Optimization of rituximab for the treatment of DLBCL (I):
dose-dense rituximab in the DENSE-R-CHOP-14 trial
of the DSHNHL

N. Murawski1, M. Pfreundschuh1*, S. Zeynalova2, V. Poeschel1, M. Hänel3, G. Held1, N. Schmitz4, A. Viardot5, C. Schmidt6, M. Hallek7, M. Witzens-Harig8, L. Trümper9, T. Rixecker1 & C. Zwick1

1Klinik für Innere Medizin I, Universitätsklinikum des Saarlandes, Homburg; 2IMISE, University Leipzig, Leipzig; 3Internal Medicine III, Klinikum Chemnitz, Chemnitz; 4Department of Haematology, Oncology and Stem Cell Transplantation, Asklepios Klinik St Georg, Hamburg; 5Innere Medizin, Universitätsklinikum Ulm, Ulm; 6Klinikum Großhadern, Munich; 7Universitätsklinik Köln, Cologne; 8Universitätsklinik Heidelberg, Heidelberg; 9Universitätsklinikum Göttingen, Göttingen, Germany

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Background: To improve outcome of elderly patients with diffuse large B-cell lymphoma, dose-dense rituximab was evaluated in the prospective DENSE-R-CHOP-14 trial.

Patients and methods: Rituximab (375 mg/m²) was given on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99 together with six CHOP-14 cycles. Results were to be compared with patients who had received the same chemotherapy in combination with eight 2-week applications of rituximab in RICOVER-60.

Results: One hundred twenty-four patients are assessable. Dose-dense rituximab resulted in considerably higher serum levels during the first 50 days of treatment, but rituximab exposure time was not prolonged. Grade 3 and 4 infections were exceptionally high in the first 20 patients without anti-infective prophylaxis, but decreased after introduction of prophylaxis with aciclovir and cotrimoxazole in the remaining 104 patients (from 13% to 6% per cycle and from 35% to 18% per patient; \( P = 0.007 \) and \( P = 0.125 \), respectively). Patients with international prognostic index = 3–5 had higher complete response/complete response unconfirmed rates (82% versus 68%; \( P = 0.033 \)) than in the respective RICOVER-60 population, but this did not translate into better long-term outcome, even though male hazard was decreased (event-free survival: from 1.5 to 1.1; progression-free survival: from 1.7 to 1.1; overall survival: from 1.4 to 1.0).

Conclusions: Dose-dense rituximab achieved higher rituximab serum levels, but was not more effective than eight 2-week applications in the historical control population, even though minor improvements in poor-prognosis and male patients cannot be excluded. The increased, though manageable toxicity, precludes its use in routine practice. Our results strongly support anti-infective prophylaxis with aciclovir and cotrimoxazole for all patients receiving R-CHOP.

Key words: diffuse large B-cell lymphoma, elderly, dose-dense rituximab, rituximab toxicity

introduction

Outcome of patients with diffuse large B-cell lymphoma (DLBCL) significantly improved when standard cyclophosphamide, doxorubicin, vincristin, prednisolone (CHOP)-21 [1–3] or dose-dense CHOP-14 [4] were combined with the monoclonal anti-CD20 antibody rituximab, and the combination of chemotherapy and rituximab is considered the standard treatment of DLBCL. However, further improvement is warranted in particular for elderly patients. Since further intensification of chemotherapy might be problematic in this population, further intensification of rituximab appears to be an attractive strategy due to the large therapeutic window of this antibody. However, despite its widespread use in DLBCL, the manner in which rituximab is combined with CHOP in 2-week or 3-week schedules was established by practical and/or historical reasons and not based on pharmacokinetic data conveying the risk of suboptimal dosing. In two of the few studies on rituximab pharmacokinetics in DLBCL, we recently demonstrated that rituximab serum levels increase only slowly in elderly patients with DLBCL when given at 2-week intervals (R-CHOP-14) and even slower when given every 3 weeks (R-CHOP-21) [5, 6]. In a series of prospective phase II trials, we tested different strategies
to improve the efficacy of rituximab in elderly patients with DLBCL. In the first study, designated DENSE-R-CHOP-14, we tested the hypothesis that early dose-densification of rituximab in combination with CHOP-14 might be beneficial, since early dose density of cytotoxic drugs (CHOP-14 instead of CHOP-21) had improved outcome of elderly patients treated with CHOP chemotherapy [7]. We now report on the final results of this prospective trial in elderly patients with DLBCL.

