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LETTER TO THE EDITOR

Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy

R. Pettengell · M. Schwenkglenks · A. Bosly

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Dear Editor,

Reductions in average relative chemotherapy dose intensity (ARDI; i.e. administered compared with planned) compromise patient outcomes [3], and a recent Belgian study showed that survival for non-Hodgkin lymphoma (NHL) patients receiving CHOP-21 was reduced when ARDI fell below 90% [2]. We support these findings with similar data from the UK Audit of Lymphoma Patients (n=78 patients who received CHOP-21 chemotherapy in 1999–2000) and from the combined Belgian and UK data (n=289) [4].

Patient, disease and treatment characteristics were similar between the two studies, except that the UK patients were younger (mean age ± SD was 55±15 years versus 63± 14 years) and fewer UK patients received colony stimulating factor (CSF). First cycle CSF use was 4% in the UK study compared to 25% in the Belgian study. During an average time to death or censoring of 72 months, 35% of patients in the UK study died. In the Belgian study, the average observation time was 30 months, during which 31% of patients died. After adjusting for the higher mean age of the Belgian patients, Kaplan–Meier survival functions were similar between the two populations (log-rank test stratified by 10-year age groups, p=0.38).

Kaplan–Meier plots for patients with >90% ARDI versus ≤90% ARDI showed reduced survival for the patients with ≤90% ARDI (Fig. 1). A trend towards reduced survival was apparent in the UK dataset alone (Fig. 1a; log-rank test-based p=0.090). For the combined dataset, the effect was statistically significant (p<0.001; Fig. 1b), as for the Belgian data alone [2].

Potential predictors of reduced survival were assessed using an extended Cox proportional hazards regression model with robust standard errors allowing for clustering by centre. Using the UK dataset, reduced survival was significantly associated with a higher Ann Arbor disease stage (hazard ratio (HR) at treatment initiation 2.59 per stage increase by 1, 95% CI 1.45–4.66, p=0.001) and showed a trend towards association with age (HR 1.02 per year of age, CI 1.00–1.04, p=0.058) and RDI≤90% (HR 1.42, CI 0.88–2.28, p=0.146). Using the combined dataset, reduced survival was associated with more advanced disease stage (HR 2.00, CI 1.44–2.77, p<0.001), age (HR 1.03, 95% CI 1.01–1.05, p=0.002) and RDI≤90% (HR 1.77, CI 1.12–2.79, p=0.014). In both models, the strength of the association with disease stage decreased over time.

Approximately 23% and 30% of UK and Belgian patients, respectively, received ARDI≤90% and were, therefore, at risk of reduced survival. There are many factors that result in a decision to reduce or delay chemotherapy, including local institutional practice. Particularly relevant is the higher proportion of elderly patients in the Belgian dataset; elderly patients are at high FN risk [1] and often receive lower doses of chemotherapy [3]. Despite this common practice, dose-dense CHOP-14 chemotherapy

R. Pettengell (✉)
Cellular and Molecular Medicine,
St. George's University of London,
Cranmer Terrace,
London SW17 0RE, UK
e-mail: rpetteng@sgul.ac.uk

M. Schwenkglenks
European Center of Pharmaceutical Medicine,
Executive Office, University Hospital, University of Basel,
Basel 4031, Switzerland

A. Bosly
Department of Haematology,
University Hospital of Mont-Godinne,
avenue Dr G. Therasse 1,
Yvoir 5530, Belgium

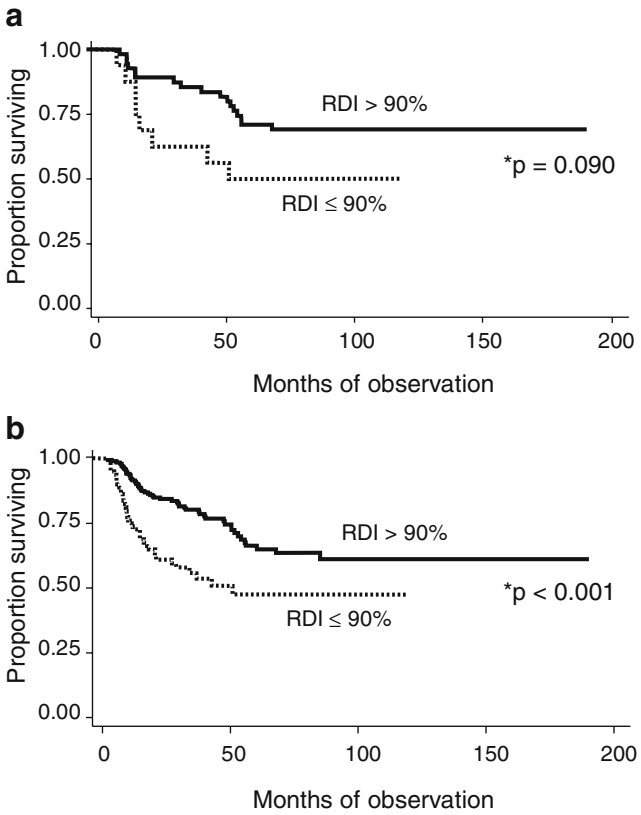

Fig. 1 Kaplan–Meier survivor estimates by RDI for UK dataset alone (**a**) and the combined UK and Belgian datasets (**b**). *Asterisk* Log-rank test-based *p* values

supported with G-CSF has been shown to be efficacious and well tolerated in both young and elderly NHL patients [5, 6].

This study highlights the potential impact of receiving ARDI≤90% on survival. While further investigation is needed, delivering full chemotherapy dose intensity remains an important goal in NHL patients who receive CHOP-21 chemotherapy.

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References

1. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, Kearney N, Lyman GH, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C (2006) EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 42:2433–2453
2. Bosly A, Bron D, Van Hoof A, De Bock R, Berneman Z, Ferrant A, Kaufman L, Dauwe M, Verhoef G; for the Lymphoma Dose Project: a National Study (2008) Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann Hematol 87:277–283
3. Marangolo M, Bengala C, Conte PF, Danova M, Pronzato P, Rosti G, Sagrada P (2006) Dose and outcome: the hurdle of neutropenia. Oncol Rep 16:233–248
4. Pettengell R, Bosly A, Bron D, Schwenkglenks M, Johnson P, Van Hoof A, Hancock B, De Brock R, Pagliuca A, Berneman Z, Thomas R, Ferrant A, Joyner M, Dauwe M, Verhoef G, Hoskin P (2006) Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy. Haematologica/Hematol J 91:69 (Abs 0185)
5. Pfreundschuh M, Trumper L, Kloess M, Schmits R, Feller AC, Rube C, Rudolph C, Reiser M, Hossfeld DK, Eimermacher H, Hasenclever D, Schmitz N, Loeffler M, The German High-Grade Non-Hodgkin's Lymphoma Study G (2004) Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 104:634–641
6. Pfreundschuh M, Trumper L, Kloess M, Schmits R, Feller AC, Rudolph C, Reiser M, Hossfeld DK, Metzner B, Hasenclever D, Schmitz N, Glass B, Rube C, Loeffler M, The German High-Grade Non-Hodgkin's Lymphoma Study G (2004) Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 104:626–633