interpretation of data and critically revised the manuscript. All authors approved the final version of the manuscript for publication.

Acknowledgements

PF is supported by a Leukaemia Foundation of Australia Clinical PhD Scholarship. ML is supported by an NHMRC PhD Scholarship. SV is supported by a Clinical Academic Fellowship, School of Clinical Sciences, Monash University. Funding for this study was provided by an educational grant from Janssen Pharmaceuticals. The company had no role in the design of the study or writing of the manuscript.

Conflicts of interest

None.

Adrian Chee[1]
Michael S. Low[1,2]
Shahla Vilcassim[1,3]
Gareth P. Gregory[1,3]
Michael Gilbertson[1]
Sumita Ratnasingam[1]
George Grigoriadis[1,3,*]
Pasquale L. Fedele[1,2,*]
[1]Monash Haematology, Monash Health, Clayton, Australia, [2]Walter and Eliza Hall Institute of Medical Research, Parkville, Australia and [3]School of Clinical Sciences at Monash Health, Monash University, Centre for Cancer Research, Hudson Institute of Medical Research, Clayton, Victoria, Australia.
E-mail: pasquale.fedele@monashhealth.org

**Contributed equally to the work.*

Keywords: multiple myeloma, bortezomib, proteasome inhibitors

First published online 31 August 2017
doi: 10.1111/bjh.14871

References

Chanan-Khan, A.A. & Giralt, S. (2010) Importance of achieving a complete response in multiple myeloma, and the impact of novel agents. *Journal of Clinical Oncology*, **28**, 2612–2624.

Durie, B.G.M., Hoering, A., Abidi, M.H., Rajkumar, S.V., Epstein, J., Kahanic, S.P., Thakuri, M., Reu, F., Reynolds, C.M., Sexton, R., Orlowski, R.Z., Barlogie, B. & Dispenzieri, A. (2017) Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *The Lancet*, **389**, 519–527.

Harousseau, J., Attal, M., Richardson, P.G., Schlag, R., Dimopoulos, M.A., Shpilberg, O., Kropff, M., Kentos, A., Cavo, M., Golenkov, A., Komarnicki, M., Mateos, M., Esseltine, D., Cakana, A., Liu, K., Deraedt, W. & van de Velde, H. (2010) Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. *Blood*, **116**, 3743–3750.

Kumar, S., Paiva, B., Anderson, K.C., Durie, B., Landgren, O., Moreau, P., Munshi, N., Lonial, S., Mateos, M.V., Dimopoulos, M., Kastritis, E., Boccadoro, M., Orlowski, R., Goldschmidt, H., Spencer, A., Hou, J., Chng, W.J., Usmani, S.Z., Zamagni, E., Shimizu, K., Jagannath, S., Johnsen, H.E., Terpos, E., Reiman, A., Kyle, R.A., Sonneveld, P., Richardson, P.G., McCarthy, P., Ludwig, H., Chen, W., Cavo, M., Harousseau, J.L., Lentzsch, S., Hillengass, J., Palumbo, A., Orfao, A., Rajkumar, S.V., San Miguel, J. & Avet-Loiseau, H. (2016) International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet Oncology*, **17**, 328–346.

Moreau, P., Attal, M., Pégourié, B., Planche, L., Hulin, C., Facon, T., Stoppa, A., Fuzibet, J., Grosbois, B., Doyen, C., Ketterer, N., Sebban, C., Kolb, B., Chaleteix, C., Dib, M., Voillat, L., Fontan, J., Garderet, L., Jaubert, J., Mathiot, C., Esseltine, D., Avet-Loiseau, H. & Harousseau, J. (2011) Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial. *Blood*, **117**, 3041–3044.

The significance of serum immunoglobulin paraprotein in diffuse large B-cell lymphoma

We read with great interest the report on the significance of serum immunoglobulin paraprotein in diffuse large B-cell lymphoma (DLBCL), by Li *et al* (2017), as we recently published on the same topic (Cox *et al*, 2014) and are currently involved in a multicentre study, in order to enlarge our series and deepen the study at a molecular level. In our recently published study (Cox *et al*, 2014), we reported on a series of 151 conventional DLBCL patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), who had been investigated for serum paraprotein. A paraprotein was detected in 23/151 (15·2%) patients and was

IgM in 19/151(12·5%) cases. In the majority of IgM+ cases (89%), the paraprotein had the same type of heavy and light chains in the serum and in the biopsy. We defined these cases as IgM-secreting DLBCL and hypothesized that they represent a new subset of non-germinal centre B-cell (GCB) subtype derived from terminally differentiated B-lymphocytes, with a poor cure rate after R-CHOP. Our results are in accordance with other studies on the same topic, reporting that: *IGHM* expression is highly discriminating between GCB and activated B-cell (ABC) DLBCL subtypes (Ruminy *et al*, 2011); an altered IgMκ/IgMλ ratio in the serum of DLBCL patients is a poor prognostic factor independent of the International Prognostic Index (Jardin *et al*, 2013).

