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Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État d'Hématologie clinique

par

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La substitution du cisplatine ou de l'oxaliplatine par le carboplatine est associée à une amélioration de la survie dans les lymphomes non hodgkiniens agressifs en rechute ou réfractaires : une étude rétrospective des centres du LYSA

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Titre : La substitution du cisplatine ou de l'oxaliplatine par le carboplatine e est associée à une amélioration de la survie dans les lymphomes non hodgkiniens agressifs en rechute ou réfractaires : une étude rétrospective des centres du LYSA.

Résumé : Le traitement par R-DHAP (rituximab, dexaméthasone, cytarabine à haute dose et cisplatine) est couramment utilisé pour le traitement des lymphomes non hodgkiniens (LNH) en rechute ou réfractaires (R/R). En l'absence de données, le cisplatine a été empiriquement remplacé par d'autres sels de platine (PS) comme le carboplatine (R-DHAC) ou l'oxaliplatine (R-DHAOx) en raison de la toxicité rénale et auditive du cisplatine. L'objectif de cette étude rétrospective multicentrique était de comparer la réponse complète (RC), la survie sans progression (SSP) et la survie globale (SG) entre ces trois traitements à base de PS. Les dossiers médicaux des patients traités pour un LNH R/R entre le 1er décembre 2006 et le 1er juillet 2013, ayant reçu soit du R-DHAP, du R-DHAC ou du R-DHAOx ont été récupérés parmi 24 centres du groupe LYSA. Parmi les 692 patients identifiés, 38 n'ont pas été inclus en raison de données manquantes, ainsi 654 patients ont été retenus dans cette analyse. Parmi eux, 146 (35%) ont été traités par R-DHAP, 190 (45%) par R-DHAOx, et 87 (21%) par R-DHAC pour un LNH agressif, après avoir exclu les patients ayant switchés de PS. Les patients traités par R-DHAP présentaient plus de LNH plus faible risque IPI (63% vs 49% respectivement, p=0,009). Le taux de RC était significativement plus élevé dans le R-DHAC que dans le R-DHAOx (46% vs 43%, p=0.04). Le R-DHAC était associé à une meilleure SSP médiane (17,5, IC 95 % : 11,3-NR vs 6,81 mois, IC 95 % : 4,9-11, p=0,01) et à une meilleure SG par rapport aux non-R-DHAC (74,7, IC 95 % : 61,3-NR vs 27,1, IC 95 % : 16,5-43,9, p=0,004). Une analyse multivariée a confirmé que le R-DHAC était associé à un risque plus faible de rechute (HR : 1,47, 95%CI : 1,06-2,03, p=0,02) et de décès (HR : 1,69, 95%CI 1,12-2,54, p=0,01) dans les LNH agressifs. Le traitement par R-DHAC était associé à moins de toxicités extra-hématologiques, en particulier à moins d'insuffisance rénale aigüe (RR 3,4, 95CI 1,4.-8,3), corrélé à moins d'arrêts de traitement (11% vs 18%, p=0,02) et moins de changement de PS (0,1% vs 8%, p<0,001). Cette étude rétrospective multicentrique en vie réelle indique que le remplacement du cisplatine et de l'oxaliplatine par le carboplatine dans le régime R-DHA-PS dans le traitement de 2ème ligne des LNH R/R est bien toléré et semble être associé à une amélioration du taux de réponse, de la SSP et de la SG.

Title: Substitution of cisplatin or oxaliplatin for carboplatin in platinum-containing chemotherapy is associated with improved survival in relapsed/refractory aggressive non-Hodgkin's lymphoma: a retrospective study from centers of the LYSA

Abstract: *Background*. The R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) regimen is commonly used for relapsed/refractory (R/R) non-Hodgkin's lymphoma (NHL). In the absence of data, cisplatin has been empirically substituted with other platinum salts (PS), such as carboplatin (R-DHAC) or oxaliplatin (R-DHAOx), because of commonly encountered renal and auditive toxicity. *Methods*. The aim of this retrospective multicenter study was to compare the complete response (CR), progression-free survival (PFS), and overall survival (OS) between three PS-based regimens. Twenty-four centers of the LYSA group retrieved medical records of patients who received PS for R/R NHL between December 1, 2006, and July 1, 2013, with R-DHAP, R-DHAC, or R-DHAOx. *Results*. Among the 692 patients identified, 38 were not included due to missing data. Thus 654 patients were retained in this analysis. Among them, 146 (35%) were treated with R-DHAP, 190 (45%) with R-DHAOx, and 87 (21%) with R-DHAC for aggressive NHL, after removal of patients with a PS switch. Patients treated with R-DHAP more often had low-risk NHL (63% vs 49%, p=0.009). The CR rate was significantly higher for R-DHAC than R-DHAOx (46% vs 43%, p=0.04). R-DHAC was associated with better median PFS (17.5 [95%CI: 11.3-NR] *vs.* 6.81 [95%CI: 4.9-11] months, p=0.01) and OS than non-R-DHAC (74.7 [95%CI: 61.3-NR] *vs.* 27.1 [95%CI: 16.5-43.9] months, p=0.004). Multivariate analysis confirmed that a carboplatin-based regimen was associated with a lower risk of relapse (HR: 1.47 [95%CI: 1.06-2.03], p=0.02) and death (HR: 1.69 [95%CI 1.12-2.54], p=0.01) in aggressive NHL. There was no difference in terms of response rate, PFS, or OS in indolent NHL. A non-carboplatin-based regimen was associated with less extra-hematological toxicity, especially acute kidney injury (RR 3.4 [95%CI 1.4.-8.3]) and correlated with less discontinuation of treatment (11% vs 18%, p=0.02) and fewer PS switches (0.1% vs 8%, p<0.001). These results remained similar after considering patients with a PS switch. *Conclusion*. This retrospective real-life multicenter study shows that cisplatin and oxaliplatin replacement by carboplatin in the R-DHA-platinum salt regimen for R/R NHL salvage treatment is safe and may be associated with improved response rate, PFS, and OS.

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.
Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.
Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les moeurs ni à favoriser le crime.
Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.
Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

Vu, le Directeur de Thèse

Vu, le Doyen

De la Faculté de Médecine de Tours

Tours, le

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Abstract.

Background. The R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) regimen is commonly used for relapsed/refractory (R/R) non-Hodgkin's lymphoma (NHL). In the absence of data, cisplatin has been empirically substituted with other platinum salts (PS), such as carboplatin (R-DHAC) or oxaliplatin (R-DHAOx), because of commonly encountered renal and auditive toxicity. Methods. The aim of this retrospective multicenter study was to compare the complete response (CR), progression-free survival (PFS), and overall survival (OS) between three PS-based regimens. Twenty-four centers of the LYSA group retrieved medical records of patients who received PS for R/R NHL between December 1, 2006, and July 1, 2013, with R-DHAP, R-DHAC, or R-DHAOx. Results. Among the 692 patients identified, 38 were not included due to missing data. Thus 654 patients were retained in this analysis. Among them, 146 (35%) were treated with R-DHAP, 190 (45%) with R-DHAOx, and 87 (21%) with R-DHAC for aggressive NHL, after removal of patients with a PS switch. Patients treated with R-DHAP more often had low-risk NHL (63% vs 49%, p=0.009). The CR rate was significantly higher for R-DHAC than R-DHAOx (46% vs 43%, p=0.04). R-DHAC was associated with better median PFS (17.5 [95%CI: 11.3-NR] *vs.* 6.81 [95%CI: 4.9-11] months, p=0.01) and OS than non-R-DHAC (74.7 [95%CI: 61.3-NR] *vs.* 27.1 [95%CI: 16.5-43.9] months, p=0.004). Multivariate analysis confirmed that a carboplatin-based regimen was associated with a lower risk of relapse (HR: 1.47 [95%CI: 1.06-2.03], p=0.02) and death (HR: 1.69 [95%CI 1.12-2.54], p=0.01) in aggressive NHL. There was no difference in terms of response rate, PFS, or OS in indolent NHL. A non-carboplatin-based

regimen was associated with less extra-hematological toxicity, especially acute kidney injury (RR 3.4 [95%CI 1.4.-8.3]) and correlated with less discontinuation of treatment (11% vs 18%, p=0.02) and fewer PS switches (0.1% vs 8%, p<0.001). These results remained similar after considering patients with a PS switch. Conclusion. This retrospective real-life multicenter study shows that cisplatin and oxaliplatin replacement by carboplatin in the R-DHA-platinum salt regimen for R/R NHL salvage treatment is safe and may be associated with improved response rate, PFS, and OS.

Background

First-line treatment of non-Hodgkin's lymphoma (NHL) is based on the association of an anti-CD20 monoclonal antibody and polychemotherapy, most often CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone(1,2). In the relapsed/refractory setting, the DHAP (dexamethasone, high-dose cytarabine and cisplatin) regimen is commonly used(3,4) and has been shown to improve progression-free survival (PFS) over the ICE regimen (ifosfamide, cyclophosphamide, and etoposide) in germinal center B (GCB)-like lymphoma(5). Second-line treatment of aggressive lymphomas and sometimes indolent lymphomas includes chemotherapy intensification followed by autologous stem-cell transplantation (ASCT) in cases of chemosensitive relapse(6,7).

Platinum salts (PS) are alkylating antineoplastic agents that interfere with DNA repair mechanisms, causing DNA damage, leading to the activation of apoptosis in malignant cells(8). Several toxicities have been reported for cisplatin-based-regimens, including renal, neurological (peripherical neuropathy), hematological, and gastro-intestinal(7). The mechanisms for cisplatin-related renal toxicity are not completely understood. Renal accumulation of the drug is likely to damage the human renal organic cation transporter(9,10). Alternative PS, such as carboplatin and oxaliplatin, have been used empirically to mitigate such adverse events.

A French retrospective study compared the toxicity of cisplatin (DHAP), carboplatin (DHAC), and oxaliplatin (DHAOx) in 276 patients with NHL and Hodgkin lymphoma (HL) (11). Although frequently reversible, renal failure was reported in 50% of patients who received DHAP, with 8.9% grade III or IV acute renal failure. The cumulative dose of cisplatin was found to be a significant risk factor for renal failure. Concerning hematological toxicity, thrombopenia was more frequent with DHAP (62%) and DHAC (72%) than DHAOx (39%) and febrile

neutropenia was reported in 29%, 10%, and 15% of patients, respectively. However, oxaliplatin was involved in neurotoxicity cases (59%), mainly grade I-II (45%).

No head-to head comparison of the efficacy of PS in hematological malignancies is available in the literature. In a retrospective study on 91 patients, including relapsed/refractory (R/R) NHL treated with R-DHAOx, the complete response rate (CRR) was 57% and progression free survival (PFS) was 43% and overall survival (OS) 75% at two years (12). Rigacci et al(13) reported similar findings in a retrospective study for 70 cases of R/R NHL and HL treated with DHAOx ± rituximab, with a CRR of 43%, two-year PFS of 44%, and two-year-OS of 71%. A recent study showed similar findings for the carboplatin-containing regimen, R-DHAC(14). The PARMA study(3), which prospectively evaluated the efficacy of DHAP (with no R) followed by ASCT in 50 patients with R/R NHL, showed a 58.5% CRR, with two-year PFS of 40% for patients who underwent ASCT. Similarly, the CORAL Study (7), showed three-year PFS of 42% for patients treated with the R-DHAP regimen. The absence of renal toxicity makes carboplatin and oxaliplatin attractive for patients eligible for autologous stem-cell transplantation and elderly patients. However, their respective efficacy has not yet been directly compared. We hypothesized that the substitution of cisplatin for oxaliplatin or carboplatin in the R-DHAP regimen would not be inferior in terms of efficacy and tolerance to the standard R-DHAP.

