Original article

Survival advantage of adding thalidomide as compared with chemotherapy only in the treatment of symptomatic myeloma in Kurdistan/Iraq

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ABSTRACT

Background: Multiple myeloma is an incurable plasma cells neoplasm. Chemotherapy by the alkylating agent Melphalan was introduced in 1958 and with the addition of prednisolone in 1964 the combination (MP) improved the survival of these patients and remained the standard treatment for over twenty years. In 1998 the antiangiogenic reagent thalidomide was tried and claimed to further improve survival of these patients including those with advanced disease.

Objectives: This study was conducted to determine the difference in survival of multiple myeloma patients in Nanakaly Hospital in Erbil city before and after the use of thalidomide.

Patients and Methods: This retrospective study was carried out at Nanakaly Hospital over a period of six years from January 2007 to March 2013. The records 123 patients with symptomatic multiple myeloma who were treated in this period were reviewed, including their clinical and laboratory profiles, as well as the survival of each group. All patients were selected according to the WHO diagnostic criteria.

Results: The patients had a median age of 59 years and the male: female ratio of 1.2:1, Chemotherapy based treatment was used in 38 patients as compared with 85 patients who used thalidomide based therapy.

Median survival was 34 months for thalidomide compared to 19 months for chemotherapy-only treated group (P= 0.001)

Conclusions: The introduction of Thalidomide as a therapeutic option in Iraqi patients improved survival of symptomatic myeloma significantly compared to chemotherapy alone.

Keywords: Multiple myeloma, thalidomide, Erbil, Iraq.

Introduction

Multiple myeloma (MM) is a neoplastic plasma-cell disorder characterized by clonal proliferation of malignant plasma cells in the bone marrow. It accounts for approximately 1% of neoplastic diseases and 13% of hematologic cancers.[1] In Western countries; the annual age adjusted incidence is 5.6 cases per 100,000 persons. The median age at diagnosis is approximately 70 years.[2] Ethnic variations in the incidence of multiple Myeloma is well known, with a lower incidence rate and median age (62 years) in Asian countries than in western countries. [3].

Myeloma is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction, including hypercalcemia, renal insufficiency, anemia, and bone disease [4]

In spite of recent advances in its treatment, multiple myeloma remains incurable[5]. Since the late fifties of the last century, Melphalan was the first chemotherapeutic agent to be used with significant activity against the disease[6]. In 1998, thalidomide, originally a sedative withdrawn from markets for its teratogenicity[7], was shown to have a reproducible activity even in end-stage myeloma[8, 9, 10]; this activity is related to its antiangiogenic effects[11]. It produced more than 50% reduction in serum or urine myeloma protein in one-third of relapsed patients after autotransplantation[8].

Studies have shown that thalidomide treated patients had a significantly higher rate of both complete remission (CR) (62 % versus 43 %) and five-year event free survival (EFS) (56 % versus 44 %) compared to non-thalidomide containing chemotherapy treated patients. However, it is important to note that the increased response rate with thalidomide-based regimens is balanced with an increased risk of venous thrombosis (DVT) and neuropathy. [12, 13]

Studies from developing countries on the use of Thalidomide in MM are scanty and very limited from Iraq, and since the latter drug became available in 2007, the notion of comparing the survival of patient with symptomatic MM treated before and after thalidomide era in our hospital was a necessity, and this was the aim of the current study

Patients and Methods

Hospital records of 123 patients with previously untreated symptomatic multiple myeloma who attended Nanakaly Hospital for Blood Diseases in Erbil city from March 2007 to March 2013 were studied. Records were reviewed for the following data:

1. Clinical data.

2. Hematological profile: Full blood count, erythrocyte sedimentation rate, and bone marrow aspirate and trephine biopsy findings.

