Long-term outcomes in light chain deposition disease- analysis of a UK cohort

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Pure light chain deposition disease (LCDD) is a rare condition associated with a clonal plasma cell or monoclonal B-cell dyscrasia. Renal involvement is nearly universal. [1,2] The heart and the liver are the other extra-renal organs involved in the process. LCDD typically presents as a glomerular disorder with proteinuria. Other clinical manifestations may also be present depending on the extra-renal involvement. The systemic nature of the condition may be under-recognised- some case series have reported extra-renal involvement of < 10% [1,3] while others have reported extra-renal involvement in 30-35% of cases. [2,4]

Treatment strategies are aimed at suppressing the underlying clone and novel anti-myeloma therapy has vastly improved the outlook of this condition. [1,2,5] Studies show that haematologic response is a crucial determinant of outcome in LCDD.

We present the long-term outcome data of 77 LCDD (Table SA 1) patients seen at the UK National Amyloidosis Centre between 1999-2018 and define their clinical characteristics, treatments, and outcomes. Details of the investigations performed at diagnosis/follow-up and statistical methods are available in the supplementary appendix.

The median age at diagnosis was 59 years (range 26-81 years). All 77 patients had renal involvement at diagnosis. 54 patients (70.1%) had eGFR < 30 ml/min. 10 patients (13%) had proteinuria < 0.5 gm/24h. 11 (14.3%) and 10 (13%) patients had cardiac and liver involvement. Eight patients (10.4%) had ESRD and were on dialysis at diagnosis. None of the patients had evidence of concomitant amyloidosis. 4 patients (5.2%) had cast nephropathy on the renal biopsy. The median dFLC and bone marrow plasma cells were 450.8 mg/l (range 2.4-25690 mg/l) and 8% (range 1-70%). 12/77 (15.5%) patients had evidence of myeloma by the standard criteria.

The median treatment line was 1 (range 1-5, table SA2). 69/77 (89.6%) patients received 1st line treatment. Eight patients had ESRD at diagnosis and did not have extra-renal involvement or evidence of myeloma; therefore, they did not receive any treatment. Bortezomib (37.7%) based chemotherapy was the commonest regimen used in 1st line, followed by Thalidomide (24.6%) and alkylators (21.7%). Most patients diagnosed after 2011 received 1st line bortezomib. Patients received a median of 6 cycles (range 1-12).

The overall response rate (ORR, CR+VGPR+PR) to 1st, 2nd and 3rd lines of treatment was 75.3%, 69.6% and 40%, respectively (Table SA3 & 4). 53.5%, 47.9% & 10% of patients had achieved ≥ VGPR after 1st, 2nd, and 3rd line treatments, respectively. 18/69 (26.1%) and 10/69 (14.5%) patients had achieved dFLC < 10 mg/l and iFLC < 20 mg/l after 1st line, respectively. In 1st line, 77% of patients achieved ≥ VGPR after Bortezomib therapy. In the 2nd line, 55.6% of patients achieved ≥ VGPR after Bortezomib-based therapy.

The median OS of the entire cohort was 134 months (Figure SA1 Supplementary Appendix). Patients achieving ≥ VGPR after 1st line treatment had significantly better survival than those with < VGPR- median OS not reached vs 91 months, p=0.001 (Figure 1A). We also analysed the impact of dFLC (< 10 mg/l) & iFLC (iFLC < 20 mg/l) response in patients with ≥ VGPR (n=37) after 1st line treatment. There was no difference in survival between patients based on their dFLC or iFLC response (Figures SA2 & SA3). The presence of myeloma did not significantly impact OS (median OS 160 months vs 123 months, p=0.377).