We launched this retrospective DHAP&CO multicenter study to evaluate cisplatin replacement with oxaliplatin or carboplatin on the response to salvage therapy, toxicity, and outcome of R/R NHL patients.

Methods

Patient selection and treatment.

Twenty-four centers of the LYSA group retrieved the medical records of patients treated between December 1, 2006, and July 1, 2013, with 100 mg/m^2 R-DHAP and 100 to 130 mg/m^2 R-DHAOx or R-DHAC area under the curve (AUC) = 5 mg/ml/min at day 1, at 21-day intervals. The study retrospectively included adult patients who received PS for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL), transformed indolent NHL (both regrouped as aggressive NHL), follicular lymphoma (FL), or other indolent lymphomas (both regrouped as indolent NHL). Exclusion criteria were patients with mantle-cell lymphoma, those with Richter's syndrome (defined as transformation of chronic lymphocytic leukemia), and those who received more than five previous treatment regimens. A standardized electronic case report form (CRF) was completed by a single clinical research assistant (CRA) who visited the centers and controlled the accuracy of all data. Comorbidities were identified according to the medical records and listed as follows: no comorbidity, at least one renal comorbidity, or comorbidity other than renal.

Complete and partial response (CR and PR, respectively) were defined by the Deauville(15) score or Cheson(16) score, according to the image-based response (PET or CT, chosen by the clinician) after the third or fourth cycle of the PS-based regimen. Dose intensity (DI) was calculated using the following formula: relative PS dose = (applied dose of PS)/(theorical dose of PS); relative cycle interval = 21/(number of days between each cycle); DI = (relative PS dose)*(relative intercourse interval). AUC were calculated using Calvert's formula for the carboplatin-based regimen and the body surface area was calculated using Mosteller's formula for the cisplatin- and oxaliplatin-based regimens.

Adverse events (AEs) after cycle 1 (C1), cycle 2 (C2), and cycle 3 (C3) were recorded and assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0. To overcome biases induced by a PS switch, each AE was counted after each treatment cycle according to the PS used and divided by the total number of cycles of each PS for which AE data were available (AEs were not equally reported for each cycle). An outcome of acute kidney injury (AKI) after receiving PS was only considered for patients with plasma creatinine (PCr) levels available before and after each cycle (at days 3, 5, and/or 7) and considered to be the case if the PCr level was >26.5 µmol/L higher than before treatment, according to international recommendations (KDIGO).

The results were dichotomized according to aggressive NHL (including DLBCL and transformed indolent NHL) and indolent NHL (including FL and other indolent NHL) due to a large difference in outcome between NHL histological subtypes. Finally, results were first analyzed after first excluding patients who switched PS at C2 or C3 ("no switch cohort"), due to a significant proportion of patients who switched PS at C2 and C3, to evaluate solely the impact of the PS in the regimen, and then including all patients ("whole cohort").

Statistical analyses

Results are expressed as the means and standard deviations for continuous variables and numbers and percentages for categorical variables. Numeric variables were compared using Student's t-test if the appropriate conditions were met. Qualitative variables were compared using the χ^2 test if the conditions were met or by Fisher's exact test if they were not. PFS was calculated from the first cycle of chemotherapy that included a PS to progression, relapse, or death from any cause. OS was calculated from the first cycle of chemotherapy that included a PS to death from any cause. PFS and OS were analyzed using the Kaplan-Meier

method and compared using the Log-rank test. Multivariate Cox models were adjusted for prognostic factors previously found to be significant in univariate analysis to estimate the risk of death and relapse. The significance level was set to 0.05. Statistical analysis was performed using R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Ethical considerations

This study was approved by the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (CCTIRS) on October 23, 2014, according to French regulations.

Results

Patient characteristics of the whole cohort

Between December 1, 2006, and July 1, 2013, 692 patients were identified to have been treated with a R-DHAP-like regimen in 24 centers. After exclusion of 38 patients with missing data or inclusion criteria violations, 654 patients were included in the analysis, regardless of PS switch (Figure 1). The chosen PS for the first cycle was overrepresented by cisplatin at the beginning of inclusion, 69% in 2007, progressively decreasing in favor of oxaliplatin (74% in 2012), with a consistently low use of carboplatin throughout the period (Figure 2). Among the 654 included patients, 448 (69%) had aggressive NHL and 206 (31%) indolent disease. Among them, 43 patients (14%) experienced a PS switch at C2 or C3 (mainly from a cisplatin-based regimen, 37/43), leading to the two first analyzed cohorts, the aggressive (n = 423) and indolent NHL (n = 188) without PS switch cohorts.

Aggressive NHL

The aggressive NHL cohort included 423 patients without a PS switch, with 307 (73%) cases of DLCBL and 116 (27%) of transformed indolent NHL. Among them, 146 (35%) were treated with R-DHAP, 190 (45%) with R-DHAOx, and 87 (21%) with R-DHAC. Patient characteristics are summarized in Table 1. Briefly, patients treated with the R-DHAOx regimen were older at the time of relapse (61 vs 58 y, p=0.01) and less frequently had no comorbidities (50% vs 63%, p=0.02), whereas patients in the R-DHAP subgroup presented with lower-risk NHL based on the IPI score (63% vs 49%, p=0.009). Follow-up was longer in the R-DHAC group (29.4 ± 24.5) than in the R-DHAOx (17.5 ± 15.3, p<0.001) and R-DHAP (22.9 ± 21.6, p=0.03) groups. Patient characteristics for those with aggressive NHL, regardless of PS switch, are summarized in Supplemental Table 1.

The overall response rate (ORR) was similar between the three groups in the "no-switch" cohort: 56% in the R-DHAP group, 54% in R-DHAOx group, and 65% in the R-DHAC group (p=0.2). The CRR was significantly higher in the R-DHAC than R-DHAOx group (46% vs 33%, p=0.04), without a statistical difference from that of the R-DHAP group (37%, p = 0.2) (Figure 3A).

The median PFS of the R-DHAP, R-DHAOx, and R-DHAC groups were 8.3 [95%CI: 5.5-14.0], 5.3 [95%CI: 3.7-12.2], and 17.5 [95%CI: 11.3-NR)] months, respectively, in the "no-switch" cohort, with significantly longer PFS in the R-DHAC than non-R-DHAC (6.81 [95%CI: 4.9-11], p=0.01) groups (Figure 4A). R-DHAC remained associated with PFS (HR: 1.47 [95%CI: 1.06-2.03], p=0.02) in a multivariate analysis after adjustment for confounding factors (age, rituximab use, refractory NHL, number of previous lines, and IPI) (Table 2). Median OS in the R-DHAP, R-DHAC, and R-DHAOx groups were 26.5 [95%CI: 14.8-55.2], 29.2 [95%CI: 14.5-NR], and 74.7 [95%CI: 61.3-NR] months (Figure 4C) in the "no-switch" cohort, with significantly better

median OS for the carboplatin-based regimen than the non-carboplatin-based regimens (27.1 [95% CI: 16.5-43.9]). The R-DHAC regimen remained associated with better OS (HR: 1.69 [95% CI 1.12-2.54], p=0.01) in a multivariate analysis adjusted for the previously described cofounding factors (Table 3).

ASCT was initially planned for 270 (78%) patients under 70-years of age (75% in the R-DHAP, 74% in the R-DHAOx, and 75% in the R-DHAC group, p=0.9). The number of patients who underwent the procedure was 63 (58%) in the cisplatin, 58 (54%) in the oxaliplatin, and 33 (61%) in the carboplatin-based regimen (p=0.6). The main reason for not performing the ASCT was an insufficient response (80, 92, and 67%, respectively), followed by the regimen's toxicity (7, 6, and 14%). Of note, ASCT was not performed because of a hematopoietic stem-cell collection failure for 4 (9%) patients in the R-DHAP, 0 in the R-DHAOx, and 2 (9%) in the R-DHAC group (Supplemental Table 4).

Considering all patients with aggressive NHL, including those with a PS switch at C2 or C3, R-DHAC patients still had a higher CRR than R-DHAOx patients (47% vs 33% p=0.04) and DHAC remained associated with better PFS (HR: 1.51 [95%CI: 1.09-2.08], p=0.01, Supplemental Table 2 and Supplemental Figure 2A) and OS (HR: 1.71 [95%CI: 1.14-2.56], p=0.01, Supplemental Table 3 and Supplemental Figure 2C) than non-R-DHAC in a multivariate analysis.

Indolent NHL

The indolent NHL cohort included 188 patients who did not switch PS, with 73 (39%) treated with R-DHAP, 97 (51%) with R-DHAOx, and 18 (10%) with R-DHAC. Among them, 175 (73%) had FL and 13 (27%) another indolent NHL. The characteristics of patients who did not switch PS are summarized in Table 4.

The ORR was similar between the three groups in the "no-switch" cohort: 85% in the R-DHAP group, 78% in R-DHAOx group, and 83% in the R-DHAC group (p=0.5). There was also no

statistical difference in the CRR between the three groups (52%, 62%, and 44%, respectively, p=0.3) (Figure 3B).

There was no difference in median PFS between the R-DHAP, R-DHAOx, and R-DHAC groups: 57.3 [95%CI: 32.5-NR], NR [95%CI: 45.5-NR], and 17.5 [95% CI: 11.3-NR)], respectively (p=0.09), (Figure 4B), nor in median OS (p=0.2) (Figure 4D).

ASCT was planned less frequently for R-DHAC (72%) patients than for R-DHAP (94%) and R-DHAOx (85%, p=0.03) patients, but the rates of ASCT were similar among them (71, 72, and 69%, respectively, p=0.9).

Toxicity profiles

Toxicities were analyzed for the whole cohort and compared between the R-DHAC and non-R-DHAC groups (Figure 5). Neurotoxicity of any grade (RR 4.0 [95%CI 1.3-12.3] and grade 4 gut toxicity (RR 3.4 [95%CI 1.4.-8.3]) were more frequent in the non-R-DHAC than R-DHAC group. A detailed face-to-face comparison of PS is reported in Supplemental Figures 3-5. AKI was found in 3/83 (3.6%) cycles of R-DHAC *vs* 119/820 (14.5%) cycles of non-R-DHAC (RR 4.0 [95%CI 1.3-12.3]). In particular, AKI was found in 99/487 cycles (20%) after a cisplatin-based regimen and 74 patients (29%) treated with R-DHAP had at least one episode of AKI, versus 17 (6%) and 2 (2%) in the R-DHAOx and R-DHAC groups, respectively. Of note, the outcome of at least one episode of AKI during treatment was associated with significantly worse median OS than for patients without an AKI episode (31 [95%CI: 14.4-NR] *vs* 75 [95%CI: 65-NR] months, p=0.001; Supplemental Figure 6B). More specifically, the AKI outcome was associated with more early deaths within the first six months following the first PS cycle (27% vs 16%, p=0.01), with 58% of deaths related to the disease and 10% to PS toxicity (vs 5%).

