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Full Length Article

A descriptive study of plasma cell dyscrasias in Egyptian population

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Abstract *Background:* Plasma cell dyscrasias (PCDs) refer to a spectrum of disorders character-ized by the monoclonal proliferation of lymphoplasmacytic cells in the bone marrow and, some-times, tissue deposition of monoclonal immunoglobulins or their components. These disorders include multiple myeloma (MM) and Waldenström's macroglobulinemia, as well as rare conditions such as light-chain deposition disease (LCDD) and heavy-chain diseases (HCDs). The worldwide annual incidence of MM is estimated at 86,000, which is approximately 0.8% of all new cancer cases.
Purpose: Our retrospective study aims to highlight the immunologic and epidemiological features of PCDs mainly MM in Egyptian patients and compare our results with those of other populations.
Methods: Two hundred seventeen Egyptian patients with PCD were enrolled in the study. Serum, urine protein electrophoresis and immunofixation were used to demonstrate M protein.
Results: One hundred thirty-eight patients (63.6%) had IgG monoclonal band, 38 patients (17.5%) had IgA, 12 patients (5.5%) had Waldenström's macroglobulinemia (IgM monoclonal band) and 29 patients (13.4%) were light chain myeloma. One hundred fifty-one (70%) were Kappa chain positive and 66 patients (30%) were lumbda positive. Conventional cytogenetics was available for 40 patients; of them 12 patients (30%) showed 13q-. Mean OS was 37.5 months (1–84 months). Survival analysis was statistically insignificant according to age, sex and ISS or type of treatment (*P* value > 0.05).

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Conclusion: Long term follow up is required to further define the role of different therapeutic lines of treatment including ASCT in the various stages of PCD based on OS data.

Introduction

Plasma cell dyscrasias (PCDs) constitute a broad spectrum of diseases characterized by clonal proliferation and accumulation of cells producing monoclonal immunoglobulins (M component) and include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), smoldering multiple myeloma (SMM), plasma cell leukemia (PCL), Waldenström's macroglobulinemia (WM), POEMS syndrome, plasmacytoma, heavy chain disease (HCD), and amyloidosis [1].

Multiple myeloma is the most serious and prevalent plasma cell dyscrasia and accounts for approximately 10% of all hematologic cancers [2,3]. It usually evolves from an asymptomatic premalignant stage of clonal plasma cell proliferation termed "monoclonal gammopathy of undetermined significance" (MGUS). MGUS is present in more than 3% of the population above the age of 50 and progresses to myeloma or related malignancy at a rate of 1% per year [4,5]. In some patients, an intermediate asymptomatic but more advanced premalignant stage, referred to as "smoldering multiple myeloma", is clinically recognized [6].

The worldwide annual incidence of MM is estimated at 86,000, which is approximately 0.8% of all new cancer cases [7]. Approximately 63,000 deaths are reported annually, which is 0.9% of all cancer-related deaths [7]. The American Cancer Society estimates that in 2013, there will be 22,350 cases of MM diagnosed (12,440 in men and 9910 in women) and 10,710 deaths related to MM (6070 in men and 4640 in women) in the United States. The incidence rate of multiple myeloma was significantly higher among people living in urban areas than those from rural areas. Residents of urban areas may expose to some carcinogenic factors especially those related to the development of multiple myeloma. Previous studies suggested that exposure to engine exhaust, asbestos and benzene may increase the risk of multiple myeloma [8].

Diagnosis of MM is based on the presence of a monoclonal protein, bone manifestations and on bone marrow (BM) plasma cell infiltration. Patients with multiple myeloma must be distinguished from those with monoclonal gammopathy of undetermined significance [< 10% BM plasma cell infiltration, low M-component levels (< 3 g/dl) and no osteolytic bone lesions] and those with amyloidosis or other lymphoproliferative disorders with paraproteinemia. Recent guidelines recommend differentiating between symptomatic and asymptomatic myeloma. Symptomatic patients present with one or more of the CRAB criteria (hypercalcemia, renal failure, anemia, bone lesions) and need active treatment, in contrast to asymptomatic patients, which should be followed only [9].

The disease is relatively rare and the prognosis is poor with a 5-year relative survival of 38.5%. The older age, male gender, black race, family history of the disease and MGUS are all risk factors [10]. The increase in mortality rate has been reported in Japan, Italy, France, Germany, and Wales. Overall, mortality rates are highest among patients older than 85 years. In England and Wales, the mortality rates for men and women aged 70–74 years were higher during the period 1981–1985 compared with 1970–1980, whereas the corresponding rates stabilized over time in the younger age groups [11].

