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Treatment outcomes of multiple myeloma in patients requiring renal replacement therapy

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ABSTRACT

Introduction: Renal impairment is a recognised complication of multiple myeloma (MM). Bortezomib and dexamethasone are used as first line therapy but are associated with important side effects.

Objectives: We investigated outcomes of patients with MM requiring renal replacement therapy (RRT), assessed renal and haematological responses, and compared effects of different chemotherapy regimens.

Patients and Methods: Retrospective study of 67 patients with MM with associated renal impairment managed at our centre from 2007–2017. Approximately 29 patients required RRT and were included in the final analysis.

Results: Bortezomib was administered to treat 65.5% patients; overall response rate was 84.2% (complete 21.1%, partial 63.1%). The remaining patients were treated with other agents; of these 50% responded to therapy, all with partial response. Bortezomib was associated with improved survival ($P=0.02$), however a higher proportion of patients experienced side effects ($P=0.02$). Of the patients who received bortezomib, 47% came off RRT, compared to 10% of patients who did not ($P=0.04$). Independence from RRT had the best association with survival ($P=0.07$). Patients who came off RRT had significant reduction in serum free light chains after two cycles of chemotherapy; those remaining dialysis-dependent showed variable changes in free light chain levels ($P=0.02$).

Conclusion: Bortezomib treatment resulted in a significant improvement in survival, albeit with more side effects. Gaining independence from RRT was associated with better patient survival. A greater degree of reduction of free light chains corresponded to an increased likelihood of being independent of dialysis; this could be used as a marker for renal recovery and overall prognosis.

Original

Implication for health policy/practice/research/medical education:
Current treatment regimens for multiple myeloma include bortezomib and dexamethasone. These regimens, although effective, are associated with side effects. We reviewed the outcomes of treatment of patients with multiple myeloma requiring renal replacement therapy in our centre. Our study highlights that bortezomib therapy is associated with improved renal and mortality outcomes, with greater chance of gaining dialysis independence compared to regimens including thalidomide or conventional chemotherapy alone. However, it is associated with significant side effects. Better light chain response to chemotherapy is a potential marker for recovery of renal function and overall improved prognosis in patients with multiple myeloma and renal impairment. We found bortezomib is associated with more favourable renal and mortality outcomes in patients with renal failure needing renal replacement therapy. However, the drug's side effect profile adds to clinical morbidity. A greater degree of reduction of light chains corresponds to an increased likelihood of being independent of dialysis. This reinforces the importance of timely and prompt treatment of multiple myeloma, as renal failure, particularly dialysis dependence, is associated with a higher mortality.

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Introduction

Renal impairment is a recognised complication of multiple myeloma (MM) and can range from acute kidney injury (AKI) to end-stage renal failure (1). The incidence of renal impairment at diagnosis of myeloma is between 20% to 50% (1); of these patients, approximately 10% present with severe AKI requiring dialysis (2). This is usually due to myeloma cast nephropathy as a result of the toxic effects of the light chain component of the immunoglobulin paraproteins (1,2).There are other factors which contribute to the development of renal injury in MM including hypercalcaemia, dehydration and nephrotoxic drugs, all of which can exacerbate the toxic effect of light chains (1).

The use of novel chemotherapeutic agents has led to quicker disease response and a considerable increase in the survival of MM patients who experience renal injury (1). Treatment regimens including the proteasome inhibitor bortezomib and dexamethasone are now commonly used as first line therapy in such patients. These regimens have improved the overall prognosis of these patients, and successful therapy can also result in partial or full recovery of renal function. These novel agents, although effective, are associated with side effects such as infection, cytopenia, peripheral neuropathy and thrombosis (1).

With previous 'conventional' chemotherapy for MM such as melphalan and prednisolone, renal injury was associated with a median survival time of approximately two years (1). Furthermore, the median overall survival for MM patients with dialysis-dependent end-stage renal failure was less than one year (3). This is in contrast to other randomised controlled trials evaluating bisphosphonate and thalidomide-based chemotherapy regimens, where overall survival was over four years (4,5). Although promising, there remains significant morbidity and early mortality in patients requiring ongoing renal replacement therapy (RRT). Renal impairment is also associated with an increased risk of treatment associated toxicity and premature death (6).