Dose-intensity and treatment modification:

The mean DI was higher in the R-DHAC than non-R-DHAC group at C1 (91% vs 81% of the theorical dose, p=0.001) and C2 (89% vs 80% of the theorical dose, p<0.001) in the whole cohort. Treatment modifications, including ending the regimen, dose reduction, and PS switch following cycle 1 and cycle 2 are reported in Table 5. R-DHAC was associated with less discontinuation of treatment than non-R-DHAC regimens (11% vs 18%, p=0.02) and R-DHAP was associated with more PS switching than non-R-DHAP regimens (8% vs 0.1%, p<0.001). Among the 37 PS-switches from cisplatin, 21 were replaced by oxaliplatin and 16 by carboplatin. Among the five patients who switched from the oxaliplatin group, the underlying cause was neurological toxicity for four, and hepatic toxicity for one.

Causes of death

The causes of death for the whole cohort are shown in Table 6. Lymphoma-related deaths were equally reported for both groups, with 69% in the R-DHAP, 76% in the R-DHAOx, and 74% in the R-DHAC (p=0.2) group. The rate of toxicity- or ASCT-related deaths was 9% for the cisplatin, 6% for the oxaliplatin, and 0% for the carboplatin-based regimen. Two cases of death following secondary acute myeloid leukemia were observed for the DHAP group, and none in the other groups, and two cases of death were reported during ASCT after R-DHAOx induction.

Discussion

We show, for the first time, that the R-DHAC regimen is associated with a higher CRR and significantly prolonged PFS and OS relative to R-DHAP and R-DHAOx regimens, even after adjusting for known prognosis factors in aggressive NHL.

This study highlights the preferential choice of oxaliplatin, used in 44% of cases in clinical practice in France and Belgium between 2007 and 2012. Importantly, oxaliplatin was

preferentially chosen over time, highlighting the need in clinical practice to replace cisplatin, despite the lack of comparative data.

In our study, there was a trend towards a higher CRR in aggressive NHL for R-DHAC relative to other PS-based regimens (47% vs 35%, p=0.05), with a significant difference between the R-DHAC and R-DHAOx groups (p=0.04). Furthermore, we found an adverse outcome for patients treated with cisplatin or oxaliplatin relative to carboplatin on PFS and OS in aggressive NHL, which has never before been described. However, the clinical outcomes described in our study were similar to those found in the literature. In the CORAL study, the ORR after three cycles of R-DHAP was 62.8%, with three-year PFS of 42% and three-year OS of 51%, with three-year OS of 53% for patients who underwent ASCT. Meyer et al (17) found a similar response profile, with an ORR of 62.3% after four cycles of R-DHAP and median PFS and OS of 7.6 and 8.5 months, respectively. A retrospective study of Tessoulin et al. found equivalent efficiency with carboplatin in terms of CR (57%), with less toxicity than a cisplatin-based regimen.(14) However, this study included several histological subgroups, such as mantle-cell lymphoma and Hodgkin's lymphoma, that were not included in our study, and did not directly compare the ORR, OS, or PFS between PS groups. Lignon et al. showed a safe and effective profile when oxaliplatin was associated with rituximab, cytarabine, and dexamethasone in R/R lymphoma(12). In this study, the ORR was 75%, with a CRR of 57% and PFS and OS at two years of 43% and 75%, respectively.

There are several possible explanations for the worse outcome of patients treated with cisplatin or oxaliplatin described here. First, patients treated with R-DHAP showed significantly greater extra-hematological toxicity, in particular auditory toxicity and AKI. Renal insufficiency after cisplatin is known to be generally reversible(11). However, in our study, an outcome of at least one episode of AKI was associated with a higher frequency of treatment discontinuation

and poorer OS, underlying the dramatic impact of AKI on the proper course of treatment. Second, patients treated with R-DHAOx were older and had more comorbidities than those treated with R-DHAP or R-DHAC. Furthermore, those in the R-DHAP group had a higher IPI score, but not those in the R-DHAC group, underlying a possible preferential choice of oxaliplatin over cisplatin for unfit patients, possibly contributing to their poorer outcome. Another explanation could be that uncontrolled confounding factors, such as the proportion of activated B-cell (ABC) DLBCL or adverse mutational profiles, may have influenced the outcome of these patients. Indeed, Thieblemont et al. showed the prognostic impact of germinal-center (GC) derived DLBCL in the R-DHAP regimen relative to that of ABC-derived DLBCL(5). Data on the cell of origin and mutational data were unavailable in our study. Histological heterogeneity of our cohort was avoided by separating our analyses into aggressive and indolent NHL, which could not be directly compared in terms of response rate or survival, except for toxicity profiles. Additionally, we found a similar rate of patients intensified with ASCT in the cisplatin (64%), oxaliplatin (63%), and carboplatin (56%) groups, for those for whom intensification was planned before treatment.

In the indolent NHL cohort, consisting mostly of FL, there were no differences in terms of response rate, PFS, or OS between regimens. We cannot rule out the statistical impact of the size of the indolent cohort, which was smaller than the aggressive cohort. Moreover, as recently shown, oxaliplatin appears to have a specific in vitro and in silico activity against mantle-cell lymphomas cells(18) and we cannot discard specific activity of one of the PS on FL cells. However, there is currently no data to support this hypothesis.

We hypothesize that cisplatin and oxaliplatin may limit the ability to aggressively treat relapses that occur after R-DHAP because of their toxicity, leading to lower treatment DI for both treatments and possibly for more unfit patients among those treated with R-DHAOx. Our

findings are supported by the higher number of PS switches with cisplatin use (15%) than for oxaliplatin (2%) or carboplatin (1%).

Of note, sinusoidal obstruction syndromes (SOS) were not observed in our cohort, in contrast to a recent national alert(19), underlying a possible association between SOS and ASCT after oxaliplatin exposure among 22 patients. However, these 22 cases occurred after 2012, the more recent time boundary of our study. In any case, analysis of the outcome according to PS switch still showed an improvement in CRR, PFS, and OS for patients treated with R-DHAC in aggressive NHL, suggesting a long-term impact of toxicity on outcome, despite a PS switch at C2 or C3.

The strength of our study was the large patient sample and its multicentric design, likely mitigating center bias. Furthermore, there have been no prospective clinical trials randomizing PS in the field of lymphoma. Such studies are highly unlikely to be launched given the active development of alternate salvage options, such as checkpoint inhibitors, CAR-T cells, bispecific antibodies, signaling inhibitors, and adoptive immunotherapies(20).

Conclusion

In this retrospective study, we found R-DHAC to be associated with less toxicity than non-carboplatin-based regimens, with better PFS and OS in aggressive NHL. These data support the substitution of cisplatin and oxaliplatin by carboplatin for the salvage treatment of aggressive NHL.

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Authors' contributions

Conception and design: EG and AI. Collection and assembly of the data: AT and ME. Data analysis and interpretation: ET, EG, and ME. Writing of the manuscript: all authors. Final approval of the manuscript: all authors.

Conflict of interest disclosure.

GC reports consulting activities (from Roche and Celgene) and royalties (from Abbvie, Sanofi, Gilead, Jansen, Roche, and Celgene). EG has received honoraria from Roche and research support from Novartis. No other potential conflict of interest relevant to this article was reported.

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Tables

	R-DHAP	R-DHAOx	R-DHAC	overall p-value
n	146	190	87	
Age over 60 y (%)	73 (50.0)	110 (57.9)	44 (50.6)	0.288
Age at relapse (mean (SD))	57.03 (12.60) *	60.66 (12.81) *	58.64 (12.15)	0.032
Male gender (%)	88 (60.3)	109 (57.4)	51 (58.6)	0.866
Comorbidities (%)				0.069
None	88 (62.4)	92 (50.0)*	50 (65.8)	0.02
Any but renal	37 (26.2)	59 (32.1)	19 (25.0)	0.4
Renal	16 (11.3)	33 (17.9)*	7 (9.2)	0.09
Histology				0.7
DLBCL	105 (71.9)	141 (74.2)	61 (70.1)	
Transformed indolent NHL	41 (28.1)	49 (25.8)	26 (29.9)	
IPI score 0,1, or 2 (%)	92 (63.0)*	91 (47.9)*	45 (51.7)	0.020
Previous line over one (%)	37 (25.3)	42 (22.1)	13 (14.9)	0.175
Refractory NHL (%)	64 (43.8)	84 (44.2)	35 (40.2)	0.813
Rituximab use (%)	122 (88.4)	165 (88.2)	76 (90.5)	0.854
Dose-intensity at C1 (mean (SD))	0.84 (0.34)	0.79 (0.20)**	0.94 (0.23)**	<0.001
Dose-intensity at C2 (mean (SD))	0.83 (0.22)	0.77 (0.21)**	0.93 (0.25)**	<0.001
Follow-up (mean (SD))	22.85 (21.62)	17.54 (15.28)**	29.45 (24.51)**	<0.001

Table 1. Patient characteristics according to each regimen for aggressive NHL patients after the removal of patients who switched PS.

*p < 0·05 compared to other regimens **p < 0·001 compared to other regimens.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, SD: standard deviation, y: year

	Univariate analysis				Multivariate analysis			
	OR	lower CI	upper CI	p	OR	lower CI	upper CI	p
Regimen								
R-DHAP	1.05	0.83	1.33	0.70				
R-DHAC	0.66	0.48	0.90	0.01	1.47	1.06	2.03	0.02
R-DHAOx	1.25	0.99	1.58	0.06				
Age > 60 y	1.41	1.11	1.80	0.01	1.18	0.89	1.56	0.26
Rituximab	0.44	0.31	0.62	<0.001	0.50	0.35	0.71	<0.001
Refractory NHL	1.79	1.42	2.25	<0.001	1.78	1.39	2.29	<0.001
Dose-intensity at C1	1.25	0.83	1.87	0.28				
Male sex	1.01	0.80	1.28	0.92				
more than one previous line	1.39	1.06	1.82	0.02	1.18	0.87	1.61	0.29
IPI low (0, 1, or 2)	0.59	0.47	0.74	<0.001	0.69	0.53	0.90	0.01
Comorbidities								
No comorbidities	0.94	0.74	1.19	0.58				
Renal comorbidities	1.09	0.79	1.51	0.60				
Other comorbidities	1.03	0.79	1.34	0.85				

Table 2. Risk factors associated with progression-free survival in univariate and multivariate analysis (logistic regression) in the aggressive lymphoma cohort without platinum salt switch. Each regimen is compared to the others.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, Ref: reference.

