ORIGINAL ARTICLE

THERAPEUTIC EFFICACY AND PHARMACOECONOMICS EVAULATION OF PAMIDRONATE VERSUS ZOLEDRONIC ACID IN MULTIPLE MYELOMA PATIENTS

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ABSTRACT

Sixty patients of multiple myeloma were randomized into two equal groups to receive Pamidronate and Zoledronic acid intravenously every month for a total of six months. The primary endpoint was to compare the therapeutic efficacy of both drugs by the resolution of hypercalcemia, prevention of skeletal related events and pathological fractures. The secondary endpoints were to assess patient compliance on the basis of quality of life score before and after treatment with Pamidronate and Zoledronic acid and to analyze the cost effectiveness of both drugs., Pamidronate was found to be more effective in the resolution of hypercalcemia as compared to Zoledronic acid, whereas Zoledronic acid reduced the overall proportion of skeletal related events (45.9%) in comparison with Pamidronate (54.1%). Overall Quality of life scores were not significantly influenced by either the response or the occurrence of adverse event but were statistically significant (P=0.000), with in the treatment groups. Patients on Zoledronic acid were more comfortable due to short administration time of l5minutes as compared to 2 hours of Pamidronate. The average cost of six months' treatment with Zoledronic acid was significantly higher (PKR=90, 000 or USD 1,052) in comparison with Pamidronate (PKR=39, 000 USD 456. Zoledronic acid reduced the risk of developing skeletal complications including hypercalcemia and was significantly more effective in reducing the incidence of hypocalcemia. The incidence of renal impairment among patients treated with Zoledronic acid was significantly higher, but severity of nephrotoxicity was more with Pamidronate. The most common adverse effects were pain, vomiting and fatigue in both treatment groups. Comparatively, Pamidronate was more effective in resolution of hypercalcemia, while Zoledronic acid have better therapeutic effects in reduction of skeletal related events and pathological fractures.

Key word*: Pamidronate, Zoledronic acid, Efficacy, Pharmacoeconomics, Multiple myeloma*
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INTRODUCTION

Multiple Myeloma is a plasma-cell neoplasm that is characterized by skeletal destruction, anemia, hypercalcemia and renal failure. One of the most common symptoms that lead patients with multiple myeloma to first seek medical attention is bone pain. This pain is caused by destruction of bone material induced by myeloma cells with in the center of bone. The bones can then become weak and eventually result in small or more substantial fractures, most commonly with in the spine or ribs [1]. Fortunately, there are now medications that can limit this process. There are now treatments for multiple myeloma bone disease which has made skeletal related complications, such as, fractures less common. Treatment of the myeloma itself is one of the most effective ways of controlling further bone breakdown. Often patients at diagnosis will be discovered to have hypercalcemia. With successful treatment, the calcium level often fall, the patient's pain often improves as well.

Bisphosphonates are a group of synthetic stable analogues of pyrophosphate drugs known to suppress osteoclast activity in multiple myeloma patients. The early treatments used in multiple myeloma were relatively weak agents, like Etidronate and Clodronate. [2]. The first bisphosphonate approved by FDA to reduce bony complication in multiple myeloma patients was Pamidronate. Recently, a newer more potent agent, Zoledronic acid has become available in the market. The therapeutic activity of bisphosphonate is attributable to its potent anti-osteoclastic activity on bone [3-5].

The objective of the study was to compare Zoledronic acid and Pamidronate in terms of efficacy, patient compliance and cost benefits in multiple myeloma patients at Shaukat Khanum Memorial Cancer Hospital and Research Centre Additionally, to check the therapeutic efficacy of Zoledronic acid in comparison with Pamidronate, resolution of hypercalcemia, prevention of skeletal related events, pathological fractures, patient compliance and to compare the cost benefits analysis of Pamidronate and Zoledronic acid.

MATERIAL AND METHODS

Sixty patients of multiple myeloma were randomly divided into two equal groups to receive Pamidronate and Zoledronic acid. The parameters to evaluate the therapeutic efficacy of study drugs were the resolution of hypercalcemia, prevention of pathological fractures and skeletal related events during six months treatment. A skeletal related event (SRE) was defined as a pathologic fracture, spinal cord compression, radiotherapy, or surgery of bone. For this purpose, serum calcium levels were monitored for six months. In case of suspected SRE based on signs and symptoms, skeletal surveys and bone scans were ordered and checked [6]. Quality of Life Score questionnaire of Spitzer WO (7) were adopted, which is comprised of fifty questions, were completed before and after receiving Pamidronate and Zoledronic acid randomly in all patients

Cost benefit analysis was done by comparing the mean total cost of the treatment for six months in either study group, including patient and organization perspective and the occurrence of adverse events to evaluate the benefits of the treatment. Total cost of the treatment include charges for all lab tests, bone scans, skeletal surveys and cost for preparation, dispensing and administration of the study drugs.