Objectives

Although renal impairment is a recognised consequence of MM, there are few studies reporting the outcomes of patients who require RRT, and these patients are often excluded from trials. In this study, we investigated the outcomes of patients with MM and associated renal impairment requiring RRT from 2007-2017 within our renal centre at St Helier Hospital. Within our patient cohort, 650 patients are established on haemodialysis and 150 patients are established on peritoneal dialysis.

We assessed the renal and haematological responses in patients undergoing chemotherapy and identified factors which necessitated initiating RRT. We also analysed the side effects the patients experienced whilst undergoing treatment, which also significantly contributes to morbidity. The timeframe of our study coincided with the introduction of bortezomib as first-line treatment for MM in 2010, and we evaluated the impact this had on renal recovery and overall prognosis for our patient cohort.

Patients and Methods

Study design

Patients diagnosed with MM with associated renal impairment at St. Helier Hospital between January 2007 to December 2017 were identified within our electronic database. Patients who required RRT (including haemodialysis, filtration or peritoneal dialysis) either at presentation or after diagnosis of myeloma were included in the final analysis. Patients diagnosed with MM with normal renal function, impaired renal function but not requiring RRT, and those diagnosed outside the specified timeframe were excluded. Data including demographics, renal function, renal biopsy results, duration of dialysis, type of myeloma, chemotherapy regimens, associated complications, response to treatment and survival rates were obtained from electronic patient records. As this was a retrospective review of our clinical practice rather than clinical research, individual patient consent was not obtained.

Time to dialysis independence was measured from the date of initiation of chemotherapy to the date when dialysis was discontinued due to recovery of renal function. Patient survival was measured from date of diagnosis of MM until date of death, or endpoint of our analysis (August 2018).

Statistical analysis

Statistical analysis including bar charts, Kaplan Meier plots, log-rank and chi-square test were performed using IBM SPSS software version 27 and Microsoft Excel software. *P* values <0.05 were considered to be statistically significant.

Results

Baseline characteristics

We identified 67 patients with renal impairment secondary to myeloma who were either reviewed in renal clinics or required hospital admission at St Helier Hospital between 2007-2017. Of these, 29 patients required RRT and were included in our final analysis. Their demographics and clinical characteristics are outlined in Table 1. The cohort was followed for a median time of 39 months (range one month–100 months).

Median age at diagnosis was 64 years with a male-to-female ratio of 1.4:1. The types of MM diagnosed included kappa light chain (34.5%, n = 10), lambda light chain (44.8%, n = 13), myeloma associated with AL amyloidosis (17.2%, n = 5) and oligo-secretory (3.5%, n = 1). Lytic bone disease was present in 14 out of 29 (48.3%) patients. Out of 29 patients, 11 (37.9%) died during the study period with a median time of 17 months from diagnosis of myeloma (range 1 month–100 months). Causes of death included disease progression (45.4%, n = 5), sepsis, (27.3%, n = 3), complications following fractured neck of femur repair

Table 1. Demographics of patients with MM requiring RRT at our centre from 2007-2017

Demographic	Number of patients (N = 29)
Age (y)	
Median	64
Range	45-86
Gender, No. (%)	
Male	17 (58)
Female	12 (41)
Ethnicity	
Caucasian	21 (72)
Black African/Caribbean	6 (21)
Asian	2 (7)
Type of myeloma diagnosed	
Kappa light chain	10 (35)
Lambda light chain	13 (45)
AL amyloid	5 (17)
Oligo-secretory	1 (3)
Serum free light chains (Kappa) in mg/L	
Median	1210
Range	474-12,900
Serum free light chains (Lambda) in mg/L	
Median	1620
Range	152-17,400
Bence Jones proteins (%)	
Present	34
Absent	66
Haemoglobin (g/dL)	
Median	105
Range	61-157
Creatinine on starting RRT (µmol/L)	
Median	539
Range	235-1352
Albumin at start of RRT (g/L)	
Median	30
Range	16-47
Corrected calcium on starting RRT (mEq/L)	
Median	2.41
Range	1.96-3.41

(9.09%, n = 1), small bowel obstruction (9.09%, n = 1) and cerebrovascular accident (9.09%, n=n = 1).

