Original article

Renal outcome of patients with newly diagnosed multiple myeloma in a resource-limited setting

Anan Promrattanakun

Department of Medicine, Saraburi Hospital, Thailand

Background: *Effective anti-myeloma therapy is crucial for managing multiple myeloma (MM) with renal impairment. Due to limited resources and data on novel agent-free treatments, we evaluated renal outcomes among patients with newly diagnosed MM in a resource-limited setting.* ***Objective:*** *The study aimed to evaluate the effectiveness of frontline therapies in improving renal function among patients with newly diagnosed MM* ***Method:*** *We retrospectively reviewed renal responses in patients with newly diagnosed MM at Saraburi Hospital from 2013 to 2022, focusing on those who had undergone a minimum of 4 cycles of frontline therapy excluding those requiring hemodialysis.* ***Results:*** *A total of 64 patients with newly diagnosed MM were included in the study. Among these, 18 cases received steroid before chemotherapy, while 46 cases did not. Frontline treatment regimens were administered including cyclophosphamide-dexamethasone (CyDex) (36 cases), bortezomib-cyclophosphamide-dexamethasone (VCD) (10 cases), melphalan-prednisolone (MP) (10 cases), bortezomib-dexamethasone (VD) (4 cases), bortezomib-thalidomide-dexamethasone (VTD) (3 cases) and cyclophosphamide-thalidomide-dexamethasone (CTD) (1 case).*

After frontline chemotherapy, the renal response rates for patients receiving steroid and no steroid therapy before chemotherapy were 21.87 and 37.5%, respectively. Among patients who received steroid therapy before chemotherapy and underwent CyDex, VCD, VD and VTD regimens, the renal response rates were 42.9, 35.7, 14.3 and 7.1%, respectively. In contrast, patients not receiving steroid therapy before chemotherapy and treated with CyDex, VCD, VD, VTD, MP and CTD revealed renal response rates of 70.8, 4.2, 4.2, 4.2, 12.5 and 4.2%, respectively. ***Conclusion:*** *CyDex regimen can be used as frontline therapy for newly diagnosed MM and can improve renal function, particularly in resource-limited settings.*

Keywords : ● *Multiple myeloma* ● *Renal impairment* ● *Renal response*
● *Cyclophosphamide-dexamethasone (CyDex)*
● *Bortezomib-Cyclophosphamide-Dexamethasone (VCD)*

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Correspondence should be addressed to Anan Promrattanakun, MD., Department of Medicine, Saraburi Hospital, Saraburi 18000

นิพนธ์ต้นฉบับ

ผลการตอบสนองทางไตของผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดมัยอีโลมารายใหม่ในบริบทที่มีทรัพยากรจำกัด

อนันต์ พรหมรัตนกุล
กลุ่มงานอายุรกรรม โรงพยาบาลสระบุรี

บทคัดย่อ

บทนำ *ผู้ป่วยมะเร็งเม็ดเลือดขาวชนิดมัยอีโลมา (multiple myeloma, MM) ที่มีภาวะไตวายร่วมด้วยนั้นจำเป็นต้องได้รับยาเคมีบำบัดที่มีประสิทธิภาพ แต่เนื่องจากมีข้อจำกัดในการเข้าถึงการใช้ยากลุ่มใหม่ รวมไปถึงข้อมูลการรักษาผู้ป่วยกลุ่มนี้ด้วยยาเคมีแบบดั้งเดิมยังมีจำกัด จึงเป็นที่มาของการศึกษานี้* ***วัตถุประสงค์*** *เพื่อศึกษาประสิทธิภาพของยาเคมีบำบัดขนานแรกในการเพิ่มการทำงานของไตในผู้ป่วย MM ที่ได้รับการวินิจฉัยใหม่* ***วิธีการศึกษา*** *รวบรวมข้อมูลย้อนหลังเพื่อประเมินผลการตอบสนองทางไตในผู้ป่วย MM ที่ได้รับการวินิจฉัยใหม่และได้รับยาเคมีบำบัดมาตรฐานในประเทศไทยขนานแรกอย่างน้อย 4 รอบ ที่รักษาในโรงพยาบาลสระบุรี ระหว่างปี 2556 ถึง 2565 โดยยกเว้นผู้ป่วยที่ได้รักษาด้วยการฟอกไต* ***ผลการศึกษา*** *พบผู้ป่วย MM ที่ได้รับการวินิจฉัยใหม่จำนวน 64 ราย โดยมีผู้ป่วยที่ได้รับและไม่ได้รับยาสเตียรอยด์ก่อนให้ยาเคมีบัดบัดขนานแรก จำนวน 18 และ 46 ราย ตามลำดับ และได้รักษาด้วยยาเคมีบำบัดขนานแรกสูตรต่างๆ ได้แก่ cyclophosphamide-dexamethasone (CyDex) (36 ราย) bortezomib-cyclophosphamide-dexamethasone (VCD) (10 ราย) melphalan-prednisolone (MP) (10 ราย) bortezomib-dexamethasone (VD) (4 ราย) bortezomib-thalidomide-dexamethasone (VTD) (3 ราย) และ Cyclophosphamide-thalidomide-dexamethasone (CTD) (1 ราย)*

