RESEARCH ARTICLE

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Treatment Pattern and Outcome of Newly Diagnosed Multiple Myeloma Patients in a Resource-Limited Setting

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Abstract

Background: Multiple myeloma is the third most common hematologic malignancy in Malaysia. The introduction of novel agents over the past decades has improved patient outcome and survival substantially. However, these agents incur significant economic burden, thus leading to limited use in less developed countries. This study aims to report on the real-world treatment pattern and outcome of newly diagnosed multiple myeloma (NDMM) patients from a resource-constraint setting. **Methods:** This is a retrospective study on NDMM patients diagnosed between 1 January 2008 and 31 December 2022 in a single academic center. Patients' demographic and treatment details were included for analysis of progression free survival (PFS) and overall survival (OS). **Results:** One hundred and thirty-six NDMM patients with a median age of 64.0 years (ranged from 38 to 87 years old) were included. Bortezomib-containing regimens were the most commonly used induction agent, followed by thalidomide. Almost half of the patients (47.1%) achieved very good partial response (VGPR) or complete remission (CR), while 31.6% achieved partial response (PR). Bortezomib containing regimen was associated with significantly deeper and more rapid response, (p=0.001 and p=0.017, respectively) when compared to other agents. Only 22.8% of these patients proceeded to upfront autologous haematopoietic stem cell transplantation. The median OS and PFS were 60.0 months and 25.0 months, respectively. Best initial response and upfront autologous stem cell transplantation (ASCT) were significantly associated with better PFS. **Conclusion:** Achieving at least a VGPR significantly associated with better outcome in NDMM patients. In a resource constrain country, we recommend incorporating bortezomib in the induction therapy followed with an upfront ASCT.

Keywords: Newly diagnosed multiple myeloma- Asia- bortezomib- limited resources- treatment outcome

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Introduction

Over the past decades, major advances in the management of multiple myeloma (MM) which see the mushrooming of novel agents had significantly improved the overall survival of MM patients [1-4]. These include newer proteasome inhibitors (PI) e.g. carfilzomib; immunomodulatory drugs (IMiDs) like lenalidomide or pomalidomide, and newer class of anti-CD38 monoclonal antibody such as daratumumab.

Information on treatment pattern and clinical outcome for newly diagnosed multiple myeloma (NDMM) patients in Asia is limited and even scarcer in Southeast Asian (SEA) region. Most countries in Asia are in the low- or middle-income category and hence not all the novel agents are accessible due to the relatively high cost. This is demonstrated in a study by Kim et al where only 36% of NDMM patients reported to receive novel agents [5]. Recent real world studies had also demonstrated the variability in the frequency of use of lenalidomide, where up to 39% of patients in developed countries such as Japan and Korea had lenalidomide as part of their induction therapy, whereas majority of the less developed nations use a cheaper option of IMiDs such as thalidomide [6-9]. Due to the disparity in the usage of novel agents in Asian countries, the median survival among NDMM patients also varies. This is demonstrated in the superior survival of patients in Japan and Korea, compared to those who were diagnosed in SEA [10, 11, 7, 12].

In Malaysia, MM is the third most common haematological malignancy but information on patients' survival is scarce [13]. Being a middle-income country, the high cost associated with the novel therapies incur enormous burden to patients and government. Most of the recommended treatments such as lenalidomide and daratumumab are generally not reimbursable in the public

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sectors. Therefore, treatment of NDMM patients remains a challenge where cost and optimal patient's outcome needs to be balanced.

This study aims to report on the real-world data of the treatment outcome of NDMM patients treated in a resource-limited setting. It is hoped that the finding of this study can provide further information to best tailor best treatment for our patients.

Materials and Methods

This is a retrospective observational study where medical records of patients with NDMM from 1 January 2008 to 31 December 2022 treated at a teaching hospital in Kuala Lumpur, Malaysia were reviewed. This study was registered with the local institution ethics committee with approval number MREC ID NO: 201511-1909.

Patients with the diagnosis of MM according to the criteria set by International Myeloma Working Group (IMWG) were included [14]. Other inclusion criteria were patients aged 18 years and older and those who proceeded to have treatment after initial diagnosis. Patients who did not have adequate information for response assessment after induction therapy, those who had other cancers or those diagnosed with primary plasma cell leukemia were excluded.

