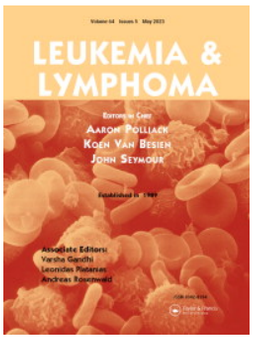

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ABSTRACT

High dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT) remains the standard consolidation in transplant eligible multiple myeloma (MM) patients. The timing between HDM administration and hematopoietic stem cell return (HSCR) varies among institutions, with a 'rest period' of 48 hours (h) employed by some for patients with renal impairment (RI). We investigated the differences in hematopoietic recovery and HDM toxicity between MM patients with RI who had HSCR after 24 vs 48 h from HDM. Fifty MM patients with RI (48 h group; $n = 31$ and 24 h group; $n = 19$) were included. No statistically significant differences were noted in surrogates for hematopoietic recovery and HDM toxicity between both groups. Only one death occurred in the 24 h group. No patients required renal replacement therapy. Therefore, a 24 h period between HDM and AHSC infusion appears safe for MM patients with RI.

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Multiple myeloma; renal impairment; autologous stem cell transplantation

Introduction

Patients with multiple myeloma (MM) constitute about 2% of all cancer cases in the UK, with approximately 6,000 new diagnoses annually. Age specific incidence rates rises sharply between 60 and 64 years, to peak in the 85–89 age group [1]. Renal impairment (RI) is one of the diagnostic criteria of MM ('R' in the 'CRAB' criteria), affecting nearly half of patients with MM at some stage of their disease [2], and is primarily secondary to cast nephropathy and hypercalcaemia [3].

Consolidative autologous stem cell transplantation (ASCT), incorporating high dose melphalan (HDM) for conditioning, is the standard of care for transplant eligible MM patients [4]. The time between hematopoietic stem cell return (HSCR) and high dose melphalan (HDM) administration is not standardized with variation between institutions [5–8]. Published data about the effect of these differences is sparse and contradicting [9–11], with no data focusing on patients with renal impairment.

Melphalan, L-phenylalanine mustard (L-PAM) or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard with a bifunctional alkylating activity that was initially discovered in 1959 [12]. It exerts its cytotoxic effect through covalent DNA cross-linkage and interference with polymerases. In addition, melphalan reduces the level of IL-6 which is crucial to the survival and proliferation of malignant plasma cells and elicits an inflammatory milieu that aids immune mediated killing of neoplastic cells [13].

In terms of pharmacokinetics, melphalan is highly bound to plasma proteins (40–60% to albumin and 20% to α1-acid glycoprotein) [14], has a volume of distribution of 0.66 L/kg, a distribution half-life of 5–15 min, and an elimination half-life of 17–75 min, and is mainly eliminated through spontaneous hydrolysis to its mono- and dihydroxy- metabolites [15–17]. Renal handling of melphalan plays a negligible role in its clearance and include both active renal tubular secretion, possibly by a pathway responsible for the active transport of some of the dietary amino acids,

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as well as reabsorption [18]. Nevertheless, despite the minimal difference in melphalan clearance following intravenous administration in patients with RI as compared to those with normal renal function [19,20], a higher mortality and non-haematological toxicity was reported in the former group [21–24]. Furthermore, El Fakih et al. reported more non-haematological toxicities in dialysis-dependant patients receiving melphalan at a dose of 200 mg/m^2 as compared to those receiving lower doses (180 and 140 mg/m^2) [25]. As such, dose modifications are usually instated based on the patient's eGFR. Similarly, a 'rest period' has been incorporated in the ASCT protocol of some institutions to limit possible HSC toxicity.

We investigated the differences in clinical outcomes, related to resource utilization and patient safety in MM patients with RI, defined as those with an estimated glomerular filtration rate (eGFR) of < 60 ml/min, who had HSCR after 24 hours (h) *vs* 48 h from HDM administration.