หลังการรักษาด้วยยาเคมีบำบัดขนานแรก ในกลุ่มที่ได้รับและไม่ได้รับยาสเตียรอยด์ก่อนยาเคมีบำบัดพบการตอบสนองทางไต ร้อยละ 21.87 และ 37.5 ตามลำดับ ในกลุ่มที่ได้รับยาสเตียรอยด์ก่อนรักษาเมื่อได้รับยาเคมีบำบัดสูตร CyDex, VCD, VD และ VTD มีการตอบสนองของไตร้อยละ 42.9, 35.7 14.3 และ 7.1 ตามลำดับ ส่วนกลุ่มที่ไม่ได้รับยาสเตียรอยด์ก่อน หลังได้รับยาเคมีบำบัดสูตร CyDex, VCD, VD ,VTD, MP และ CTD มีการตอบสนองของไตร้อยละ 70.8, 4.2, 4.2, 4.2, 12.5, 4.2 ตามลำดับ ***สรุป*** *การรักษาด้วยยาเคมีบำบัดสูตร CyDex เป็นยาขนานแรกในผู้ป่วย MM ที่ได้รับการวินิจฉัยใหม่ ทำให้เกิดการฟื้นตัวของไต โดยเฉพาะในบริบทที่มีทรัพยากรจำกัด*

คำสำคัญ : ● *มะเร็งเม็ดเลือดขาวชนิดมัยอีโลมา* ● *การตอบสนองทางไต* ● *Cyclophosphamide-dexamethasone (CyDex)* ● *Bortezomib-Cyclophosphamide-Dexamethasone (VCD)*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2567;34:33-43.

Background

Multiple myeloma (MM) is common hematologic malignancy with significant global impact. In 2017, the USA reported 30,280 newly diagnosed cases[1], while Thailand indicated a incident rate of 0.74% in 2020[2]. The pathophysiology of MM involves abnormal plasma cell proliferation in the bone marrow, leading to anemia, bone destruction, bone pain and fractures, as well as generating monoclonal proteins causing hyperviscosity and renal failure. Renal impairment affects 20 to 50% of MM cases due to excessive production of monoclonal immunoglobulins especially free light chains, which accumulate in the renal tubules, causing cast nephropathy and inflammatory reaction. Hypercalcemia, hyperuricemia, sepsis and nephrotoxin exposure also contribute to renal impairment in MM[3].

The definition of renal impairment in MM relies on criteria by the International Myeloma Working Group (IMWG), considering creatinine levels exceeding 2 mg/dL or an eGFR less than 40 ml/min/1.73m^2 with stable creatinine levels. Renal function was calculated using the Modification of Diet in Renal Disease (MDRD) formula or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which should be used to evaluate renal function among patients with MM and stabilized serum creatinine. CKD-EPI formula is more accurate than MDRD due to being calculated using serum creatinine or cystatin C that affects accurated tumor burden. Renal impairment severity is evaluated using a classification system with five stages (CKD 1-5) or categorized using RIFLE (Risk, Injury, Failure, Loss, and End Stage Kidney Disease) or AKIN (Acute Kidney Injury Network) and IMWG criteria classify renal response as complete, partial or minor based concerning eGFR levels before and after treatment[4].

Effective management of MM with renal impairment requires control of triggering factors, particularly hypercalcemia by providing hydration at least three litres daily along with bisphosphonates to reduce serum calcium. Moreover, high cutoff hemodialysis or plasmapheresis could be initiated when hyperviscosity syndrome occurs. Hemodialysis was considered for severe renal impairment. Otherwise, treatment to reduce the monoclonal light chain involved chemotherapy, that constituted the cornerstone treatment. One novel agent for MM with renal impairment included bortezomib-based regimen, which rapidly reduced the monoclonal light chain compared with other chemotherapy regimen and created more renal recovery. Furthermore, other novel agents such as thalidomide, lenalidomide, pomalidomide and carfilzomib were used as core-drug combinations[3]. MM with renal impairment exhibits substantial tumor burden at an advanced disease stage and limited treatment response, resulting in critical complications and increased mortality rates for patients with MM. Early detection and appropriate interventions offer potential for renal recovery and long term survival. Chemotherapy selection and effective supportive care also influence outcomes.

