Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in the management of Primary Mediastinal B-cell Lymphoma (PMBL): A subgroup analysis of the UK NCRI R-CHOP 14 *versus* 21 trial

Running Title: R-CHOP in PMBL

Mary Gleeson[1], Eliza A Hawkes[2], David Cunningham[1], Nick Chadwick[3], Nicholas Counsell[3], Anthony Lawrie[3], Andrew Jack[4], Paul Smith[3], Paul Mouncey[3], Christopher Pocock[5], Kirit M Ardeshna[6,7], John Radford[8], Andrew McMillan[9], John Davies[10], Deborah Turner[11], Anton Kruger[12], Peter W.M. Johnson[13], Joanna Gambell[3] and David Linch[6]*

[1]The Royal Marsden Hospital, London and Surrey, United Kingdom, [2]Department of Oncology and Clinical Haematology, Austin Health, Heidelberg, Melbourne, Australia, [3]Cancer Research UK and UCL Cancer Trials Centre, UCL Cancer Institute, London, United Kingdom, [4]HMDS, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [5]East Kent Hospitals, Canterbury, United Kingdom, [6]University College London, London, United Kingdom, [7]Mount Vernon Cancer Centre, Northwood, United Kingdom, [8]The University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom, [9]Nottingham City Hospital, Nottingham, United Kingdom, [10]Western General Hospital, Edinburgh, United Kingdom, [11]Torbay Hospital, Torquay, United Kingdom, [12]Royal Cornwall Hospital, Truro, United Kingdom, [13]Cancer Research UK Centre, Southampton, United Kingdom

*Corresponding author: Department of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, United Kingdom.

Tel: 0207 808 2132, Fax: 0207 808 2688,

Email: David.Cunningham@rmh.nhs.uk

Word Count: 1,474

Summary: 95

Manuscript: 1,379

Summary

We performed a subgroup analysis of the phase III UK NCRI R-$CHOP_{14}$ *versus* R-$CHOP_{21}$ trial to evaluate the outcomes for patients meeting the WHO 2008 criteria for primary mediastinal B-cell lymphoma (PMBL). Fifty patients meeting the criteria were identified from the trial database. At a median follow-up of 7.2 yrs the 5-yr PFS and OS were 79.8% and 83.8% respectively. An exploratory analysis raised the possibility of a better outcome in those who received R-$CHOP_{14}$ and time intensification may still, in the rituximab era, merit testing in a randomised trial in this subgroup of patients.

Keywords

Primary Mediastinal B-cell Lymphoma

Diffuse large B-cell lymphoma

R-CHOP

Non-Hodgkin lymphoma

Clinical trials

Introduction:

Primary Mediastinal B-cell Lymphoma (PMBL) is a distinct subtype of diffuse large B-cell lymphoma (DLBCL) arising from putative thymic B-cells in the mediastinum and comprises 2-4% of all non-Hodgkin lymphomas (NHLs) (Gaulard *et al*, 2008). PMBL has unique clinicopathologic and genotypic features and is characterised by a bulky antero-superior mediastinal mass, which often directly invades local structures including lungs, pleura or pericardium, and is frequently associated with superior vena cava syndrome. In contrast to DLBCL, PMBL patients are typically younger (median age 35 years) and there is usually a female predominance. Spread to supraclavicular or cervical lymph nodes can occur but absence of other lymph node or bone marrow involvement is required to exclude DLBCL with secondary mediastinal involvement (Gaulard *et al*, 2008).

Combination chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) with or without consolidative radiotherapy (RT) is the most commonly used regimen in the first-line management of PMBL with reported 5-yr OS rates of 79-89% (Savage *et al*, 2006; Rieger *et al*, 2011; Soumerai *et al*, 2014). However with the exception of the MInT trial (which evaluated patients with PMBL aged ≤60 years with an age-adjusted International Prognostic Index of 0-1) (Rieger *et al*, 2011); the evidence-base for R-CHOP in PMBL comes from retrospective studies.