Renal replacement therapy

All patients within this cohort required RRT. Of these, 58.6% (n = 17) required dialysis at presentation, 24.14% (n = 7) started RRT within a year of diagnosis and 17.2% (n = 5) started RRT more than 12 months after the diagnosis of myeloma. For those patients who started RRT after diagnosis of myeloma, the time interval between myeloma diagnosis and commencement of RRT ranged from 30-3650 days (median of 456 days).

Additional factors which contributed to a need to commence RRT included infection (20.7%, n = 6 [5/6 = 83.3% at presentation of myeloma diagnosis]), hypercalcaemia (17.2, n = 5, all at presentation of myeloma diagnosis) and fluid overload (10.34%, n=3, all during follow up after myeloma diagnosis). Median creatinine at the start of RRT was 550 µmol/L (range 235-1372 µmol/L).

The majority of patients (96.6%) were established on haemodialysis, with 1/29 patient (3.4%) established on peritoneal dialysis. No patients underwent plasma exchange.

In total, 14 patients underwent renal biopsy which identified: cast nephropathy (50%, n = 7), amyloidosis (42.9%, n = 6) and light chain deposition disease (7.1%, n = 1).

Did patients gain independence from RRT?

Ten patients (34.5%) became independent of RRT with a median time to dialysis independence of 28 days (confidence interval 1.66–54.34) as shown in Figure 1. Of these patients, 2 gained complete renal remission (best estimated glomerular filtration rate [eGFR] >60 mL/min/1.73 m^2), five patients gained partial renal remission (best eGFR 30-59 mL/min/1.73 m^2, and one patient gained minimal renal remission (best eGFR 15-29 mL/min/1.73 m^2, as defined by the International Myeloma Working Group (1). The remaining 2 patients had best eGFR <15 mL/min/1.73 m^2 but had recovered urine output and did not require ongoing RRT. By the endpoint of our study (August 2018), the median eGFR of patients who gained independence from RRT was 42 mL/min (range 12–78 mL/min/1.73 m^2. These patients were defined as having stable or improving kidney function for at least four weeks after stopping dialysis.

We assessed whether there was a relationship between

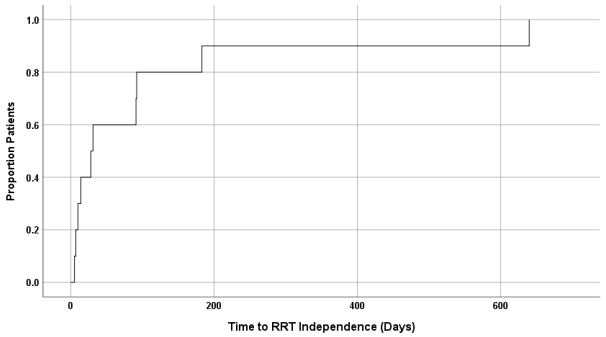

Figure 1. Kaplan Meier plot depicting time to RRT independence in those patients who recovered enough renal function to come off dialysis. Overall, 34.48% (n=10) of the patients became independent of RRT with a median time to dialysis independence of 28 days (confidence interval 1.66 – 54.34).

the likelihood of gaining independence from RRT, and whether RRT was started at the same time as the diagnosis was made, or started a while after the diagnosis of myeloma. This is illustrated in Figure 2. Of the patients who required dialysis at presentation of myeloma diagnosis, 47.1% subsequently became independent of dialysis; by contrast, only 16.7% of patients who required dialysis following diagnosis of myeloma became independent of dialysis (chi-square test, P = 0.09).

Dialysis dependence and survival

Figure 3 shows the relationship between dialysis dependence and mortality. It demonstrates that recovery of renal function and the consequent independence from RRT was associated with better patient survival (log rank $P = 0.03$).