The combination of melphalan and prednisone produces responses in approximately 50% of patients and a disease-free survival (DFS) of approximately 15 months. Meta-analysis comparing combination chemotherapy with melphalan and prednisone has shown no statistically significant difference in survival, despite a higher response rate with more aggressive combination chemotherapy. The VAD regimen (infusional vincristine and doxorubicin combined with dexamethasone) results in a response rate of about 70% and does not compromise stem cell collection unlike melphalan [12].

Thalidomide, an oral immunomodulatory drug, is efficacious for patients with relapsed and refractory multiple myeloma. It has been combined with dexamethasone, and a recent clinical trial noted a higher response rate (70%) with that combination when compared with dexamethasone alone (50%) [13]. More recently, lenalidomide (a thalidomide analog), and bortezomib (a proteasome inhibitor) are evaluated in different combinations with chemotherapy, dexamethasone, or both. Survival information is as yet inconclusive for these combinations [14].

In this retrospective study, we try to review the epidemiological features and survival of PCDs patients diagnosed and treated in the period between 2000 and 2010 and compare our results with other studies.

Patients and methods

Study population

The current study was carried out on 217 Egyptian patients with PCDs. Patients were chosen during the period between "2000 and 2010" among cases referred to the clinical oncology department, Cairo University. The research was approved by the IRB of the clinical oncology department, Cairo University. They were 128 males and 89 females. Their ages ranged between 27 and 80 years with a mean age of 58.5 years and median of 53.5 years.

All patients were subjected to: *1. Routine Laboratory Tests including*, Complete blood count with differential count, complete metabolic panel (calcium, albumin, and creatinine) and coagulation testing. *2. Myeloma-Specific Testing including*, serum protein electrophoresis, monoclonal protein analysis by immunofixation, urine protein electrophoresis, serum β2-microglobulin, CRP, and LDH, BM aspirate and biopsy, flow cytometry (CD38 & CD138) and *3. Skeletal bone survey including*, plain X-ray films of the spine, pelvis, skull, humeri, and femurs.

Prognostic criteria for MM were applied according to the International Staging System (ISS) (Table 1), which provides two advantages over the traditional Durie–Salmon system. The ISS relies on widely available laboratory parameters and allocates patients to equally sized patients groups with

markedly different prognoses. In contrast, the Durie–Salmon system depends on the subjective evaluation of the extent of bone involvement and usually results in an imbalanced distribution of patients (more patients are categorized as stage III than as stage I or II) [15].

Statistical method

Data showed non-parametric distribution & Mann–Whitney U test was used for comparisons between two groups. This test is the non-parametric alternative to Student's t-test.

Chi-square (χ^2) test was used for studying the comparisons and associations between different qualitative variables. Spearman's correlation coefficient was used to determine significant correlations between different variables.

The Kaplan–Meier survival curve was constructed for survival analysis.

The significance level was set at $P \leqslant 0.05$.

Statistical analysis was performed with IBM/SPSS Statistics Version 20 for Windows.

Results

The study included 128 (59%) males and 89 (41%) females. Their ages ranged between 27 and 80 years with a mean age of 58.5 years and median of 53.5 years (Table 2).

Regarding immunoglobulin subtypes, one hundred thirty-eight patients (63.6%) had IgG monoclonal band, 38 patients (17.5%) had IgA, 12 patients (5.5%) had Waldenström's macroglobulinemia (IgM monoclonal band) and 29 patients (13.4%) were light chain myeloma. One hundred fifty-one (70%) were Kappa chain positive and 66 patients (30%) were lumbda positive.

Survival analysis calculated for 116 patients: Mean overall survival was 37.5 ± 16.89 months (1–84 months) and median survival was 15.8 months. Thirty-one patients (27%) with ISS = I mean survival was 21.9 ± 13.8 months and median survival was 15.8 months. Seventy-eight patients (67%) with ISS stage II mean survival was 20.5 ± 15.9 months and median survival was 14.5 months. Seven patients (6%) with ISS = III mean survival was 16.6 ± 9.09 months and median survival was 12 months. ANOVA test for comparison of difference according to age, sex and ISS was used. Survival analysis was statistically insignificant (P value > 0.05). Fig. 1 demonstrates survival difference according to ISS (P value 0.4). Figs. 2 and 3 compare survival difference between two age groups (below 50 and above 50 years) and sex, respectively and was statistically insignificant (P value > 0.05).

Conventional cytogenetics was available for 40 patients. 12 patients (30%) were 13q- by the FISH technique.

Table 1 The International Staging System.

Stage	Definition
I	Albumin > 3.5 g/dl and β2-Microglobulin < 3.5 mg/dl
II	Albumin < 3.5 g/dl and β2-Microglobulin < 3.5 mg/dl or β2-Microglobulin 3.5–5.5 mg/dl
III	β2-Microglobulin > 5.5 mg/dl

Table 2 Age distribution of 217 patients with plasma cell dyscrasias.