Patients were followed-up until the date of death or date of last clinic visit. Demographic data, such as gender, age at presentation, and ethnicities were captured. Other data for example type of MM, calcium level, renal function, haemoglobin level, bone lesions, and marrow findings including cytogenetic abnormalities were also collected. Patients were categorized into different stages according to Durie Salmon Staging (DSS) or Revised International Staging System (RISS) of patients [15, 16]. Treatment modalities including autologous stem cell transplantation (ASCT) and treatment response were also recorded. Patients who had serum beta-2 microglobulin and cytogenetic results were categorized according to RISS staging system. The cytogenetic abnormalities were classified into high and standard risk based on mSMART 3.0 classification of active MM [17].

The response criteria to induction therapy were defined according to IMWG 2016 consensus criteria for response [18]. Patients were classified into complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), progressive disease (PD) or clinical relapse according to IMWG [18]. Response assessment in the study population was determined every 2 to 3 cycles of therapy. Minimal residual disease (MRD) was not included as part of the assessment as this service was not available.

Survival analysis

Overall survival (OS) was defined as the time from diagnosis to the date of death of any cause. Progression free survival (PFS) was defined as the time from diagnosis to disease progression or death due to any cause, whichever occurs first. Patients were censored at the date of last contact.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Science (SPSS) software version 23.0 (New York, United States). Response to treatment was analysed and compared between groups using chi-square test, with Fisher's exact test applied when appropriate. Mean time to best response was compared between groups using T test or one-way analysis of variance (ANOVA). The log-rank test was used to compare survival differences among categorical variables. Cox regression was used for multivariate analysis to compare factors that affect survival and disease progression. Tests were two sided and $P < 0.05$ was indicative of statistical significance.

Results

Baseline characteristics

One hundred and thirty-six patients were included in this study. There were 77 (56.6%) males and 59 (43.4%) females, age ranged from 38 years to 87 years, with median age of 64.0 years at diagnosis. Table 1 showed the patients' demographic and disease characteristics.

Table 1. Demographic Data, Disease Characteristics and Treatment Regimens Used

	n (%)
Gender	
Male	77 (56.6)
Female	59 (43.4)
Age at diagnosis (years)	64.0 (38 – 87)a
Ethnicity	
Chinese	56 (41.2)
Malay	53 (39.0)
Indian	26 (19.1)
Others	1 (0.7)
Immunoglobulin type	
IgG	83 (61.0)
Others	53 (39.0)
Target organ damage	
Hypercalcaemia	32 (23.5)
Renal impairment	34 (25.0)
Anaemia	92 (67.6)
Lytic bone lesions	109 (80.1)
DSS Stage	
Stage 1	5 (3.7)
Stage 2	56 (41.2)
Stage 3	75 (55.1)
RISS Stage	
Stage 1	9 (6.6)
Stage 2	46 (33.8)
Stage 3	17 (12.5)
Not Available	64 (47.1)
mSMART 3.0 risk category	
Standard risk	80 (58.8)
High risk	22 (16.2)
Not Available	34 (25.0)

Table 1. Continued

	n (%)
Number of agents used	
Doublet therapy	56 (41.2)
Triplet therapy	80 (58.8)
Agents used	
MP	10 (7.4)
TD	28 (20.6)
VD	18 (13.2)
MPT	7 (5.1)
VMP	2 (1.5)
CTD	6 (4.4)
VCD	59 (43.4)
VTD	2 (1.5)
VRD	4 (2.9)

Median duration of follow-up was 30.5 months, ranging from 3 to 176 months.

All patients were staged based on DSS but only 72 patients were able to be staged according to RISS (Table 1). Twenty-two (21.6%) and eighty (78.4%) patients were categorised as high risk and standard risk respectively based on mSMART 3.0 criteria.

Treatment regimens

Fifty-six patients (41.2%) received doublet therapy while the remaining had triplet therapy as induction therapy. The treatment regimens used are shown in Table 1. Eighty-five patients (62.5%) received PI-containing regimens while forty-three patients (42.4%) received IMiDs, including thalidomide and lenalidomide. Only ten patients (7.4%) received non-novel agent combination as induction therapy.