By Cox-Regression analysis, independence from RRT appeared to have the best association with survival ($P = 0.07$), in comparison with other variables including age ($P = 0.83$), gender ($P = 0.74$), albumin ($P = 0.10$), creatinine ($P = 0.95$) and corrected calcium ($P = 0.29$); however, we note this is not statistically significant.

Chemotherapy, renal recovery and patient survival

All patients within our cohort received chemotherapy. Bortezomib was used as part of first-line chemotherapy for 19 patients (65.5%). Meanwhile, 10 patients (34.5%) did not have bortezomib as part of initial chemotherapy (as this was before it came into use as first line treatment in 2010) and were instead treated with other agents including thalidomide and melphalan.

Figure 4 highlights the treatment response of these patients to chemotherapy. Overall, there was a better response rate in terms of complete and partial response to chemotherapy with bortezomib as first line therapy when compared with the group who did not receive bortezomib as initial therapy. The difference was not statistically significant however, when calculated with the chi-square test ($P = 0.05$).

Figure 5 depicts the main side effects the patients experienced with their therapy regimens. A greater percentage of patients who received bortezomib as initial

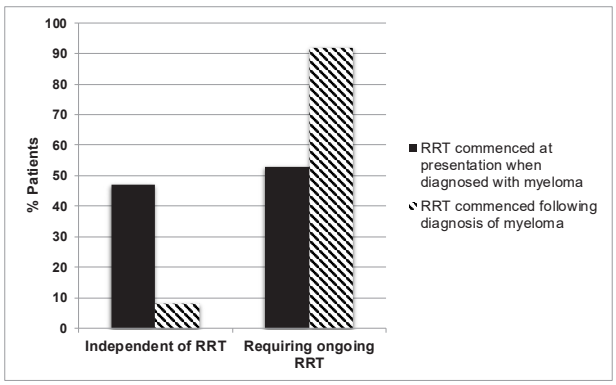

Figure 2. Graph assessing relationship between commencing RRT and subsequent dialysis independence or ongoing dependence. 47.06% of patients who required dialysis at presentation of myeloma diagnosis subsequently became independent of dialysis, compared to 16.67% of patients who required dialysis following diagnosis of myeloma (Chi-square test, P = 0.09).

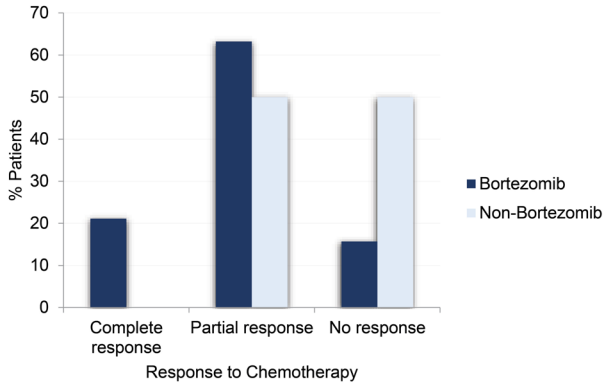

Figure 4. Graph comparing responses of patients to bortezomib or non-bortezomib chemotherapy. Overall response rate was 84.21% in patients who received bortezomib (complete 21.05%, partial 63.16%). By contrast, 50% of patients who were treated with other agents responded to therapy, all with partial response (Chi-square test, P = 0.05).

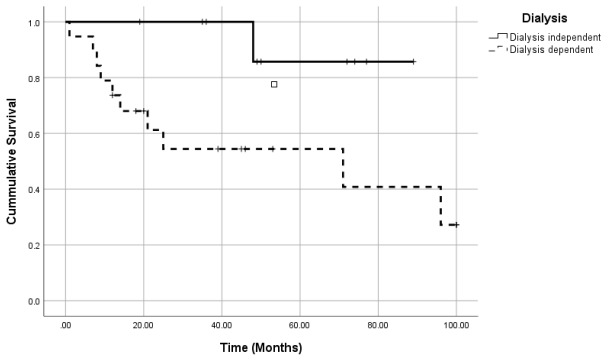

Figure 3. Kaplan Meier plot assessing relationship between mortality and independence or continued dependence on RRT (Log rank, P = 0.03).