**methods**

**patients**

The study was conducted in accordance with the Helsinki declaration. DENSE-R-CHOP-14 was conducted according to an amendment of the RICOVER-60 protocol, which was approved by the ethical review committee of each participating center after the RICOVER-60 trial had been closed early after the second planned interim analysis. All patients gave written informed consent. Patients were eligible if they had previously untreated, biopsy-confirmed aggressive non-Hodgkin’s lymphoma of the B-cell type according to the WHO classification [8] and were between 61 and 80 years old. Histological diagnosis was reviewed centrally by a panel of five expert hematopathologists. Patients with previous lymphoma associated with the acquired immunodeficiency syndrome, a diagnosis or history of indolent lymphoma or other neoplasms, marked impairment of cardiac, pulmonary, hepatic, or renal function, WHO performance status >2, initial white blood cell (WBC) <2.5 × 10^3/l, initial platelet <100 × 10^3/l, or inability to comply with study requirements were excluded. The patients had mandatory baseline examinations including clinical examination, relevant laboratory tests (i.e. hemoglobin, platelets, total WBC count, differential WBC count, serum protein, albumin, serum creatinine, urea, uric acid, calcium, potassium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, lactate dehydrogenase, β2-microglobulin, and urinalysis), computed tomography of chest and abdomen, and a bone marrow biopsy.

**treatment**

A ‘prephase’ treatment [single injection of 1 mg vincristine (i.v.) and 100 mg prednisone (p.o.) for 7 days] was mandatory to improve the performance status of the patients and to ameliorate the side-effects of the first chemotherapy cycle. For patients who complained of fatigue after tapering the prednisone, hydrocortisone (20 mg p.o. in the morning and 10 mg at noon) recommended. The CHOP regimen [1] consisted of cyclophosphamide (750 mg/m^2 i.v.), doxorubicin (50 mg/m^2 i.v.), vincristine (2 mg i.v.) on day 1 and prednisone (100 mg p.o.) given on days 1–5. CHOP-14 was recycled every 2 weeks for a total of six cycles on days 1, 15, 29, 43, 57, and 71. Rituximab 375 mg/m^2 was given on days 0, 1, 4, 8, 15, 22, 29, 43, 57, 71, 85, and 99. All patients received recombinant human granulocyte colony-stimulating factor (filgrastim or lenograstim) starting on day 4 of each cycle until recovery of leukocytes. The next chemotherapy cycle was scheduled for day 15, after recovery of WBC (>2.5 × 10^3/l) and platelets (>80 × 10^3/l). Patients with initial bulky disease (defined as lymphoma masses or conglomerates with a diameter ≥7.5 cm) or extranodal involvement received radiotherapy (36 Gy) to these areas irrespective of the result of chemotherapy.

All patients underwent restaging after three cycles of therapy and at the end of therapy. Follow-up examinations were carried out every 3 months during the first 2 years, and every 6 months during the third to fifth year by use of physical examination, relevant laboratory tests (as those done for staging) and CT of the chest and abdomen. Response was assessed by the treating physician and classified as complete response (CR), complete response unconfirmed (CRu), partial response (PR), stable disease, or progressive disease according to the International Workshop criteria [9]. Adverse events reported by the patient or observed by the treating physician were coded on the case-report forms according to NCI-CTC v 2.0 grades. An adverse event was defined as any adverse change from the patient’s baseline condition after the initiation of therapy, whether or not it was considered related to treatment. The WHO grades for hematotoxicity were assessed from blood counts within treatment-specific nadir windows.

