	0·21-0·57	
Regimens and Regions in aaIPI ≥ 2 (N = 265)	Regimen			0·006
	R-CHOP	1		
	R-CHOEP	0·50	0·24-1·05	
	R-VIC	0·35	0·17-0·70	
	Region			0·0007
	Regions 1+2	1		
	Regions 3+4	0·46	0·21-0·99	
	Regions 5+6	0·32	0·18-0·59	
Ordered regimens in aaIPI < 2 (N = 341)	Regimen			0·025
	R-CHOP	1		
	R-CHOEP	1·00	0·13-7·52	
	R-VIC	3·28	1·41-7·70	

Note: In all multivariable models, competing variables were gender, age, aaIPI, and bulky disease.
Abbreviations: CI, confidence interval; aaIPI, age-adjusted international prognostic index; R-CHOP, rituximab combined with cyclophosphamide-doxorubicin-vincristine-prednisone; R-CHOEP, rituximab combined with CHOP-etoposide; R-VIC, rituximab combined with very intensive chemotherapy.

Table III. Distribution of factors in patients with aaIPI ≥ 2.

Factor			Regimen				Regions		
		All n = 338	R-CHOP n = 162	R-CHOEP n = 34	R-VIC n = 74	P *	Moderate n = 165	Intensive n = 173	P **
Male sex		57%	55%	68%	58%	0·45	58%	56%	0·64
Median age, years		52	53	49	52	0·016	52	53	0·66
Age groups	18-40	16%	13%	26%	26%		17%	15%	
	41-50	28%	28%	32%	16%		28%	27%	
	51-60	57%	59%	41%	58%		55%	58%	
LDH elevated		99%	99%	100%	99%	0·65	98%	99%	0·96
WHO ≥ 2		26%	23%	32%	20%	0·93	21%	31%	0·037
Ann Arbor stage III-IV		96%	96%	100%	97%	0·50	98%	94%	0·058
Age-adjusted IPI = 3		21%	19%	32%	16%	0·93	18%	24%	0·17
Extranodal sites ≥ 2		22%	20%	18%	30%	0·14	26%	18%	0·070
Bulky disease		29%	25%	44%	33%	0·11	26%	31%	0·36

* Test for difference between treatment algorithms
** Test for difference between Regions
Abbreviations: ICQR, interquartile range (25th to 75th percentile); R-CHOP, rituximab combined with cyclophosphamide-doxorubicin-vincristine-prednisone; R-CHOEP, rituximab combined with CHOP-etoposide; R-VIC, rituximab combined with very intensive chemotherapy; LDH, lactate dehydrogenase; WHO, World Health Organization performance status; IPI, international prognostic index.

Table IV. Regional treatment intensity in patients with aaIPI ≥ 2.

N = 338	R-CHOP	R-CHOEP	R-VIC	Intensity score	Rank (1 = most moderate)
Region 1 (n = 67)	72·6%	6·5%	21·0%	38·0	1
Region 2 (n = 69)	67·7%	11·3%	21·0%	42·8	2
Region 3 (n = 29)	68·2%	4·6%	27·3%	45·6	3
Region 4 (n = 32)	63·0%	14·8%	22·2%	48·1	4
Region 5 (n = 79)	48·2%	30·4%	21·4%	62·5	5
Region 6 (n = 62)	39·0%	2·4%	58·5%	90·2	6

Note: The intensity score in each Region was calculated using a simple algorithm in which each Region's percentage of R-CHOEP was multiplied by 1 and of R-VIC by 1·5.
Abbreviations: aaIPI, age-adjusted international prognostic index; R-CHOP, rituximab combined with cyclophosphamide-doxorubicin-vincristine-prednisone; R-CHOEP, rituximab combined with CHOP-etoposide; R-VIC, rituximab combined with very intensive chemotherapy.

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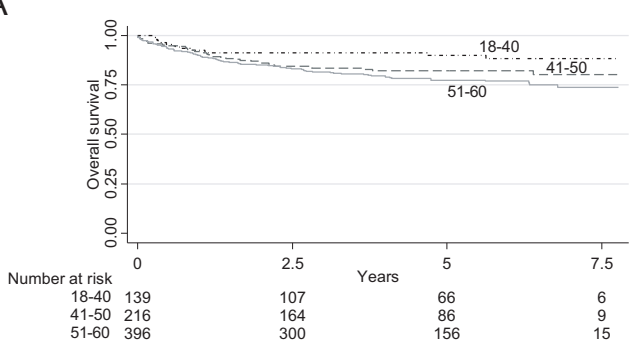
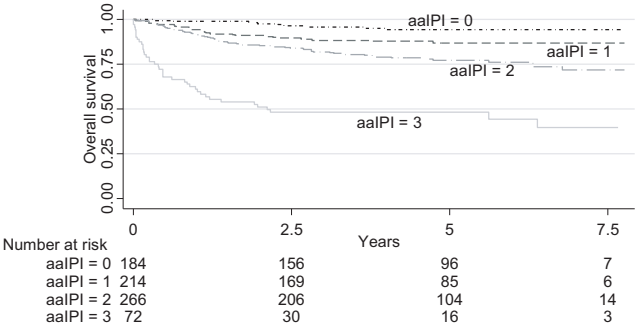