In our series, the majority of IgM-secreting DLBCL cases were de-novo (89·3%) and all patients were treatment-naïve. They were characterised by: immunoblastic features ($P < 0·0001$), non-GCB-type ($P = 0·002$), stage III–IV ($P = 0·003$), ≥2 extra nodal sites ($P < 0·0001$), bone-marrow ($P = 0·002$), central nervous system involvement at disease onset or relapse ($P < 0·0001$), IPI-score 3–5 ($P = 0·009$) and failure to achieve complete remission ($P = 0·005$). *MYC* rearrangements were not detected while *BCL2* and *BCL6* translocations were found in only 13% and 6·5% respectively. Thirty-six-month event-free (11·8% vs. 66·4% $P < 0·0001$), progression-free (23·5% vs. 75·7%, $P < 0·0001$), and overall (47·1% vs. 74·8%, $P < 0·0001$) survivals were significantly worse than in non-secreting DLBCL.

The major difference with the results reported by Li *et al* (2017) concerns the prevalence of the paraprotein isotype: they found that the IgG isotype was the prevalent subtype, whereas in our and other series IgM was the most common one (Jardin *et al*, 2013; Cox *et al*, 2014). The discrepancy, also reported previously by others (Kim *et al*, 2014), may be due to either the different methodology used to determine the immunoglobulin isotype or racial differences between Asiatic and European DLBCL patients. Furthermore Li *et al* (2017) hypothesized that the poor prognosis of DLBCL patients who harbour a paraprotein may be due to the *MYD88* L265P mutation. We think this might not be the right explanation, as we failed to find this mutation in our series (Cox *et al*, 2014).

At variance with Li *et al* (2017), we investigated immunoglobulin expression also at the level of lymphoma biopsy, using immunohistochemistry. This, we believe, is an important clue, given that monoclonal gammopathy of undetermined significance (MGUS) is a rather common finding in the random population and rises with age. Thus, patients with MGUS who develop a non-clonally related DLBCL may have a worse prognosis because of older age and a dysfunctional immune system.

The significance of serum immunoglobulin paraprotein in DLBCL still needs to be definitely assessed. However in the era of precise medicine, we need to identify possible differences between truly immunoglobulin secreting cases from patients who harbour a non-clonally related paraprotein.

Author contributions

All authors wrote the paper.

M. Christina Cox[1]
Arianna Di Napoli[2]
Alberto Fabbri[3]
Emanuele Cencini[3]
Luigi Ruco[2]

[1]Haematology Unit, Azienda ospedaliera universitaria Sant'Andrea, Rome, Italy, [2]Department of Clinical and Molecular Medicine, Pathology Unit, La Sapienza University, Azienda ospedaliera universitaria Sant'Andrea, Rome, Italy and [3]Unit of Haematology and Transplants, Azienda Ospedaliera Universitaria Senese, Siena, Italy.
E-mail: chrisscox@gmail.com

Keywords: paraprotein, DLBCL, prognosis, IgM, lymphoma, immunoglobulin

First published online 17 August 2017
doi: 10.1111/bjh.14873

References

Cox, M.C., Di Napoli, A., Scarpino, S., Salerno, G., Tatarelli, C., Talerico C Lombardi, M., Monarca, B., Amadori, S. & Ruco, L. (2014) Clinicopathologic characterization of diffuse-large-B-cell lymphoma with an associated serum monoclonal IgM component. *PLoS ONE*, **9**, e93903.

Jardin, F., Delfau-Larue, M.H., Molina, T.J., Copie-Bergman, C., Briere, J., Petrella, T., Canioni, D., Fabiani, B., Jais, J.P., Figeac, M., Leroy, K., Mareschal, S., Salles, G.A., Coiffier, B., Delarue, R., Peyrade, F., Bosly, A., André, M., Ketterer, N., Haioun, C. & Tilly, H. (2013) Immunoglobulin heavy chain/light chain pair measurement is associated with survival in diffuse large B-cell lymphoma. *Leukemia & Lymphoma*, **54**, 1898–1907.

Kim, Y.R., Kim, S.J., Cheong, J.W., Kim, Y., Jang, J.E., Lee, J.Y., Min, Y.H., Song, J.W., Yang, W.I. & Kim, J.S. (2014) Monoclonal and polyclonal gammopathy measured by serum free light chain and immunofixation subdivide the clinical outcomes of diffuse large B-cell lymphoma according to molecular classification. *Annals of Hematology*, **93**, 1867–1877.

Li, Y., Wang, L, Zhu, HY, Liang, JH, Wu, W, Wu, JZ, Xia, Y, Fan, L, Li, JY & Xu, W. (2017) Prognostic significance of serum immunoglobulin paraprotein in patients with diffuse large B cell lymphoma. *British Journal of Haematology*, https://doi.org/10.1111/bjh.14735

Ruminy, P., Couronné, L., Parmentier, F., Rainville, V., Mareschal, S., Bohers, E., Burgot, C., Cornic, M., Bertrand, P., Lenormand, B., Picquenot, J.M., Jardin, F., Tilly, H. & Bastard, C. (2011) The isotype of the BCR as a surrogate for the GCB and ABC molecular subtypes in diffuse large B-cell lymphoma. *Leukemia*, **25**, 681–688.