Patients Inclusion Criteria

- Adult patients (Age 18 to 65 years)
- Patients with definitive diagnosis of Multiple Myeloma disease
- Patients with bone metastases
- Patient having tumor induced hypercalcemia

Patients Exclusion Criteria

- Patients with pre-existing renal impairment
- Adult patients at high risk for complications (e.g. ONJ (Osteo-necrosis of the jaws))
- Patients with a history of hypersensitivity reactions to Pamidronate/Zoledronic acid or other agents of the class

Dosage Regimen

Pamidronate: Standard Dose: 90mg Intravenously over 2 Hours Monthly

Zoledronic Acid: Standard Dose: 4mg intravenously over 15 minutes Monthly

EVALUATION

Evaluation of Response

- Disappearance/Resolution of hypercalcemia with overall clinical improvement
- Disappearance of clinical and lab evidence of hypercalcemia and skeletal related events

Failure of Treatment

- Occurrence of skeletal related events
- Increased serum Calcium levels
- Fragility (e.g. pathological factures)
- Nephrotoxicity (AUC is tripled in the presence of severe renal impairment (CrCL< 30); experience is limited in this setting and Pamidronate/Zoledronic acid should be used with extreme caution.)

Initial Assessment

Prior to commencement of therapy, history, physical examination, Urine Analysis, Complete Blood Count, Bone scan from appropriate sites were done to evaluate Bone metastases and Hypercalcemia. Consider full dental assessment and completed any dental procedures before starting treatment to minimize risk of Osteonecrosis of the jaws.

After commencement of drugs

- Regular Physical Examination
- Monitored plasma concentrations of electrolytes, including calcium, magnesium and phosphate during treatment
- Monitored CBC profile especially Hematocrit and Hemoglobin
- Checked serum creatinine before each dose; if renal function deteriorated further

dose was withheld until serum creatinine returned to within 10% of baseline value

- Restored and maintained adequate hydration with sodium chloride 0.9% in hypercalcemia
- Bone scans were performed
- Patients were examined during therapy for clinical symptoms and signs of side effects.

Drugs related nephrotoxicity was defined as Increase in Sr.Cr by 0.5mg/dl from baseline value, other causes of nephrotoxicity (hypotension, Amphotericin or Aminoglycosides or other nephrotoxic drugs) had been excluded.

Statistical Analysis:

ANOVA test was utilized to compare the means of normally distributed interval dependent variable for two independent groups, the Pamidronate and Zoledronic acid treatment groups at every month. Values changed were compiled and analyzed using test for Paired Analysis. ANOVA generalizes Independent Sample T-test [9, 10].

An Independent Sample T-test was used to compare the Quality of life of multiple myeloma patients receiving Pamidronate and Zoledronic acid and paired analysis was also done with in each study group before and after treatment. Cost analysis was done by comparing average cost of the treatment for six months in either study group and percentage of adverse events occurred was calculated to conclude benefits of the treatment in comparison [11].

RESULTS

The base line investigations including complete blood cell counts, urea and electrolytes and serum calcium levels were carried, which showed no significant differences before treatment in each study group and were similar in both groups. Statistically, there was no significant difference observed in white blood cell counts ((P=0.192) between the two

groups (Table 1) prior to treatment, whereas a significant difference (P=0.039) was observed at second month of the treatment. .The mean value (7.2756) was significantly higher with Pamidronate therapy than Zoledronic (mean=5.6836). Comparing white blood cell counts before treatment and at month 6 of treatment, no significant differences were found within two groups (Table 1).

Table 1 White blood cell count trend with Pamidronate and Zoledronic acid therapy

	Pamidronate		Zoledronic acid		
Time(Months)	**Mean (x10.e 3/µl)**	**SEM**	**Mean (x10.e 3/µl)**	**SEM**	**P-Value[2]**
Month 0	7.1648	0.4995	6.3165	0.3847	**0.192**
Month 1	6.0862	0.4878	5.2450	0.5423	**0.263**
Month 2	7.2756	0.4956	5.6836	0.5430	**0.039**
Month 3	5.5482	0.4974	6.0244	0.6434	**0.559**
Month 4	6.0144	0.5571	7.0071	0.6566	**0.226**
Month 5	5.6536	0.1007	5.4575	0.8071	**0.780**
Month 6	6.5800	0.4974	5.2400	0.7081	**0.189**
P-Value[1]	**0.912**		**0.480**		

*** P-Value[1]** *Comparison of mean values observed before therapy with that of at month 6*
*** P-Value[2]** *Independent Comparison of mean values for two regimens at every month*