3. Biochemical profile: Serum calcium, urea, creatinine, total proteins, albumin, globulins and paraprotein.

4. Radiological findings.

The study included all patients diagnosed as myeloma who showed features of related organ or tissue impairment (CRAB: hypercalcemia, renal insufficiency, anemia and bone lesions) or myeloma related symptoms (hyperviscosity and recurrent infection)

Patients were divided into two groups:

Group I: Included patients treated by chemotherapy only i.e. (before the availability of thalidomide in our area, March 2007 until December 2008.total number 38 patients.

Group II: Patients treated with thalidomide based regimens, total number 85 patients.

Patients with incomplete data , had autologous bone marrow transplant or received other novel agents were excluded.

Statistical tools: Data analyses were carried out using computer statistical analysis software (SPSS 18). Survival assessed using Kaplan-Meir plots and median survival compared using log rank test. A p value < 0.05 was considered indicative of statistically significant difference.

Results

Studied patients included 67 males and 56 females with a male: female ratio of 1.2:1. Their ages ranged from 27 to 87 years with a mean age of 60.02 ± 13.1 (median 59 years).

The mean Hb level was 9.54 ± 2.3gm/dL, median erythrocyte sedimentation rate was 111mm/hour and mean serum calcium was 9 ± 1 mg/dL. (Table 1)

Serum paraprotein was present in 91 patients (74%). In the majority of the latter patients (62%) the paraproteins was of IgG type (figures 1). Urine was positive for BJ protein in 40% of cases, and around 23% had positive monoclonal band both in urine and blood.

Skeletal involvement was shown radiologically in 78% while renal impairment (serum creatinine ≥2 mg/dL) was present in 37%. (Figure 1).

Males had a slightly longer survival than females but the difference was not significant (p = 0.076) statistically (figure 3). Likewise, renal impairment at presentation did not affect survival significantly (p = 0.16), though the mean survival was longer among those with normal renal function. (Figure 4).

Studying survival according to the treatment used , comparing thalidomide treated patients with non-thalidomide treated group , showed significant longer survival for thalidomide treated group (median survival 34 months) as compared with non-thalidomide treated group (median survival 19 months) (p =0.001) (figure 5)

It's worth noting that 20 /60 (33%) patients who survived more than 1 year on thalidomide had evidence of peripheral neuropathy, while 11 of 85 (13%) of those on Thalidomide has at least one thrombotic episode mainly in the form of venous thrombosis (8 patients) or arterial thrombosis (2 patients had cardiac ischemia and one ischemic stroke) despite the prophylactic use of antiplatelet agents (acetyl salicylic acid or clopidogrel) and/or anticoagulation with low molecular weight heparin and warfarin.

Discussion

Multiple myeloma, the second most common blood cancer[14], is generally considered incurable. In Iraq, where autologous stem cell transplant is not practicable yet, the treatment of myeloma was by chemotherapy only, until and quite recently thalidomide became available and was introduced for the management of these patients.

In this retrospective study we compared the survival of symptomatic myeloma patients treated by chemotherapy alone with that of patients treated by thalidomide based regimens.

The general characteristics of both groups were nearly similar, although females were more frequent in the non- thalidomide group but overall there was a slight male predominance which is in accordance with other studies[5, 15, and 16].

The mean age of studied patients was 60.02 ± 13.1 years ranging from 27 to 87 years; this age distribution is comparable with the age range of Asian myeloma patients as compared with older age group in western countries[3].

Most of our patients were paraprotein secretors with IgG subtype predominating which is also in agreement with other studies[16.]

In relevance to survival, sex carried no survival difference in our patients which is also reported in other studies.[17] Furthermore, and while renal impairment at presentation is known to adversely affect survival [18,19], however, in this series elevated serum creatinine at presentation did not significantly affect survival, the latter discrepancy may be due the fact that in many patients in this series renal impairment was mild and was correctable by vigorous rehydration , treating hypercalcemia , hyperuricemia and controlling the disease as it have been shown that early detection and treatment of acute kidney injury(AKI) would improve outcomes.[20]

Lastly, the survival benefit of using thalidomide as compared with the group without using thalidomide is obvious and in parallel with the other studies that show survival advantage of thalidomide in MM [21,22,23,24.25,26] and supports the use of this drug in the initial treatment of non-transplant illegible patients.