The selection of an appropriate antimyeloma regimen requires careful consideration of various factors, especially in settings with limited resources. Given the limited data on novel agent-free regimens and the restricted availability of novel agents for all patients, we conducted an interesting evaluation of renal outcomes among patients with newly diagnosed MM in a resource-limited setting.

Methods

We evaluated renal responses among patients with newly diagnosed MM following IMWG criteria at Saraburi Hospital between 2013 and 2022. A retrospective review of electronic medical records was conducted. Patients underwent at least four cycles of frontline chemotherapy at the physician's discretion, excluding those requiring hemodialysis. Steroids were administered before chemotherapy, except for patients treated with the MP or CTD regimen. Patients were divided in two groups based on steroid therapy. Renal function, assessed by eGFR (CKD-EPI formula), was compared before and after steroid therapy and frontline therapy.

The primary objective of this study was to evaluate the effectiveness of frontline therapies in improving renal function among patients with newly diagnosed MM. Additionally, secondary objective pertains to assessing the depth of disease response.

Statistical analysis was conducted using SPSS Software. Continuous variables were expressed as mean with standard deviation when normally distributed and as median and interquartile range (IQR) for data exhibiting a nonnormal distribution, while categorical data were presented as numbers and percentages. The odds ratio was calculated using logistic regression. *P*-values < 0.05 were considered statistically significant. The protocol of this study was approved by the Saraburi Hospital Human Research Ethics Committee.

Definition

Renal response in this study refers to a significant improvement in posttreatment eGFR, at least 25% higher than pretreatment levels. Unchanged eGFR refers to an increase or decrease of eGFR by less than 25%, and a declined eGFR means a decrease of at least 25% compared with pretreatment levels.

Results

A total of 64 patients with newly diagnosed MM were included in this study. The number of frontline treatment regimens totaled 6, with CyDex, VCD, MP, VD, VTD and CTD being administered to 56.25, 15.62, 15.62, 6.25, 4.68 and 1.56%, respectively. The number of male and female patients accounted for 51.6, and 48.4%, respectively. The mean age was 61.61±10.57 years. Almost all patients were in the advanced stage, with 9.4% of ISS I, 29.7% of ISS II and 48.4% of ISS III. The most common subtype of monoclonal protein was kappa light chain (57.8% of cases). In the context of myeloma-defining events, the study revealed a median hypercalcemia level of 9.25 (8.6, 10) mg/dL, a median hemoglobin level of 8.05 (6.35, 9.3) g/dL, a median serum creatinine level of 1.27 (0.89, 1.9) mg/dL and a median estimated glomerular filtration rate (eGFR) of 49.5 (32, 77.5) mL/min, as indicated in Table 1.

Before initiating frontline chemotherapy, steroids were administered to 28.12% of the entire population, except for patients who were treated with the MP or CTD regimen. The rationale for using steroids before chemotherapy including acute kidney injury (AKI) (61.11%), transitioning to other definitive chemotherapy (27.77%), managing severe hypercalcemia (5.55%), and alleviating spinal cord compression due to plasmacytoma (5.55%). The steroid therapy group had an unchanged eGFR and an improved eGFR (55.55% and 44.44%). No one in this group experienced a decline in eGFR. Conversely, in the non-steroid therapy group exhibited unchanged eGFR, an improvement in eGFR and a declined in eGFR by 58.69%, 28.26% and 13.04%, respectively.

After completion of the frontline therapy, patients who did not receive steroids therapy prior to chemotherapy demonstrated a renal response in 37.5% of cases, while 32.81% had an unchanged eGFR, and only 1.56% experienced a declined eGFR. In contrast, those who received steroids therapy prior to chemotherapy exhibited a lower renal response rate of 21.87%. Among patients without steroid therapy, the CyDex regimen showed a renal response in 70.8% of cases, with 52.4% having an unchanged eGFR. Among patients with steroid therapy, the CyDex regimen demonstrated a renal response in 42.9% of cases and an unchanged eGFR in 52.4% of cases. Notably, none of the patients who received the CyDex regimen experienced a declined eGFR, as indicated in Table 2.

