Multiple Myeloma in Indonesia

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ABSTRACT

Aim: to overview the clinical characteristics of multiple myeloma patients in Indonesia. Methods: We conducted descriptive method, crosssectional multicentre study on November 2008 until November 2009. Data of seventy multiple myeloma patients was taken from Indonesia's Multiple Myeloma Study Group.

Results: Over sixty percent of MM patients were at the age of more than fifty years old (65.71%), gender approximately equal between male and female. Approximately half of the patients were Javanese, senior high school educational background, and unemployeed.

Fifty-three percent patients have less then 30% plasma cells in the bone marrow with seventy percent patients had negative Bence Jones proteinuria and positive monoclonal gammopathy serum in more than eighty percent patients. The percentage of plasma cells in the bone marrow were more frequent among younger patients (34.05% vs 24.24% vs 7.5%).

We reported that almost half of the patients had IIIA stage based on Durie-Salmon staging system. A higher stage associated with older patients according to International Myeloma Working Group System classification. Melphalan/prednisone was the most chemotherapy regimen that used for the treatment (59.7%) while forty five percent patients had a partial response as the most frequent best response to primary chemotherapy.

Conclusion: Multiple myeloma patients characteristics in Indonesia predominantly Javanese ethnicity, senior high school background and unemployeed status. Based on clinical characteristics, most of the patients had less than 30% palsma cells in the bone marrow with negative Bence Jones proteinuria and positive monoclonal gammopathy serum. Almost half of the patients had IIIA stage with melphalan/prednisone as the most chemotherapy regimen used with a result of partial response as the most frequent best response found.

Keyword : *Multiple myeloma, clinical characteristics, Indonesia*

ABSTRAK

Tujuan: Melihat karakteristik klinis pasien mieloma multipel di Indonesia.

Metode: studi deskriptif, potong lintang, multisenter, dilakukan pada November 2008 sampai dengan November 2009. Tujuh puluh data pasien mieloma multipel diambil dari seluruh Indonesia, dari kelompok studi mieloma multipel di Indonesia.

Hasil: Lebih dari enam puluh persen pasien mieloma multipel di Indonesia berusia lebih dari 50 tahun (65,71%) dengan perbadingan jenis kelamin yang kurang lebih sama antara pria dan wanita. Kurang lebih lima puluh persen pasien bersuku Jawa, dengan tingkat pendidikan Sekolah Menengah Atas (SMA) dan tidak bekerja.

Lima puluh tiga persen pasien memiliki kurang dari 30% sel plasma di sumsum tulangnya dengan 70% pasien tidak memiliki proteinuria Bence Jones dan 80% pasien memiliki serum *monoclonal gammopathy* yang positif. Persentase sel plasma di sumsum tulang lebih banyak ditemukan pada pasien yang berusia lebih muda (34,05% vs. 24,24% vs. 7,5%). Dilaporkan bahwa hampir lima puluh persen pasien memiliki stadium IIIA berdasarkan klasifikasi *Durie Salmon Staging system*. Stadium penyakit yang lebih tinggi berkaitan dengan usia yang lebih tua berdasarkan klasifikasi *International Myeloma Working Group*. Melphalan/prednisone merupakan pilihan kemoterapi yang paling banyak digunakan (59,7%) dengan hasil pengobatan terbanyak adalah respons parsial.

Kesimpulan: karakteristik pasien mieloma multipel di Indonesia didominasi oleh suku Jawa, dengan tingkat pendidikan SMA dan tidak bekerja. Sebagian besar pasien memiliki sel plasma kurang dari 30% di sumsum tulang, proteinuria Bence Jones yang negatif, dan serum *monoclonal gammopathy* yang positif. Hampir lima puluh persen pasien memiliki stadium IIIA dengan melphalan/prednison sebagai jenis kemoterapi terbanyak yang diberikan dengan hasil terbaik sebagian besar adalah respon parsial.