Conclusion

It's our opinion that despite the expected provision of newer novel agents and the probable availability of stem cell transplant (SCT), there will still be an important role for thalidomide in the treatment of myeloma patients as it is relatively cheap and effective.

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Table 1: Characteristics of the studied patients (Number of patients 123)

Variable	Range	Mean ± SD	Median
Age in years	27 – 87	60.02 ± 13.1	59
Hemoglobin level (gm/dl)	3.4 – 16.8	9.54 ± 2.3	9.2
ESR (mm / 1st h)	8 -180	99.4 ± 44.7	111
S. Calcium (mg/dl)	5.8 – 12.9	8.98 ± 1.15	8.9

Table 2. A comparison of patient characteristics between thalidomide and non-talidomide-based treatment groups.

Characteristic	Non-thalidomide	Thalidomide	p-value
Number of patients	**38**	**85**	
Age in years	62.5 (35-85)	60 (27-87)	**0.165**
Gender M:F ratio	**0.65:1**	**1.5:1**	
Hemoglobin in g/dl	9.56	9.5	**0.964**
Lytic bone lesions	73%	82%	**0.332**
Mean Serum calcium mg/dL	**8.5**	**9.0**	**0.148**
Mean Serum creatinine in mg/dL	1.98	**2.1**	**0.769**
Creatinine > 2 mg/dl (no. of patients)	**8 (21%)**	**26 (30%)**	**0.5**
Serum M-protein			
IgA	15.7%	21%	**0.58**
IgG	57.8%	52%	**0.84**
Urine M-protein	36%	29%	**0.537**
Median Survival (months)	**19**	**34**	**P<0.001**

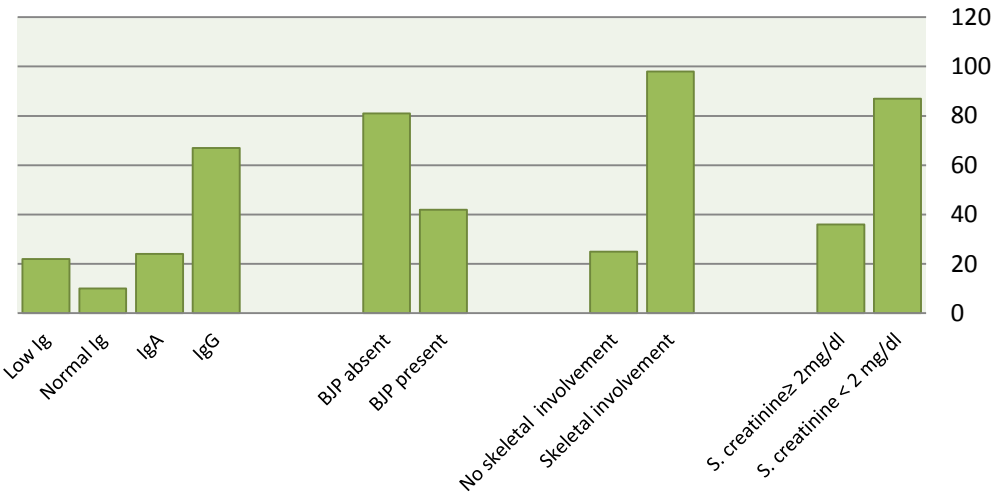

Figure1; Lab Charecteristics

Table 3; Outcome of Patients according to some variables

Variable	Mean survival (in months)	P value
Gender		
Male (N=67)	**37.7**	**0.076**
Female (N=56)	**26.7**	
S. Creatinine in mg/dl		
< 2 (N= 87)	**35.7**	**0.160**
≥ 2 (N=36)	**29.5**	
Thalidomide based Therapy		
Yes (n=85)	**44.09**	**0.001**
No (n= 38)	**17.18**	