The depth of disease response after completion of frontline therapy is comprehensively outlined in Table 3. The overall response rates were 80.45% and 72.22% for the non-steroid and steroid therapy prior to chemotherapy groups, respectively. Among patients who received steroids therapy prior to chemotherapy, those treated with the VCD regimen demonstrated the highest ORR of 38.88%, followed by CyDex of 22.22%. On the other hand, in the non-steroid therapy prior to chemotherapy group, CyDex displayed the highest ORR of 47.82%, with

Table1 Baseline characteristics

		Treatment regimen					
Variable	**Total**	**VCD**	**VTD**	**CyDex**	**MP**	**VD**	**CTD**
Number (n)	**64**	**10 (15.62 %)**	**3 (4.68%)**	**36 (56.25%)**	**10 (15.62%)**	**4 (6.25%)**	**1 (1.56%)**
Sex							
Male	33 (51.6%)	4 (40%)	3 (100%)	19 (52.8%)	4 (40%)	2 (50%)	1 (100%)
Female	31 (48.4%)	6 (60%)	0 (0%)	17 (47.2%)	6 (60%)	2 (50%)	0 (0%)
Age (year)*	61.61 ± 10.57	65.4 ± 10.2	57 ± 9.64	57.97 ± 9.79	69.1 ± 7.22	66 ± 13.74	76
ISS stage							
Not done	8 (12.5%)	2 (20%)	0 (0%)	4 (11.1%)	1 (10%)	0 (0%)	1 (100%)
Stage 1	6 (9.4%)	0 (0%)	1 (33.3%)	4 (11.1%)	1 (10%)	0 (0%)	0 (0%)
Stage 2	19 (29.7%)	4 (40%)	0 (0%)	12 (33.3%)	2 (20%)	1 (25%)	0 (0%)
Stage 3	31 (48.4%)	4 (40%)	2 (66.7%)	16 (44.4%)	6 (60%)	3 (75%)	0 (0%)
Type of M-protein							
IgG	38 (59.4%)	8 (80%	0 (0%)	21 (58.3%)	6 (60%)	3 (75%)	0 (0%)
IgA	17 (26.6%)	0 (0%)	1 (33.3%)	11 (30.6%)	3 (30%)	1 (25%)	1 (100%)
Light chain only	8 (12.5%)	2 (20%)	2 (66.7%)	4 (11.1%)	0 (0%)	0 (0%)	0 (0%)
Nonsecretory	1 (1.6%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
Light chain							
Kappa	37 (57.8%)	7 (70%)	1 (33.3%)	20 (55.6%)	6 (60%)	3 (75%)	0 (0%)
Lambda	24 (37.5%)	3 (30%)	2 (66.7%)	15 (41.7%)	3 (30%)	1 (25%)	0 (0%)
Unknown	3 (4.7%)	0 (0%)	0 (0%)	1 (2.8%)	1 (10%)	0 (0%)	1 (100%)
Serum Calcium** (mg/dL)	9.25 (8.6, 10)	9.3 (8.5, 11.5)	8.2 (7.9, 13)	9.05 (8.8, 9.8)	9.5 (9.4, 9.7)	10.8 (9.05, 12.65)	9.7
Hemoglobin** (g/dL)	8.05 (6.35, 9.3)	7.05 (5.9, 9.5)	8.5 (5.9, 13.6)	8 (6.95, 9.95)	8.2 (5.5, 9)	8.45 (6.45, 9.2)	0.6
Creatinine level** (mg/dL)	1.27 (0.89, 1.9)	1.39 (1, 4.09)	1.47 (0.99, 4.89)	1.26 (0.9, 1.83)	0.88 (0.59, 1.4)	2.38 (1.77, 3.01)	1.23
eGFR** (mL/min)	49.5 (32, 77.5)	47 (15, 60)	49 (12, 85)	54 (35.5, 82)	73 (49, 95)	24 (19, 36)	61
NO. of steroid therapy before chemotherapy	18 (28.125%)	7 (70%)	1 (33.3%)	8 (22.2%)	0 (0%)	2 (50%)	0 (0%)

*Mean±SD for data normal distribution, and **Median (IQR) for data nonnormal distribution.
Bortezomib-Cyclophosphamide-Dexamethasone (VCD); Bortezomib-Thalidomide-Dexamethasone (VTD); Cyclophosphamide-Dexamethasone (CyDex); Melphalan-Prednisolone (MP); Bortezomib-Dexamethasone (VD); Cyclophosphamide-Thalidomide-Dexamethasone (CTD)

MP following closely at 13.04%. It is important to note that the change in eGFR was not found to be associated with the ORR, as indicated in Table 4.