Number at risk

18-40	139	107	66	6
41-50	216	164	86	9
51-60	396	300	156	15

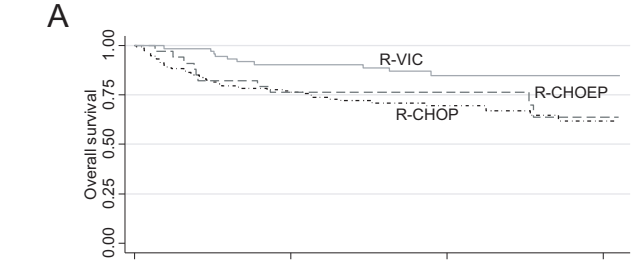
B



Number at risk

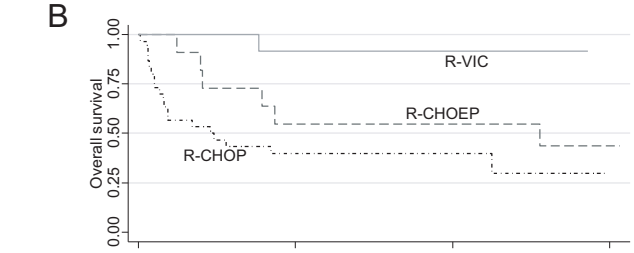
aaIPI = 0	184	156	96	7
aaIPI = 1	214	169	85	6
aaIPI = 2	266	206	104	14
aaIPI = 3	72	30	16	3

A



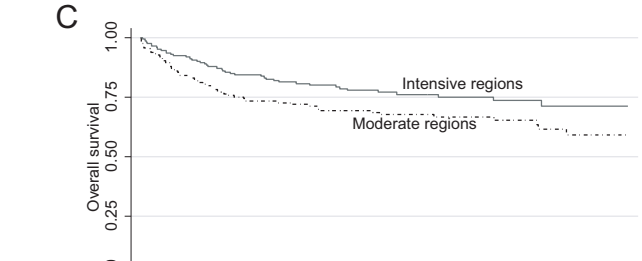
Number at risk				
R-CHOP	162	115	62	6
R-CHOEP	34	22	14	4
R-VIC	74	63	36	6

B



Number at risk				
R-CHOP	30	11	7	0
R-CHOEP	11	6	5	2
R-VIC	12	9	3	0

C



Number at risk				
Mild regions	165	111	57	9
Intensive regions	173	125	63	8

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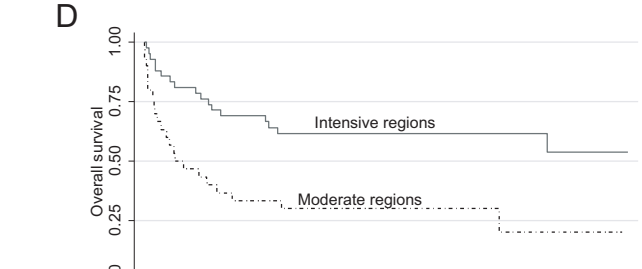
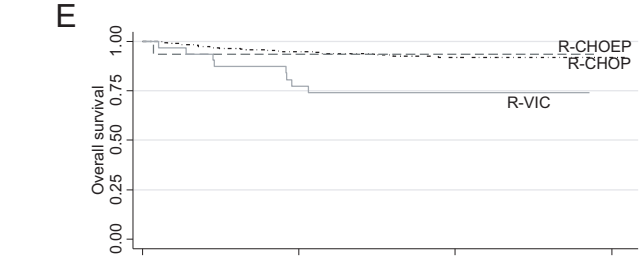


Number at risk				
Mild regions	30	7	5	1
Intensive regions	42	23	11	2

E



Number at risk				
R-CHOP	294	254	152	12
R-CHOEP	16	13	8	0
R-VIC	32	23	11	0