Treatment outcome of newly diagnosed multiple myeloma patients: A retrospective analysis in a resource-limited setting

Chin Sum Cheong[1], Tengku Ahmad Hidayat Tengku K Aziz[2], Nur Adila Anuar[3], bee chong[1], Edmund Fui Min Chin[1], Shasha Khairullah[1], Chee Chiat Liong[1], and Gin Gin Gan[1]

[1]University of Malaya
[2]Beacon Hospital
[3]Universiti Malaya

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Abstract

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. The usage of novel agents can be financially taxing, and hence resources limit its use. This study aims to report on the real-world treatment outcome when resources are limited. This is a retrospective study on newly diagnosed multiple myeloma (NDMM) patients diagnosed between 1 January 2008 and 31 December 2018 in a single academic center. Patients demographic and type of treatment were included for analysis of progression free survival and overall survival. Ninety-eight NDMM patients with a median age of 63.5 (ranged from 38 to 87 years old) were included. Half of the total patients received bortezomib-containing regimens while 40.8% received thalidomide-containing regimens, and remaining 9.2% had other agents as induction. Forty-seven patients (48.0%) achieved very good partial response (VGPR) or complete remission (CR), while remaining 51 patients (52.0%) have achieved partial response (PR) at best during induction therapy. Bortezomib use was associated with significantly deeper (p=0.001) and more rapid response (p=0.005) compared to other agents. Five-year OS and PFS were 45.3% and 18.4%, respectively. Triplet regimen, best initial response and upfront ASCT were significantly associated with better PFS. In conclusion, deep response significantly affects PFS and OS in NDMM patients. Thus, one of the goals of treatment is to ensure earlier and deeper response by including bortezomib as part of triplet combination in upfront therapy, followed by ASCT for those who are fit. This is feasible in a resource limited country such as Malaysia, especially there is a cheaper generic formulation.

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In conclusion, deep response significantly affects PFS and OS in NDMM patients. Thus, one of the goals of treatment is to ensure earlier and deeper response by including bortezomib as part of triplet combination in upfront therapy, followed by ASCT for those who are fit. This is feasible in a resource limited country such as Malaysia, especially there is a cheaper generic formulation.

Keywords: newly diagnosed multiple myeloma, Asia, bortezomib, novel agents, limited resources, treatment outcome

What's known

***** The pillar of treatment of myeloma is induction treatment followed by consolidation with autologous haematopoietic stem cell transplantation

* Triplet therapy has shown better response rate compared to doublet therapy in multiple myeloma treated patients.

* There is sparse information available concerning the survival outcome of multiple myeloma in South East Asia regions. Reports on the survival outcome were mainly from developed countries.

What's new?

* We present the disease characteristic and treatment outcome of multiple myeloma patients in Malaysia (the first report from Malaysia), whereby newer data in resource-limited countries within South East Asia regions are deprived of.

***** Bortezomib-based treatment is associated with deeper and quicker response, and it is recommended to be included as first-line treatment, in a resource-limited setting followed by AHSCT as a cost-effective strategy especially with the avaibility of generic form.

Background

Multiple myeloma (MM) is a haematological cancer characterized by the proliferation of neoplastic plasma cells in the bone marrow, resulting in lytic bone lesions, hypercalcaemia, anaemia and renal impairment. It is the third most common haematological malignancy in Malaysia, after non-Hodgkin's lymphoma and leukemia [1].

There have been major advances in the treatment of MM over the past 15 years. Introduction of novel agents has improved survival in MM significantly, from median survival of 2.5 years to 6 years, and even longer in certain subset of patients who had autologous stem cell transplantation (ASCT) [2-4]. These novel agents include immunomodulatory agents (IMiDs) such as, lenalidomide and pomalidomide; proteasome inhibitors (PI) for instance bortezomib, carfilzomib and ixazomib; daratumumab, a monoclonal antibody that target CD38 protein on myeloma cells, among others. These agents, which are now being used in both upfront and relapsed settings, have shown to retard disease progression and prolong patient survival [5-9].

