Therapy for Immunoglobulin D Plasma Cell Myeloma

Robert Peter Gale

Haematology Research Centre, Division of Experimental Medicine, Department of Medicine,
Imperial College London, London, UK

There is a circularity to life. My PhD advisor at UCLA was Prof. John Fahey who, in 1965 with David Rowe, discovered immunoglobulin D (IgD) in the serum of a young man with previously undiagnosed plasma cell myeloma [1]. Fifty years later I am asked to comment on an article in this journal by Kang et al. [2] describing therapy advances they attribute to new anti-myeloma drugs.

IgD plasma cell myeloma is rare (<2% of cases) [3]. It typically occurs in young males and is characterized by a small or absent M-protein spike on serum protein electrophoresis, extra-medullary involvement, osteolytic lesions, systemic amyloidosis, hypercalcaemia, a λ -light-chain bias, Bence Jones proteinuria, kidney failure, and a worse prognosis than IgG and IgA forms of plasma cell myeloma [4]. This worse prognosis reflects these adverse biological features as well as more advanced disease at diagnosis. Part of this diagnostic delay is attributed to the absent M-spike on routine blood examinations for unrelated reasons [5].

The question posed by the authors is whether persons with IgD plasma cell myeloma receiving what they term *novel* drugs (is something novel if it has been used for 15 years?) and an autotransplant are better than persons receiving conventional therapy and an autotransplant. They conclude that this is likely so; they are probably correct. However, the issue for me is to comment on whether the data they present prove this conclusion, which is an entirely different matter.

A real statistician could have a field day highlighting problems with this study: its retrospective nature, few, non-consecutive subjects, selection biases, historical controls (obviously novel drugs were given to the most recent subjects), etc. There is no statistical comparison of the cohorts for progression-free survival (PFS) or survival. The authors' explanation is that there were too few subjects. I agree. However, with wide 95% confidence intervals we cannot accurately say whether the statistical model typically tested for significance with a *p* value, the null hypothesis, is a good explanation of the data observed or more extreme results [6]. As for performing multivariate analyses on a sample size of 22: forget about it.

One curiosity in the data reported is that although median PFSs were similar (7 and 8 months) for subjects receiving or not receiving novel drugs, survivals were seemingly vastly different (13 and 39 months). This means that if novel drugs are effective in improving survival their efficacy is after progression, not before. We must, of course, be cautious in accepting these data as PFS is typically (but not always) a somewhat reasonable surrogate of survival. Data regarding the efficacy of maintenance therapy after autotransplant in this typescript in very few subjects should be ignored; the issue has been addressed in large randomized trials [7, 8].

Others have studied a slightly different question: whether persons with IgD plasma cell myeloma have a different outcome than others with or without high-dose

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Fig. 1. Weight of evidence on the efficiency of new drugs in immunoglobulin D plasma cell myeloma.

therapy and an autotransplant. Results are contradictory [9–12]. In a study from the Centre for Blood and Marrow Research (CIBMTR) in 36 subjects my colleagues and I found similar outcomes to persons with IgG and IgA

plasma cell myeloma [13]. However, another study in 17 subjects reported worse outcomes [14].

The bottom line of all this? Members of a jury are instructed to consider the *balance of evidence* in reaching an opinion. This concept acknowledges the fact that the truth cannot be known with absolute certainty: did the defendant kill the victim if there are no eye witnesses and the defendant denies the killing? What we are asked to do is to imagine a balance scale where evidence for and against a hypothesis is weighed. Which way does the balance tilt? In this instance, it is in favour of *novel* drugs, with or without high-dose therapy and an autotransplant, improving outcomes of persons with IgD plasma cell myeloma. Can I prove it? No. Can the authors prove it? No. However, this typescript tilts the balance a bit further towards a benefit (Fig. 1).

Acknowledgements

R.P.G. acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme.

Disclosure Statement

R.P.G. is a part-time employee of Celgene Corp.

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