Subjects and methods

In our institution, the time between HDM administration and HSCR was reduced from 48 to 24 h in patients with an eGFR of < 60 ml/min in March 2020. The aim of this change in practice was to reduce the length of inpatient stay and utilize the available resources more efficiently without compromising patient safety. We retrospectively identified MM patients with an eGFR <60 ml/min before (June–December 2019) and after (July 2020–July 2021) this change was implemented.

The majority of the patients start their ASCT as ambulatory patients, with subsequent admission to the inpatient ward as and when needed. Only a minority have their ASCT started as inpatients based on comorbidities, mobility and language barriers.

Mobilization protocols used included single agent G-CSF at a dose of 10 µg/kg administered subcutaneously for 5 consecutive days; or cyclophosphamide at a dose of 1.5 g/m^2 intravenously, followed by G-CSF for 8 days. Plerixafor is administered if needed depending on the CD34+ cell count on the harvest day for up to 2 doses. The target stem cell dose for a single ASCT is 2×10^6/kg. Melphalan dose is adjusted according to age, comorbidities and eGFR. Patients with an eGFR < 40 ml/min routinely had melphalan dose reduced from 200 to 140 mg/m^2 [26]. Melphalan is administered as an IV infusion over 30 min. G-CSF (5 µg/kg) is administered form day +6 until neutrophil engraftment. All patients are started on prophylactic antivirals unless otherwise contraindicated. Preemptive platelet transfusion threshold is $<10\times10^9$/l and $<20\times10^9$/l in afebrile and feverish patients, respectively.

eGFR was assessed using ^{51}Cr-EDTA. The cut off of < 60 ml/min was chosen as demonstrating moderate and severe renal impairment, and renal failure according to the consensus statement of the International Myeloma Working Group (IMWG) [26].

Clinical outcomes used surrogates for bone marrow recovery and HDM side effects. The former included time to neutrophil engraftment (TTNE) and time to platelet engraftment (TTPE). TTNE was defined as the time, in days, between HSCR and the date of the first of 3 consecutive days with a neutrophil count $>0.5\times10^9$/l. TTPE was defined as the time, in days, between HSCR and the date of the first of 3 consecutive days with a platelet count $\geq20\times10^9$/l, with no platelet transfusion in the preceding 7 days.

Surrogates for HDM side effects included the occurrence of diarrhea secondary to intestinal mucositis and its grade (as per the CTCAE version 5 [27]), occurrence of neutropenic fever and bacteremia, the need for continuous subcutaneous infusion (CSCI) for oro-pharyngeal mucositis pain and/or nausea and vomiting, the need for total parental nutrition (TPN), admission to the intensive care unit (ICU) and the need for renal replacement therapy (RRT).

The length of hospital stay was calculated from the date of HDM administration to discharge.

Disease response before ASCT and high risk cytogenetics (CGs) were defined as per the IMWG [28].

Median and range were used to describe non-parametric data. Independent samples Mann–Whitney U and χ^2/Fisher's Exact tests were used to compare non-parametric quantitative and qualitative data, respectively. A two-sided p value of < 0.05 was considered to be statistically significant. SPSS version 28 was used for the statistical analyses.

Results

We identified 239 patients with MM who underwent ASCT in our institution during the aforementioned periods. Of these, 50 (20.9%) had an eGFR < 60 ml/min; 19 (38%) and 31 (62%) had their HSCR after 24 h and 48 h from HDM, respectively (Figure 1). Patients demographics and disease characteristics at diagnosis were broadly similar in both groups. Patients in the 24 h group were older, but this difference was not statistically significant ($p = 0.17$). The majority of patients in both groups had stage 3 RI (Table 1).

The majority of patients received a bortezomib based induction and had 1 therapy line before ASCT. About two thirds had a VGPR or deeper response

before ASCT (Table 2). Two patients in the 48 h group had a second ASCT.

The median melphalan dose (in mg/m^2) in both groups was 140. A higher proportion of patients in the 48 h group had a dose of 200 mg/m^2. There was no statistically significant difference in the HSC dose between both groups ($p = 0.107$) (Table 3).