The median time to dialysis (TTD) of the entire cohort was 62 months (Figure SA4, Supplementary Appendix). Patients with eGFR < 30 ml/min had a significantly

shorter TTD than those with eGFR > 30 ml/min- median TTD 19 months vs median not reached, p=0.002 (Figure 1B). Patients achieving ≥ VGPR after 1st line treatment had a significantly improved TTD- median TTD not reached vs 14 months, p=0.001 (Figure 1C). In patients with eGFR < 30 ml/min, patients with ≥ VGPR after 1st line had a significantly improved TTD than those with < VGPR- median TTD not reached vs 8 months, p< 0.005 (Figure 1D). We also analysed the impact of dFLC (<10 mg/l) and iFLC (< 20 mg/l) response on TTD in patients with ≥ VGPR. There was no significant difference in the TTD based on dFLC/iFLC response (Figures SA5 & SA6). Table SA5 shows the significant predictors of OS and TTD

Detailed organ response data is available in the supplementary appendix. Overall, the renal function improved or remained stable in 66.4% of patients and proteinuria improved or remained stable in 94.3% of patients. A significant proportion of patients with improved or stable serum creatinine had achieved ≥VGPR to 1st line therapy (84% vs 60%, p<0.005). There was an inverse correlation between proteinuria reduction and TTD that tended towards statistical significance (Pearson co-relation -0.289, p=0.083).

23/69 (33.3%) patients underwent an autologous stem cell transplant (ASCT). The median age at the time of ASCT was 50 years (range 29-69 years) and the median dFLC was 22 mg/l (range 2-2250 mg/l). 8/23 (34.8%) patients were in a CR at the time of ASCT. 12/23 (52.1%) had eGFR < 30 ml/min at the time of ASCT. 6/12 (50%) of these patients were already on dialysis at the time of ASCT. There were no transplant-related deaths. There were also no instances of renal failure during ASCT. Patients who received ASCT at diagnosis or as a consolidation procedure after 1st line had significantly superior survival compared to those who did not receive ASCT-

median OS not reached vs 107 months (95% CI 63.42-150.57 months, p=0.018) (Figure SA 7).

7/77 (9.1%) patients received a renal transplant. The median age at the time of renal transplant was 46 years (range 32-65 years). 6/7 (85.7%) patients were <60 years old at the time of the transplant. 5/7 (71.4%) patients were in CR at the time of the transplant. 5/7 (71.4%) patients had received an autologous stem cell transplant before the renal transplant. 1/7 (14.3%) patients received Bortezomib-based chemotherapy following the transplant. As of this analysis, 2/7 (28.6%) renal grafts had failed, and these patients started dialysis 8 and 22 months following the renal transplant (one failure due to recurrence, cause unknown in other). The true median graft survival was 35 months (range 8-137 months). The 1-year, 5-year, and 10-year graft survival were 86%, 70% and 70%, respectively.

This data from the largest UK cohort confirms that the haematologic response and degree of renal dysfunction at diagnosis are the critical determinants of outcomes (OS & TTD) in LCDD. Unlike systemic AL amyloidosis, deep light chain response (dFLC < 10 mg/l or iFLC < 20 mg/l) did not significantly improve outcomes.

Renal disease in monoclonal immunoglobulin deposition disease is heterogeneous and may present as a slowly progressive chronic kidney disease without much proteinuria. [2] 13% of patients in the present cohort had proteinuria < 0.5 gm/24h. Therefore, a high index of suspicion is needed to identify cases early, particularly as early treatment can vastly improve outcomes.

1/3rd of the present cohort underwent an autologous stem cell transplant with no transplant-related mortality or renal failure. Also, the survival of patients who received a stem cell transplant was significantly better than those who did not

receive the procedure. The patients who received the stem cell transplant were younger and may have been in a better functional state; therefore, a selection bias cannot be ruled out. Nevertheless, these data show that autologous stem cell transplant is a valuable arsenal in our armamentarium. Given the high rates of haematologic response with novel agents, the role of autologous stem cell transplant needs further clarification in prospective studies.