	Univariate analysis				Multivariate analysis			
	OR	lower CI	upper CI	p	OR	lower CI	upper CI	p
Regimen								
R-DHAP	1.18	0.89	1.57	0.26				
R-DHAC	0.57	0.38	0.84	0.00	1.69	1.12	2.54	0.01
R-DHAOx	1.22	0.92	1.62	0.16				
Age > 60 y	1.41	1.11	1.80	0.01	1.04	0.74	1.45	0.83
Rituximab	0.45	0.32	0.63	<0.001	0.55	0.37	0.81	<0.001
Refractory NHL	1.86	1.46	2.37	<0.001	1.70	1.27	2.28	<0.001
Dose-intensity at C1	1.20	0.79	1.83	0.40				
Male sex	0.99	0.78	1.27	0.96				
more than one previous line	1.47	1.11	1.95	0.01	1.45	1.02	2.05	0.04
IPI score 0, 1, or 2	0.59	0.46	0.75	<0.001	0.69	0.50	0.95	0.02
Comorbidities								
No comorbidities	0.97	0.76	1.24	0.81				
Renal comorbidities	0.99	0.70	1.41	0.96				
Other comorbidities	1.04	0.80	1.37	0.76				

Table 3. Risk factors associated with overall survival in univariate and multivariate analysis (logistic regression) in the aggressive lymphoma cohort without platinum salt switch. Each regimen is compared to the others.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, CI: confidence interval

	R-DHAP	R-DHAOx	R-DHAC	overall p-value
n	73	97	18	
Age over 60 y (%)	23 (31.5)*	45 (46.4)	11 (61.1)	0.03
Age at relapse (mean (SD))	55.76 (8.70)*	58.71 (10.59)	60.85 (7.76)	0.05
Male gender (%)	40 (54.8)	69 (71.1)*	8 (44.4)	0.02
Comorbidities (%)				
None	44 (63.8)	54 (58.1)	9 (52.9)	
Any but renal	18 (26.1)	23 (24.7)	5 (29.4)	
Renal	7 (10.1)	16 (17.2)	3 (17.6)	
Histology				
DLBCL	68 (93.2)	90 (92.8)	17 (94.4)	
Transformed indolent NHL	5 (6.8)	7 (7.2)	1 (5.6)	
FLIPI score 0,1, or 2 (%)	43 (58.9)	64 (66.0)	7 (38.9)	0.09
Previous line over one (%)	17 (23.3)	28 (28.9)	6 (33.3)	0.6
Refractory NHL (%)	23 (31.5)	27 (27.8)	5 (27.8)	0.9
Rituximab use (%)	62 (87.3)	85 (91.4)	17 (94.4)	0.6
Dose-intensity at C1 (mean (SD))	0.79 (0.19)	0.82 (0.19)	0.76 (0.15)	0.4
Dose-intensity at C2 (mean (SD))	0.79 (0.17)	0.81 (0.19)	0.74 (0.15)	0.4
Follow-up (mean (SD))	38.28 (22.46)**	26.84 (20.69)*	32.53 (13.76)	0.002

Table 4. Patient characteristics according to each regimen for indolent NHL patients after the removal of patients who switched PS.

*p < 0·05 compared to other regimens **p < 0·001 compared to other regimens.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, SD: standard deviation, y: year

	R-DHAP	R-DHAOx	R-DHAC	overall p-value
n	452	553	212	
No change	306 (67.7) **	440 (79.6) *	174 (82.1) *	<0.001
Treatment discontinuation	88 (19.5) *	88 (15.9)	23 (10.8) *	0.01
Disease-related	18 (4.0)	29 (5.2)	7 (3.3)	
Toxicity	42 (9.3)	36 (6.5)	7 (3.3)	
Other	7 (1.5)	3 (0.5)	3 (1.4)	
Unknown	21 (4.6)	20 (3.6)	6 (2.8)	
Dose reduction	21 (4.6)	20 (3.6)	14 (6.6)	0.2
Toxicity	20 (4.4)	20 (3.6)	14 (6.6)	
Other	1 (0.2)	0 (0.0)	0 (0.0)	
PS switch	37 (8.2)**	5 (0.9)**	1 (0.5)*	<0.001
Disease-related	1 (0.2)	0 (0.0)	0 (0.0)	
Toxicity	33 (7.3)	5 (0.9)	1 (0.5)	
Other	3 (0.7)	0 (0.0)	0 (0.0)	

Table 5. Regimen modification after pooled cycle 1 and cycle 2 according to each regimen for the whole cohort.

*p < 0·05 compared to other regimens **p < 0·001 compared to other regimens.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin

	R-DHAP	R-DHAOx	R-DHAC
n	106	106	31
Lymphoma-related	73 (68.9)	81 (76.4)	23 (74.2)
ASCT toxicity	0 (0.0)	2 (1.9)	0 (0.0)
PS-based regimen toxicity	9 (8.5)	6 (5.7)	0 (0.0)
Graft versus Host Disease	0 (0.0)	2 (1.9)	4 (12.9)
Late infection	2 (1.9)	4 (3.8)	2 (6.5)
Secondary malignancy	2 (1.9)	0 (0.0)	0 (0.0)
Other	2 (1.9)	2 (1.9)	0 (0.0)
Unknown	18 (17.0)	9 (8.5)	2 (6.5)

Table 6. Causes of death according to regimen for the whole cohort.

*p < 0·05 compared to other regimens **p < 0·001 compared to othe regimens.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin

Figure legends

Figure 1. Flow chart.

Figure 2. Relative frequencies of each regimen over time of inclusion in the whole cohort. The regimens in 2006 and 2013 are not shown due to the very low number of events (n = 2). *DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin*

Figure 3. Response rate according to regimen in the "no switch" cohort in aggressive lymphoma (A) and indolent lymphoma (B). *DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, CR: complete response, PR: partial response*

Figure 4. Kaplan-Meier curves of progression free-survival in aggressive lymphoma (A) and indolent lymphoma (B) and overall survival in aggressive lymphoma (C) and indolent lymphoma (D) according to regimen in the no-switch cohort.
DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin

Figure 5. Forest plot of the comparison of toxicity between R-DHAC and non-R-DHAC (R-DHAOx and R-DHAP) regimens.
DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, RR: relative risk, CI: confidence interval

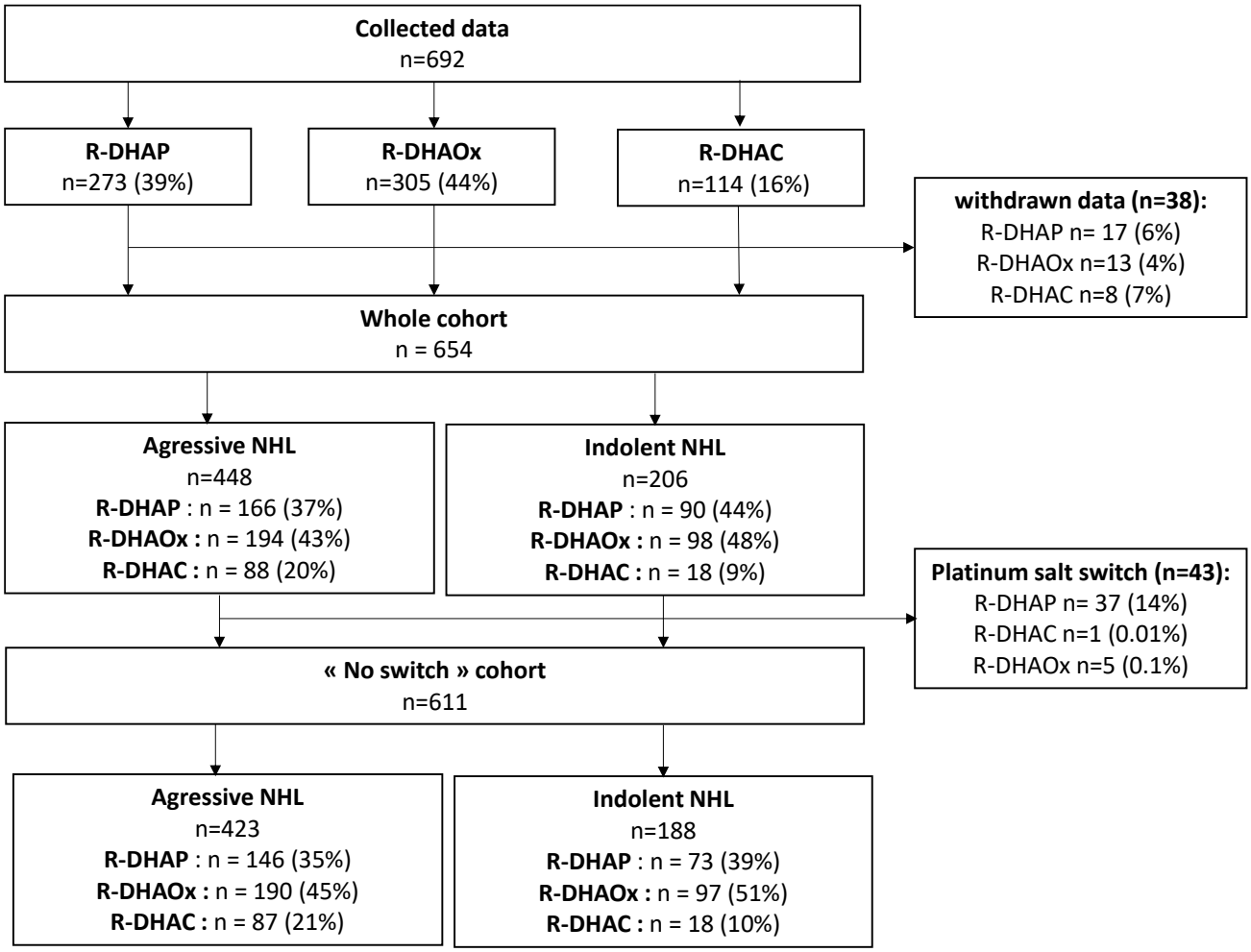


Figure 1. Flow chart.

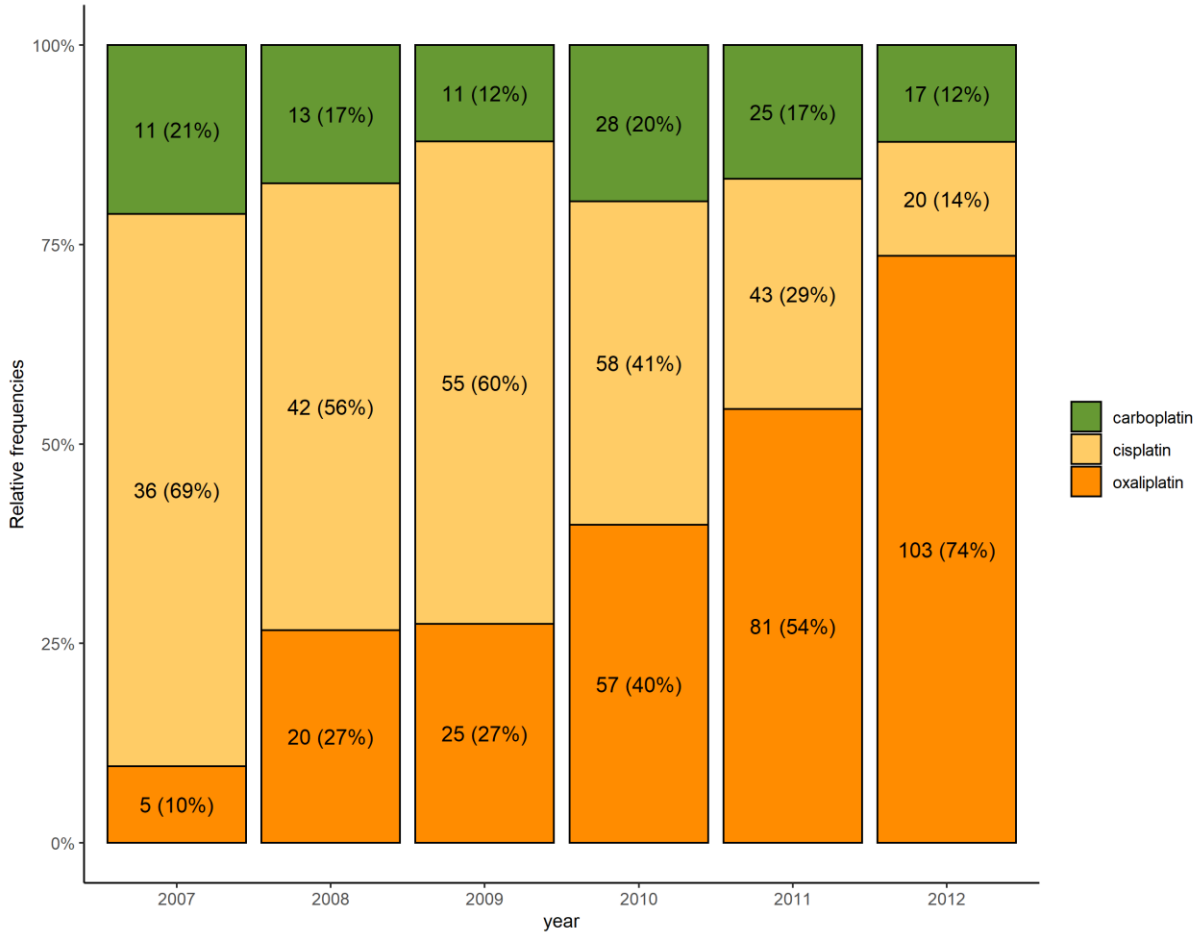


Figure 2. Relative frequencies of each regimen over time of inclusion in the whole cohort. The regimens in 2006 and 2013 are not shown due to the very low number of events (n = 2). *DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin*