Kata kunci : mieloma multipel, karakteristik klinis, Indonesia

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INTRODUCTION

Multiple myeloma is characterized by malignant plasma cells infiltrating the bone marrow, and some patients a malignant plasma cells infiltrate other organs and extramedullary tissues. Based on a laboratory view, plasma cells neoplasma are distinguished by an idiotypic rearrangement of the immunoglobulin gene, which occurs prior to the malignant transformation of an early plasma cell precursor. The clone that develops must increase to about 5 x 10^9 cells before it produces enough of the idiotypic immunoglobulin to be recognized as a monoclonal "spike" (M protein or paraprotein) in a serum electrophoresis pattern. Most subjects with a serum M-protein can be ruled out, they are labeled as monoclonal gammopathies of undermined significance (MGUS). By definition, the monoclone in MGUS is stable and the serum M-protein concentration remains more or less at the same level for many years. However, prolonged follow up of a large group of MGUS subjects at the Majo Clinic has shown that about 2% of these patients progress per year to develop symptomatic multiple myeloma (MM), macroglobulinemia, malignant lymphoma, chronic lymphocytic leukemia or amyloidosis. Almost all the genetic aberrations identified in MM (aneuplody, monosomy 13, 14q13 chromosome translocations) are also present in MGUS. Additional neoplastic changes are required to convert this large stable clone into MM, a progressively expanding tumor with malignant characteristics.[1-3]

In most cases, monoclonal immunoglobulin molecules or immunoglobulin light chains can be measured in the serum or urine and used as a specific marker for diagnosis and follow up. Presenting symptoms depend on tumor burden and individual complications induced by each myeloma plasma cells clone. The clone may produce and secrete monoclonal immunoglobulin, different cytokines, and less defined biological and physically active factors, which interfere with bone metabolism, renal function, hematopoeisis, immune mechanisms, and other organ systems. Different patterns of such complications contribute to the heterogeneity of MM patients in terms of symptoms, treatment strategy, and prognosis.[1,4,5]

Epidemiologic approaches can be used to track the occurrence of disease, to characterize natural history, and to identify determinants of disease. These evidences are needed as foundation to develop better therapy inspites all the limitations of current therapy in the treatment of the disease. The objectives of the study is to overview the clinical characteristics of multiple myeloma patients in Indonesia.

MATERIAL AND METHODS

We conducted descriptive method, crosssectional multicentre study on November 2008 until November 2009. Data of seventy multiple myeloma patients was taken from Indonesia's Multiple Myeloma Study Group.

Basic characteristics data was taken from patients including: age, gender, ethnicity, educational background and employment status. Clinical characteristics's data that evaluated including : percentage of plasma cells in bone marrow, Bence Jones proteinuria, monoclonal gammopathy serum frequency and multiple myeloma staging. This study also evaluated the type of chemotherapy that used for treatment and the best response to treatment. The data collected were analyzed by SPSS programme.

RESULTS

Basic Characteristics

The multiple myeloma demographic data in Indonesia is presented in table 1. It is acknowledged that over sixty percent MM patients were at the age of more than fifty years old and the gender approximately equal between male and female. Approximately half of the patients were Javanese, senior high school educational background, and unemployeed.

Table 1: Basic characteristics of multiple myeloma in Indonesia

CHARACTERISTICS	FREQUENCY (%)
Age	
• < 30 years	2.86
• 30 – 50 years	31.43
• > 50 years	65.71
Gender	
• Male	52.86
• Female	47.14
Ethnicity	
• Balinese	37.14
• Buginese	28.6
• Chinese	2.86
• Gorontalo	5.71
• Javanese	51.42
Educational background	
• Elementary school	26.67
• Senior high school	57.78
• University	15.56
Employment status	
• Unemployeed	56.0
• Employeed, part time	12.0
• Employeed, full time	30.0

Clinical Characteristics

We also collected the percentage of plasma cells in bone marrow. More than fifty percent of the Indonesian MM patients have less than thirty percent of plasma cells in bone marrow, and only fifteen percents have plasma cells more than forty percents in the bone marrow.

Table 2: Percentage of plasma cells in bone marrow

Percentage of plasma cells in bone marrow	Frequency (%)
• < 30%	35 (53.03)
• 30 - 40 %	21 (31.82)
• > 40%	10 (15.15)

Table 3: Percentage of plasma cells in bone marrow based on age and gender classification

Variables	Percentage of plasma cells in the bone marrow		
	< 30	30 – 40	>40
Age classification			
< 30 years	1.52	16.67	34.05
30 – 50 years	0	7.5	24.24
> 50 years	0	7.5	7.5
Gender			
Male	22.73	19.7	10.61
Female	30.30	12.12	4.55

Based on plasmacytoma examination (10 patients), we found positive results in 8 patients (80%) and negative results in 2 patients (20%).