A subgroup analysis of the patients in the 48 h group who received a higher dose of melphalan (200 mg/m^2; $n = 14$) and those receiving a lower dose (140 and 110 mg/m^2; $n = 17$) showed no statistically differences in all the clinical outcomes compared (Supplementary Table 1).

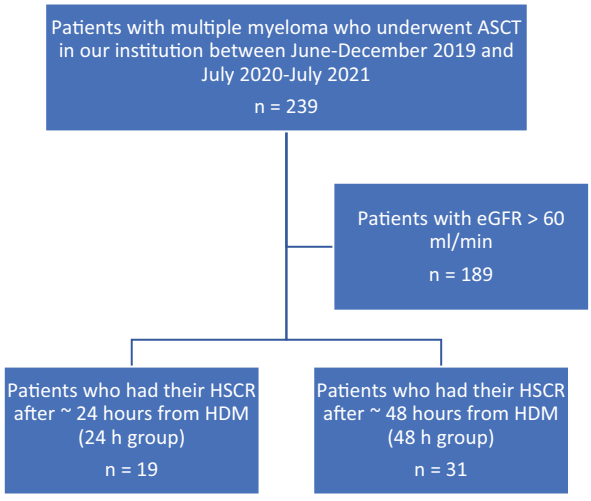

Figure 1. Study flow chart.

Clinical outcomes are listed in Table 4. There was no difference in the length of hospital stay, TTNE, TTPE, occurrence of neutropenic fever or diarrhea, use of TPN or CSCI between both groups. No patients required RRT. One patient in the 24 h group died during the first 100 days post transplant. This patient received HDM at 140 mg/m^2, engrafted on $D+10$ and was discharged, but developed type 1 respiratory failure due to a lower respiratory tract infection on $D+25$. Despite being transferred to ITU, continued deterioration ensued leading to death on $D+38$. No deaths or ITU admissions occurred in the 48 h group during the same period post transplant.

Discussion

Despite the availability of many therapeutic agents (proteasome inhibitors, immunomodulatory agents, anti CD 38 and anti B cell maturation antigen monoclonal antibodies, steroids and alkylators), MM remains incurable with HDM followed by stem cell rescue offering the best overall and progression free survival rates [29].

Efficacy and safety of HDM in MM patients with RI are varied in the literature. Sweiss et al. [30] reported more non-haematological toxicities, comparable OS and longer median treatment-free survival in patients with RI (defined as a CrCl < 60 ml/min), as compared to those with CrCl ≥ 60 ml/min. Carlson [23] noted no relationship between GFR and stem cell yield, engraftment, incidence of neutropenic fever

Table 1. Patients' demographics and disease characteristics at diagnosis.

	24 h group ($n = 19$)	48 h group ($n = 31$)
Males (%)	47.4	54.8
Age, years (median, range)	65.7 (55.6–71.4)	61.3 (40.4–75.6)
>60, *n* (%)	18 (94.7)	18 (58.1)
>70, *n* (%)	1 (5.3)	3 (9.7)
>75, *n* (%)	0	1 (3.2)
Uncorrected GFR, ml/min (median, range)	48 (33–58)	49 (26–59)
Stage of renal impairment (*n*, %)		
3 (Moderate reduction of GFR; 30–59 ml/min)	19 (100)	28 (90.3)
4 (Severe reduction of GFR; 15–29 ml/min)	0	3 (9.7)
5 (Renal failure; GFR < 15 ml/min or on dialysis)	0	0
Disease isotype		
IgA	3	4
IgD	1	0
IgG	10	14
Polyclonal	1	0
KLC	1	10
LLC	3	2
Oligosecretory	0	1
ISS, *n* (%)		
1	5 (26.3)	6 (19.4)
2	2 (10.5)	4 (12.9)
3	3 (15.8)	11 (35.5)
Unknown	9	10
High risk cytogenetics, n (%)	6 (31.6)	6 (19.4)

KLC: kappa light chain; LLC: lambda light chain.

Table 2. Treatments and responses before ASCT.