**rituximab pharmacokinetics**

A pharmacokinetic study was carried out in the first 10 male and 10 female patients recruited on to DENSE-R-CHOP-14. All patients included in the pharmacokinetic study had normal kidney and liver functions and were representative for the entire study population. Blood sampling and rituximab enzyme-linked immunosorbent assay were carried out as described previously [5]. Pharmacokinetic properties (population model building, pharmacokinetic analysis, and model validation) of rituximab were processed and analyzed using the nonlinear mixed-effect approach nonlinear mixed effect modeling software as described previously [5]. The statistical analysis of demographic data of the pharmacokinetic study was done using IBM SPSS version 19.0. 2010 (SPSS, Inc., Ehningen, Germany).

**study design and statistical analysis**

DENSE-R-CHOP-14 was an open-label prospective phase II trial to assess the pharmacokinetics as well as the clinical effects of dose-dense rituximab. The primary end point was the assessment of the pharmacokinetics (in the first 20 patients) and the safety of dose-dense rituximab in a historical comparison with patients treated with eight 2-week applications in combination with the same six cycles CHOP-14 in the RICOVER-60 trial. Secondary endpoints were the rate of complete remissions/complete remissions unconfirmed (CR/CRu), event-free (EFS), progression-free (PFS), and overall survival (OS). Only three centers were opened for the first 20 patients, after whom a planned toxicity analysis was carried out, and 43 centers recruited the remaining 125 patients. EFS was defined as the time from start of therapy to either disease progression, initiation of salvage therapy, additional (unplanned) treatments, relapse or death from any cause; progression-free survival as the time from start of therapy to progression, relapse or death from any cause; and OS as the time from start of therapy to death from any cause. These end points were analyzed according to Kaplan and Meier and are given at 3 years with the 95% confidence limits. The results of the DENSE-R-CHOP-14 trial were to be compared with the results of 306 patients who had been included to the same inclusion and exclusion criteria and had been treated in the RICOVER-60 trial with 6xR-CHOP-14 + 2R [4]. With 6% therapy-associated deaths in the historical comparison, 100 patients were necessary to detect the difference between the null hypothesis proportion P0 of 6% and the alternative proportion PA of 13.5% with a power of 80% and a nominal 5% one-sided significance level. The cutoff value for rejecting the null hypothesis at the end of the trial was 11 treatment-related deaths. The rate of complete responses was 78% for six cycles CHOP-14 within the RICOVER-60 trial. Assuming the rate of complete remissions which would be observed in this trial to be 88%, an estimation of the 95% confidence interval for the CR/CRu rate with a precision of ±6% would be possible with 100 patients. This comparison was to be carried out for the entire populations and separately for good (1–2) and poor (international prognostic index (IPI) = 3–5) prognosis groups, because we expected potential improvements to be easier detectable in this subgroup the outcome of which was poor in RICOVER-60 [4]. All tests for significance were two-sided. Patient characteristics, NCI-CTC toxicities, therapeutic interventions, and responses between treatment arms were compared by χ^2 tests and if required by Fisher’s exact tests. Dose reductions, treatment duration for patients with at least two courses chemotherapy and relative dose intensity were assessed according to Kaplan–Meier as described elsewhere [10].
subgroup analyses by good- and poor-prognosis patients according to the IPI were preplanned; the subgroup analyses according to gender were done retrospectively. Statistical analyses were carried out with SPSS (version 19.0). RICOVER-60 and the DENSE-R-CHOP-14 amendment were registered as DSHNHL-1999-1 with the registration numbers EU-20243 and NCT00052936.

results

Between July 2004 and April 2007, 43 centers recruited 125 consecutive patients for DENSE-R-CHOP-14. From one patient, the informed consent form was missing, leaving 124 patients assessable for response and toxicity. The characteristics of patients are shown in Table 1.

adherence to protocol

The adherence to protocol was excellent, with a relative median dose intensity of the dose-dense rituximab schedule of 98%. Similarly, relative doses of doxorubicin and cyclophosphamide were 98% (supplementary Figure S1, available at Annals of Oncology online), and 100% for prednisone (data not shown); however, due to polyneuropathy, the median total dose of vincristine was only 75%.