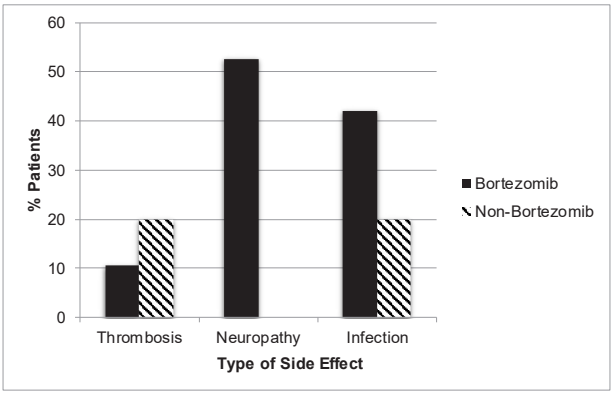

Figure 5. Graph comparing side effects of bortezomib or non-bortezomib chemotherapy (Chi-square test, P = 0.02).

therapy experienced side effects including thrombosis, peripheral neuropathy, and infection requiring hospital admission, compared to patients who did not receive bortezomib. This was statistically significant using the chi-square test ($P=0.02$).

In total, 47.4% of patients who received bortezomib as initial therapy recovered enough renal function to cease RRT compared to only 10% of patients who did not have bortezomib as part of their initial chemotherapy regimen (Chi-square test, $P=0.04$). Patients who became independent of dialysis had a significant reduction of free light chains following two cycles of chemotherapy (median 85%, range 61%-99%). Those who remained dialysis-dependent by contrast had quite a variable change in free light chains, ranging from -99% to +63 %. This is shown in Figure 6, where $P=0.02$ by Pearson's correlation.

Autologous stem cell transplantation was performed in 5/29 patients (17.2%). Three of these patients presented with AKI requiring RRT; they were commenced on bortezomib as first line chemotherapy and recovered sufficient renal function to become independent of RRT. The remaining two patients were not initiated on bortezomib therapy (instead treated with cyclophosphamide, thalidomide, and dexamethasone). Both patients did not require RRT at presentation, but unfortunately relapsed following stem cell transplant. They were both subsequently treated with bortezomib, however their renal function deteriorated with disease progression, necessitating establishment on RRT. All patients who received a stem cell transplant were still alive at the endpoint of this study (August 2018).

Overall, administering bortezomib as first-line chemotherapy resulted in improved survival of patients compared to those who did not receive bortezomib as first line therapy; this is shown in Figure 7, where by the Log rank test, $P = 0.02$.

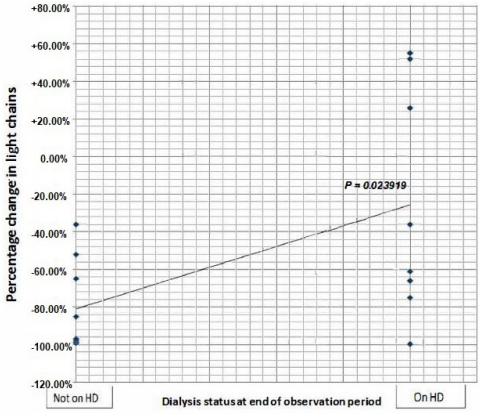

Figure 6. Graph showing relationship between % change in light chains after two cycles of chemotherapy and state of dialysis dependence, (by Pearson's correlation, $P = 0.02$).

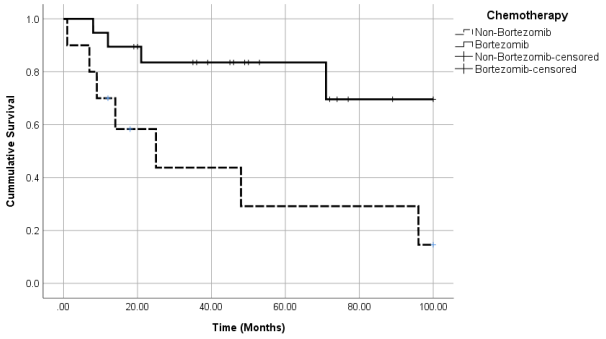

Figure 7. Kaplan-Meier plot assessing relationship between type of chemotherapy and patient survival (Log rank, $P = 0.02$).