	24 h group ($n=19$)	48 h group ($n=31$)
Induction therapy, *n* (%)		
Bortezomib based	14 (73.7)	25 (80.6)
Bortezomib based followed by lenalidomide based for COVID planning	3 (15.8)	0
KCd	1 (5.3)	2 (6.5)
Lenalidomide based /Dexamethasone	1 (5.3)	1 (3.2)
	0	1 (3.2)
PAD	0	2 (6.5)
Therapy lines before ASCT, *n* (%)		
1	11 (57.9)	22 (71)
2	6 (31.6)	7 (22.6)
3+	2 (10.5)	2 (6.5)
Disease response before ASCT, *n* (%)		
sCR	1 (5.3)	4 (12.9)
CR	7 (36.8)	6 (19.4)
VGPR	6 (31.6)	11 (35.5)
PR	5 (26.3)	8 (25.8)
SD	0	2 (6.5)

KCd: carfilzomib, cyclophosphamide, and dexamethasone; PAD: bortezomib, adriamycin and dexamethasone.

Table 3. ASCT parameters.

	24 h group ($n=19$)	48 h group ($n=31$)
Melphalan dose (mg/m^2), median (range)	140 (140–200)	140 (110–200)
HDM dose (mg/m^2), *n* (%)		
110	0	3 (9.7)
140	16 (84.2)	14 (45.2)
200	3 (15.8)	14 (45.2)
Time between HDM and HSCR, hours (median, range)	25 (22.8–26.4)	46.4 (40.9–49.3)
HSC dose, CD34 $\times 10^6$/kg (median, range)	2.8 (1.7–16.8)	3.4 (1.5–12.1)

HDM: high dose melphalan; HSCR: hematopoietic stem cell return.

Table 4. Clinical outcomes.

	24 h group ($n=19$)	48 h group ($n=31$)	*p* value
Length of hospital stay, median (range)	16.4 (14.4–41.4)	16.4 (13.4–34.4)	0.569
Time to neutrophil engraftment, median (range)	11.3 (9.3–12.3)	10.5 (9.3–13.4)	0.509
Time to platelet engraftment, median (range)	15.4 (8.36–20.3)	15.4 (9.4–61.3)	0.436
Diarrhea, *n* (%)			1
Y	19 (100)	30 (96.8)	
N	0	1 (3.2)	
Diarrhea grade, *n* (%)			0.693
Grade 1	6 (31.6)	9 (29)	
Grade 2	10 (52.6)	13 (41.9)	
Grade 3	3 (15.8)	8 (25.8)	
Neutropenic fever, *n* (%)			0.637
Y	18 (94.7)	27 (87.1)	
N	1 (5.3)	4 (12.9)	
Bacteremia, *n* (%)			0.756
Y	7 (36.8)	9 (29)	
N	12 (63.2)	22 (71)	
Use of TPN, *n* (%)			1
Y	0	1 (3.2)	
N	19 (100)	30 (96.8)	
Need for CSCI, *n* (%)			0.727
Y	5 (26.3)	6 (19.4)	
N	14 (73.7)	25 (80.6)	

TPN: total parenteral nutrition; CSCI: continuous subcutaneous infusion; Y: yes; N: no.

or infectious complications, but a higher incidence of severe mucositis and worse survival in patients with RI. Tricot [24] et al. reported longer durations of fever and hospitalization in patients with RI, but no negative impact on the quality of collected HSC, engraftment, transfusion requirements, incidence of severe mucositis, or overall survival. The heterogeneity of the method used to assess renal function and the definition of RI in the aforementioned studies is acknowledged.

Although worsening renal function has been reported in the post transplant period, it was mild, did not adversely impact PFS or OS, and recoverable in the majority of patients [31,32].

Various dosing schedules for HDM were reported, ranging from a single dose given on day − 2 or −1, or split doses given on days −3 and −2. The superiority of these regimens has not been tested in prospective trials and the choice remains at the discretion of the treating center. Moreover, of the published retrospective studies comparing the outcomes of HSCR at day −2 vs day −1 [9–11], none focused on patients with RI.