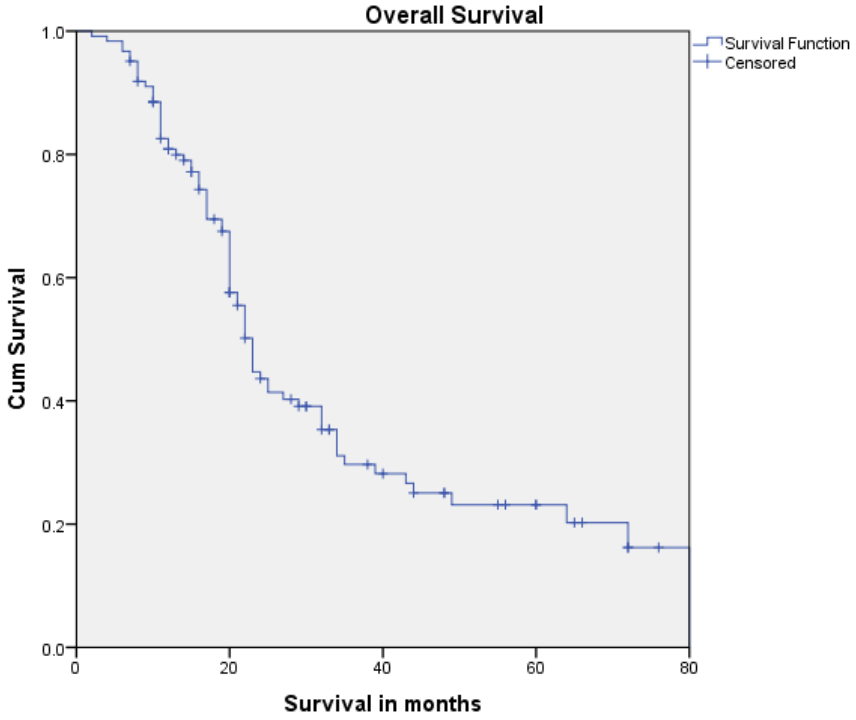

Figure 2: Overall survival of all patients

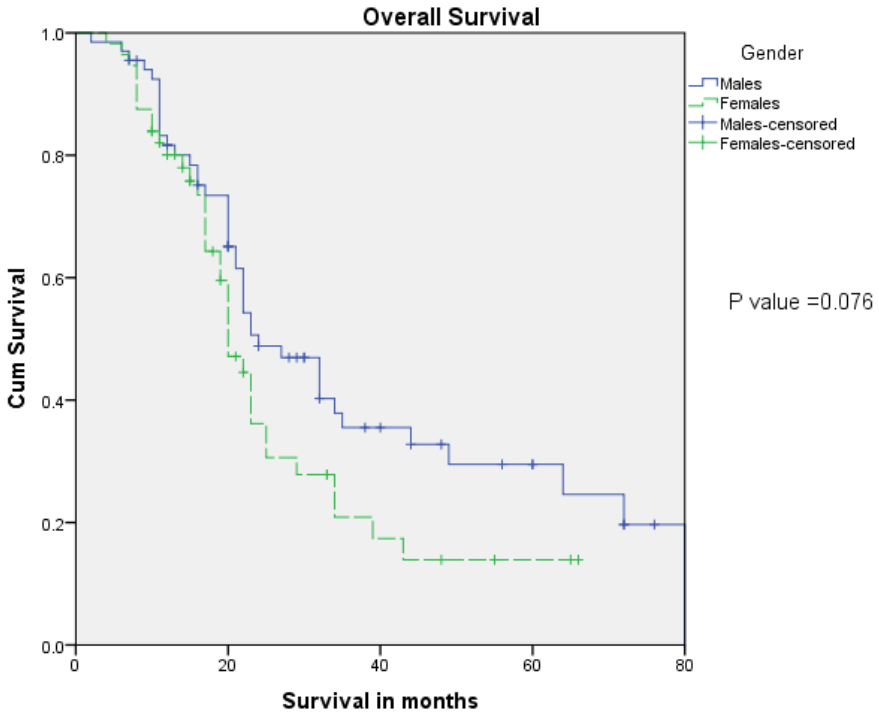

Figure 3: Overall survival of all patients by gender

