1st-line treatment with R-CHOP-14 or R-CHOP-21 in patients with high-grade non-Hodgkin's lymphoma is similarly effective: Data from the German prospective TLN Registry

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Introduction

Combination immunochemotherapy with cyclophosphamide, doxorubicine, vincristine, prednisone and the anti-CD20 monoclonal antibody rituximab (R-CHOP) is the standard of care for patients with previously untreated high-grade (aggressive) non-Hodgkin's lymphoma (aNHL). Dose intensification of CHOP has shown ambiguous results (Pfreundschuh, 2004; Ohmachi, 2011), but the dose-dense two-weekly schedule (R-CHOP-14) was not found to be superior to the three-weekly schedule (R-CHOP-21) (Cunningham, 2013). Since clinical trials are restricted to highly selected patients, we investigated effectiveness of R-CHOP-14 and R-CHOP-21 in unselected patients with aNHL treated in routine practice by German office-based haematologists.

Methods

The open, longitudinal, multicentre, clinical registry on lymphoid neoplasms (TLN Registry, ClinicalTrial.gov registry NCT00889798) prospectively collects data on the treatment of patients with lymphoid B-cell neoplasms as administered by a network of over 260 German office-based haematologists. The choice of therapy is upon the discretion of the treating physician. All patients give their informed consent before onset of therapy. Patients are followed for 5 years. A broad set of data regarding patient and tumour characteristics, co-morbidities, all systemic treatments and response rates, date(s) of progression(s) and date of death are recorded. In the TLN it is not specified when, how often and according to which criteria the treating physician monitors the course of disease. Therefore, the determination of "registry PFS" (PFS_{REG}) is not identical with the PFS determined in clinical trials. Automated plausibility and completeness checks with subsequently generated queries by the electronic data capture system ensure data reliability. In addition, data managers regularly check for plausibility and issue queries. Between May 2009 and August 2014 (date of present interim analysis), a total of 3,798 patients have been recruited.

Results

R-CHOP-21 is used more often than R-CHOP-14

Of 565 patients with aNHL (95% DLBCL), recruited at the start of 1st-line therapy and treated with R-CHOP, 41% were treated with the two-weekly schedule (R-CHOP-14) and 59% received the three-weekly schedule (R-CHOP-21), with a tendency in favour of R-CHOP-21 over time (Figure 1).

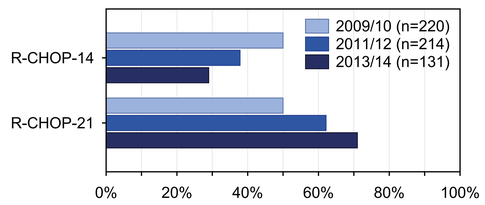

Figure 1: Frequency over time

Patients were 68 years old (median, 31% ≤ 60 years), 46% female, 28% presented with tumour stage I (Ann Arbor), 25% with stage IV and 64% with at least one co-morbidity. 36% patients were of low risk according to the International Prognostic Index, IPI (Figure 2).

Patient characteristics showed no considerable differences between patients treated with R-CHOP-14 or R-CHOP-21 (Figure 2). In a multivariate logistic regression model of all parameters tested (age, sex, ECOG, co-morbidities (yes/no), tumour stage) only tumour stage had a significant impact on treatment decision (R^2 = 0.0305). Patients diagnosed with Ann Arbor Stage I were significantly more likely treated with R-CHOP-21 than patients with Ann Arbor Stage II (OR: 0.45, p = 0.003).

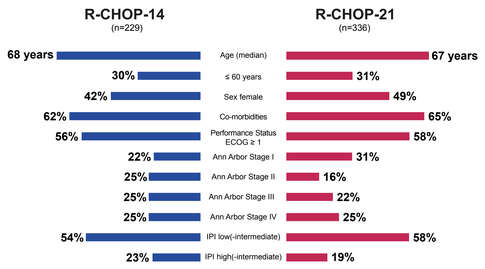

Figure 2: Patient characteristics

CHOP is given a median of six cycles

In patients who had completed their 1st-line therapy at the time of this analysis, CHOP was applied for a median of 6 cycles, independent of schedule, while rituximab was applied for a median of 8 cycles in R-CHOP-14 and 6 cycles in R-CHOP-21. Less than 6 cycles of CHOP were applied in 18% and 22% of patients, respectively (Table 1).

Data on the application of Granulocyte-colony stimulating factor (G-CSF) were available for 443 patients. G-CSF was applied in 98% of patients treated with R-CHOP-14 and 63% of patients treated with R-CHOP-21. Patients treated with R-CHOP-21 and G-CSF were older (median 71 vs. 61 years) than patients treated with R-CHOP-21 and no application of G-CSF (data on file).