Several studies in PMBL from the pre-rituximab era suggested a benefit for third-generation regimens such as etoposide/methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisolone and

bleomycin (V/MACOP-B) over CHOP (Lazzarino *et al*, 1993; Zinzani *et al*, 2002; Todeschini *et al*, 2004). These weekly regimens were intended to be dose-intensified, based on the Skipper model (Hryniuk *et al*, 1998) but they typically involved reduction of the total dose of anthracyclines which are the most effective class of lymphoma drugs (Hasenclever *et al*, 2001). These regimens were, however, time-intensified with the cytotoxic drugs delivered over 11 weeks rather than the 15 weeks with 6 cycles of CHOP. Recently excellent results have been reported in a small single-arm prospective phase 2 study from National Cancer Institute (NCI) with the infusional regimen of dose-adjusted etoposide, doxorubicin, cyclophosphamide with vincristine, prednisolone plus rituximab (DA-EPOCH-R) (Dunleavy *et al*, 2013), but it is unclear whether these results are significantly better than can be achieved with R-CHOP.

The aim of this subgroup analysis was to evaluate the outcomes for patients with PMBL treated with R-CHOP with or without RT within the randomised prospective UK NCRI R-CHOP 14 *versus* 21 trial. An exploratory analysis was also carried out on the impact of time-intensification with the R-$CHOP_{14}$ regimen.

Methods:

The phase III UK NCRI R-CHOP-14 *versus* 21 trial compared R-CHOP given 2-weekly versus 3-weekly in previously untreated patients aged ≥18 years with bulky stage I-IV histologically proven DLBCL. A total of 1,080 patients from 119 centres across the United Kingdom were enrolled from 2005-2008 and randomised in a one-to-one ratio to receive either 6 cycles of R-CHOP every 14 days (R-

CHOP-14) plus 2 cycles of rituximab or 8 cycles of R-CHOP every 21 days (R-CHOP-21). We previously reported that R-CHOP-14 was not superior to R-CHOP-21 for OS, progression free survival (PFS), response rate or safety (Cunningham *et al*, 2013).

Response following induction chemotherapy with R-CHOP was evaluated by a CT scan of the thorax, abdomen, and pelvis with or without neck. ^{18}F-fluorodeoxyglucose-positron-emission-tomography-CT (FDG-PET-CT) scans were not mandated by the trial protocol and therefore no FDG-PET-CT data were collected as part of the main study. Administration of consolidation RT on study was permitted at the discretion of the local investigator.

Patients with PMBL were not excluded from enrollment and cases were identified by searching the trial database for patients with a "bulky" mediastinal mass at baseline (a minimum cut-off of 5cm diameter was used) who also fulfilled the World Health Organization (WHO) 2008 criteria for sites of involvement at presentation, that is absence of disease involvement outside of the thorax with or without cervical / supraclavicular lymph node involvement (Gaulard *et al*, 2008).

Statistical Analysis:

The outcomes in this subgroup analysis are the same as in the overall study: the primary endpoint was OS and the secondary endpoints were PFS and response rate. PFS and OS were calculated from the date of randomisation, censored at the date last seen, and analysed using Kaplan-Meier and Cox regression models. End of treatment response was assessed according to the 1999 International Working Group (IWG) criteria (Cheson *et al*, 1999).

Results:

Fifty of 1,080 (4.6%) patients from the R-CHOP 14 versus 21 study database met the WHO 2008 clinical criteria. Baseline characteristics are demonstrated in Table I. The median age at diagnosis was 38.5 years and 50.0% of patients were female. All patients had stage I or II disease and the median mediastinal mass diameter was 11.1cm. Twenty-eight patients (56.0%) were treated with R-CHOP-21 and 22 patients (44.0%) received R-CHOP-14. On completion of R-CHOP chemotherapy response by CT was complete in 42.9% (n=21), partial in 49.0% (n=24), stable disease in 2.0% (n=1) and progressive disease in 6.1% (n=3). End of treatment response was not evaluable for 1 patient. Radiotherapy was administered to 58.0% of patients (n=29).