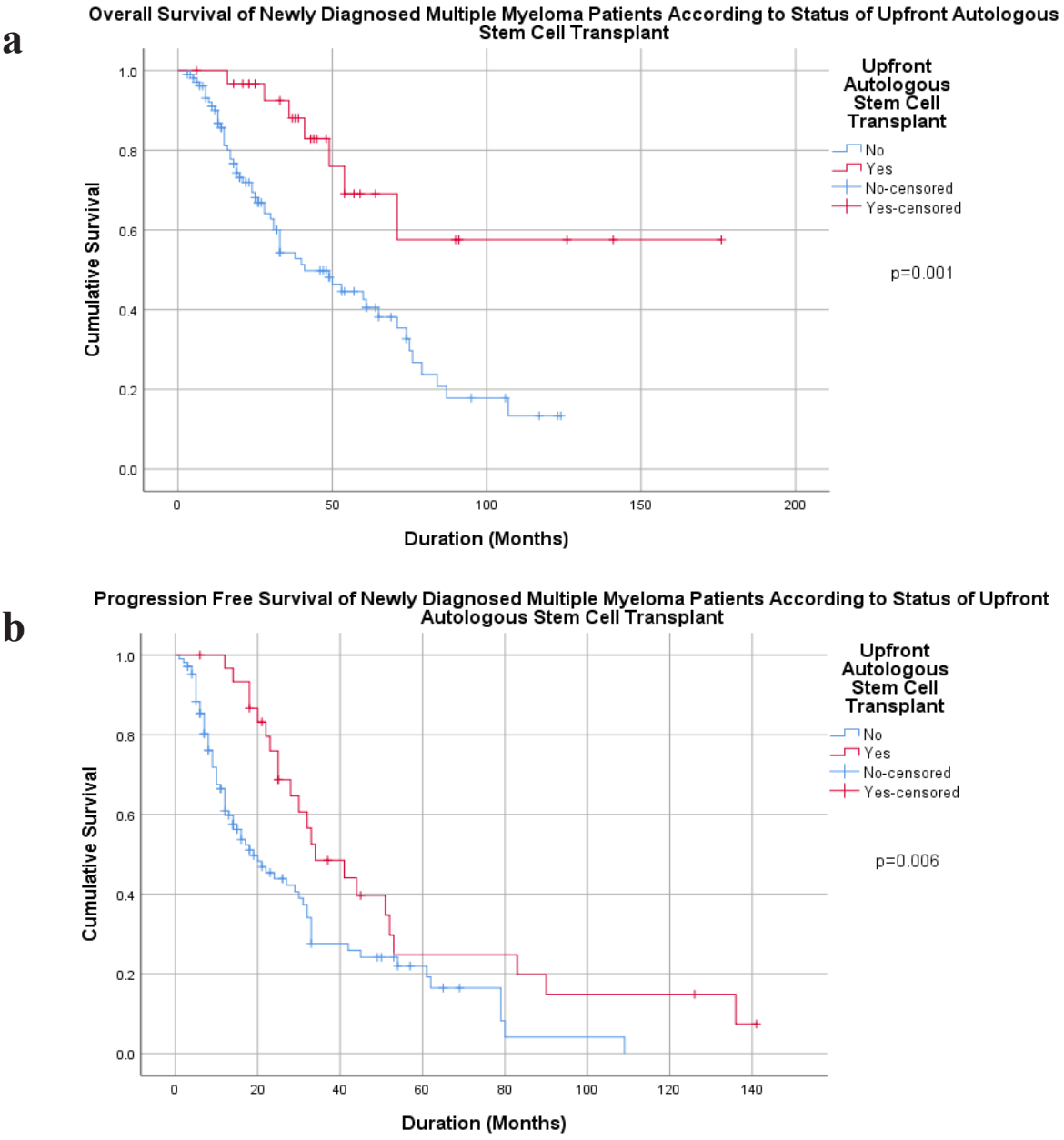

Figure 1. a) overall survival and b) progression free survival of patients with and without upfront autologous stem cell transplant

Table 2. Association of Disease Characteristics, Treatment Regimens Used and Best Treatment Response