pharmacokinetics

Twelve dose-dense applications of rituximab resulted in high trough serum levels from day 4 on which were significantly higher than those achieved with the 2-week schedule in RICOVER-60 during the first 50 days of treatment (Figure 1). Later on, rituximab trough serum levels in DENSE-R dropped faster than in RICOVER and became superimposable resulting in a total exposure time of rituximab which was not different from the one achieved with eight rituximab applications every 2 weeks.

toxicity

Toxicity was a primary end point of this study, and an interim toxicity analysis was planned and carried out after the first 20 patients. The rate of grade 3 and 4 infections in this population was unexpectedly high (13% per cycle and 35% per patient). Seven of the first 20 patients without prophylaxis had to be referred to an intensive care unit due to interstitial pneumonitis and three of them (15%) died. Interestingly, the majority of these cases became manifest only after recovery of the leukocytes from the nadir to normal levels, and three cases occurred after recovery from the last R-CHOP-14 cycle. In the bronchial lavage, fluid from these patients with interstitial pneumonitis Pneumocystis jirovecii was detected in one and cytomegalovirus in another patient. Therefore, for the last 104 patients in DENSE-R, prophylaxis with aciclovir (daily 4 × 400 mg p.o.) and cotrimoxazole (two double-strength doses a day twice every week p. o.) was made mandatory, resulting in a significant reduction of grade 3 and 4 infections per cycle (13% versus 6%; \(P = 0.007\)) and in a considerable and clinically relevant reduction of patients with severe infections (35% versus 18%; \(P = 0.125\); Figure 2). The therapy-associated death rate also went down from 3/20 (15%) to 4/104 (4%; \(P = 0.083\)) in DENSE-R-CHOP-14 after the introduction of prophylaxis; excluding one patient in the prophylaxis cohort who committed suicide, this difference was borderline significant (\(P = 0.053\)).

response to therapy

The response to therapy is shown in Table 2. One hundred two of 124 patients (82%) achieved CR/CRu and 9 (7%) patients progressed under therapy. 3-year EFS was 65% in the entire DENSE-R-CHOP-14 population (69% in patients with IPI = 1–2 and 62% in patients with IPI = 3–5); 3-year PFS was 67% for all patients (72% for IPI = 1–2 and 63% for patient with IPI = 3–5). 3-year rates for OS were 71% for all, 77% for IPI = 1–2, and 67% for IPI = 3–5.

comparison of DENSE-R rituximab schedule with eight 2-week applications (RICOVER-60)

As planned in the protocol, the results of the 124 assessable DENSE-R patients were to be compared with the 306 patients

![Figure 1. Trough serum levels of rituximab in the DENSE-R-CHOP-14 and RICOVER-60 trials. Black (blue online) curve: trough serum levels of 20 patients (11 females, 9 males) with eight 2-week applications in RICOVER-60; grey (green online) curve: trough serum levels of 20 patients (13 females, 7 males) with 12 dose-dense applications in DENSE-R-CHOP-14.](image-url)
in the best arm of RICOVER-60 who had been randomized to six cycles of CHOP-14 in combination with eight 2-week administrations. Despite identical inclusion criteria, patients in DENSE-R presented with worse prognostic factors compared with the respective RICOVER-60 population, with more patients presenting with >1 extralymphatic sites of involvement, advanced stages 3 and 4 and a higher IPI (Table. 1).

A prerequisite for the historical comparison of two treatment strategies is the adherence to the respective protocols. As can be seen from supplementary Figure S1, available at Annals of Oncology online, adherence to the rituximab schedules was excellent in both trials, with a median relative dose of 98% and 99%, respectively, in the two populations. Similarly, the relative doses of the cytotoxic drugs cyclophosphamide and doxorubicin

![Figure 2](image_url). Grade 3 and 4 infections without and with anti-infective prophylaxis. Starting with patient #21 (light grey (blue online) columns), patients received anti-infective prophylaxis with aciclovir and cotrimoxazole. This resulted in a significant reduction of chemotherapy cycles with grade 3 and 4 infections (left graph), and a considerable decrease of patients with grade 3 and 4 infections (left graph).