Discussion

Advances in therapies for MM have improved the prognosis and the quality of life of patients. The time frame of our study coincides with the introduction of bortezomib as first-line treatment for MM in 2010. Previous studies have demonstrated that bortezomib has improved treatment response rates, including dialysis independence in patients with MM (1,7). The rapid reduction in tumour load together with bortezomib's non-renal metabolism has resulted in it being the mainstay of MM therapy, particularly in those with myeloma-related renal injury (1,7).

Response to chemotherapy has shown to be one of the main determinants of patient survival in MM (1,8). In our cohort, bortezomib resulted in a significant improvement in renal recovery and survival compared to those who did not receive bortezomib as first line therapy, which is in concordance with the literature. Furthermore, recovery of renal function and gaining independence from RRT was associated with better mortality. Our data therefore supports the International Myeloma Working Group recommendation for a bortezomib-based regimen as the most desirable therapy for MM patients with acute renal injury (1,9). In our study, independence from RRT had the best association with patient survival, in comparison with other variables including age, gender, albumin, creatinine and corrected calcium, confirming the relationship between recovery of renal function and reduced mortality.

We found that patients who became independent of dialysis had a significant reduction of free light chains following two cycles of chemotherapy (median 85%, range 61%-99%). Those who were still dialysis-dependent had greater variation in change in free light chains, ranging from -99% to +63%. This is similar to findings in a study by Rezk et al, which demonstrated in patients with renal amyloidosis, that the speed and magnitude of clonal response in patients presenting with a low GFR directly influences overall survival and dialysis duration (10). Our study also shows that a greater degree of reduction of light chains corresponds to an increased likelihood of being independent of dialysis, which is corroborated in other studies from other units (11,12). This reinforces the importance of timely and prompt treatment of MM,

as renal failure, particularly dialysis dependence, is associated with a higher mortality (13).

Although therapies such as bortezomib for the treatment of MM have had significant effects on patient survival and treatment response rate (14), they can be associated with a high side effect profile. Our study showed that there was a statistically significant increase in side effects of bortezomib when compared to non-bortezomib regimens. These side effects included thrombosis, neuropathy, and bacterial infections requiring hospital admission as shown in Figure 5. The bacterial infections constitute a serious adverse event, grade 3. In this respect, our data highlights a significant burden and risk of side effects with bortezomib therapy. We sought to compare this to what has been previously reported in the literature.

San-Miguel et al (15) outlined the findings of the APEX study, whereby patients were randomised (1:1) to receive either bortezomib or dexamethasone. Bortezomib was found to be effective in patients with renal impairment, with response rates similar across all the sub-groups of patients with varying degrees of renal function. We found 17/329 who received bortezomib had a creatinine clearance (CrCl)<30 mL/min. In these patients, common side effects of therapy included diarrhoea (71%), nausea (65%) and constipation (47%). Over half (53%) of patients experienced pyrexia, however none of the patients developed associated grade 3 adverse effects of sepsis including neutropenia, and hospital admission for intravenous antibiotics. Only 6% patients had peripheral neuropathy (in comparison to 52.6% in our study), and none of the patients experienced thrombosis. Of note in the APEX study, patients were required to have calculated CrCl >20 mL/min; as the patients in our study all required RRT, they all had CrCl <20 mL/min during the course of their disease.

Chanan-Khan et al (16) performed a retrospective study assessing outcomes of 24 patients diagnosed with MM, treated with bortezomib who had renal failure requiring dialysis at the time of bortezomib treatment. They concluded that the overall response rate of bortezomib-based treatments was comparable to MM patients with primarily normal renal function. Adverse events were experienced by 75% of patients including neuropathic pain (6%), infection (11%) and thrombocytopenia (39%). The main serious adverse event was noted to be progressive disease (33%). The only serious adverse events linked to treatment were neuropathic pain (6%) and peripheral neuropathy (6%). They described toxicities as manageable and similar to those seen in patients with relapsed and/or refractory MM in the phase 2 SUMMIT (17) and CREST (18) trials.