Age (ys)	Patient (%)
<40	4
40–49	9
50–59	39
60–69	38
70–79	9
⩾80	1

Data regarding treatment were complete for 55 patients mentioned in Table 3. Around 50% of patients received endoxan/steroids or melphalan/steroids. Survival analysis according to treatment type was statistically insignificant (Fig. 4).

Discussion

The aim of this study is to highlight the immunologic and epidemiological features of PCDs in Egyptian patients and compare our results with those of other populations. This study included 205 MM patients presented to Cairo University between ''2000 and 2010''. Mean age studied was 58.5 years (27–80 years). This is not consistent with most western published reports that confirmed the rising incidence of MM and the hypothesis that myeloma is a genetically evolutionary disease [16]. However, our mean age was similar to a Chinese study where the median onset age was 58 years with a spike of 55–65 years [17]. In US age-adjusted incidence rates according to age group, MM is rarely diagnosed prior to age 40, after which the incidence increases rapidly until age 84 and then declines [18,19]. The median age in England (Thames region) was 72 years [20] and Swedish study, did report a median age of 72 years [21].

Males' percentage was higher than females (59% vs. 41%). This is similar to what was reported in the South Thames area
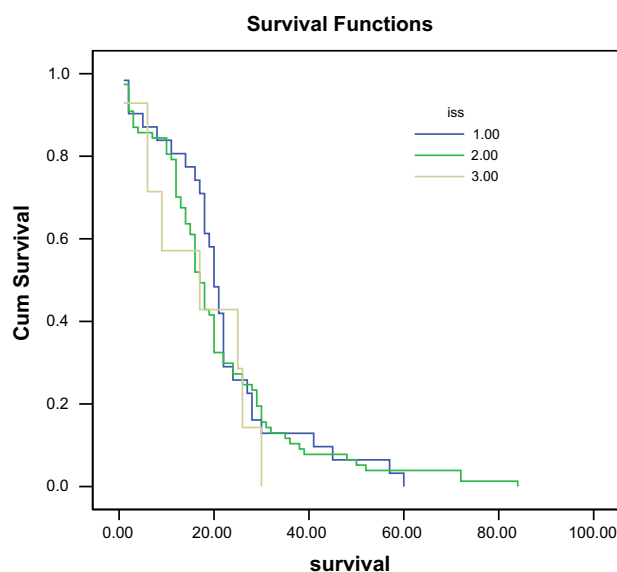

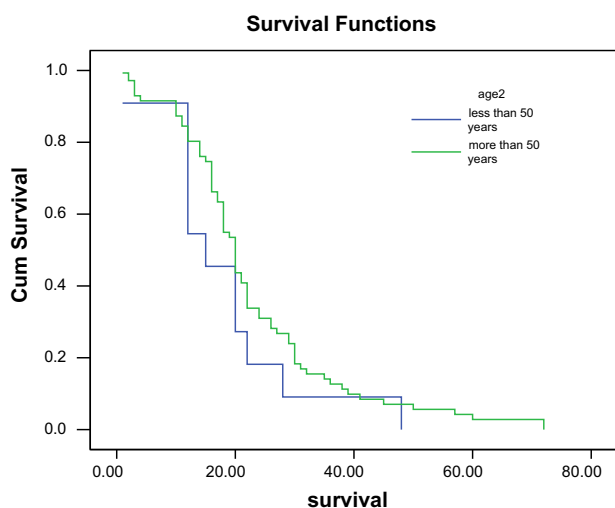**Figure 1** Survival according to ISS score of 116 patients with plasma cell dyscrasias.

Survival Functions

Figure 2 Kaplan survival according to age group of 217 patients with plasma cell dyscrasias.
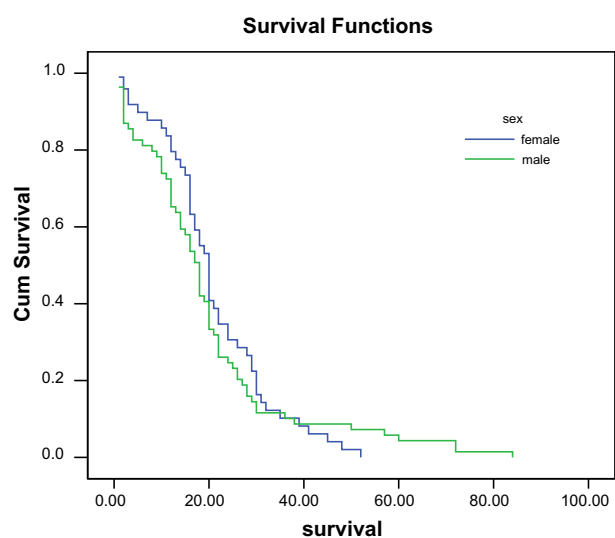
Survival Functions

Figure 3 Kaplan–Meier survival curve according to sex of 217 patients with plasma cell dyscrasias.