Significant decrease in the number of thrombocytes were observed in both two groups at fourth month of treatment (P=0.032). Mean values observed before and at sixth month of treatment was found to be significant (P=0.020) in Pamidronate group only. (Table 2)

Table 2 Absolute number of Thrombocytes before and after treatment with Pamidronate and Zoledronic acid

	Pamidronate		Zoledronic acid		
Time(Months)	**Mean (x10.e 3/µl)**	**SEM**	**Mean (x10.e 3/µl)**	**SEM**	**P-Value[2]**
Month 0	326.2414	15.7233	316.1231	25.0488	**0.728**
Month 1	208.5385	34.0188	214.6000	45.7027	**0.914**
Month 2	329.8125	22.4333	271.6429	29.9653	**0.126**
Month 3	252.6364	30.1678	298.5556	44.8191	**0.392**
Month 4	268.0000	25.0849	356.2857	27.0297	**0.032**
Month 5	346.5455	23.2920	302.5000	22.7133	**0.207**
Month 6	232.5000	24.4305	278.5000	1.5000	**0.342**
P-Value[1]	**0.020**		**0.109**		

*** P-Value[1]** *Comparison of mean values observed before therapy with that of at month 6*
*** P-Value[2]** *Independent Comparison of mean values for two regimens at every month*

Absolute neutrophil count was significantly decreased in Pamidronate group (P= 0.057) versus Zoledronic acid (P= 0.077) over six months of treatment, whereas statistically there was no significant difference found between the two groups (Table 3).

Table 3 Absolute neutrophil count before and after treatment with Pamidronate and Zoledronic acid

	Pamidronate		Zoledronic acid		
Time(Months)	**Mean (x10.e 3/µl)**	**SEM**	**Mean (x10.e 3/µl)**	**SEM**	**P-Value[2]**
Month 0	5.9427	0.4761	5.0350	0.4333	**0.166**
Month 1	3.5876	0.6871	3.3810	0.6551	**0.213**
Month 2	4.7119	0.5835	3.6900	0.7066	**0.317**
Month 3	3.7182	0.4977	3.7222	0.3985	**0.272**
Month 4	3.9822	0.6070	4.2614	0.1137	**0.696**
Month 5	3.5055	0.1129	3.2188	0.7661	**0.669**
Month 6	2.7583	0.1939	2.4450	0.2150	**0.427**
P-Value[1]	**0.057**		**0.077**		

*** P-Value[1]** *Comparison of mean values observed before therapy with that of at month 6*
*** P-Value[2]** *Independent Comparison of mean values for two regimens at every month*

Serum potassium level were observed in both treatment group and statistically no significant difference present between the mean Potassium levels (compared before the start of therapy with that of sixth
month)) for Zoledronic Acid.

Table 4 Serum Potassium levels before and after treatment with Pamidronate and Zoledronic acid

	Pamidronate		Zoledronic acid		
Time(Months)	**Mean** (mmol/L)	**SEM**	**Mean** (mmol/L)	**SEM**	**P-Value[2]**
Month 0	4.3781	0.1032	4.53820	0.1141	**0.295**
Month 1	4.4340	0.1293	4.2822	0.1210	**0.398**
Month 2	4.3095	0.1265	4.4423	0.1126	**0.200**
Month 3	4.3990	0.1187	4.4283	0.1226	**0.723**
Month 4	4.4884	0.1172	4.5688	0.1135	**0.627**
Month 5	3.9556	0.1768	4.3154	0.1347	**0.100**
Month 6	4.3055	0.1307	4.3045	0.1301	**0.995**
P-Value[1]	**0.503**		**0.035**		

*** P-Value[1]** *Comparison of mean values observed before therapy with that of at month 6*
*** P-Value[2]** *Independent Comparison of mean values for two regimens at every month*

Therapeutic Efficacy

There was a statistically significant difference (P=0.011 at fourth month, P=0.035 at sixth month) in calcium levels were observed between two groups with mean values for Zoledronic acid was higher (9.3614 at fourth month, 9.0445 at sixth month) as compared to Pamidronate (8.8539 at fourth month, 8.6391 at sixth month). (Table 5)

Resolution of hypercalcemia and occurrence of skeletal related events over a period of six months were comparable in both treatment groups (Table 6).

