Dialysis-dependent renal failure at diagnosis continues to be associated with very poor outcome in multiple myeloma

We read with great interest the study by Pozzi *et al* (2013), using data collected from the Modena Cancer Registry from 1989 to 2009, that shows improvement in survival of multiple myeloma (MM) patients over time, especially after 2006. Although several studies have now shown improved overall survival (OS) for MM patients treated in the era of novel agents (bortezomib, lenalidomide, thalidomide), it is not yet clear if patients presenting with renal failure, severe enough to warrant dialysis at diagnosis, have also benefitted in terms of improved survival. We have calculated median OS for all patients diagnosed with MM at our centre over the preceding 18 years and also found improvement in median OS over time for both younger and older age groups. However, MM patients presenting with severe renal failure, requiring dialysis at diagnosis, continue to have a particularly poor prognosis.

262 patients (60·3% male) were diagnosed with MM at our centre between January 1995 and December 2012. We constructed Kaplan-Meier curves and used the Wilcoxon (Breslow) test to evaluate OS functions (diagnosed in three calendar periods: 1995–2000; 2001–2006; 2007–2012) for our total patient population as well as the subset of patients who required dialysis within 4 weeks of diagnostic bone marrow test. For all patients, median OS significantly increased, from 13·2 months during 1995–2000 to 27 months between 2001–2006 with median OS not yet reached throughout 2007–2012 ($P < 0·0001$) (Fig 1). In patients ≤70 years old, median OS significantly increased, from 25·4 months in 1995–2000 to 46·7 months throughout 2001–2006 with median OS not yet reached between 2007–2012 ($P = 0·0395$). Improved median OS was also seen in patients >70 years old: 4·4 months during 1995–2000, 17·4 months between 2001–2006 and 25·1 months throughout 2007–2012 ($P < 0·0001$).

In contrast, patients requiring dialysis within 4 weeks of diagnosis ($n = 44$) had much worse outcomes: median OS in the period 1995–2000 was 2·8 months and although there was some improvement in median OS during 2001–2006 measured at 11 months, there was a reversal in median OS to 6 months throughout 2007–2012 (Fig 2) (P value = 0·0538). At our centre, bortezomib in combination with high dose dexamethasone was first used as initial therapy for MM patients with severe renal impairment in 2007 and nine of the ten MM patients presenting with dialysis-dependent renal failure in between 2007 and 2012 received this regimen.

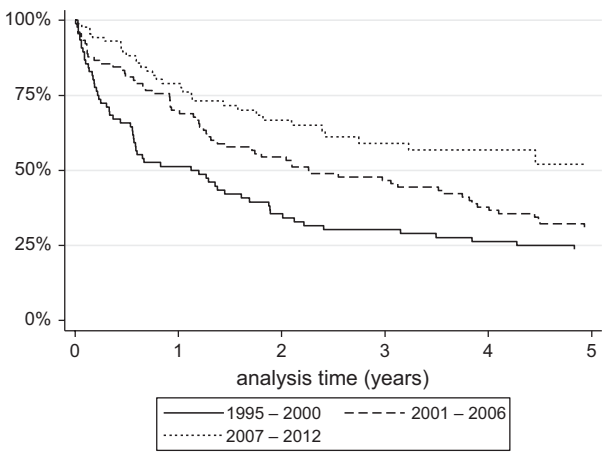

Fig 1. Overall Survival of all multiple myeloma patients for the periods 1995–2000, 2001–2006 and 2007–2012.

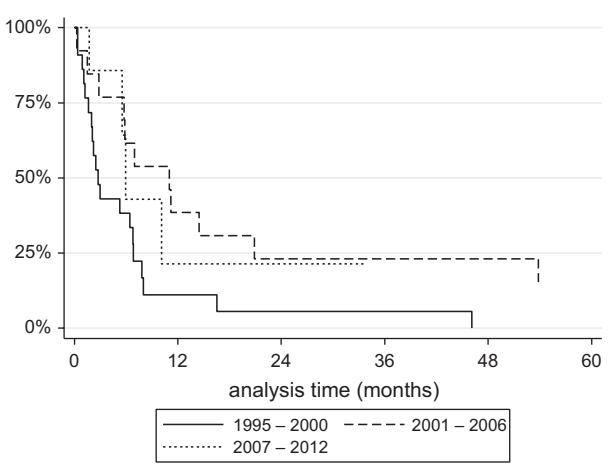

Fig 2. Overall Survival of multiple myeloma patients requiring dialysis at diagnosis for the periods 1995–2000, 2001–2006 and 2007–2012.