Based on age classification (table 3), we found that the percentage of plasma cells in bone marrow is more frequent among younger patients. Based on gender classification, it seems that female tendency have fewer percentage plasma cell than male.

Table 4: Frequency of Bence Jones proteinuria and monoclonal gammopathy serum

Variables	Frequency (%)
Bence Jones proteinuria	
Negative	34 (73.91)
Positive	12 (26.09)
Serum protein electrophoresis (monoclonal gammopathy)	
Negative	11 (15.71)
Positive	59 (84.29)

We found that over seventy percent of MM patients have negative Bence Jones proteinuria and more than eighty percent have positive monoclonal gammopathy serum, reversely (table 4).

Stage of multiple myeloma as initial diagnosis can be assessed by two types of staging system which are Durie-Salmon staging system and International Myeloma Working Group Staging (IMWG) System.[4,13] Based on Durie-Salmon staging system, we found that almost half of patients have IIIA stage at first diagnosis and that result was similar if we used International Myeloma Working Group system (table 6).

According to International Myeloma Working Group system classification (table 7), we found that a higher stage associated with older and female MM patients.

Table 5: Percentage of Bence Jones proteinuria and monoclonal gammopathy serum based on age and gender classification

Variables	% of plasma cells in bone marrow		Monoclonal gammopathy (%)	
	Negative	Positive	Unknown	Positive
Age classification				
< 30 years	0	0	0	2.86
30 – 50 years	26.09	4.35	0	31.43
> 50 years	47.83	21.74	15.71	50.00
Gender				
Male	39.13	15.22	7.14	45.71
Female	34.78	10.87	8.57	38.57

Table 6: Multiple myeloma stage based on Durie-Salmon staging system and International Working Group staging system

Multiple myeloma stage	Frequency (%)
Durie-Salmon Staging System	
IA	1 (1.47)
IB	1 (1.47)
IIA	10 (14.71)
IIB	6 (8.82)
IIIA	32 (47.06)
IIIB	18 (26.47)
International Myeloma Working Group Staging System	
Unknown	2 (8.33)
I	2 (8.33)
II	5 (20.83)
III	15 (62.50)

Table 7: Distribution of Durie-Salmon staging system of multiple myeloma by age and gender classification

Variables	Stage of multiple myeloma based on international myeloma working group staging system (%)		
	I	II	III
Age classification			
< 30 years	0	0	4.17
30 – 50 years	4.17	0	29.17
> 50 years	4.17	20.38	29.17
Gender			
Male	4.17	4.17	25.00
Female	4.17	16.67	37.50

Table 8: Type of chemotherapy and response on first line chemotherapy

Variables	Frequency (%)
Chemothrapy protocols	
Melphalan/prednison	40 (59.70)
VAD	15 (22.39)
VBMPC	2 (2.99)
Thalidomide/dexametasone	3 (4.48)
Other protocols	7 (10.45)
Best respons on first line treatment with primary chemotherapy	
Complete response	3 (8.57)
Partial response	16 (45.71)
Minimal response	4 (11.43)
Stable disease	3 (8.57)
Progressive disease	9 (25.71)

Based on type of chemotherapy that used for the treatment, we found the most frequent regiment for chemotherapy was melphalan/prednisone (59.70%), the others were VAD, VBMC, thalidomide/dexametasone. Forty five percent patients had a partial response as the most frequent best response to primary chemotherapy (table 8).

DISCUSSION

Cytomorphology of Peripheral Blood and Bone Marrow

The finding of plasma cells which produce a "mass" effect indicates displacement of normal tissue through plasma cells infiltration, evidencing the uncontrolled growth of a malignant clone. This pathologic micro-anatomic property contrasts with the usual randomly dispersed, non-aggregated plasma cells in a benign reactive plasmacytosis. Beyond a "mass effect", additional cytologic properties favor a neoplastic process. Specifically, these include the findings of multinucleated plasma cells and plasma cell immaturity or anaplasia. Since 1-5% of reactive plasma cells may be binucleate or, rarely, trinucleate, it is the finding of bizzare multinucleate (greater than trinucleate) forms that is mostly considered pathologic. The findings of immaturity include dispersed nuclear chromatin, high nuclear/cytoplasmic ratio and prominent nucleoli, giving a "blastic" appearance indicative of plasmablasts. Since nuclear-cytoplasmic asynchrony and immaturity rarely occur in reactive circumstances, they are realiable indicators of "atypical" or pleomorphic plasmacytosis greatly favoring a diagnosis of neoplasia.[6] In this study, we found that over fifty percent of the Indonesian MM patients have less than thirty percent of plasma cells in bone marrow, and only fifteen percents have plasma cells more than forty percents in the bone marrow (table 2).

