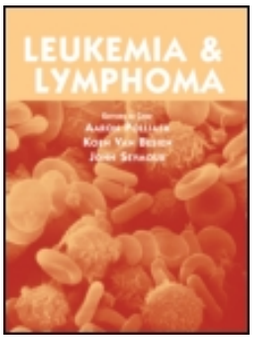

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: Carsten Zwick & Michael Pfreundschuh (2012) Fourteen-day rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP-14): use it right or do not use it at all, Leukemia & Lymphoma, 53:5, 758-759, DOI: 10.3109/10428194.2011.647316

To link to this article: https://doi.org/10.3109/10428194.2011.647316

Leukemia & Lymphoma, May 2012; 53(5): 758–759

ISSN: 1042-8194 print/1029-2403 online
DOI: 10.3109/10428194.2011.647316

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COMMENTARY

Fourteen-day rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP-14): use it right or do not use it at all

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In their retrospective study on the use of granulocyte-colony stimulating factor (G-CSF) prophylaxis in patients with diffuse large B-cell lymphoma (DLBCL), Johnsen and colleagues [1] report that the primary prophylaxis with G-CSF after rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone given every 14 days (R-CHOP-14) varies widely, despite the fact that treatment guidelines published by the European Organisation for Research and Treatment of Cancer (EORTC) recommend G-CSF support for patients with lymphomas or solid tumors receiving a dose-dense regimen [2]. While the omission of primary G-CSF prophylaxis (after the first R-CHOP-14) was not clearly associated with an increased incidence of febrile neutropenia, the need for G-CSF was highlighted by the fact that 61 of the 64 patients who had not received primary prophylaxis with G-CSF were subsequently administered G-CSF. Moreover, chemotherapy dose delays >3 days (75% vs. 47%) and dose reductions $>10\%$ (19% vs. 12 %) were observed more frequently in patients not receiving primary G-CSF prophylaxis, and most important, the absence of primary G-CSF prophylaxis (in addition to higher International Prognostic Index [IPI] score and increased age) was a highly significant risk factor for predicting $<90\%$ relative dose intensity (RDI).

The study of Johnsen and colleagues is in line with recently presented and published data underlining the importance of primary G-CSF prophylaxis when a 2-week R-CHOP-14 is intended. While one would expect that $<90\%$ RDI compromises the therapeutic potential of R-CHOP-14, the formal proof of this assumption remains to be demonstrated, and it is unclear whether falling below the margin of 96% or 98% of RDI with six or eight cycles of R-CHOP-14 as achieved in the RICOVER-60 trial of the German High-Grade Non-Hodgkin-Lymphoma Study Group (DSHNHL) in elderly patients with DLBCL [3] is the reason why R-CHOP-14 was not better than R-CHOP-21 in two randomized trials, one performed by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) in elderly patients with DLBCL [4,5] and a second by the British National Cancer Research Institute (NCRI) [6]. It must, however, be kept in mind that not giving primary prophylaxis after R-CHOP-14 puts patients with DLBCL, in particular elderly patients with DLBCL, at risk, as shown by the French experience: while the therapy-associated death rate in the French trial was as high as 9% in the first 100 patients treated with R-CHOP-14, it fell to 2.5% in the last 200 patients in that trial. Similarly, the first 500 patients in the RICOVER-60 trial who received G-CSF prophylaxis starting on day 6 had a considerably higher therapy-associated death rate than the patients who received G-CSF starting on day 4, later in the trial. In contrast, a randomized trial of peg-filgrastim in elderly patients with DLBCL treated with R-CHOP-14 showed a significantly reduced therapy-associated death rate when pegfilgrastim was given on day 4 instead of day 2, as recommended on the label. The superiority of day-4 over day-2 peg-filgrastim is most likely due to the fact that the higher number of neutrophils on day 2 clear more and leave less free pegfilgrastim than the lower number of neutrophils that encounter peg-filgrastim when given on day 4 [7]. A comparison of filgrastim, lenograstim and peg-filgrastim in DSHNHL trials in elderly patients with DLBCL suggests that best protection is provided with peg-filgrastim on day 4, the least with peg-filgrastim on day 2, and the daily filgrastim or lenograstim applications ranging in between (manuscript in preparation). Finally, after an increased toxicity (in particular interstitial pneumonia) of six cycles of CHOP-14 was observed when combined with 12 dose-dense applications of rituximab in the DENSE-R-CHOP-14 trial [8], the introduction of prophylactic acyclovir (against cytomegalovirus [CMV]) and cotrimoxazole led to a significant reduction of severe infections and therapy-associated deaths. More than 700 elderly patients have now been treated with R-CHOP-14 in prospective phase II and phase III trials of the DSHNHL, with combined primary G-CSF as well as acyclovir and cotrimoxazole prophylaxis. The therapy-associated death rate has been consistently below 3% and the RDI of $6 \times$ RCHOP-14

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This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

was > 95%. These figures should be considered the benchmark for quality delivery of R-CHOP-14 in elderly patients with DLBCL in future trials.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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