After a median follow-up of 7.2 years, the 5-year PFS was 79.8% (95% CI 68.6-91.0) and 5-year OS was 83.8% (95% CI 73.4-94.2) [Figure 1A and 1B]. Where disease progression occurred 9/10 events occurred within the first-year of follow-up. For the 9 patients who died in our cohort the causes of death were documented as progressive disease (n=7), cardiac-related (n=1) and in one case the cause of death was unknown. Eight out of ten progressions and 8/9 deaths occurred in patients who received R-CHOP-21 [Figure 1C and 1D]. The difference in OS between the two treatment arms approached statistical significance (p=0.06). Five out of ten progressions and 4/9 deaths occurred in patients who had received RT consolidation post-R-CHOP.

Discussion: Our data confirms the efficacy of R-CHOP (with or without RT) in the management of PMBL and serves as a benchmark for future studies. This is, to our knowledge, the largest reported cohort of patients with PMBL treated with R-CHOP within a prospective trial. The additional strength of the data lies in the strict selection of patients according to the WHO 2008 clinical criteria for PMBL, the inclusion of all patients ≥18 years without an upper age limit, and the long duration of follow-up. Compared to the study of DA-EPOCH-R our patients were older (median age 38.5 years versus 30 years) and our trial was multicentre, but despite this the 83.8% OS at 5 years is within the 95% confidence limits of the DA-EPOCH-R results (Dunleavy *et al*, 2013).

More events occurred in patients treated with R-CHOP-21, and the difference in survival approached significance. However it should be noted that the number of patients in this subgroup analysis was small and this prevents a meaningful multivariate analysis to address the impact of any potentially confounding factors. **As with other trial populations, it is also worth noting that very unwell patients presenting with PMBL were potentially excluded from study enrolment.** There is also no compelling biological reason why time-intensification in the rituximab era should be more efficacious in this form of NHL than in other types of DLBCL, where time-intensification has not impacted on outcome (Cunningham *et al*, 2013). Nonetheless, together with the previous experience from the pre-rituximab era, this suggests that the impact of time-intensification should be considered in future trials of this specific subtype of DLBCL. In our study RT was given at the clinician's discretion, so it is not possible to draw conclusions about the value of

this modality of therapy. The currently accruing IELSG-37 randomised phase III trial (NCT 01599559), will address this important clinical question by evaluating the role of RT in FDG-PET-CT negative patients following rituximab-containing induction chemotherapy, although it should be noted that a positive end of treatment PET scan, **seen in approximately 40% of R-CHOP-treated patients (Vassilakopoulos *et al*, 2016)** is not indicative of impending disease progression (Dunleavy *et al*, 2013; Woessmann *et al*, 2013).

In conclusion our analysis demonstrates that R-CHOP is an efficacious regimen in the management of PMBL. Although excellent results have been reported with the combination of DA-EPOCH-R in PMBL, the benefit of such regimens over R-CHOP needs to be evaluated in prospective randomised trials and consideration should be given to further exploring the value of R-$CHOP_{14}$ in this group of patients.

ACKNOWLEDGEMENTS

Cancer Research UK provided endorsement and funding and the National Health Service (NHS) provided funding to the National Institute for Health Research (NIHR) Biomedical Research Centres at both University College London and the Royal Marsden Hospital/Institute of Cancer Research, London, UK. Chugai Pharmaceuticals provided an educational grant and lenograstim.

AUTHOR CONTRIBUTIONS

M.G., E.A.H., D.C., A.J., and D.L. designed the study; M.G., E.A.H., D.C. and D.L. interpreted the data, performed literature searches and

wrote the report. N.C., A.L., P.S., J.G., P.M. gathered and interpreted the data; N.C. and N.C. analysed and interpreted the data, produced figures and wrote the report; E.A.H., A.J., C.P., K.M.A., J.A.R, A.M., J.D., D.T., A.K., P.J., D.L. gathered and interpreted the data. All authors reviewed and approved the final manuscript.