In our report, the extra 'rest' day in the 48h was canceled out by a 1 day shorter TTNE resulting in an equal length of hospital stay in both groups. However, the difference in TTNE between both groups was not statistically significant. Similarly, there was no difference in the aforementioned outcomes between both groups. These results are in keeping with the findings of Talamo et al. [9] wherein no statistically significant differences were noted between patients who had HDM at days −2 and −1 from HSCR in TTNE, TTPE, occurrence of neutropenic fever, rate of use of patient-controlled analgesia and TPN, and rate of grade 3–4 diarrhea. However, it is worth highlighting that the renal functions of the reported cohort were not clearly defined in their study.

On the other hand, Al Saleh et al. [10] found a longer duration of hospital admission, higher rates of fever, and longer TTPE in the day −1 cohort as compared to the day −2 cohort. In their study, they used a platelet threshold of 50×10^9/l to define platelet engraftment, rather than the 20×10^9/l threshold employed by us and by Talamo et al. This higher threshold might explain the reported longer TTPE in the day −1 cohort. Whether the lack of routine administration of G-CSF at $D+6$ by Al Saleh et al. would explain the differences in duration of hospital admission and occurrence of fever is difficult to ascertain. More importantly, the median creatinine clearance in Al Saleh et al. report was 86 and 87 ml/min, as compared to 49 and 48 ml/min in our report, in the day −2 and −1 cohorts, respectively. The lack of data on the method devised to measure/calculate creatinine clearance in the former study is acknowledged.

Mahindra et al. [11] reported on the results of a similar analysis. A statistically significant difference was found in the TTNE (median of day 11 (range, 10–12) *vs* day 13 (range, 11–17; $p<0.001$) in patients receiving HDM on day −2 as compared to day −1. Mucositis (as assessed by the oral mucositis assessment scale) was more severe in the day −1 cohort. These findings again contradicts the current analysis. The difference in assessing mucositis severity between both studies is acknowledged. Again, the renal functions of both groups were not reported in their abstract.

Although the single ITU admission and death occurred in the 24 h group, the patient received the lower dose of melphalan, did not experience a delay in neutrophil engraftment and was actually discharged after his transplant. It is therefore unlikely that the shorter period between HDM and HSCR would have contributed to the outcome.

The major limitation of our study is its retrospective nature. Given melphalan undergoes spontaneous hydrolysis in aqueous solution, comparing the duration from its constitution to infusion between both groups would have been useful to eliminate possible confounders. We assessed GFR using a radiolabelled tracer, rather than the inulin infusion method with concomitant urine collection, which is considered the gold standard for measuring GFR. This is however justified given the complexity of the latter method. A higher proportion of patients in the 24 h group received the lower dose of melphalan (140 mg/m^2 rather than 200 mg/m^2) as compared to the 48 h group. This difference might have confounded our results in favor of the former group. Nevertheless, a subgroup analysis within the 48 h group between patients receiving melphalan at a dose of 200 mg/m^2 *vs* those at doses of 140 and 110 mg/m^2 failed to show any statistically significant differences in the clinical outcomes compared. Lastly, the subjectivity of the surrogates for HDM toxicity is acknowledged.

In conclusion, we reported on the outcomes of 2 groups of MM patients with RI who had their HSCR after 24 and 48 h from HDM infusion. Although there was no difference in the length of hospital stay between both groups; no significant differences were found in surrogate markers of hematopoietic recovery or HDM toxicity. The shorter duration between HDM and HSCR was unlikely to have contributed to the single ITU admission and death in our cohort. To the best of our knowledge, this is the first report focusing on patients with an eGFR < 60 ml/min. Our findings support the safety of HSCR after 24 h from HDM which might allow easier planning and more efficient use of the available resources. Further studies with larger sample sizes, especially for patients with more severe RI, are needed to confirm/refute our findings.

Authors' contributions

GN: collected and analyzed the data, and wrote the manuscript. NR and RS: conceived the idea, collected the data, critically appraised the manuscript. CK, JS, RP, KY, BW, KX, AW, LL, SI, XP, SM, AM, JH, FN, JM, LA, SA, SC: critically appraised the manuscript.

Disclosure statement

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Data availability statement

All data generated or analyzed during this study are included in this published article.

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