Various induction regimens are available for newly diagnosed multiple myeloma (NDMM) patients. Triplet therapy has shown better response rate compared to doublet therapy [3, 8] and is now considered standard of care [10, 11]. Bortezomib-based three-drug regimens are considered the best option as induction therapy in transplant eligible patients [10]. Similarly, superiority in terms of progression free survival (PFS) and overall survival (OS) were also demonstrated in transplant ineligible patients when bortezomib was combined with melphalan or lenalidomide [7, 12]. Other first line treatment options include lenalidomide- and daratumumab-based combinations, which have similarly shown to be effective [6, 8, 13].

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, co-morbidities, previous treatment and the interval since the last therapy. Bortezomib-based doublets or triplets are recommended in relapse after IMiD-based induction, whereas patients who relapse after bortezomib-based induction are recommended to receive doublets or triplets with lenalidomide and dexamethasone as backbone [10].

Several studies have demonstrated that a quality response at any stage of treatment, including induction, ASCT and during consolidation; is associated with improved outcome [14, 15]. However, usage of these novel therapies to achieve deep response, although are associated with better PFS and OS, has increased health cost exponentially. In the United States, total healthcare cost has increased from USD$3263 per patient per month (PPPM) in 2000 to USD$14656 PPPM among patients with newly diagnosed multiple myeloma in 2014. Treatment related drug costs, which accounted for 10.6% from the total expenses in year 2000, have increased to 28.5% in 2014 [16].

In Asia, where most countries are in the low- or middle-income category, not all of these novel agents are available due to limited resources. Therefore, cheaper options such as thalidomide-based or bortezomib-based therapy are frequently used as first line treatment in patients with NDMM [17, 18]. The usage of novel agent use is relatively low where only about 36% of NDMM patients received them [19].

A recently published consensus from the Asian countries made several recommendations based on affordability, apart from efficacy of the combination therapy. Three-drug combination that includes a second generation IMiD like lenalidomide and a PI is recommended as front line treatment for transplant eligible and transplant ineligible patients who are fit, or any bortezomib-based triplet if reimbursement disallows. Two-drug regimen with an aim to achieve maximum response with minimal treatment-related toxicity is recommended for unfit patients who are transplant ineligible. Bortezomib- or lenalidomide-based triplet therapy is recommended in relapsed setting [20].

In Malaysia, we encounter similar problems in the management of patients with multiple myeloma. Being a middle-income country, the high cost associated with the novel therapies incur enormous burden to patients and government. The Total Expenditure on Health (TEH) for Malaysia ranged from 3.05% to 4.21% of total Gross Domestic Product (GDP) from 1997 to 2016. The government and private insurance and out-of pocket expenditures shared almost equal proportion in financial resources to support TEH [21]. Therefore, treatment of myeloma patients remains challenging for physicians to strike a balance between cost of treatment and patient outcome.

Thus, we decide to embark on this study with the aims to determine the efficacy, overall survival and progression free survival of patients treated with various induction agents, in a resource limited setting. It is hoped the finding of this study can provide information to best tailor treatment for our patients.

Material and methods

This is a retrospective study, which involved patients who were diagnosed of MM from 1 January 2008 to 31 December 2018 in University Malaya Medical Center. The diagnostic criteria for multiple myeloma were according to the criteria set by International Myeloma Working Group (IMWG) [22]. Ethics committee approval was obtained from Medical Research Ethics Committee, University Malaya Medical Center (MREC ID No: 201511-1909).

Patients included in this study were age 18 years and older and those who proceeded to have treatment after initial diagnosis. Patients who did not return for follow-up prior to first assessment after treatment initiation, those who had another primary cancer before diagnosis of MM or presented with primary plasma cell leukemia, were excluded from the study.

Patients were followed up until the date of death or date of last clinic visit with a minimum of 3 months follow up. Medical records of these patients were reviewed and demographic data, clinical features on presentation, Durie-Salmon Staging (DSS) or International Staging System (ISS) of patients, treatment modalities including autologous stem cell transplantation, treatment response and survival were captured.

ISS staging data was captured for a subset of patients as serum beta-2 microglobulin test was only available in our center from January 2015.

Response to treatment

The response criteria to induction therapy were defined according to IMWG 2016 consensus criteria for response [23]. These 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 [23].

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. All patients including those who lost to follow-up 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. 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). Cumulative survival curves were plotted according to the Kaplan-Meier method. 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

Ninety-eight patients were included in this study. There were 52 (53.1%) males and 46 (46.9%) females, age ranged from 38 to 87 years old, with a median age of 63.5 years old at diagnosis. These patients comprise 39 (39.8%) Chinese, 36 (36.7%) Malays and 23 (23.5%) Indians. The median duration of follow-up was 33 months in this study, ranging from 3 to 154 months. Table 1 showed the patients' demographic and disease characteristics.