The study found no statistically significant differences in renal response between patients with MM ISS II and III compared to MM ISS I. Type of M-protein, light chain type, and steroid therapy prior to chemotherapy also showed no significant associations with renal response. However, significant renal responses were observed in patients with hypercalcemia levels above 11 mg/dL (OR 7.76; 95%CI: 0.93, 353.34; *p*-value 0.032) and those with a baseline eGFR below 30 mL/min (OR 44; 95%CI: 4.88, 397.03), as well as in patients with eGFR between 30-59 mL/min (OR 17.81; 95%CI: 4, 79.28). These responses were statistically significant compared to patients with higher baseline eGFR.

Table 2 Renal response of patients with newly diagnosed multiple myeloma before and after frontline therapy

Treatment regimen/Renal outcome	Unchanged eGFR (< 25%)	Improved eGFR (≥ 25%)	Declined eGFR (≥ 25%)
Before frontline therapy			
Steroid therapy	N = 10 (55.55%)	N = 8 (44.44 %)	N = 0
Nonsteroid therapy	N = 27 (58.69 %)	N = 13 (28.26%)	N = 6 (13.04%)
After frontline therapy			
Steroid therapy before chemotherapy	N = 3 (4.68%)	N = 14 (21.87%)	N = 1 (1.56%)
VCD	1 (33.3%)	5 (35.7%)	1 (100%)
VTD	0 (0%)	1 (7.1%)	0 (0%)
CyDex	2 (66.7%)	6 (42.9%)	0 (0%)
VD	0 (0%)	2 (14.3%)	0 (0%)
Nonsteroid therapy before chemotherapy	N = 21 (32.81%)	N = 24 (37.5%)	N = 1 (1.56%)
VCD	2 (9.5%)	1 (4.2%)	0 (0%)
VTD	1 (4.8%)	1 (4.2%)	0 (0%)
CyDex	11 (52.4%)	17 (70.8%)	0 (0%)
MP	6 (28.6%)	3 (12.5%)	1 (100%)
VD	1 (4.8%)	1 (4.2%)	0 (0%)
CTD	0 (0%)	1 (4.2%)	0 (0%)

Bortezomib-Cyclophosphamide-Dexamethasone (VCD); Bortezomib-Thalidomide-Dexamethasone (VTD); Cyclophosphamide-Dexamethasone (CyDex); Melphalan-Prednisolone (MP); Bortezomib-Dexamethasone (VD); Cyclophosphamide-Thalidomide-Dexamethasone (CTD)

Table 3 Depth of disease response after frontline therapy

Treatment regimen/ Renal outcome	Not done	sCR	CR	VGPR	PR	SD	PD	ORR (sCR+CR+VGPR+PR)
Steroid therapy before CMT	N = 0	N = 2	N = 3	N = 3	N = 5	N = 2	N = 3	13 (72.22%)
VCD	0 (0%)	2 (100%)	2 (66.7%)	1 (33.3%)	2 (40%)	0 (0%)	0 (0%)	7 (38.88%)
VTD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (5.55%)
Cydex	0 (0%)	0 (0%)	0 (0%)	2 (66.7%)	2 (40%)	1 (50%)	3 (100%)	4 (22.22%)
VD	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	1 (5.55%)
Nonsteroid therapy before CMT	N = 2	N = 2	N = 13	N = 8	N = 12	N = 4	N = 5	37 (80.45%)
VCD	0 (0%)	1 (50%)	1 (7.7%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	3 (6.52%)
VTD	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	1 (8.3%)	0 (0%)	0 (0%)	2 (4.34%)
Cydex	1 (50%)	0 (0%)	8 (61.5%)	7 (87.5%)	7 (58.3%)	2 (50%)	3 (60%)	22 (47.82%)
MP	1 (50%)	0 (0%)	1 (7.7%)	1 (12.5%)	3 (25%)	2 (50%)	2 (40%)	6 (13.04%)
VD	0 (0%)	1 (50%)	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (4.34%)
CTD	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.17%)

ORR between steroid therapy and nonsteroid therapy before CMT, p-value 0.4749

sCR: stringent complete remission; CR: complete remission; VGPR: very good partial remission; PR: partial remission; SD: stable disease; PD: progressive disease; ORR: overall response rate