| Table 2. Response to therapy in the DENSE-R-CHOP-14 trial and the reference population in the RICOVER-60 study |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 6xCHOP + 12R (DENSE-R) \( N = 124 \)                      | 6xCHOP + 8R (RICOVER-60) \( N = 306 \)                      | \( P \) value                                               |
| A: All patients                                             |                                                               |                                                               |
| CR/Cru                                                      | 102 (82%)                                                     | 238 (78%)                                                    | 0.301 |
| CR                                                          | 43 (35%)                                                      | 122 (40%)                                                    | |
| PR; NC                                                      | 0 (0.0%)                                                      | 11 (4%)                                                      | |
| PRO                                                         | 9 (7%)                                                        | 20 (7%)                                                      | |
| Therapy-associated deaths                                   | 7 (6%)                                                        | 17 (6%)                                                      | |
| Unknown                                                     | 4 (3%)                                                        | 15 (5%)                                                      | |
| CR/CRu and additional treatment                             | 2 (2%)                                                        | 5 (2%)                                                       | |
| DENSE-R \( N = 51 \)                                        |                                                               |                                                               |
| B: Patients with IPI = 1–2                                 |                                                               |                                                               |
| CR/Cru                                                      | 42 (82%)                                                      | 154 (84%)                                                    | 0.758 |
| CR                                                          | 25 (49%)                                                      | 92 (50%)                                                     | |
| PR; NC                                                      | 0 (0.0%)                                                      | 4 (2%)                                                       | |
| PRO                                                         | 3 (6%)                                                        | 8 (4%)                                                       | |
| Therapy-associated deaths                                   | 3 (6%)                                                        | 6 (3%)                                                       | |
| Unknown                                                     | 2 (4%)                                                        | 8 (4%)                                                       | |
| CR/CRu and additional treatment                             | 1 (2%)                                                        | 3 (2%)                                                       | |
| 6xCHOP + 12R DENSE-R \( N = 73 \)                          | 6xCHOP + 8R (RICOVER-60) \( N = 123 \)                       |                                                               |
| C: Patients with IPI = 3–5                                 |                                                               |                                                               |
| CR/Cru                                                      | 60 (82%)                                                      | 84 (68%)                                                     | 0.033 |
| CR                                                          | 18 (25%)                                                      | 30 (24%)                                                     | |
| PR; NC                                                      | 0 (0.0%)                                                      | 7 (6%)                                                       | |
| PRO                                                         | 6 (8%)                                                        | 12 (10%)                                                     | |
| Therapy-associated death                                    | 4 (6%)                                                        | 11 (9%)                                                      | |
| Unknown                                                     | 2 (3%)                                                        | 7 (6%)                                                       | |
| CR/CRu and additional treatment                             | 1 (1%)                                                        | 2 (2%)                                                       | |
were also 98% and 99%, respectively. The dose reductions of vincristine (75% of the planned dose) were also not different in the two populations.

With respect to toxicity, the rate of grade 3 and 4 infections was higher in the first 20 patients treated without anti-infective prophylaxis, and considerably higher than in the respective RICOVER-60 population (who had not received anti-infective prophylaxis either), where the figures had been 7% and 28%, respectively ($P_{cycle} = 0.012$; $P_{patient} = 0.472$). However, after the introduction of anti-infective prophylaxis with aciclovir and cotrimoxazole, the rate of the grade 3 and 4 infections in the last 104 patients of the DENSE-R study was even somewhat lower than in RICOVER-60 (6% versus 7% per cycle; 18% versus and 28% per patient). Also, the therapy-associated death rate for all patients in DENSE-R which went down from 3/20 (15%) to 4/104 (4%; $P = 0.083$) after the introduction of anti-infective prophylaxis was comparable with the rate of therapy-associated deaths in RICOVER-60 (6%).