A previous study has suggested that renal allograft survival is significantly reduced in patients with LCDD. [6] The present data suggests renal transplant is a viable option in patients with a deep haematologic response and is consistent with the data published by Joly et al. [2]

The present data is different from previously published studies in the extent of extra-renal involvement. [1-4] The incidence of cardiac involvement in the present cohort is significantly lower than in some previous studies. [2,4] The nature of the underlying clone is a possible explanation for the discrepancy between the previous reports and the present data (the median dFLC was much higher in these cohorts than in the present cohort).

There are many limitations to the present study. It is retrospective; patients were diagnosed and treated over 20 years with disparate regimens. As patients had their diagnostic bone marrow performed at their local centres, we do not have the bone marrow clonal burden and cytogenetic profile of all patients. We also do not have the data on dose intensity, toxicity, progression free survival (PFS) and transplant-related morbidity of the patients in this cohort. We acknowledge these limitations of our study.

In conclusion, LCDD is a rare chronic glomerulopathy presenting with advanced renal dysfunction in most instances. Early diagnosis is key to improving outcomes. Haematologic response is a crucial determinant of outcomes, even in patients with advanced renal dysfunction. ASCT and renal transplants are valuable arrows in our quiver and should be considered in appropriately selected patients.

Authorship declaration

SR collected/analysed the data and wrote the manuscript.

SL, SM, BW, DF, MF, AMN, CW, PNH, JDG, and HJL reviewed and approved the final manuscript.

ADW supervised the study, reviewed, and approved the final manuscript.

Conflict of Interest declaration

Prof. Wechalekar has received honoraria from Janssen, GSK, Celgene, and Takeda. The other authors do not have any conflict of interest to disclose.

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Figure Legends

Figure 1A: Kaplan-Meier curve showing the impact of haematologic response (≥ VGPR vs < VGPR) on overall survival. Patients who achieved ≥ VGPR after 1st line treatment had significantly improved survival- median OS not reached vs 91 months (95% CI 61.41-120.58 months), p=0.001. 100%, 100%, 93%, and 59% of patients with ≥ VGPR after the 1st line were alive at the end of 1, 2, 5, & 10 years from diagnosis.

Figure 1B: Kaplan-Meier curve showing the impact of renal function at diagnosis on time to dialysis (TTD). Patients with eGFR< 30 ml/min have a significantly poorer TTD than those with eGFR > 30 ml/min- median TTD 19 months (95% CI 0-42.20 months) vs median not reached, p=0.002 (Figure 1B). 100%, 100%, 83%, and 58% of patients with eGFR > 30 ml/min at diagnosis had not required dialysis at the end of 1, 2, 5 and 10 years.

Figure 1C: Kaplan-Meier curve showing the impact of haematologic response (≥ VGPR vs < VGPR) on time to dialysis (TTD). Patients who achieved ≥ VGPR after 1st line treatment had significantly improved dialysis-free survival- median TTD not reached vs 14 months (95% CI 0-30.24 months), p=0.001. 84%, 84%, 68%, and 59% of patients with ≥ VGPR after 1st line treatment had not required dialysis at the ned of 1, 2, 5, & 10 years from diagnosis.

Figure 1D: Kaplan-Meier curve showing the impact of haematologic response (≥ VGPR vs < VGPR) on time to dialysis (TTD) in patients with advanced (eGFR < 30 ml/min) renal dysfunction at diagnosis. Haematologic response after 1st line was a significant predictor of TTD in patients with eGFR < 30 ml/min at diagnosis. Patients with ≥VGPR after 1st line had a significantly better TTD- median TTD not reached vs 8 months (95% CI 4.38-11.61 months), p< 0.005. 76%, 76%, 61% and 61% of

patients with eGFR < 30 ml/min at diagnosis and ≥VGPR after 1st line treatment had not required dialysis at the end of 1, 2, 5 & 10 years, respectively.