Table 4 Factors correlated with renal response

	Renal response (n = 38)	Nonrenal response (n = 26)	OR 95%CI	*p*-value
Age (year)				
< 65	26 (68.4%)	16 (61.5%)	1.35 (0.42, 4.35)	0.569
≥ 65	12 (31.6%)	10 (38.5%)	Reference	1
ISS stage*				
Stage 1	1 (2.6%)	5 (19.2%)	Reference	1
Stage 2	12 (31.6%)	7 (26.9%)	8.57 (0.83, 89.04)	0.072
Stage 3	19 (50%)	12 (46.2%)	7.92 (0.82, 76.28)	0.073
Type of M-protein (g/L)				
IgG	26 (68.4%)	12 (46.2%)	2.53 (0.8, 8.03)	0.075
IgA	8 (21.1%)	9 (34.6%)	0.5 (0.14, 1.8)	0.228
Light chain	4 (10.5%)	4 (15.4%)	0.65 (0.11, 3.89)	0.564
Nonsecretory	0 (0%)	1 (3.8%)	N/A	0.223
Light chain (mg/L)				
Kappa	24 (63.2%)	13 (50%)	1.71 (0.55, 5.31)	0.295
Lambda	13 (34.2%)	11 (42.3%)	0.71 (0.23, 2.25)	0.511
No	1 (2.6%)	2 (7.7%)	0.32 (0.01, 6.67)	0.347
Prior steroid therapy before chemotherapy				
No	24 (63.2%)	22 (84.6%)	Reference	1
Yes	14 (36.8%)	4 (15.4%)	3.21 (0.82, 15.17)	0.061
eGFR (mL/min)				
< 30	14 (36.8%)	1 (3.8%)	44 (4.88, 397.03)	0.001
30-59	17 (44.7%)	3 (11.5%)	17.81 (4, 79.28)	<0.001*
≥ 60	7 (18.4%)	22 (84.6%)	Reference	1
Serum calcium (mg/dL)				
< 11	29 (76.3%)	25 (96.2%)	Reference	1
≥ 11	9 (23.7%)	1 (3.8%)	7.76 (0.93, 353.34)	0.032*
Hemoglobin (g/dL)				
< 10	34 (89.5%)	19 (73.1%)	3.13 (0.68, 16.25)	0.088
≥ 10	4 (10.5%)	7 (26.9%)	Reference	1
Treatment regimen				
VCD	6 (15.8%)	4 (15.4%)	1.03 (0.21, 5.57)	0.965
VTD	2 (5.3%)	1 (3.8%)	1.39 (0.07, 85.16)	0.792
CyDex	23 (60.5%)	13 (50%)	1.53 (0.5, 4.72)	0.404
MP	3 (7.9%)	7 (26.9%)	0.23 (0.04, 1.19)	0.040*
VD	3 (7.9%)	1 (3.8%)	2.14 (0.16, 116.91)	0.511
CTD	1 (2.6%)	0 (0%)	N/A	0.404
Change of eGFR				
Unchanged eGFR	15 (31.3%)	7 (50%)	Reference	1
Increased eGFR > 25%	32 (66.7%)	6 (42.9%)	2.49 (0.71, 8.7)	0.153
Declined eGFR > 25%	1 (2.1%)	1 (7.1%)	0.47 (0.03, 8.6)	0.608

p-value by logistic regression; *The patient's unidentified ISS stage has not undergone analysis

Bortezomib-Cyclophosphamide-Dexamethasone (VCD); Bortezomib-Thalidomide-Dexamethasone (VTD); Cyclophosphamide-Dexamethasone (CyDex); Melphalan-Prednisolone (MP); Bortezomib-Dexamethasone (VD);

The treatment regimen significantly influences renal response. The VD regimen showed the most substantial disease response with an ORR of 2.14 (95%CI: 0.16 to 116.91), followed by CyDex regimen and VTD regimen with ORRs of 1.53 (95%CI: 0.5 to 4.72) and 1.39 (95%CI: 0.07 to 85.16), respectively, though not clinically significant. Conversely, the MP regimen resulted in a diminished renal response with an ORR of 0.23 (95%CI: 0.04 to 1.19), *p*-value 0.040. Patients who received steroid prior to chemotherapy displayed a markedly renal response, approximately 3.21 times higher than those with non-steroid therapy prior to chemotherapy.