	n (%)		P value	Duration to best response Mean (SD)	P value
	Less than VGPR (n=72)	At least VGPR (n=64)			
Age group					
Less than 65	33 (46.5)	38 (53.5)	0.115		
65 and above	39 (60.0)	26 (40.0)			
Immunoglobulin type					
IgG	52 (62.7)	31 (37.3)	0.005*		
Others	20 (37.7)	33 (62.3)			
DSS Stage					
Stage 1	1 (20.0)	4 (80.0)	0.219		
Stage 2	28 (50.0)	28 (50.0)			
Stage 3	43 (57.3)	32 (42.7)			
RISS Stage					
Stage 1	3 (33.3)	6 (66.7)	0.395		
Stage 2	25 (54.3)	21 (45.7)			
Stage 3	7 (41.2)	10 (58.8)			
Not Available	37 (57.8)	27 (42.2)			
mSMART 3.0 category					
Standard risk	42 (52.5)	38 (47.5)	0.615		
High risk	10 (45.5)	12 (54.5)			
Not Available	20 (58.8%)	14 (41.2)			
Number of agents used					
Doublet	35 (62.5)	21 (37.5)	0.081	7.38 (6.295)	0.016*
Triplet	37 (46.3)	43 (53.8)		6.12 (3.110)	
Agents used					
Bortezomib-containing regimens	37 (46.8)	42 (53.2)	0.001*	5.64 (2.920)	0.017*
Thalidomide-containing regimens	24 (58.5)	17 (41.5)		8.26 (7.022)	
Mixed	1 (16.7)	5 (83.3)		6.17 (3.656)	
Non-novel agent	10 (100.0)	0 (0.0)		9.13 (3.871)	

Ig, immunoglobulin; DSS, Durie-Salmon Staging; RISS, Revised International Staging System; VGPR, very good partial response; SD, standard deviation; *P<0.05 is statistically significant

Best initial treatment response

Almost half of the patients (47.1%) achieved VGPR or CR. Patients who have non-IgG subtype (p=0.005) and who were treated with bortezomib-containing regimens as induction (p=0.001) had significant better treatment response (Table 2). Those who were treated with triplet therapy including bortezomib as one of the agents achieved clinical response significantly faster compared to those who did not have (p=0.016 and p=0.017, respectively) (Table 2). Neither age, stage of disease nor mSMART risk category were associated with treatment response.

Overall survival

The median OS was 60.0 months (95% confidence interval [CI] 44.1 – 75.9). Univariate analysis showed that age group, DSS stage, RISS stage, mSMART 3.0 risk category, number of agents used, induction regimens, best initial treatment response and upfront ASCT affected OS. However, after multivariate analysis, only best initial treatment response was demonstrated as an independent predictor of better OS (p=0.004) (Table 3).

Progression free survival

The median PFS was 25.0 months (95% CI 18.03.7 – 32.0). Factors which were demonstrated to be associated with better PFS after multivariate analysis include best initial treatment response and upfront ASCT (Table 3).

Autologous stem cell transplantation

Thirty-one (22.8%) patients underwent upfront ASCT as consolidation therapy. The mean ages of patients who had upfront ASCT were younger, 56.3 years compared to 66.6 years in those who did not (p<0.001). Patients who had upfront ASCT have significantly better median OS (not reached vs. 41.0 months, p=0.001) and median PFS (34.0 months vs. 19.0 months, p=0.006) (Figure 1).

Discussion

The development and introduction of novel therapy for treatment of NDMM over the past decades has improved patient outcome and survival substantially. As more evidence surfaced over the years, international recommendations have been updated to include newer agents [19]. However, this can be financially taxing to

Table 3. Univariate Analysis of Factors Affecting Overall Survival and Progression Free Survival

		Overall Survival			Progression Free Survival		
	n	Died	Median (Months)	P value	Progressed	Median (Months)	P value
Age							
Less than 65	71	26	71	0.005*	51	25	0.571
65 and above	65	37	40		41	27	
Immunoglobulin type							
IgG	83	39	53	0.889	56	29	0.625
Others	53	24	74		36	23	
DSS Stage							
Stage 1	5	3	60	0.008*	3	45	0.14
Stage 2	56	16	107		38	29	
Stage 3	75	44	41		51	20	
RISS Stage							
Stage 1	9	0	-	0.012*	5	62	0.236
Stage 2	46	13	-		32	20	
Stage 3	17	8	-		9	25	
Not Available	64	42			46	27	
mSMART 3.0 category							
Standard risk	80	26	74	0.004*	52	30	0.293
High risk	22	12	33		14	13	
Not Available	34	25	41		26	27	
Number of agents used							
Doublet	56	38	33	0.010*	42	21	0.504
Tripleyt	80	25	71		50	30	
Agents used							
Bortezomib-containing regimens	79	26	74	<0.001*	55	23	0.232
Thalidomide-containing regimens	41	29	49		29	32	
Mixed	6	1	-		2	NR	
Non-novel agent	10	7	21		6	20	
Best initial treatment response							
Less than VGPR	72	40	33	<0.001*	49	12	<0.001*
At least VGPR	64	23	76		43	33	
Upfront ASCT							
No	105	56	41	0.001	70	19	0.006*
Yes	31	7	NR		22	34	

Ig, immunoglobulin; DSS, Durie-Salmon Staging; RISS, Revised International Staging System; VGPR, very good partial response; ASCT, autologous stem cell transplantation; P<0.05 is statistically significant

the healthcare system, especially in Asian countries where most of the countries fall in the low and middle income group [20].