Figure 1A

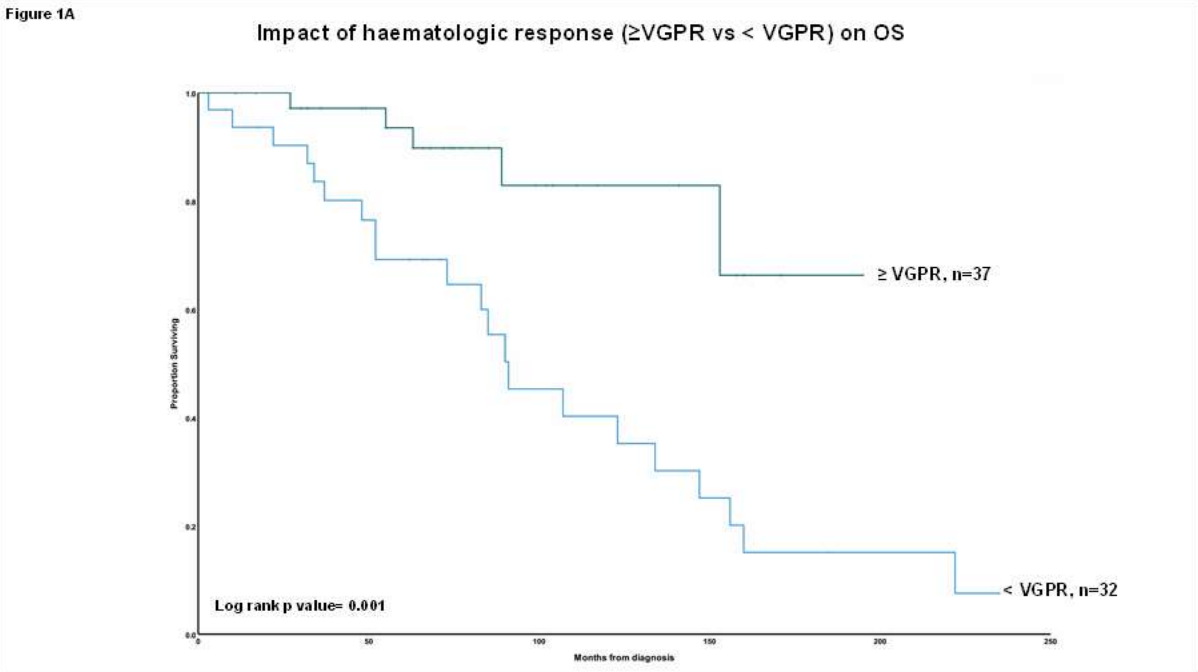

Figure 1B