Zannetti et al (19) performed a retrospective study evaluating the outcomes of 21 newly diagnosed MM patients with severe renal impairment due to myeloma kidney, who were primarily treated with bortezomib-based therapy with high cut-off haemodialysis. In their study, 67% of patients had CKD stage 5 or required RRT. They showed that the overall renal response rate was 57%, with 76% of patients gaining independence from RRT. They found that the bortezomib therapy was well-tolerated; the most frequent adverse event was peripheral neuropathy grade 1-2 in 57% of patients, and grade 3 in 9% of patients. Haematological toxicity was rare, with only one patient developing neutropenia grade 4 and thrombocytopenia grade 3. No episodes of severe sepsis requiring hospital admission were recorded.

There are studies which suggest that a greater proportion of side effects are seen in patients with renal impairment. Jagannath et al (20) assessed outcomes of bortezomib in recurrent and/or refractory MM. They concluded that renal function did not impact on response rates to bortezomib but did note a trend towards an increased rate of serious adverse events including thrombocytopenia, neutropenia, and peripheral neuropathy with decreasing renal function. Kaygusuz et al (21) also reported similar findings with overall response rates comparable between patients with normal renal function and renal impairment but those with reduced renal function having more adverse events. However, both studies did not study patients who required RRT.

A unique finding from our study was the high bacterial infection rate requiring hospital admission in the bortezomib-treated group. The high bacterial infection rate was surprising to us, as bortezomib tends to be associated with increased viral infection/reactivation of latent viruses. We wonder whether the high dose of dexamethasone given with the bortezomib, and the patients' underlying renal impairment could have been contributory factors. Therefore, although mortality outcomes associated with bortezomib are more favourable compared to non-bortezomib regimens, there is still a relatively high morbidity associated with this treatment.

Conclusion

Our study is in keeping with others which show that bortezomib chemotherapy appears to be associated with more favourable renal and survival outcomes (22). We found that better light chain response to chemotherapy is a potential marker for recovery of renal function and overall improved prognosis in patients with MM and renal impairment.

However, we feel that it is important to emphasize that bortezomib therapy in the dialysis requiring patient is also associated with significant side effects, which in turn can have a negative impact on patient morbidity and quality of life.

Due to the paucity of clinical trials conducted in patients with MM and end-stage renal failure requiring dialysis, there remains limited understanding of factors which contribute to renal recovery. Patients with severe AKI requiring RRT have often been excluded from randomised controlled trials when studying the effects of

chemotherapy on renal or survival outcomes and further studies are required in this area. Our study provides further insight into this group of patients, particularly with regard to the potential toxicity of the commonly used first line treatment regimen in dialysis-dependent patients.

Limitations of the study

We acknowledge that due to the small sample size, our study is underpowered to truly show whether there is a relationship between haematological outcomes and a chemotherapy regimen.

Authors' contribution

Conceptualization: Aruni Ratnayake, Mukunthan Srikantharajah, Simon Stern, David Makanjuola.
Data curation: Aruni Ratnayake, Mukunthan Srikantharajah.
Formal analysis: Aruni Ratnayake.
Methodology: Aruni Ratnayake, Mukunthan Srikantharajah, Simon Stern, David Makanjuola.
Supervision: Simon Stern, David Makanjuola.
Validation: Aruni Ratnayake.
Writing–original draft: Aruni Ratnayake, Mukunthan Srikantharajah.
Writing–review and editing: Simon Stern, David Makanjuola.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was a retrospective review of our data assessing service evaluation in our centre. As outlined by the NHS Health Research Authority, service evaluation does not require ethical approval as it is not deemed to be research. Meanwhile, informed written consent was obtained from all participants during their admission in the hospital or for MM drug therapy. Nonetheless, other ethical issues (including plagiarism, data fabrication, double publication) have been taken into consideration and the authors can confirm that none of these are a part of this article.

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