As our hospital is the national referral centre for both renal transplantation and neurosurgery in the Republic of Ireland, it is likely that our patient population has a higher percentage of poor prognostic, advanced cases, compared to the Modena Cancer Registry. Despite this, we have also seen marked improvements in OS over time for patients over 70 years old as well as for younger, autologous transplant

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eligible patients. However, we have also identified patients requiring dialysis at time of diagnosis as a subgroup with an especially poor prognosis. As anti-myeloma therapy for this subgroup did not substantially change between time periods 1995–2000 and 2001–2006, we suspect that the improvement in median OS in the period 2001–2006 probably reflects better supportive care. Although the numbers of patients in this subgroup over the three time periods is small, the lack of further improvement in median OS in the period 2007–2012 is noteworthy, given that all but one of the patients received bortezomib and high dose dexamethasone as first line therapy. These findings are disappointing, given previous evidence for the efficacy of bortezomib-based regimens in MM with renal impairment (Piro & Molica, 2011).

Our findings are similar to those of a recently published analysis from a single centre that examined the survival of MM patients presenting with severe renal impairment (serum creatinine >500 μmol/l) over a 20-year period (Haynes *et al*, 2010). In this study, a median OS of 10·2 months was observed, with those patients that remained dialysis-dependent having an even worse outcome (Haynes *et al*, 2010). Although the introduction of novel agents and high cut-off haemodialysis has been reported to improve the outcome of MM patients presenting with renal failure (Dimopoulos *et al*, 2009; Hutchison *et al*, 2009), a substantial number of patients do become permanently dialysis-dependent. Importantly, to date, MM patients with severe renal failure have been excluded from the majority of clinical trials of novel agents in MM. The results of the European Trial of Free Light Chain Removal by Extended Haemodialysis in Cast Nephropathy (EuLITE; NCT00700531) are eagerly awaited and will help guide future treatment.

In summary, our data suggest that MM patients presenting with dialysis-dependent renal failure continue to have a very poor outlook despite the improvements seen in the OS of MM patients as a whole. In our experience, although our numbers are small, the introduction of bortezomib as part of first line anti-MM therapy in this subgroup has not led to improved median OS. Achieving dialysis-independence may be a crucial factor in improving survival in this high-risk patient group and such patients should be treated aggressively at presentation.

Author contributions

Philip Murphy performed the research, designed the study and wrote the paper.Cherisse Baldeo performed the research. Patrick O'Kelly analysed the data. Jeremy Sargant, Patrick Thornton, Mary McCloy, Peter Conlon, Colm Magee, Mark Denton, and John Quinn designed the study and wrote the paper.

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References

Dimopoulos, M.A., Richardson, P.G., Schlag, R., Khuageva, N.K., Shpilberg, O., Kastritis, E., Kropff, M., Petrucci, M.T., Delforge, M., Alexeeva, J., Schots, R., Masszi, T., Mateos, M.V., Deraedt, W., Liu, K., Cakana, A., van de Velde, H. & San Miguel, J.F. (2009) VMP (Bortezomib, Melphalan and Prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *Journal of Clinical Oncology*, **27**, 6086–6093.

Haynes, R.J., Read, S., Collins, G.P., Darby, S.C. & Winearls, C.G. (2010) Presentation and survival of patients with severe acute kidney injury and multiple myeloma: a 20-year experience from a single centre. *Nephrology Dialysis Transplantation*, **25**, 419–426.

Hutchison, C.A., Bradwell, A.R., Cook, M., Basnayake, K., Basu, S., Harding, S., Hattersley, J., Evans, N.D., Chappel, M.J., Sampson, P., Foggensteiner, L., Adu, D. & Cockwell, P. (2009) Treatment of acute renal failure secondary to multiple myeloma with chemotherapy and extended high cut-off hemodialysis. *Clinical Journal of the American Society of Nephrology*, **4**, 745–754.

Piro, E. & Molica, S. (2011) A systematic review on the use of bortezomib in multiple myeloma patients with renal impairment: what is the published evidence? *Acta Haematologica*, **126**, 163–168.

Pozzi, S., Marcheselli, L., Bari, A., Liardo, E.V., Marcheselli, R., Luminari, S., Quaresima, M., Cirilli, C., Ferri, P., Federico, M. & Sacchi, S. (2013) Survival of multiple myeloma patients in the era of novel therapies confirms the improvement in patients younger than 75 years: a population-based analysis. *British Journal of Haematology*, **163**, 40–46.