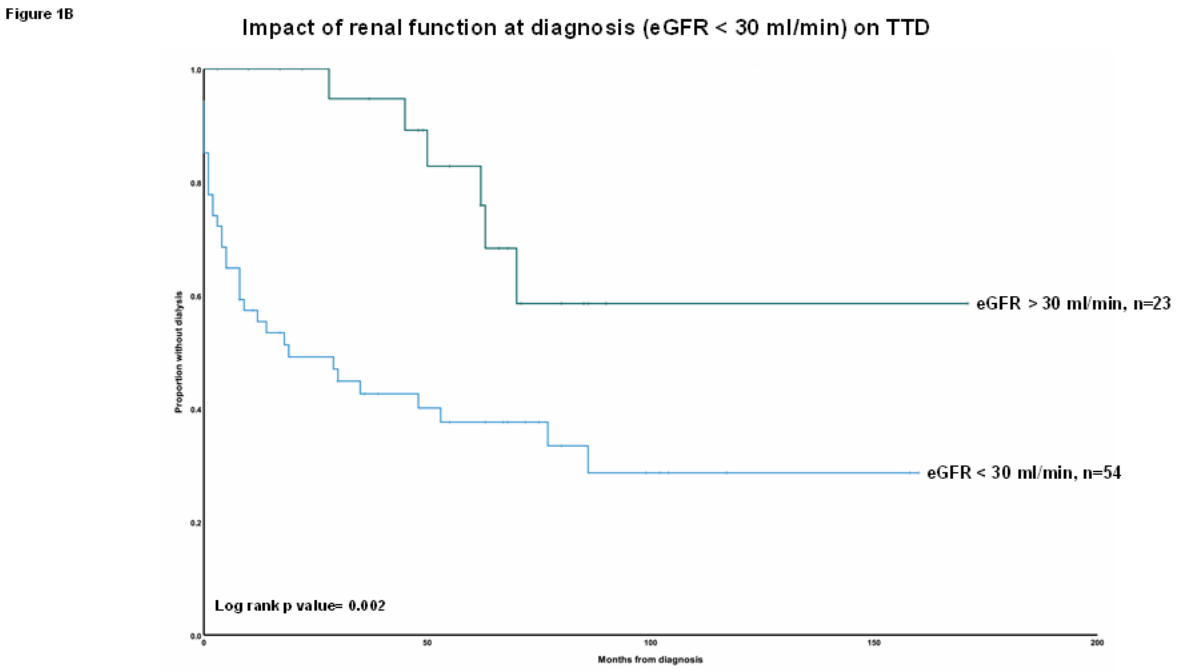

Figure 1C

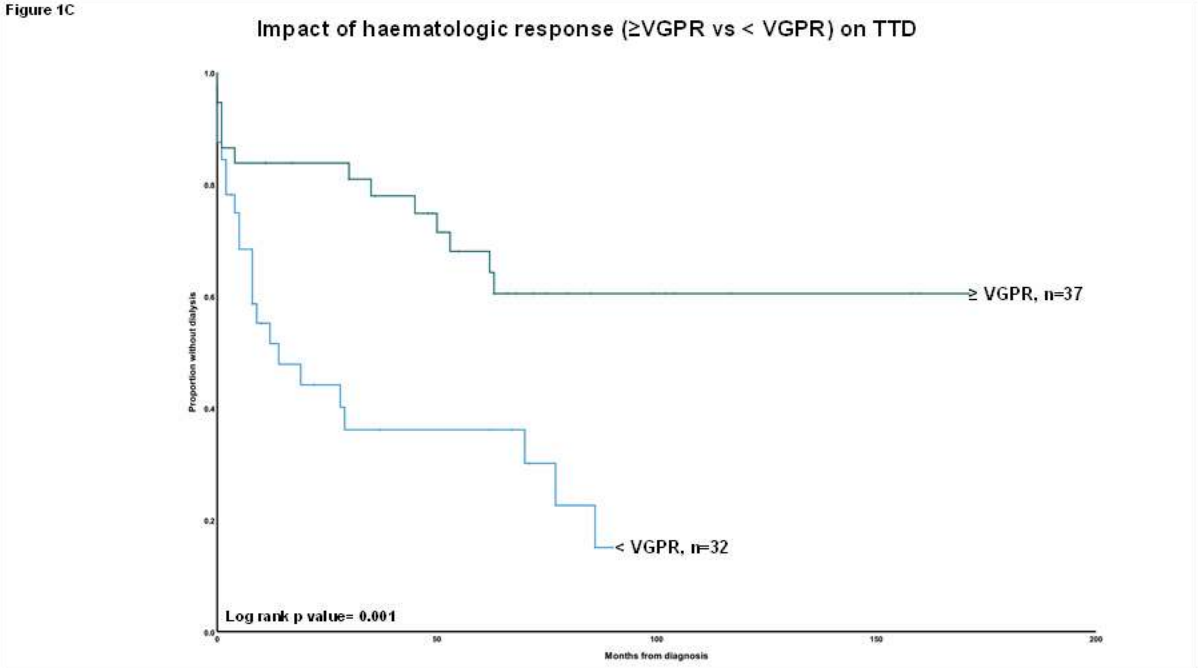

Figure 1D