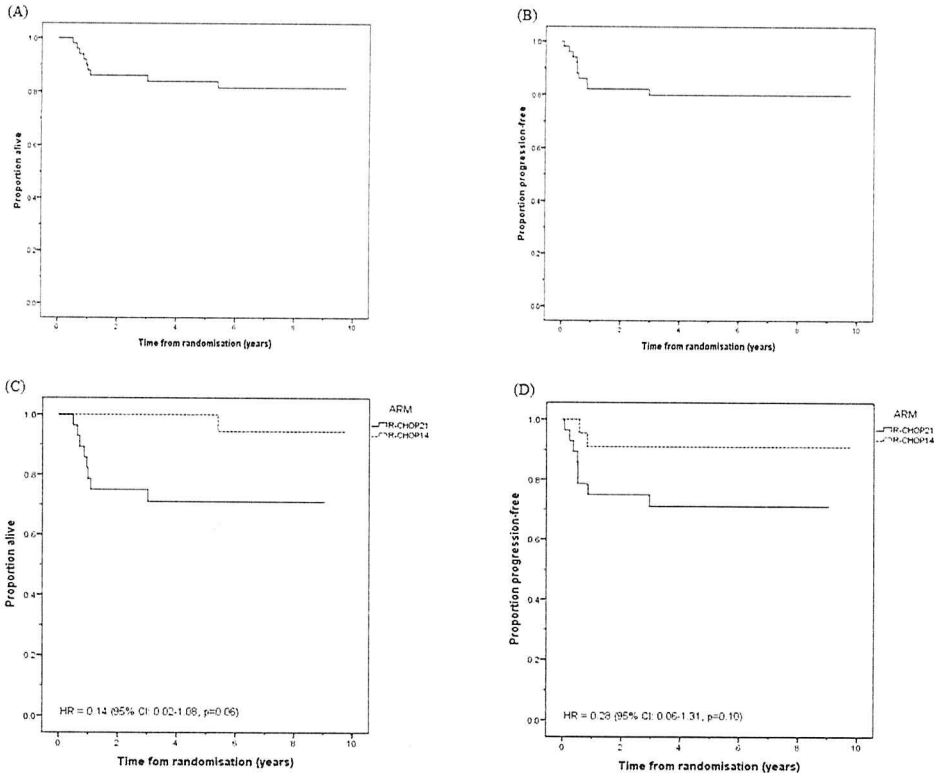
DISCLOSURES OF CONFLICT OF INTERESTS

D.C. has received research funding from Amgen, Astra Zeneca, Bayer, Celgene, Medimmune, Merrimack, Merck Serono and Sanofi. K.M.A. has received research funding, conference expenses and honoraria for attending or chairing advisory boards. All other authors declare that they have no conflicts of interest to report.

Table I: Baseline Characteristics

	n=50	%
Gender		
Male	25	50
Female	25	50
Age (yrs)		
Median (range)	38.5	22-78
< 60	46	92
≥ 60	4	8
Stage		
I	18	36
II	32	64
Maximum diameter of mediastinal mass		
Median (range)	11.1	6-23
≤10cm	15	30
>10 cm	35	70
B symptoms		
Absent	24	48
Present	26	52
Performance score		
0	29	58
1	15	30
2	6	12
IPI		
0	6	12
1	36	72
2	5	10
3	3	6
LDH		
Normal	8	16
Raised	42	84

Figure 1: Overall (A) and progression free survival (B) for all patients. Overall (C) and progression free survival (D) according to treatment arm.



References:

Cheson, B.D., Horning, S.J., Coiffier, B., Shipp, M.A., Fisher, R.I., Connors, J.M., Lister, T.A., Vose, J., Grillo-Lopez, A., Hagenbeek, A., Cabanillas, F., Klippensten, D., Hiddemann, W., Castellino, R., Harris, N.L., Armitage, J.O., Carter, W., Hoppe, R. & Canellos, G.P. (1999) Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. *Journal of Clinical Oncology*, **17,** 1244–1253.

Cunningham, D., Hawkes, E.A., Jack, A., Qian, W., Smith, P., Mouncey, P., Pocock, C., Ardeshna, K.M., Radford, J.A., McMillan, A., Davies, J., Turner, D., Kruger, A., Johnson, P., Gambell, J. & Linch, D. (2013) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: A phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *The Lancet*, **381,** 1817–1826.