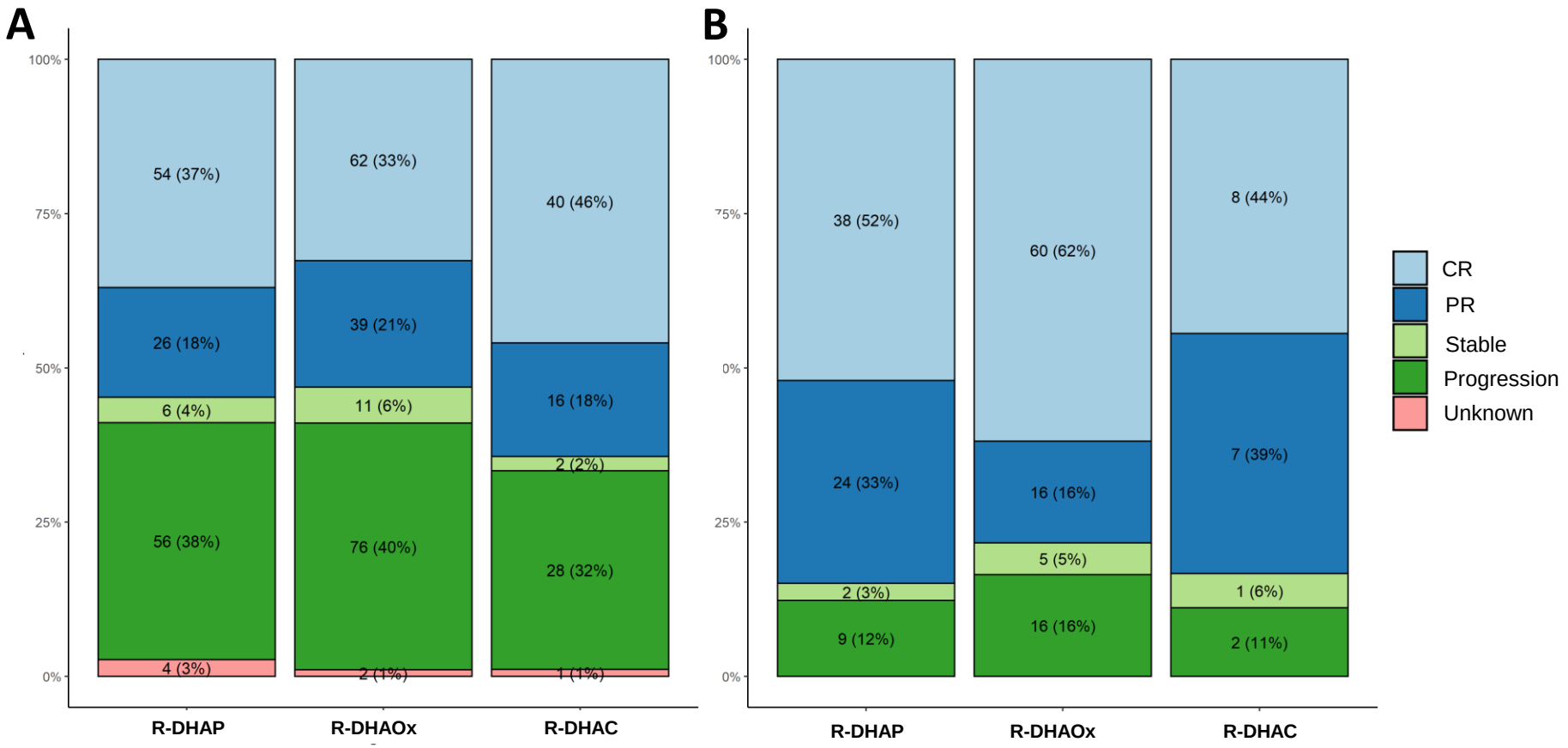


Figure 3. Response rate according to regimen in the "no switch" cohort in aggressive lymphoma (A) and indolent lymphoma (B). *DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, CR: complete response, PR: partial response*

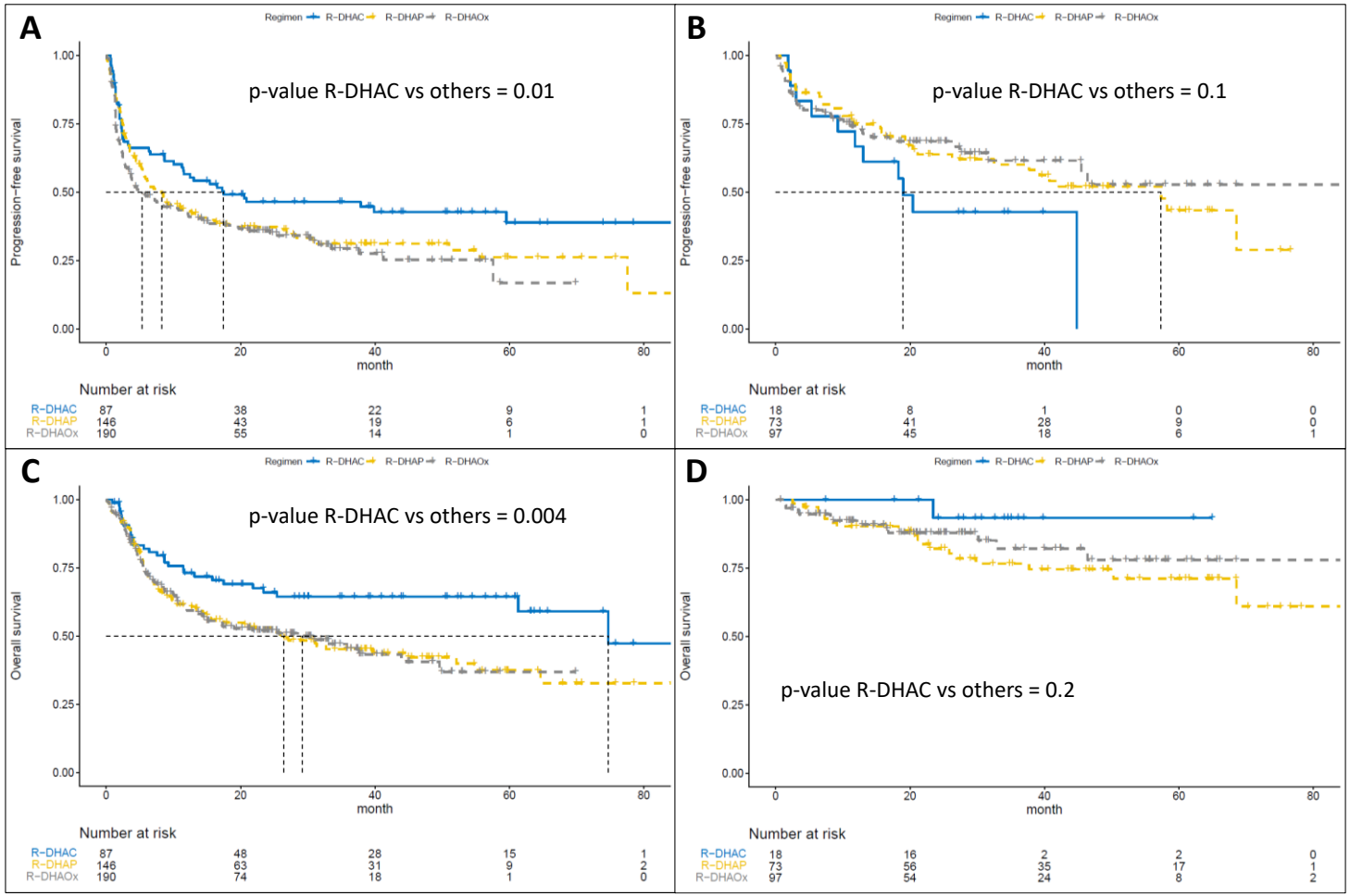


Figure 4. Kaplan-Meier curves of progression free-survival in aggressive lymphoma (A) and indolent lymphoma (B) and overall survival in aggressive lymphoma (C) and indolent lymphoma (D) according to regimen in the no-switch cohort.

DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin

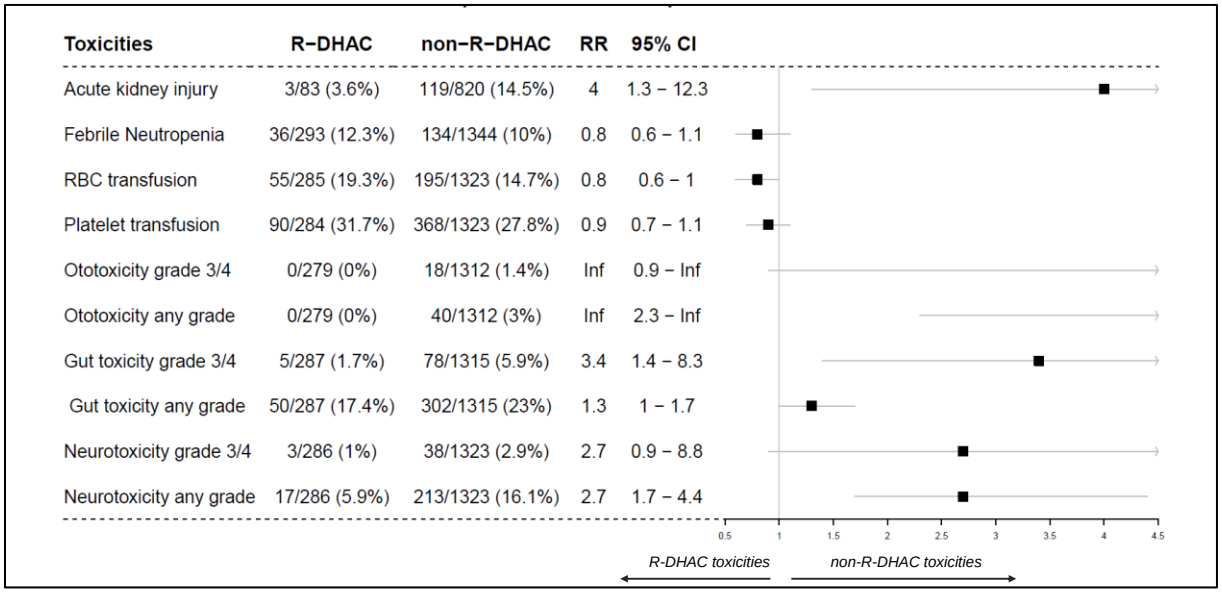


Figure 5. Forest plot of the comparison of toxicity between R-DHAC and non-R-DHAC (R-DHAOx and R-DHAP) regimens.

DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, RR: relative risk, CI: confidence interval

Supplemental Tables

	R-DHAP	R-DHAOx	R-DHAC	overall p-value
n	166	194	88	
Age over 60 y (%)	83 (50.0)	114 (58.8)	45 (51.1)	0.2
Age at relapse (mean (SD))	56.70 (13.00) *	60.79 (12.73) *	58.79 (12.16)	0.01
Male gender (%)	99 (59.6)	111 (57.2)	52 (59.1)	0.8
Comorbidities (%)				0.1
None	99 (61.5)	94 (50.0)*	50 (64.9)	0.02
Any but renal	39 (24.2)	60 (31.9)	19 (24.7)	0.2
Renal	23 (14.3)	34 (18.1)*	8 (10.4)	0.3
Histology (%)				0.5
DLBCL	119 (71.7)	145 (74.7)	61 (69.3)	
Transformed indolent NHL	47 (28.3)	49 (25.3)	27 (30.7)	
IPI score 0,1, or 2 (%)	100 (60.2)*	93 (47.9)	45 (51.1)	0.06
Previous line over one (%)	43 (25.9)	42 (21.6)	13 (14.8)	0.1
Refractory NHL (%)	72 (43.4)	85 (43.8)	35 (39.8)	0.8
Rituximab use (%)	136 (88.9)	169 (88.5)	77 (90.6)	0.8
Dose-intensity at C1 (mean (SD))	0.85 (0.32)	0.79 (0.20) **	0.93 (0.23) **	<0.001
Dose-intensity at C2 (mean (SD))	0.82 (0.21)	0.77 (0.21) *	0.92 (0.26) **	<0.001
Follow-up (mean (SD))	23.24 (21.42)	17.64 (15.52) **	29.25 (24.44) **	<0.001

Supplemental Table 1. Patient characteristics according to each regimen for aggressive NHL patients, regardless of PS-switch.

*p < 0·05 compared to other regimens **p < 0·001 compared to other regimens.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, SD: standard deviation, y: year

	Univariate analysis				Multivariate analysis			
	OR	lower CI	upper CI	p	OR	lower CI	upper CI	p
Regimen								
R-DHAP	1.05	0.83	1.33	0.70				
R-DHAC	0.66	0.48	0.90	0.01	1.51	1.09	2.08	0.01
R-DHAOx	1.25	0.99	1.58	0.06				
Age > 60 y	1.02	1.01	1.03	<0.001	1.01	1.00	1.02	0.09
Rituximab	0.44	0.31	0.62	<0.001	0.49	0.35	0.70	<0.001
Refractory NHL	1.79	1.42	2.25	<0.001	1.76	1.38	2.25	<0.001
Dose-intensity at C1	1.25	0.83	1.87	0.28				
Male sex	1.01	0.80	1.28	0.92				
more than one previous line	1.39	1.06	1.82	0.02	1.12	0.82	1.52	0.49
IPI or FLIPI 0, 1, or 2	0.59	0.47	0.74	<0.001	0.68	0.53	0.88	<0.001
Comorbidities								
No comorbidities	0.94	0.74	1.19	0.58				
Renal comorbidities	1.09	0.79	1.51	0.60				
Other comorbidities	1.03	0.79	1.34	0.85				

Supplemental Table 2. Risk factors associated with progression-free survival in univariate and multivariate analysis (logistic regression) in the aggressive lymphoma cohort, regardless of platinum salt switch.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, Ref: reference

	Univariate analysis				Multivariate analysis			
	OR	Lower CI	upper CI	p	OR	Lower CI	upper CI	p
Regimen								
R-DHAP	1.12	0.85	1.48	0.41				
R-DHAC	0.57	0.39	0.84	<0.001	1.71	1.14	2.56	0.01
R-DHAOx	1.25	0.95	1.65	0.11				
Age > 60 y	1.37	1.09	1.74	0.01	0.99	0.71	1.37	0.95
Rituximab	0.44	0.31	0.62	<0.001	0.52	0.36	0.77	<0.001
Refractory NHL	1.79	1.42	2.25	<0.001	1.59	1.20	2.12	<0.001
Dose-intensity at C1	1.25	0.83	1.87	0.28				
Male sex	1.01	0.80	1.28	0.92				
more than one previous line	1.39	1.06	1.82	0.02	1.40	0.99	1.97	0.06
IPI score 0, 1, or 2	0.59	0.47	0.74	<0.001	0.65	0.47	0.90	0.01
Comorbidities								
No comorbidities	0.94	0.74	1.19	0.58				
Renal comorbidities	1.09	0.79	1.51	0.60				
Other comorbidities	1.03	0.79	1.34	0.85				

Supplemental Table 3. Risk factors associated with overall survival in univariate and multivariate analysis (logistic regression) in the aggressive lymphoma cohort, regardless of platinum salt switch.

PS: platinum salt, R: rituximab, DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin. DLBCL: diffuse large B-cell lymphoma, NHL: non-Hodgkin lymphoma, C1: cycle 1, C2: cycle 2, C3: cycle 3, IPI: International Prognostic Index, FLIPI: Follicular Lymphoma International Prognostic Index, Ref: reference.

	R-DHAP	R-DHAOx	R-DHAC	overall p-value
n	129	144	72	
ASCT planned (%)				0.4
Yes	96 (74.4)	106 (73.6)	54 (75.0)	
No	33 (25.6)	38 (26.4)	18 (25.0)	
ASCT performed				0.8
Yes	57 (59.4)	56 (52.8)	33 (61.1)	
No	39 (40.6)	50 (47.2)	21 (38.9)	
Reason for no ASCT				
Insufficient response	32 (82.1)	46 (92.0)	14 (66.7)	
Toxicity	2 (5.1)	3 (6.0)	3 (14.3)	
HSC collection failure	4 (10.3)	0 (0.0)	2 (9.5)	
Patient refusal	1 (2.6)	0 (0.0)	1 (4.8)	
HSCT	0 (0.0)	1 (2.0)	1 (4.8)	

Supplemental Table 4. Planning and performance of ASCT according to regimen for patients under 70 years of age without a PS switch in aggressive NHL.

Supplemental Figures:

Supplemental Figure 1. Response rate according to regimen for the whole cohort for aggressive lymphoma (A) and indolent lymphoma (B).
DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, CR: complete response. PR: partial response.

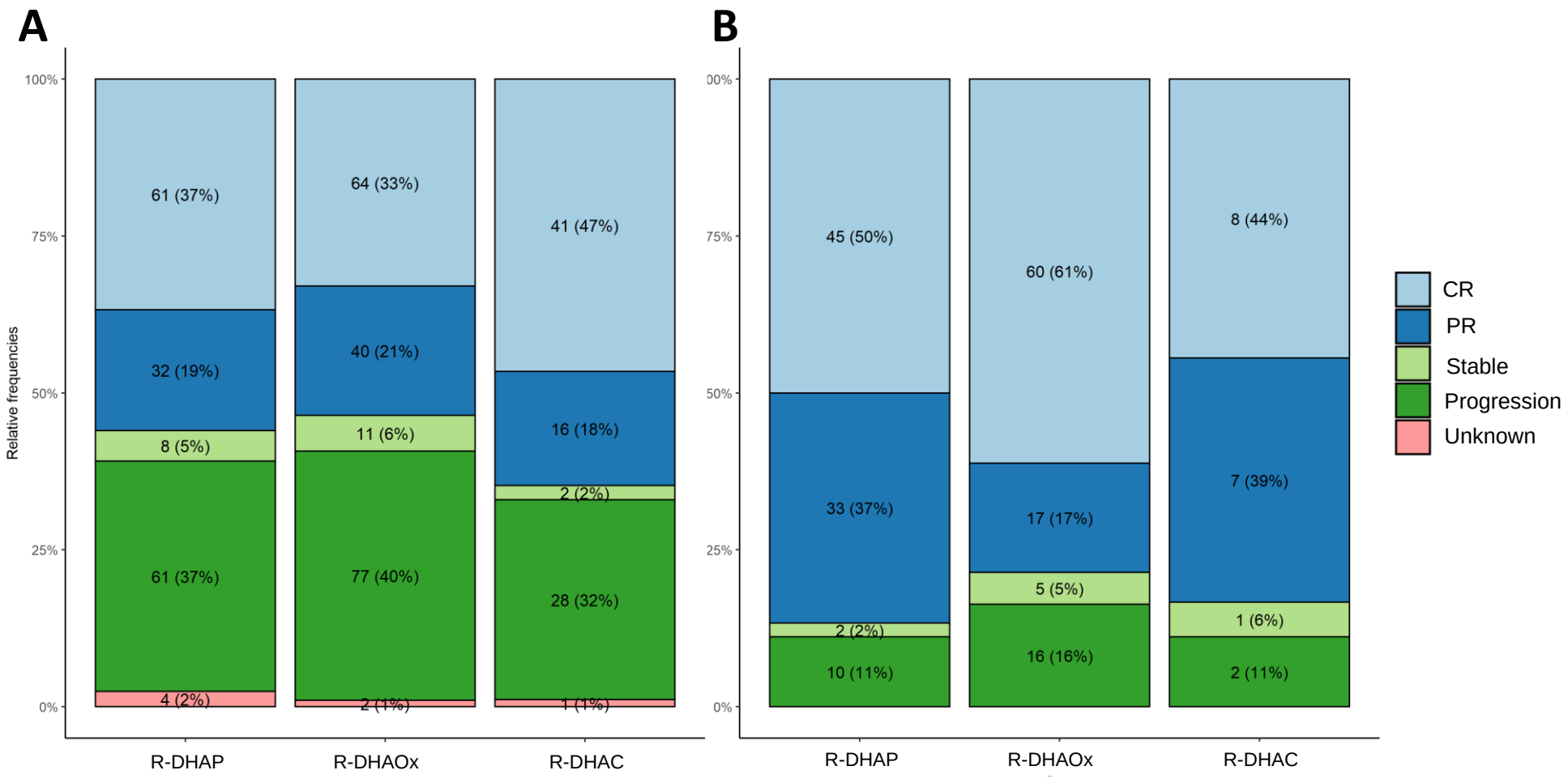
Supplemental Figure 2. Kaplan-Meier curves of progression free-survival in aggressive lymphoma (A) and indolent lymphoma (B) and overall survival in aggressive lymphoma (C) and indolent lymphoma (D) according to regimen in the no-switch cohort.
DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin,

Supplemental Figure 3. Forest plot of toxicities comparison between R-DHAOx and R-DHAP regimen.
DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, RR: relative risk, CI: confidence interval

Supplemental Figure 4. Forest plot of the comparison of toxiciy between the R-DHAC and R-DHAP regimen.
DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, RR: relative risk, CI: confidence interval