Table 3 Treatment of MM patients.

Treatment	Number of patients	Survival in months (mean ± SD)
Endoxan/melphalan steroid	27 (49%)	50 ± 4.9
VAD	12 (22%)	47.4 ± 9.8
Velcade	3 (5 %)	30.89 ± 8.4
Thalidomide	13 (24%)	25.5 ± 3.8

epidemiology study and Chinese study [18,20]. Our results are similar to those of Mayo clinic study where 59% of 1072 were males and Los Anglos [14,22]. SEER (US Surveillance Epidemiology and End Results Programme) data from 1992 to 1998 revealed a male to female ratio of 1.4–1 [20].

The commonest type of immunoglobulin in our study was IgG which was found in more than 60% followed by IgA
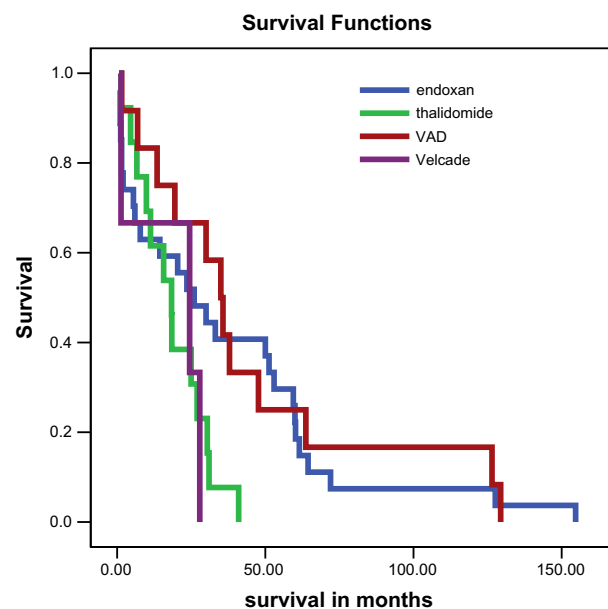
Survival Functions

Figure 4 Kaplan–Meier survival curve according to treatment of 55 patients with MM.

and light chain myeloma. This is consistent with that reported in Mayo Clinic [14].

Our mean OS was 37.5 ± 16.89 months and median survival was 15.8 months. No difference between young and elderly (cut age level was 50 years). While mean survival in the SEER study, a large study on epidemiology of MM. was 30 months (median = 19 months). Multivariate analysis did not reveal statistically significant differences in OS between patients in the white and black race ($P = 0.709$). Younger age (age less than 65, and 65–75) was associated with improved OS when compared with patients more than 75 years of age (P: 0.001) [23]. In our work we used cut level of 50 years as age level not 65 years as in the SEER due to decrease life expectancy age in our population in comparison to western countries. The lack of a significant difference in survival between different groups could be attributed to the small patient numbers in the group below 50 years in relation to the other group.

MM remains generally incurable, with most patients experiencing relapse after first-line treatment. Median survival is approximately 5 years [24]. The goals of first-line therapy are to achieve rapid disease control with prolonged remissions and to produce substantial cytoreduction. Achievement of a complete response (CR) is an important goal, because it has been shown to be prognostic for improved survival when achieved after HDT–ASCT, after induction therapy before HDT–ASCT or after induction therapy in patients not proceeding to HDT–ASCT [25].

Data regarding treatment were complete for 55 patients. Front line therapy; endoxan and dexamethasone were the main line of treatment of most of the patients (49% with OS 47 months). Twelve patients (22%) received VAD regimen (adriamycin, vincristin and decadrone). Due to financial aspects, 24% received thalidomide and only 5% received velcade either alone or in combination. That could be the cause of inability to see a statistical significant difference in overall survival among different groups according to treatment subtypes. Newer agents were preserved to those who showed unfavorable cytogenetics as 13q-.

Mean survival is a little bit lower to that reported in another Egyptian study done on 35 newly diagnosed MM patients with OS being 42 months [26], in Iranian study, survival was 44.3 months [27] and in Chinese large study was 40 months but nearer to those of western countries [17] which could be attributed to ethnic variations.

Conclusion

Long term follow up is required to further define the role of different therapeutic lines of treatment including ASCT in the various stages of PCD based on OS data. Tailoring of therapies to individual cytogenetic risk factors should also be considered. A number of anti myeloma agents are currently undergoing examination in clinical trials such as HSP90 inhibitors, HDAC inhibitors. Results from ongoing studies will certainly affect the future of the disease outcome.

Conflict of interest

None.

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