All patients were staged based on Durie-Salmon Staging System (DSS). Only 37 patients were able to be staged according to the International Staging System (ISS) (Table 1).

Treatment regimens

Fifty-three patients (54.1%) and forty-five patients (45.9%) with newly diagnosed multiple myeloma, received doublet and triplet therapy for induction therapy, respectively. The treatment regimens used are shown in Table 2.

We have further divided the treatment regimens into three groups: thalidomide-containing regimens, bortezomib-containing regimens and non-novel agents. In this study, forty-nine patients (50.0%) received bortezomib-containing regimens; forty patients (40.8%) received thalidomide-containing regimens, and nine patients (9.2%) received non-novel agent combination during induction therapy.

Treatment response

Forty-seven patients (48.0%) achieved VGPR or CR, while remaining 51 patients (52.0%) have achieved PR at best during induction therapy.

Age and clinical presentations were not found to be significantly associated with treatment response. The type of MM and stage of disease were also not associated with response (Table 3). Similarly, there was no significant difference in proportion of patients with at least VGPR with either doublet or triplet therapy

(p=0.073). However, patients who were treated with bortezomib-containing regimens had better treatment response when compared to those who were treated with thalidomide and melphalan (p=0.001) (Table 3).

Although there was no significant difference in time to best response between those who received doublet therapy and triplet therapy, patients treated with bortezomib achieved clinical response significantly faster (p=0.005) (Table 4).

Overall survival

The 5-year OS for patients with NDMM was 45.3% (Figure 1). Univariate analysis showed that age group, ISS stage, number of agents used, induction regimens, best initial treatment response and upfront ASCT affect OS. However, after multivariate analysis, only best initial treatment response was demonstrated as an independent predictor of overall survival (p=0.008) (Table 5).

Progression free survival

The 5-year PFS of patients with NDMM was 18.4% (Figure 2). Factors that affect disease progression identified on univariate and multivariate analysis include number of agents used, type of induction regimens, best initial treatment response and upfront ASCT (Table 6).

Autologous stem cell transplantation

Nineteen (19.4%) out of ninety-eight patients underwent upfront ASCT as part of treatment for multiple myeloma. The median ages of patients with and without upfront ASCT were 57 and 66 years old, respectively. In comparison, patients who had upfront ASCT have significantly better 5-year OS (p=0.039) and PFS (p=0.002) (Figure 3 and 4).

Seven patients (7.1%) had ASCT after disease progression from initial induction therapy. They were given second line or third line therapy prior to ASCT. The mean duration to ASCT from date of diagnosis was significantly longer in those who received upfront ASCT (9.38+ 3.728 months), compared to 32.69+ 25.755 months in those who had transplant later (p<0.001). However, there was no significant difference in 5-year OS between these two groups (p=0.493).

Discussion

The development and introduction of novel therapy for treatment of multiple myeloma 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 [20]. The usage of these agents as per recommendation can be financially taxing to the healthcare system, especially in Asian countries where most of the countries fall in the low and middle income group [24]. Hence, some of these new treatment options become inaccessible to patients in view of resource limitation.

The median age at diagnosis of patients in this study was 63.5 years old. This is comparable to what was reported in other parts of Asia. The most common type of myeloma in this population was of IgG type (63.3%) followed by IgA (24.5%). We found similar results as other studies [19, 25, 26]. More than half of our patients presented at late stage and this is higher than what was reported elsewhere in the world, reflecting possible lack of awareness of this disease in our general population [25-27].

Only half of our patients (49.9%) received bortezomib-containing regimens as first line therapy and none received lenalidomide as first line. This is because the relative high cost of these agents, especially lenalidomide, which is not only not reimbursable and there is also no available generic formulation in Malaysia until 2020 [18]. Other countries within Asian region reported various frequencies of lenalidomide use, ranging from 2% in Japan to 39% in Korea [28, 29]. When compared with the data from CoMMpass study involving patients from the United States and Europe, lenalidomide use was 52% [30]. The difference may be related to discrepancy in reimbursement options in these countries.