Response to therapy was not different when all patients in DENSE-R and RICOVER-60 were compared (CR/CRu 82% versus 78%; $P = 0.301$; Table 2). In patients with good prognosis (IPI = 1–2), CR/CRu rates were 82% [95% confidence interval (CI) 69–92] in the 51 patients treated in DENSE-R-CHOP-14 compared with 84% (95% CI 78–89) in the 183 patients treated in RICOVER-60 ($P = 0.758$). However, the CR/CRu rate was significantly higher in the 73 poor-prognosis (3–5) patients treated with the dose-dense rituximab schedule compared with 123 patients with IPI = 3–5 treated with the 2-week schedule [82% (95% CI 72–90) versus 68% (95% CI 59–76); $P = 0.033$].

After a median observation time of 51 months in DENSE-R and 34 months in RICOVER-60, there were no significant differences in 3-year EFS with respect to the entire population (65% versus 66%; $P = 0.828$), and neither for IPI = 1–2 (69% versus 75%; $P = 0.419$) nor for IPI = 3–5 patients (62% versus 54%; $P = 0.210$). The respective figures for 3-year PFS were 67% versus 73% ($P = 0.258$) for all patients, 72% versus 82% ($P = 0.185$) for patients with IPI = 1–2, and 63% versus 59% ($P = 0.574$) for IPI = 3–5. There was also no difference with respect to OS between DENSE-R-CHOP-14 and RICOVER-60 for the entire population. When restricted to good-prognosis patients (IPI = 1–2), the survival of the DENSE-R-CHOP-14 population tended to be even worse than in the RICOVER-60 cohort (3-year OS 77% versus 86%; $P = 0.147$; Figure 3) due to the increased toxicity in this DENSE-R subpopulation. In the poor-prognosis population, the survival in DENSE-R-CHOP-14 and RICOVER-60 was not different (3-year OS 67% versus 67%; $P = 0.598$). Results in DENSE-R and RICOVER were also similar if only the last 104 patients who received anti-infective prophylaxis in DENSE-R-CHOP-14 were compared with the respective cohort in RICOVER-60 (data not shown).

Male sex was a risk factor in RICOVER-60 for elderly patients treated with rituximab, but not for those treated without rituximab [5, 6]. An exploratory analysis of the survival curves of males and females in DENSER-CHOP-14 is shown in supplementary Figure S2, available at *Annals of Oncology* online. Interestingly, the hazard ratio for males, who had a faster rituximab clearance and hence lower serum levels and shorter exposure times which was associated with a significantly worse outcome with the eight 2-week applications in RICOVER-60, decreased in DENSE-R from 1.5 to 1.1 for EFS (sex adjusted with IPI Faktors), 1.8 to 1.1 for PFS, and from 1.6 to 1.0 for OS, respectively, suggesting that male patients had a relative benefit from the higher rituximab serum levels (supplementary Table S1, available at *Annals of Oncology* online).

**discussion**

After observing that (trough) serum levels increase only slowly with a 2-week schedule of rituximab and are below the putative efficacy threshold of 50 ng/ml until the second application (Figure 1) on day 14, we designed a dose-dense rituximab schedule by adding four additional rituximab administrations during the first 3 weeks in order to achieve high rituximab serum levels early. Indeed, this dose-dense schedule resulted in high rituximab serum levels by the time of the first CHOP application, but did not prolong the total rituximab exposure time. Unexpectedly, there was a high rate of grade 3 and 4 infections with seven cases of interstitial pneumonitis and three therapy-associated deaths among the first 20 patients treated within DENSE-R-CHOP. Because cytomegalovirus (CMV) and *P. jirovecii* were detected in the bronchial lavage fluid from one patient each, anti-infective prophylaxis with aciclovir and cotrimoxazole against CMV and pneumocystis, respectively, became mandatory in addition to levofloxacin which had already been recommended in the first 20 DENSE-R patients and in the previous RICOVER-60 study for periods with leukocytes <1.0 × 10⁹/μl. This anti-infective prophylaxis with cotrimoxazole/acyclovir until 4 weeks after the last chemotherapy and temporary levofloxacin during periods of leukocytopenia was very effective with a significant reduction in grade 3 and 4 infections and less therapy-associated deaths in the last 104 patients in DENSE-R-CHOP14 compared with the first 20 without prophylaxis; indeed, the rate of severe infections among these 104 patients was even somewhat lower than what had been observed in RICOVER-60. Moreover, the therapy-associated death rate consistently remained <3% in >500 elderly patients treated in DSHNHL trials since this prophylaxis had become mandatory. We therefore recommend this low-cost prophylaxis which causes few side-effects (consisting mostly of rare allergic skin reactions to cotrimoxazole) for all patients who receive R-CHOP.