The use of novel agents as induction therapies varies within Asia, including the more developed nations. Most countries use bortezomib rather than lenalidomide as first line induction agent. This is evident in the treatment pattern for NDMM in Korea and Singapore, where between 31.8% and 78% of patients had bortezomib while lenalidomide was used in only 21.5% to 39% respectively [7, 21]. This pattern is similar to our centre as majority of our patients (62.5%) received bortezomib-containing regimens as induction therapy and only 3% received lenalidomide. The possible reason is due to the relative higher cost of lenalidomide. However, the treatment pattern may change in view of the recent availability of generic formulation of lenalidomide in Malaysia. In other parts of SEA countries, there is also variation in the prescription pattern. For example, 35.7% and 62.2% of NDMM patients in Philippines and Myanmar received bortezomib, in contrast to patients in Indonesia where none received novel agent as part of induction therapy [10, 11, 22]. The vast difference in the first line treatment choices is most likely due to the discrepancy in reimbursement options in each country. However, it is noteworthy that some of these studies were published more than 10 years ago, and situation may have changed now.

Almost half of our patients achieved VGPR or better

and the treatment outcome correlates with the use of novel agents. Similarly, superior results were also reported in Myanmar and Singapore where more than half of their patients achieved VGPR or better although this was not observed in a study conducted in Philippines where only about a third of their patients achieved such response [22, 11].

In this study, median PFS and OS of the NDMM patients were 25.0 months and 60.0 months, respectively, which were comparable to what was reported in other Asian countries [7, 12, 23]. Meanwhile, result from a single center study from Indonesia has shown a lower median OS at 28.0 months [10]. This discrepancy may reflect the availability of novel agents for second line and beyond in each of these countries. Our findings showed that achieving at least a VGPR predicts better OS. This is consistent with other studies which have shown that deeper response including minimal residual disease (MRD) negativity, the better the OS [18, 24, 25]. Although our centre does not have the facility to determine MRD, the response determined by serum electrophoresis and serum free light chain appeared to yield similar findings.

When bortezomib is included as part of the induction therapy, treatment response is better and faster, similar with the results of a meta-analysis and this translate to improvement in both PFS and OS [26]. Despite a better treatment response among our NDMM patients, there was no significant improvement in PFS and OS, likely due the relatively small number of patients.

Nonetheless, the goal of treatment strategies for NDMM patients should be to achieve the best initial response, although cost effective of such treatment should also be taken into consideration. In a resource limited setting, bortezomib ought to be part of the three drug combinations as it has shown to be the optimal choice.

ASCT has consistently shown to significantly improve PFS of MM patients and this study demonstrates similar results [27]. However, it is noteworthy that only about 20% of our patients proceeded to have upfront ASCT. This may be due to our centre implementing an age limit of 60 years previously; other possibilities may include unwillingness of patients or progression of disease. The findings of this study re-emphasise that ASCT should be offered to those who are eligible and fit. Moreover, the relative low cost of ASCT in our centre (approximately USD5,000) is a more cost-effective strategy than those therapeutic choices which incorporate newer agents as first-line. Hence, ASCT may represent an attractive option especially in low middle-income countries where accessibility of novel agents in NDMM is limited.

There are few limitations in this study. Firstly, it was a retrospective study, and not all patients were able to categorise according to RISS due to lack of adequate information. The sample size is also relatively small and may not truly reflect the real situation in Malaysia. However, our single center study provides useful information on treatment pattern and outcome of NDMM patients within SEA, where such data are lacking.

In conclusion, we demonstrate that achieving at least a VGPR significantly associated with better outcome in NDMM patients. In a resource constrain country, we recommend induction therapy incorporating bortezomib followed with an upfront ASCT.

Author Contribution Statement

CSC was involved in study design, data collection, analysis of data and manuscript writing. TAHTA collected data. NAA, PCB, EFMC, SK, CCL were involved in review of the manuscript. GGG has developed the concept, revised and supervised the work. All authors read and approved the final manuscript.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical Declaration

This study was approved by University Malaya Medical Center-Medical Research Ethics Committee (UMMC-MREC). The reference number for approval was 201511-1909.

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