Biochemical and Immunological Investigations

Biochemical investigations play an important role in the diagnosis, prognosis and monitoring of Multiple Myeloma. The monoclonal immunoglobulin resulting from the clonal proliferation of the B cells is an important tumor marker and reliable detection, typing and quantification of the monoclonal protein (M protein or paraprotein) is vital. Measures of proteins related to B-cell function or turnover, e.g. the polyclonal background immunoglobulins or β2-microglobulin, can give indications of tumor burden and prognosis.[7] Additionally, in the investigation of patients with B-cell dyscrasiasis, a wide range of biochemical markers are useful to monitor renal function, bone and calcium metabolism, infection and the effects of treatments. Monoclonal proteins may be present at very high concentrations and often show manifestations not seen with normal polyclonal immunoglobulins, such as hyperviscosity, protein precipitation, or interference in analytical systems, where their presence can influence a variety of analyzes and methods.

In this study, we found that over seventy percent MM patients have negative Bence Jones proteinuria and more than eighty percent have positive monoclonal gammopathy serum (table 4). Although we found that over seventy MM patients have negative Bence Jones proteinuria, there are more than eighty percents have positive monoclonal gammopathy serum, reversely. This has fulfill one of the all 3 required of MM diagnostic criteria according to the Durie-Salmon staging system. Yet, to confirm the diagnosis, the Durie Salmon criteria requires the presence of monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma and one or more of myeloma-related organ dysfunction.

Cytogenetics

In recent years, considerable progress has also been made in cytogenetic and molecular genetic investigation of lymphoproliferative disorders, and most investigators believe that almost every case is characterized by chromosomally abnormal clones. This is also true for multiple myeloma (MM), but cytogenetic studies of MM cells are often hampered by the low mitotic rate of the myelomatous clone. For this reason, use of molecular cytogenetic techniques, which do not necessarily depend on dividing cells, has greatly enhanced our possibilities to investigate MM and monoclonal gammopathy of undetermined significance (MGUS) at the cytogenetic level and to derive clinically relevant information from these studies.

The ability to obtain karyotypic information in MM is greatly influenced by the aggresiveness and the

proliferative capacity of the malignant clone. Abnormal karyotypes are, therefore, almost never observed in MGUS; in MM, chromosomally abnormal clones can be found in 30-40% of patients with newly diagnosed disease, in up to 60% of patients with relapsed disease, and in up to 80% of patients with plasma cell leukemia.[8] Karyotypes in MM typically exhibit a complex set of numerical and structural abnormalities. Cytogenetic studies performed in large patient population have reproducibly shown that two main groups of MM patients can be distinguished based on the number of chromosomes in the abnormal metaphases. One group is characterized by the presence of a hyperdiploid clone (with mean chromosome numbers between 50 and 53) with frequent occurrence of trisomies of chromosomes 3, 5, 7, 9, 11, 15 and 19. Strucutural abnormalities may or may not be present along with these numerical gains.[9,10] The second group is defined by hypodiploid and pseudo-diploid karyotypes which are invariably associated with structural abberations. This pattern of chromosomal changes obviously represents distinct MM entities, which is also reflected by the different clinical course of these patient populations. In our study, cytogenetics evaluation is not routinely performed.[11,12]

Stage and Prognostic Factors

The tumor burden can be assessed by means of the Durie and Salmon classification, which was specifically obtained from mathematical models for the evaluation of tumor mass.[13] Other prognostic factors that reflect the tumor burden are the proportion plasma cells (PC). A high number of PC in BM as well as a diffuse pattern of infiltration are generally associated with a poor prognosis. However, these are not consistent prognostic factors, probably owing to the heterogenous distribution of PC in BM (these areas with bone tenderness or lytic lesions are usually more heavily infiltrated). The detection of circulating PC, identified either by morphology or immunophenotyping, is associated with advanced disease, and it has been reported that the presence of high levels of circulating PC (> 4% PC) is an independent adverse prognostic factor.[12,14]

Based on Durie-Salmon and International Myeloma Working Group staging system classification, we found that almost half of patients have III stage as first diagnosis and also showed that a higher stage associated with older and female MM patients (table 6 and 7).