Discussion

This study focuses on analysis of the renal response in patients with newly diagnosed MM. While novel agent-based regimens have shown favorable renal responses[5], limited data are available for novel agent-free regimens among patients with MM and renal impairment. The study included 64 patients undergoing frontline therapy.

Multiple chemotherapy regimens were available as frontline therapy in newly diagnosed MM. The choice of regimens depended on various factors, but limited drug accessibility emerged as the main obstacle. Typically, treatment for MM starts with hydration and steroid administration, particularly in cases involving renal impairment. Notably, this study excluded severe renal impairment necessitating hemodialysis. Additionally, plasmapheresis and high cutoff hemodialysis were not used for any patients in this study.

Among the patients in this study, 56.25% received conventional CyDex regimen, while novel agent-based regimens such as VCD, VD and CTD were limited, with only 4.68% of patients receiving VTD. Baseline serum creatinine was 1.27 (0.89, 1.9) mg/dL, and baseline eGFR was 49.5 (32, 77.5) mL/min. Additionally, the baseline eGFR for patients on VCD, VTD and VD regimens was 47 (15, 60), 49 (12, 85) and 24 (19, 36) mg/dL, respectively. Remarkably, the baseline eGFR levels for VCD, VTD and VD regimens in this study were lower compared with those of other treatments. After the novel-based frontline treatment, the renal response rates were found to be lower than those of the CyDex regimen, regardless of prior steroid therapy. However, among patients with MM and renal impairment, novel-based regimens were preferred whenever feasible.

For patients receiving novel agent-containing regimens without steroid therapy before chemotherapy, 4.2% presented observed renal responses in each regimen (VCD, VTD, VD and CTD). However, in the group of patients receiving steroids therapy before chemotherapy, the VCD treatment resulted in a significantly higher renal response rate of 35.7% compared with that of the VD and VTD regimens, exhibiting response rates of 14.3 and 7.1%, respectively.

Bortezomib significantly enhanced renal function and was independently associated with a higher probability of renal response than thalidomide- or lenalidomide-based therapy[6], especially among patients aged over 70 years It improved those presenting a baseline eGFR below 60 ml/min/1.73 m^2, with free light chain levels exceeding 1,000 mg/L and a free light chain response of > 90%[7]. Several studies have shown the favorable impact of bortezomib-based regimens on improved renal function[7-10]. Meletios A. and colleagues[11] concluded that bortezomib-based regimens may result in improved renal function among 59% of patients with MM and renal impairment, leading to a complete renal response in 30% of cases and achieving a renal response within a median duration of 11 days. Additionally, the toxicities associated with bortezomib-based regimens were comparable to those in MM treatment without renal impairment[12].

Treatment regimens demonstrate varying renal response rates due to their diverse mechanisms of action. For example, cyclophosphamide functions as an alkylating agent, mediating its cytotoxicity through DNA damage, ultimately leading to cellular necrosis, apoptosis and immunomodulatory effects[13]. Glucocorticoids exert a cytotoxic effect on myeloma cells by inhibiting nuclear

factor-κ light chain enhancer of activated B cells (NF-κB) and interleukin (IL)-6[14]. Additionally, bortezomib, the first proteasome inhibitor, disrupts the ubiquitin-proteasome pathway, resulting in the degradation of numerous intracellular proteins and programmed cell death in malignant cells[15,16]. Furthermore, bortezomib directly acts on MM cells, altering cellular interactions and cytokine secretion in the bone marrow milieu. This dual action inhibits tumor cell growth, induces apoptosis and overcomes drug resistance[17]. Consequently, bortezomib was recommended as the first-line therapy for patients with MM and renal impairment[14]. On the other hand, patients with MM treated with the novel agent-free regimen, CyDex, demonstrated promising renal response rates, with 42.9 and 70.8% in the nonsteroid and steroid therapy before chemotherapy groups, respectively. The CyDex regimen exhibited a 53% increase in the probability of renal response, with an odds ratio of 1.53 (0.5, 4.72), as shown in Table 4.

Steroids are commonly used as monotherapy for treating MM. To assess the effectiveness of steroid therapy as a treatment during the period of awaiting definitive frontline therapy, 28.12% of patients in this study received steroids before undergoing chemotherapy.

Before initiating frontline chemotherapy, the group receiving steroid therapy showed a higher renal response (44.44%) compared with that of the nonsteroid therapy group (28.26%), even though the eGFR remained unchanged (55.55%) and a renal response (44.4%) was observed after steroid therapy. Patients receiving a high dose of steroids alone experienced a 44% restoration of renal function, whereas none of the patients in the low dose/no steroid group showed such improvement[18]. On the other hand, using dexamethasone alone resulted in a response rate of 41%, which was significantly lower than the response rate observed using thalidomide and dexamethasone combined (63%)[19].