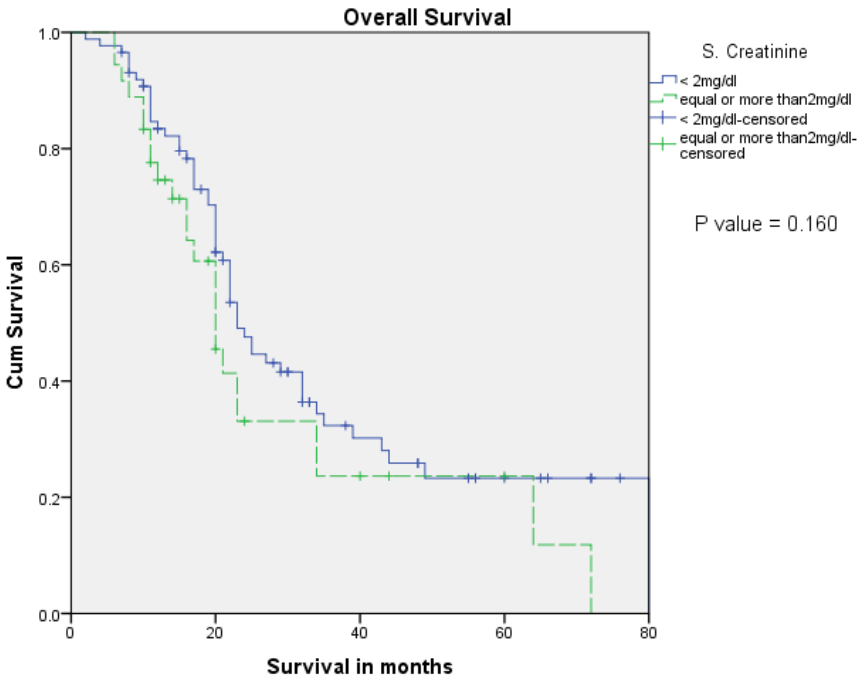

Figure 4: Overall survival of all patients by S. Creatinine level

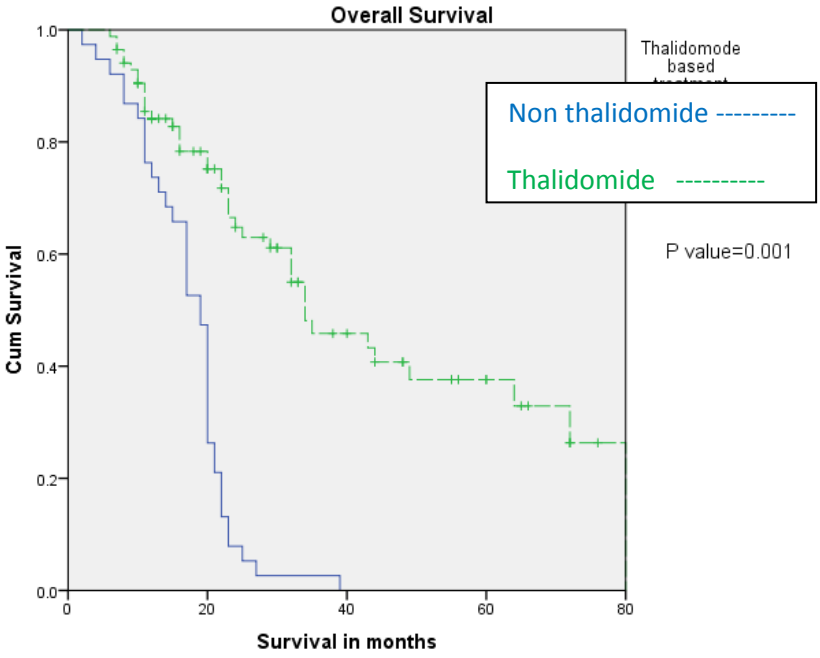

Figure 5: Overall survival of all patients by type of treatment