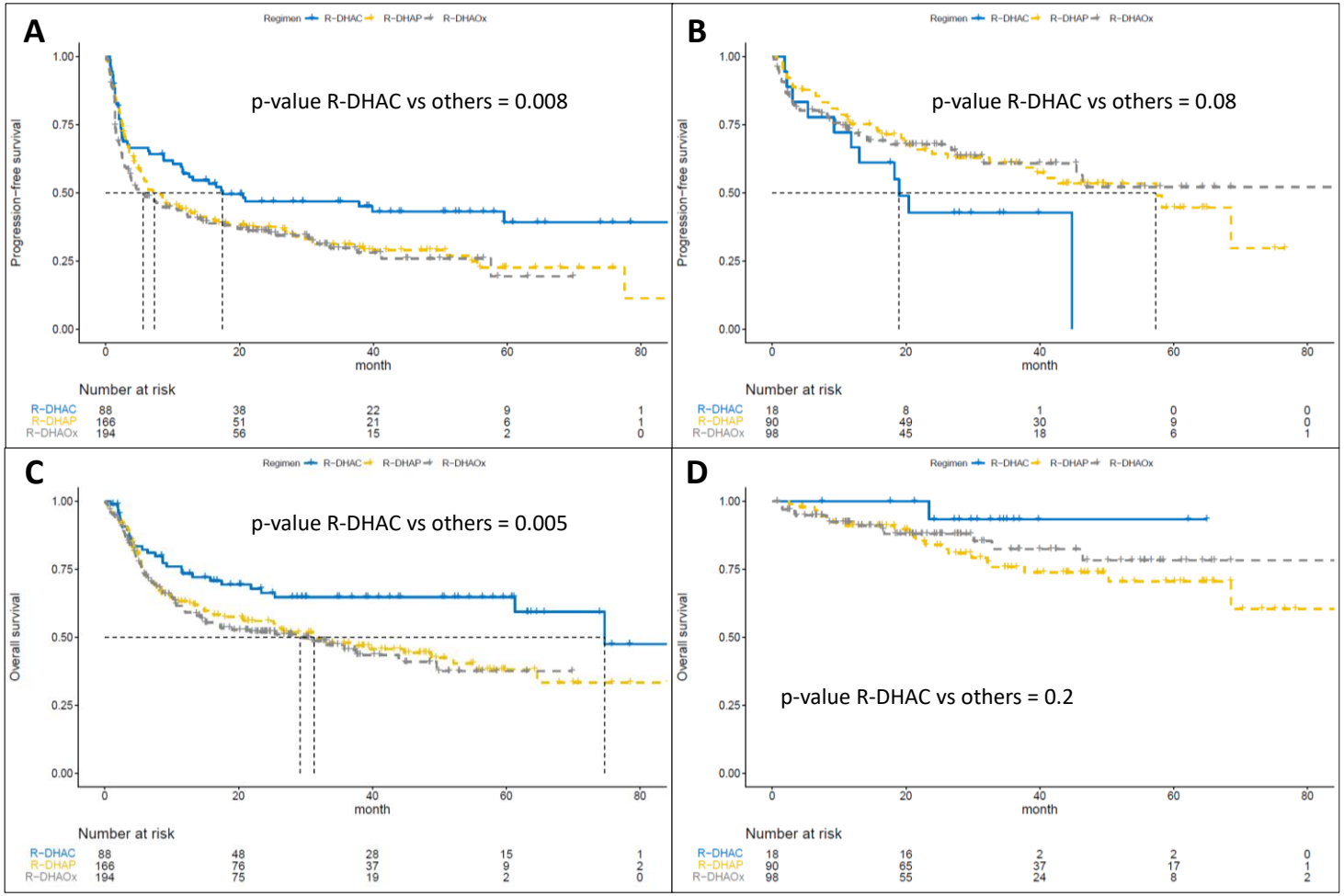
Supplemental Figure 5. Forest plot of the comparison of toxicity between the R-DHAC and R-DHAOx regimen.
R: rituximab. DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, RR: relative risk, CI: confidence interval

Supplemental Figure 6: Kaplan-Meier curves of progression free-survival (A) and overall survival (B) according to an outcome of at least one episode of acute kidney injury (AKI) or not.



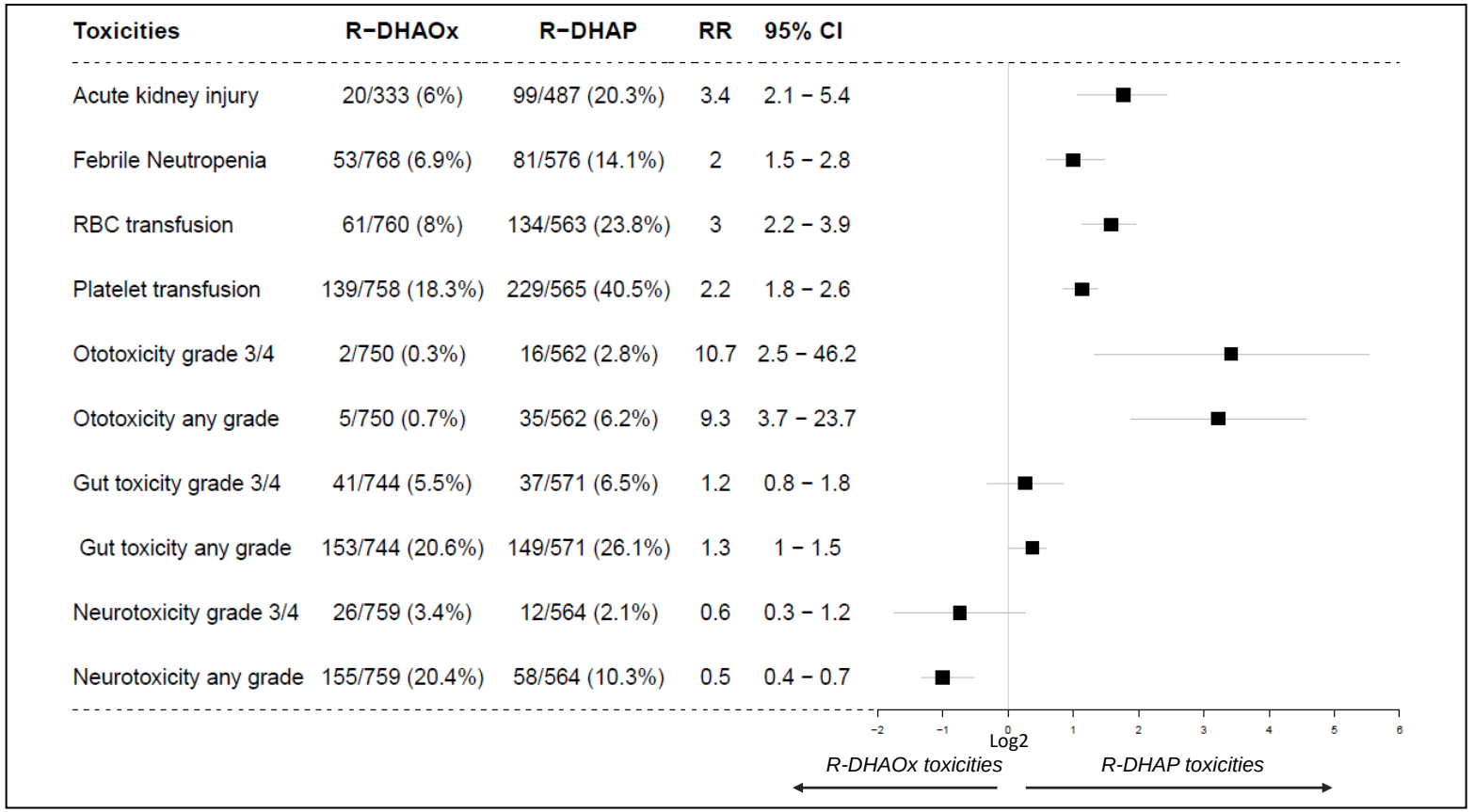
Supplemental Figure 1. Response rate according to regimen for the whole cohort for aggressive lymphoma (A) and indolent lymphoma (B).

DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose bine, and oxaliplatin, CR: complete response. PR: partial response.



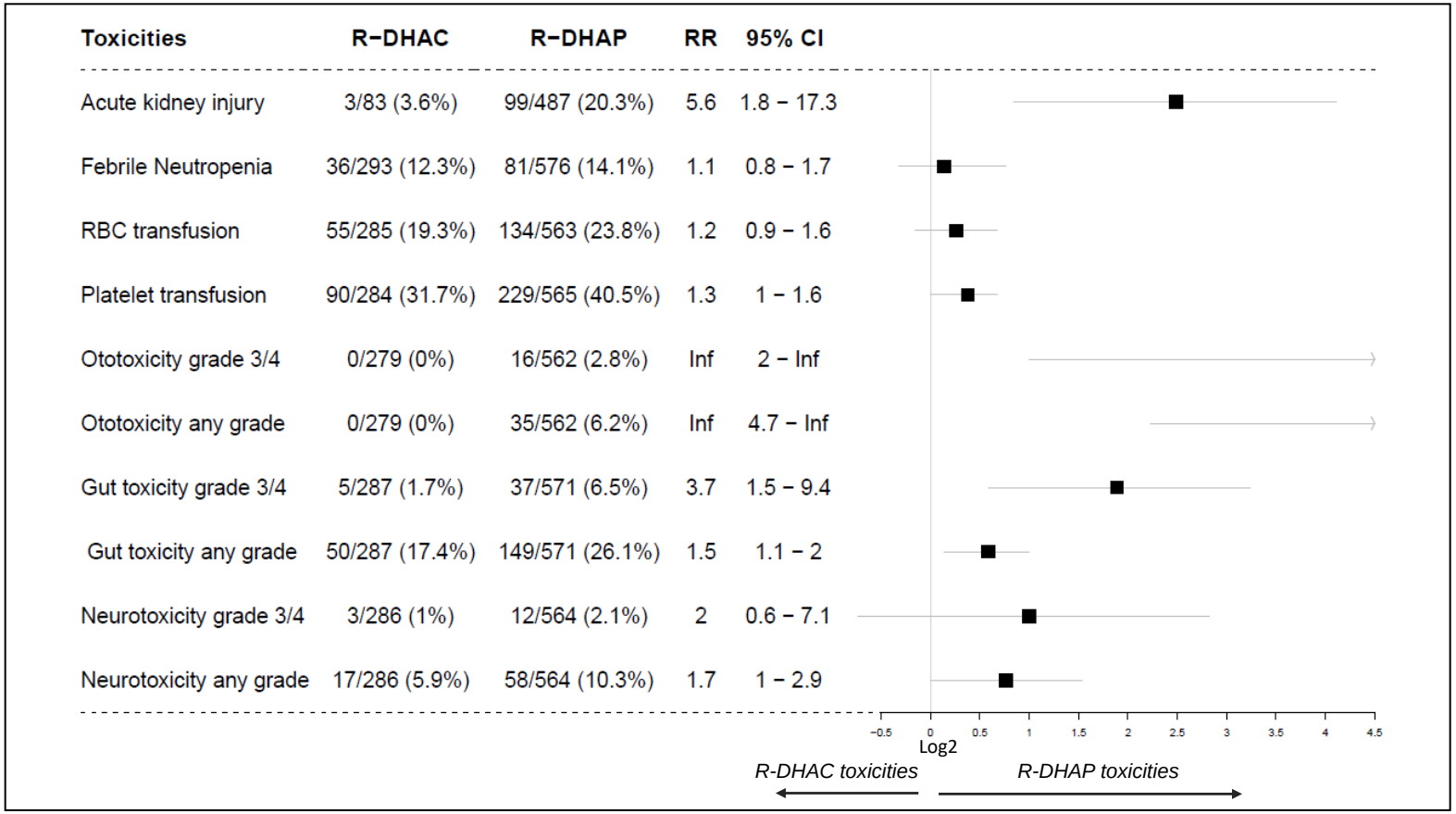
Supplemental Figure 2. Kaplan-Meier curves of progression free-survival in aggressive lymphoma (A) and indolent lymphoma (B) and overall survival in aggressive lymphoma (C) and indolent lymphoma (D) according to regimen in the no-switch cohort.

DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin



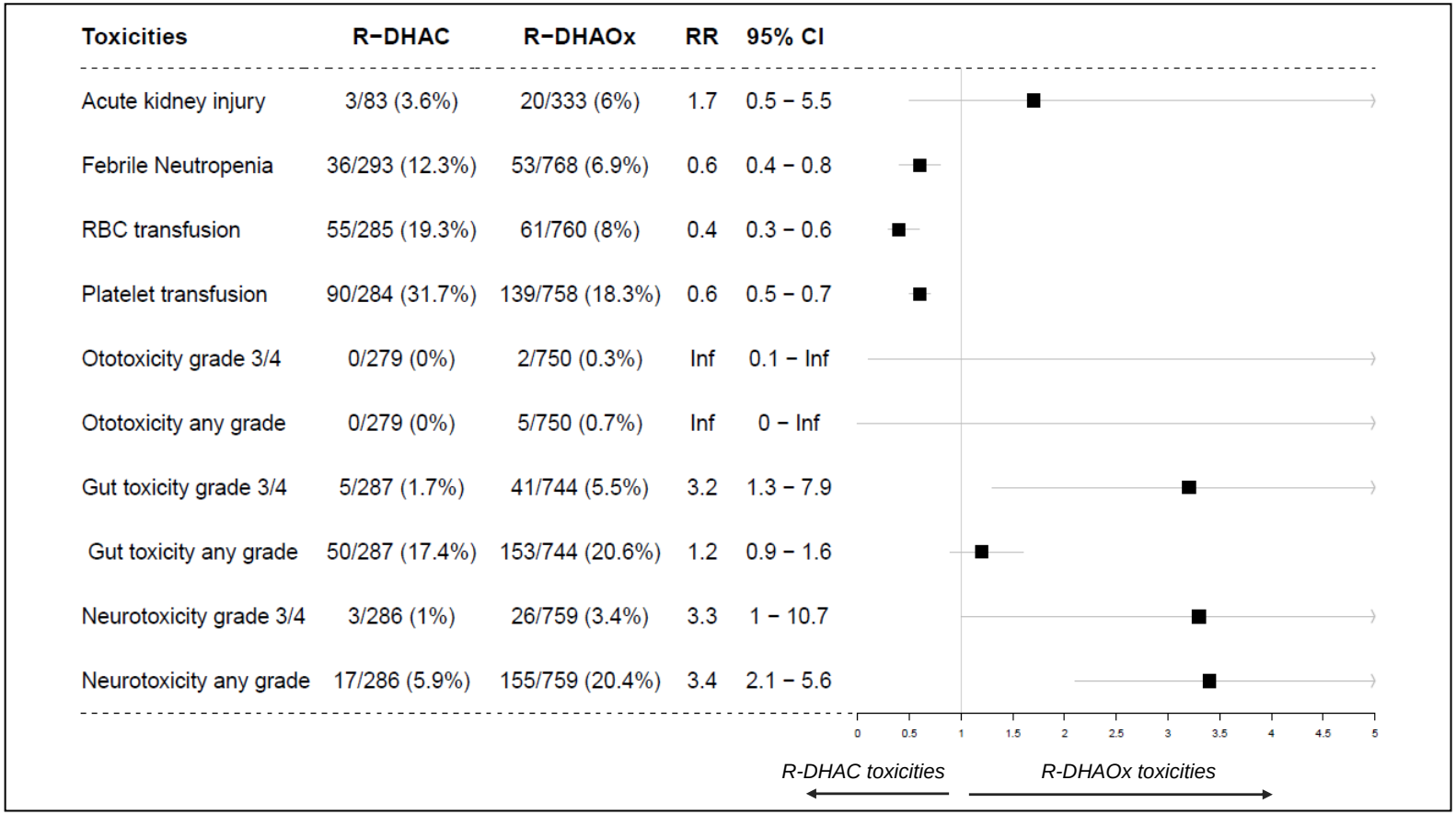
Supplemental Figure 3. Forest plot of toxicities comparison between R-DHAOx and R-DHAP regimen.

DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, RR: relative risk, CI: confidence interval



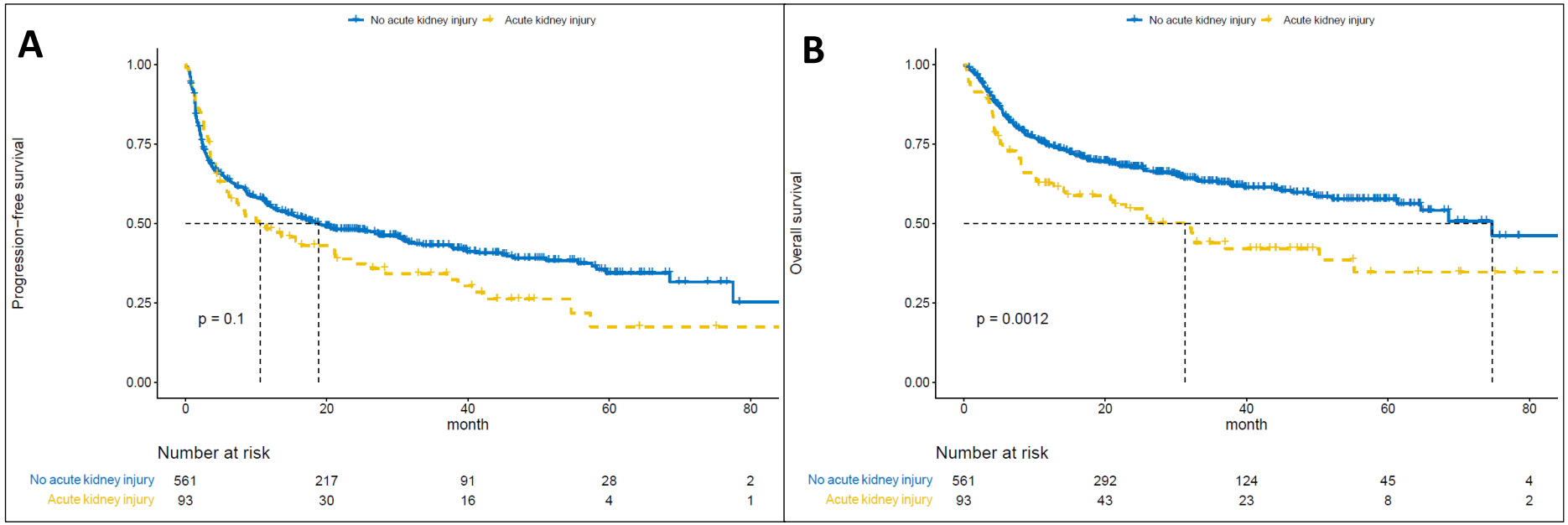
Supplemental Figure 4. Forest plot of the comparison of toxiciy between the R-DHAC and R-DHAP regimen.

DHAP: dexamethasone, high-dose cytarabine, and cisplatin, DHAC: dexamethasone, high-dose cytarabine, and carboplatin, RR: relative risk, CI: confidence interval



Supplemental Figure 5. Forest plot of the comparison of toxicity between the R-DHAC and R-DHAOx regimen.

R: rituximab. DHAC: dexamethasone, high-dose cytarabine, and carboplatin, DHAOx: dexamethasone, high-dose cytarabine, and oxaliplatin, RR: relative risk, CI: confidence interval



Supplemental Figure 6. Kaplan-Meier curves of progression free-survival (A) and overall survival (B) according to an outcome of at least one episode of acute kidney injury (AKI) or not.

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56 pages – 10 tableaux – 11 figures

Résumé :

Le traitement par R-DHAP (rituximab, dexaméthasone, cytarabine à haute dose et cisplatine) est couramment utilisé pour le traitement des lymphomes non hodgkiniens (LNH) en rechute ou réfractaires (R/R). En l'absence de données, le cisplatine a été empiriquement remplacé par d'autres sels de platine (PS) comme le carboplatine (R-DHAC) ou l'oxaliplatine (R-DHAOx) en raison de la toxicité rénale et auditive du cisplatine. L'objectif de cette étude rétrospective multicentrique était de comparer la réponse complète (RC), la survie sans progression (SSP) et la survie globale (SG) entre ces trois traitements à base de PS. Les dossiers médicaux des patients traités pour un LNH R/R entre le 1er décembre 2006 et le 1er juillet 2013, ayant reçu soit du R-DHAP, du R-DHAC ou du R-DHAOx ont été récupérés parmi 24 centres du groupe LYSA. Parmi les 692 patients identifiés, 38 n'ont pas été inclus en raison de données manquantes, ainsi 654 patients ont été retenus dans cette analyse. Parmi eux, 146 (35%) ont été traités par R-DHAP, 190 (45%) par R-DHAOx, et 87 (21%) par R-DHAC pour un LNH agressif, après avoir exclu les patients ayant switchés de PS. Les patients traités par R-DHAP présentaient plus de LNH plus faible risque IPI (63% vs 49% respectivement, p=0,009). Le taux de RC était significativement plus élevé dans le R-DHAC que dans le R-DHAOx (46% vs 43%, p=0.04). Le R-DHAC était associé à une meilleure SSP médiane (17,5, IC 95 % : 11,3-NR vs 6,81 mois, IC 95 % : 4,9-11, p=0,01) et à une meilleure SG par rapport aux non-R-DHAC (74,7, IC 95 % : 61,3-NR vs 27,1, IC 95 % : 16,5-43,9, p=0,004). Une analyse multivariée a confirmé que le R-DHAC était associé à un risque plus faible de rechute (HR : 1,47, 95%CI : 1,06-2,03, p=0,02) et de décès (HR : 1,69, 95%CI 1,12-2,54, p=0,01) dans les LNH agressifs. Le traitement par R-DHAC était associé à moins de toxicités extra-hématologiques, en particulier à moins d'insuffisance rénale aigüe (RR 3,4, 95CI 1,4.-8,3), corrélé à moins d'arrêts de traitement (11% vs 18%, p=0,02) et moins de changement de PS (0,1% vs 8%, p<0,001). Cette étude rétrospective multicentrique en vie réelle indique que le remplacement du cisplatine et de l'oxaliplatine par le carboplatine dans le régime R-DHA-PS dans le traitement de 2ème ligne des LNH R/R est bien toléré et semble être associé à une amélioration du taux de réponse, de la SSP et de la SG.

Mots clés :
Lymphome, sels de platine, cisplatine, carboplatine, oxaliplatine,

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