After frontline therapy, patients receiving steroid therapy before chemotherapy and subsequently undergoing frontline therapy demonstrated a slightly decreased renal response rate compared with that of the nonsteroid group (21.87 vs. 37.5%). Although steroids were initially used as a single agent among patients with MM, they are now often employed as an adjunct to novel treatment regimens. Despite the historical use of steroids as a standalone treatment for patients with MM, they are now frequently employed as adjuncts to novel treatment regimens. In a study by Efstathios Kastritis and colleagues[12], combining novel agents with high dose dexamethasone resulted in an 80% reversibility rate for renal impairment, which is comparable with high dose dexamethasone monotherapy. Additionally, these novel agents demonstrated a more rapid reversal of renal failure.

The factor that predicted the probability of renal recovery was eGFR < 50 mL/min/1.73 m^2, leading to a complete renal response in 50.6% of cases. This indicates a higher response rate when compared with patients with eGFR greater than 30 mL/min/1.73 m^2, ISS II, or hypercalcemia[20]. Conversely, severe renal failure, indicated by serum creatinine levels above 4 mg/dL and proteinuria exceeding 2 g/day, were linked to a lower likelihood of renal failure reversal[12]. Despite the association between renal impairment and high tumor burden[20], our study found no relationship between the stage of MM and renal response. Additionally, the type of M-protein was unrelated to renal response, differing from Alexanian R.'s study, where monoclonal IgG or IgA exhibited a higher renal response, while lambda light chain protein displayed a lower response due to renal tubule toxicity. No strong evidence supported the relationship between light chain protein and serum creatinine[5]. Serum creatinine levels before treatment, below 3.05 mg/dL or a decline of at least 60% in free light chain protein after 21 days of treatment, were related to renal response, resulting in an 80% renal recovery of patients[21]. In our study, patients with lower baseline eGFR demonstrated a higher renal response than those with higher baseline eGFR, and after completing chemotherapy, renal responders exhibited a greater disease response.

Anemia was the only factor showing a renal response in our study although without statistical significance. We found no relationship between hypercalcemia and renal response, although hypercalcemia above 11 mg/dL showed a higher response. However, hypercalcemia above 9.8 mg/dL was related to high mortality in another study[22] and showed a 5.6 times higher renal response[23]. Chemotherapy, particularly bortezomib, remains the primary treatment for patients with MM, especially those with renal impairment. The choice of chemotherapy depends on various factors including patient fitness, disease characteristics, drug accessibility and physician experience with preference given to combined regimens involving at least one novel agent. Interestingly, the overall response rate was slightly lower in the steroid therapy before chemotherapy group (ORR 22.22%) compared with that of the non-steroid therapy before chemotherapy group (ORR 47.84%). However, the nonsteroid therapy before chemotherapy group exhibited a higher response rate after complete chemotherapy (37.5 vs. 21.87%) with a similar overall response rate (80.45 vs. 72.22%).

Conclusion

Patients with MM and renal impairment reveal an unfavorable prognosis, but renal dysfunction can be reversed, leading to improved long term survival. Frontline therapy is crucial in enhancing renal function for newly diagnosed individuals. The CyDex regimen is a notable and effective alternation, especially for patients with renal impairment, offering significant advantages, particularly in resource-limited healthcare settings.

Limitations and confounding factors

Confounding factors posed challenges in the study, notably at the beginning of MM with renal impairment, where we encountered difficulties in controlling various factors including the amount, duration of fluid hydration and steroid duration. Additionally, the timing of renal reversibility assessment depends on the last creatinine measurement before initiating chemotherapy. The inability to precisely identify the cause of renal failure among patients with MM remains a significant concern. Therefore, renal reversibility may not fully affect the treatment regimen.

Furthermore, the selection of treatment regimens is significantly influenced by the availability of drugs for the patient and considerations made by the physician. This often leads to patients with MM and renal impairment receiving nonnovel-based therapies, resulting in a fluctuating numbers of patients in each regimen. This variability, in turn, diminishes the statistical power of our study, making it challenging to discern statistically significant associations among factors and renal responses. This limitation is likely attributed to the variable sample size stemming from the diverse treatment regimens employed for patients with MM and renal impairment.

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Conflict of interest

None

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