Dunleavy, K., Pittaluga, S., Maeda, L.S., Advani, R., Chen, C.C., Hessler, J., Steinberg, S.M., Grant, C., Wright, G., Varma, G., Staudt, L.M., Jaffe, E.S. & Wilson, W.H. (2013) Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma. *New England Journal of Medicine*, **368,** 1408–1416.

Gaulard, P, Harris, N.L., Pileri, S.A., Kutok, J.L, Stein, H, Kovrigina, A.M., Jaffe E.S, Moller, P. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon IARC Press 2008; 250-251.

Hasenclever, D., Brosteanu, O., Gerike, T. & Loeffler, M. (2001)

Modelling of chemotherapy: the effective dose approach. *Annals of Hematology*, **80 Suppl 3,** B89–94.

Hryniuk, W., Frei, E. & Wright, F.A. (1998) A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: Summation dose-intensity. *Journal of Clinical Oncology*, **16,** 3137–3147.

Lazzarino, M., Orlandi, E., Paulli, M., Boveri, E., Morra, E., Brusamolino, E., Kindl, S., Rosso, R., Astori, C., Buonanno, M.C., Magrini, U. & Bernasconi, C. (1993) Primary mediastinal B-cell lymphoma with sclerosis: An aggressive tumor with distinctive clinical and pathologic features. *Journal of Clinical Oncology*, **11,** 2306–2313.

Rieger, M., Österborg, A., Pettengell, R., White, D., Gill, D., Walewski, J., Kuhnt, E., Loeffler, M., Pfreundschuh, M. & Ho, A.D. (2011) Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: Results of the Mabthera International Trial Group study. *Annals of Oncology*, **22,** 664–670.

Savage, K.J., Al-Rajhi, N., Voss, N., Paltiel, C., Klasa, R., Gascoyne, R.D. & Connors, J.M. (2006) Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: The British Columbia experience. *Annals of Oncology*, **17,** 123–130.

Soumerai, J.D., Hellmann, M.D., Feng, Y., Sohani, A.R., Toomey, C.E., Barnes, J.A., Takvorian, R.W., Neuberg, D., Hochberg, E.P. & Abramson, J.S. (2014) Treatment of primary mediastinal B-cell lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone is associated with a high rate of primary refractory disease. *Leukemia & Lymphoma*,

55, 538–43.

Todeschini, G., Secchi, S., Morra, E., Vitolo, U., Orlandi, E., Pasini, F., Gallo, E., Ambrosetti, A., Tecchio, C., Tarella, C., Gabbas, A., Gallamini, A., Gargantini, L., Pizzuti, M., Fioritoni, G., Gottin, L., Rossi, G., Lazzarino, M., Menestrina, F., Paulli, M., et al (2004) Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. *British Journal of Cancer*, **90,** 372–6.

Vassilakopoulos, T.P., Pangalis, G.A., Chatziioannou, S., Papageorgiou, S., Angelopoulou, M.K., Galani, Z., Kourti, G., Prassopoulos, V., Leonidopoulou, T., Terpos, E., Dimopoulou, M.N., Sachanas, S., Kalpadakis, C., Konstantinidou, P., Boutsis, D., Stefanoudaki, E., Kyriazopoulou, L., Siakantaris, M.P., Kyrtsonis, M.-C., Variami, E., et al (2016) PET/CT in primary mediastinal large B-cell lymphoma responding to rituximab-CHOP: An analysis of 106 patients regarding prognostic significance and implications for subsequent radiotherapy. *Leukemia*, **30,** 238–260.

Woessmann, W., Lisfeld, J. & Burkhardt, B. (2013) Therapy in Primary Mediastinal B-Cell Lymphoma. *New England Journal of Medicine*, **369,** 282–284.

Zinzani, P.L., Martelli, M., Bertini, M., Gianni, A.M., Devizzi, L., Federico, M., Pangalis, G., Michels, J., Zucca, E., Cantonetti, M., Cortelazzo, S., Wotherspoon, A., Ferreri, A.J.M., Zaja, F., Lauria, F., De Renzo, A., Liberati, M.A., Falini, B., Balzarotti, M., Calderoni, A., et al (2002) Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with

sclerosis: a retrospective multinational study on 426 previously untreated patients. *Haematologica*, **87,** 1258–64.