The higher toxicity also affected the outcome of the DENSE-R patients, and was the reason why 3-year OS of DENSE-R-CHOP-14 good-prognosis patients tended to be worse (77% versus 86%) than that of RICOVER-60 patients, which was not the case when only DENSE-R-CHOP-14 patients were analyzed who received the anti-infective prophylaxis (data not shown). But, even when the first 20 DENSE-R-CHOP-14 who had not received the anti-infective prophylaxis were excluded from the analysis, the results of 12 dose-dense applications of rituximab were not suggestive of having the potential to significantly improve the results over the eight 2-week applications.

Only the CR/CRu rate was better in the poor-prognosis patients (IPI = 3–5) compared with the respective RICOVER-60 population. This might explain why a trend toward a better EFS and PFS in poor-prognosis DENSE-R-CHOP-14 was observed after an early follow-up of 18 months [11] and suggests that dose-dense rituximab leads to a faster reduction of large tumor masses without eradicating the malignant clone, resulting in
Figure 3. Outcome of patients treated in DENSE-R-CHOP-14 and RICOVER-60. Upper row: all patients [grey (blue online) curves: 124 patients in DENSE-R-CHOP-14; black (green online) curves: 306 patients in the historical control (RICOVER-60)]; middle row: patients with IPI = 1–2 [grey (blue online) curves: 51 patients in DENSE-R-CHOP-14; black (green online) curves: 183 patients in the historical control (RICOVER-60)]; lower row: patients with IPI = 3–5 [grey (blue online) curve: 73 patients in DENSE-R-CHOP-14; black (green online) curve: 123 patients in the historical control (RICOVER-60)]. EFS, event-free survival; PFS, progression-free survival; OS, overall survival.
higher relapse rates in these patients, and thus not translating into a better EFS, PFS or OS. Whether dose-dense rituximab in combination with CHOP-21 would improve results over standard R-CHOP-21 can only be speculated about, but does not seem very likely, because the higher rituximab serum levels at the start of treatment would be expected to be also associated with increased toxicity.

The optimal dose and schedule of rituximab remain to be determined, as are the minimum effective serum levels, exposure times, and area under the curve. Interestingly, the increased hazard for elderly male compared with female patients, which was observed in RICOVER-60, disappeared in DENSE-R. This suggests that at least elderly males, who have faster rituximab clearance, and hence shorter rituximab serum elimination half-lives, lower serum levels, and shorter exposure times with the eight 2-week applications, might have had some benefit from the higher serum levels in DENSE-R. However, this benefit was not sufficient to improve overall DENSE-R-CHOP-14 results to an extent that would recommend a randomized comparison of the DENSE-R with the standard schedule of rituximab. Thus, increasing rituximab serum levels is not a promising way to go when improved outcome in elderly DLBCL patients is the goal. This also suggests that antibodies that are higher dosed than rituximab (e.g. ofatumumab and obinutuzumab or GA-101) would be expected to fail unless they work not only because of their higher dose, but also by superior intrinsic mechanisms of action.

In summary, higher rituximab serum levels did not significantly improve the outcome of elderly patients with DLBCL and the increased, though manageable toxicity precludes its use in routine practice. Following DENSE-R-CHOP-14, the DSHNHL therefore started SMARTER-CHOP-14, a second phase II study where a prolonged exposure time of rituximab was investigated. Early results indicated a positive effect of the prolonged rituximab exposure time [12], but longer follow-up of SMARTER-CHOP-14 is needed before definitive conclusions can be drawn.

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disclosure

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