From our study, almost half of our patients achieved VGPR or better after first line therapy. This is higher than what was reported by Asian Myeloma Network, which included other countries within Asia regions

[19]. Novel agents were only used in 35.9% of NDMM patients. It is important to note that the study was published almost 10 years ago when most of the novel agents were expensive and generic options were not available. Preliminary result from Asia-Pacific (APAC) Myeloma and Related Diseases Registry (MRDR) showed that the usage of novel agents is now higher, with bortezomib-based regimen alone encountered for at least 45% of the first line treatment administered and this would likely results in different treatment and survival outcome. [25]. In comparison, 67.5% of patients in a Swedish registry received novel drugs, and 45.8% of them achieved VGPR or better after first line treatment [26]. The vast difference in treatment response could be due to difference in treatment regimen used during induction.

The 5-year OS of patients with NDMM was 45.3% in this study. This is similar to what was reported in other Asian countries where the OS was reported to range from 46.7% to 50.3% [29, 31]. However, when compared with a Swedish study, the OS was reported to be only 38.3% and this difference may have been due to the older patients' cohort. [26]

Five year PFS was only 18.4% in this study. Triplet regimen, best initial response and upfront ASCT were significantly associated with better PFS. These findings are consistent with other studies [12, 15, 32]. Interestingly, patients who were treated with thalidomide-containing regimens as first line had also better PFS. There is no direct comparison between bortezomib- and thalidomide-containing regimens, but previous systematic review showed no superiority of one agent over another [33]. Small sample size of this study may have affected the findings. However, it is important to realise that patients would eventually relapse as evident by the low 5 year PFS.

In this study, depth of response after induction therapy was shown to be associated with better outcome. Many studies have also consistently demonstrated the effect of achieving deeper response and its implications on clinical outcomes. Recently, minimal residual disease (MRD) has also been integrated into the response criteria as MRD negativity has been shown to improve OS in NDMM patients [23, 34, 35]. With the availability of better treatment options and assessment tools, the aim of treatment for NDMM patients is now gearing towards a deeper response for better survival outcome. In this study, the proportion of patients who have achieved at least VGPR was significantly higher with bortezomib-based treatment. The time to response was also shown to be shortest in patients who were treated with bortezomib-containing regimens. This is consistent with the result from a meta-analysis, which demonstrated significant improvement in overall response rate in patients who had bortezomib as one of their first line treatments. These findings corresponded to improvement in both PFS and OS [36]. Although our study did not demonstrate that bortezomib-containing regimen improves OS or PFS, it could be due to the relatively small number of patients.

ASCT is shown in this study to significantly improve PFS and this is consistent with previous analysis although OS was not affected [32]. In view of the potential benefit of ASCT among NDMM patients, it is recommended in the guidelines in patients who are young and fit [20, 37]. Only about 20% of patients proceeded to have upfront ASCT as part of consolidation in this study. The relatively low number is due to our previous age limit for ASCT, which was 60 years and below and hence, this inadvertently reflected in the total number of transplantation performed.

There are few limitations in this study. Firstly, it is a retrospective study and some of the information was not complete and certain laboratory investigations such as beta 2-microglobulin and serum free light chain were not available at the initial stage. Secondly, some of the novel agents are not reimbursable and this may have affected the choice of first line treatment among our NDMM patients. There is also a change in treatment used as the availability of generic drugs becomes available at the later part of this study for example, bortezomib which was relatively costly initially became one of the common first line drugs prescribed in our NDMM patients when generic formulation became available. Finally, the sample size is small and some of the conclusions cannot be confirmed with this single centre study.

In conclusion, the result from this study reflected the disease characteristics and treatment efficacy in the real world setting in an Asian developing country. It is important to note that most of our patients presented

late in the disease. Therefore, it is pertinent that education to create awareness for both patients and healthcare workers for early detection of MM. Bortezomib-based treatment is associated with deeper and quicker response, and hence it ought to be recommended to be included as first line treatment, in a resource-limited setting especially with the availability of generic form. Deep response significantly affects PFS and OS in NDMM patients and thus, one of the goals of treatment is to ensure earlier and deeper response by including bortezomib and triplet combination in upfront therapy, followed by ASCT for those who are fit. Newer novel agents definitely have their roles in the management of NDMM patients if they are more accessible to our patients.

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