Table 1: Treatment characteristics

	R-CHOP-14	R-CHOP-21
Patients (N)	229	336
Therapy completed [n(%)] [a]	218 (95%)	297 (88%)
Duration of chemotherapy (median)	14.1 weeks	17.0 weeks
Number of cycles chemotherapy		
mean ± StD	5.9 ± 1.2	5.7 ± 1.2
median	6	6
≤ 5	39 (18 %)	64 (22 %)
6	148 (68 %)	207 (70 %)
≥ 7	30 (14 %)	26 (9 %)
Number of cycles rituximab		
mean ± StD	6.7 ± 1.7	6.5 ± 1.8
median	8	6
≤ 5	34 (16 %)	50 (17 %)
6	64 (29 %)	119 (40 %)
≥ 7	118 (54 %)	128 (43 %)
Radiotherapy		
before / during 1st-line therapy	5 (2 %)	11 (4 %)
after 1st-line	36 (17 %)	28 (9 %)
Application of G-CSF (n) [b]	177	266
at least once	173 (98 %)	168 (63 %)

[a] The difference to the number of patients (N) represents the number of patients with ongoing therapy at the time of this interim analysis.

[b] Number of patients for whom data on the application of G-CSF were available.

Effectiveness of both schedules is similar

Data on best clinical response were available for 90% of patients who had completed their 1st-line therapy at the time of this analysis. Objective response rate (ORR) as assessed by the local site was: 96% for R-CHOP-14 and 93% for R-CHOP-21; the clinical (unconfirmed) complete remission rate (CRu) was 65% for R-CHOP-14 and 66% for R-CHOP-21 (Figure 3a). While ORR was similar for both schedules in patients diagnosed with different tumour stages, the rates of CRu differed between the two schedules in patients with tumour stage I/II and III/IV (Figure 3b).

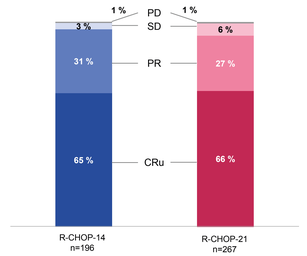

Figure 3a: Best Response

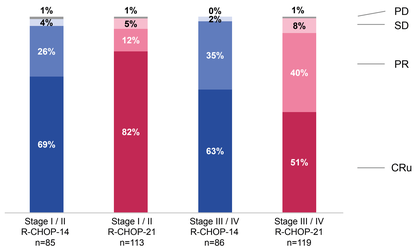

Figure 3b: Best Response by tumour stage

With a median follow-up of 25 months (maximum 62 months), 2-year progression-free survival rate (PFS_{REG}) is 77% (1-year: 84%) for R-CHOP-14 and 86% (1-year: 88%) for R-CHOP-21 (Figure 4). 2-year overall survival rate (OS) is 87% (1-year: 92%) for R-CHOP-14 and 86% (1-year: 90%) for R-CHOP-21 (Figure 5). At the time of this analysis, 10% (R-CHOP-14) and 9% (R-CHOP-21) of patients have received a 2nd-line therapy, respectively. Overall, 10% of patients have been lost to follow-up.

At this point, the high rate of patients alive without progression (>80%) precluded multivariate regression analyses regarding factors affecting PFS_{REG} or OS.

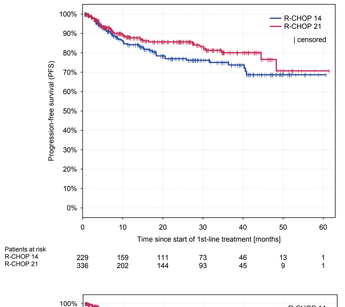

Figure 4: Progression-free Survival (PFS_{REG}) since start of 1st-line treatment

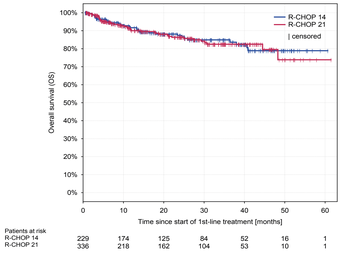

Figure 5: Overall Survival (OS) since start of 1st-line treatment

Conclusion

Our data show that in routine practice in Germany, patients with previously untreated high-grade aNHL and treated with R-CHOP are more likely to receive the three-weekly schedule R-CHOP-21, independent of age, sex, performance status or co-morbidities. Regardless of the schedule, a median of six cycles CHOP are applied. First outcome data show that the effectiveness (ORR, PFS_{REG} and OS) of both schedules is similar. Further analyses will investigate whether subgroups of patients, e.g. those with advanced tumour stage, may benefit from either schedule, and whether G-CSF or radiotherapy impact on the outcome of treatment.

In collaboration with:

AKS Arbeitskreis klinische Studien e.V.

Kompetenznetz Maligne Lymphome

Abbreviations:
G-CSF: Granulocyte-colony stimulating factor | R-CHOP: cyclophophamide + doxorubicin + vincristine + prednisone + rituximab
CRu: unconfirmed complete response | PD: progressive disease | PR: partial response | ORR: overall response rate | PFS_{REG}: progression-free survival with registry data | OS: overall survival | SD: stable disease
aNHL: aggressive (lhigh-grade) non-Hodgkin's lymphoma | DLBCL: diffuse large B-cell lymphoma | ECOG: Eastern Cooperative Oncology Group | IPI: International Prognostic Index | OR: Odds Ratio | StD: Standard deviation | TLN: Tumour Registry of Lymphoid Neoplasms

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Disclosures:
No relevant conflicts of interest to declare

Acknowledgements:
The authors would like to thank all patients at the study sites and all members of the TLN Study Group for their participation in the registry.

ASH 2014 San Francisco
Publication Number 4406
Submission ID 66894