Treatment of Myeloma

During the past decade there has been an enormous increase in knowledge of multiple myeloma and related disorders. Much of this has come about as new technologies and have made it possible to refine studies on chromosomes and genes, to gain information about gene expression. Multiple Myeloma continues to present a theurapetic challenge.

Multiple Myeloma (MM) continues to present a therapeutic challenge. Attempts have been made to utilize the new knowledge to develop targeted therapy and, although results are still modest, improvements have been obtained with thalidomide and analogues, as well as proteasome inhibitors.

In spite of new approaches to treatment, MM at present remains incurable, with a median survival of between 3 and 4 years. Treatment produces a response in approximately two-thirds of patients, with a fall in paraprotein and improvement of resolution of clinical symptoms. However, complete remission (CR) is very rare, except after high-dose therapy, and in most patients the paraprotein falls but reaches a plateau after a few months of treatment. At this stage, the patient is said to be in "plateau phase". Sooner or later the paraprotein starts to rise again, indicating relapse, or there may be a recurence of symptoms. Further treatment at this stage, perhaps with a different drug or drug combination, may again produce a response, but the duration of response is ussually shorter than that of the initial remission. Eventually, the disease becomes refractory to treatment and the patient succumbs to infection, renal failure, or other disease complication. High-dose therapy with autologous stem cell support prolongs remission and survival, but it is not curative and, at present, the only potential curative treatment approach is allogeneic transplantation, which is an option for only minority of patients. The most important aims of treatment are, therefore, to relieve symptoms and to prolong life without the treatment causing unacceptable side effects.[15]

In this study, we found that the most type of chemotherapy that used for the treatment was melphalan/prednisone with the most patients had a partial response as the best response to primary chemotherapy. Actually, multiple myeloma can be treated with several categories of medications. Principally, the treatment of choice for MM is based on the patient's age and prognostic factors. According to the literature, the first-line treatment for MM is bone marrow transplantation. Yet, because of several limitations in our country, we preferred Melphalan-Prednison (MP) as the first-line treatment. More research, which can give benefit as preliminary reports, is needed to enrich the multiple myeloma management modalities in Indonesia.

CONCLUSION

A summary of the frequency of MM in our population is presented in table 1, it showed a strongly influenced and increases with age. In our population, the frequency

of multiple myeloma is rare below 30 years old with the median age is more than 50 years old.

One of the modalities of MM diagnostic investigation is hematologic investigation by cytomorphology of peripheral blood and bone marrow. It is conducted that just over fifty percent of the Indonesian MM patients have less than thirty percent of plasma cells in bone marrow, and only fifteen percents have plasma cells more than forty percents in the bone marrow.

Based on age classification, we also found that percentage of plasma cells in bone marrow is more frequent among younger patients. Meanwhile, based on gender classification, it seems that female tendency have fewer percentage plasma cell than male.

Biochemical investigations play an important role in the diagnosis, prognosis and monitoring of multiple myeloma. Although we found that over seventy MM patients have negative Bence Jones proteinuria, there are more than eighty percents have positive monoclonal gammopathy serum.

In this study, we found that the most frequent cases in our population were at least stage IIIA with the most type of chemotherapy that used for the treatment was melphalan/prednisone and a partial response as the best response to primary chemotherapy. As consequences: early detection, recognition of potentially treatable condition and assessment of functional reserve should be improved. Because of several limitations in our country, we preferred Melphalan-Prednison (MP) as the first-line treatment.

Cytogenetic and molecular genetic investigations of lymphoproliferative disorders are not routinely performed. So, for further research we need elaboration that associated of genetic involvements and molecular findings. Improvement of these investigations is essential because it contribute in determining prognostic factors that eventually will be useful for effective treatment choice. More research, which giving benefit as preliminary report, is needed to enrich the multiple myeloma management modalities in Indonesia. ◆

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