Table 5 Serum Calcium levels before and after treatment with Pamidronate and Zoledronic acid

	Pamidronate		Zoledronic acid		
Time(Months)	**Mean** (mmol/L)	**SEM**	**Mean** (mmol/L)	**SEM**	**P-Value[2]**
Month 0	10.8723	0.2104	11.0033	0.2887	**0.717**
Month 1	9.8032	0.2422	10.4353	0.2639	**0.085**
Month 2	9.7055	0.2102	10.0937	0.2175	**0.208**
Month 3	9.3854	0.1980	9.7162	0.1943	**0.244**
Month 4	8.8539	0.1774	9.3614	0.1933	**0.011**
Month 5	9.0853	0.2440	9.0445	0.1913	**0.895**
Month 6	8.6391	0.1218	9.0494	0.1450	**0.035**
P-Value[1]	**0.000**		**0.000**		

*** P-Value[1]** *Comparison of mean values observed before therapy with that of at month 6*
*** P-Value[2]** *Independent Comparison of mean values for two regimens at every month*

Table 6 Therapeutic efficacy of Pamidronate versus Zoledronic acid in Multiple Myeloma patients

	Pamidronate	Zoledronic acid
Resolution of Hypercalcemia	**(%)**	**(%)**
• **within 24 Hrs**	0	**3.33**
• **within 3-7 days**	54.3	**45.7**
• **more than 10 days**	57.1	**42.9**
Occurrence of Skeletal related events	**54.1**	**45.9**

Patient Compliance

Patients from both groups were participated in Quality of life assessment and were found that there was no occurrence of any side effects which significantly influenced the changes in patient's quality of life. There was no significant difference in QOL score (Table 7) obtained from Pamidronate and Zoledronic acid groups (P= 0.067, P= 0.077) but a

statistically significant difference (P= 0.000) was found in paired differences in QOL score of both groups with higher mean difference (i.e.12) in patients receiving Zoledronic acid as compared to Pamidronate (i.e.11) (Table 8).

Table 7 Comparison of Quality of Life Score in Multiple Myeloma patients before and after receiving Pamidronate and Zoledronic acid

Group Statistics			
QOL Score	**Mean**	**SEM**	**P- value**
Before and after Pamidronate	194.8667 183.8667	6.6510 6.6129	**0.067**
Before and after Zoledronic acid	**190.5667** **178.4333**	**7.9247** **7.7541**	**0.077**

Table 8 Comparison of Quality of Life Score in Multiple Myeloma patients before and after receiving Pamidronate and Zoledronic acid

Paired differences			
QOL Score	**Mean**	**SEM**	**P- value**
Before and after Pamidronate	11.00	0.5252	**0.000**
Before and after Zoledronic acid	**12.00**	**0.6894**	**0.000**

* **QOL** *Quality of life*

Cost benefit analysis

Total cost of six months treatment were calculated by summing up the cost for medical resources, cost of institutional care, medications, administration and monitoring baseline

tests. Resources used were similar for both groups. The net cash flow for six months with Zoledronic acid was higher (PKR 13,053 or USD 152.6)) as compared to Pamidronate (PKR 4,950 or USD 57.9) (Table 9).

Table 9 Average Cost Comparison of six months therapy with Pamidronate and Zoledronic acid

Pamidronate		**Zoledronic Acid**	
Cash Inflow	**Cash Outflow**	**Cash Inflow**	**Cash Outflow**
PKR 34,850	39,800	76,947	90,000
USD 407.60	465.50	899.96	1052.63
Net Cash Flow =CO – CI =39,800-34,850 PKR=4,950 (USD 57.9)		Net Cash Flow =CO – CI =90,000-76,947 PKR=13,053 (USD 152.7)	

*Cost analysis includes cost of lab tests, bone scans, medicine preparation and administration charges
* **CI** Cash Inflow (Organization cost)
* **CO** Cash Outflow (Cost to the Patient)
* Net Cash Flow (Organization profitability)

The mean total cost of Pamidronate for thirty patients was PKR 39,800 (USD 465.5) and PKR 90,000 (USD 1052.63) for Zoledronic acid including patients and organizational perspective.

Benefits of the treatment with cost, adverse events were also noted in each group. Adverse events (regardless of relationship to study drug) were mild. Most commonly observed symptoms were nausea, headache, pain and vomiting. Severe adverse events were experienced by 3 patients only (5%), however, these events did not result in any discontinuations from the study and only two events were related to study medication.

Bone pain was assessed in 11% patients with higher incidence 63.6% with Zoledronic acid and 36.4% with Pamidronate (Table 10).

Table 10 Occurrence of Adverse events (%) in patients receiving Pamidronate and Zoledronic acid therapy

Adverse events	Pamidronate	Zoledronic acid
Vomiting	8.33%	**0%**
Headache	60%	**40%**
Loose motion	83.3%	**16.7%**
Bony pains	36.4%	**63.6%**
Leg pains	45%	**54.5%**
Chest pain	33.3%	**66.7%**
Hypocalcaemia	77.8%	**22.2%**
Nephrotoxicity	47.4%	**52.6%**
Fragility	60%	**40%**
SRE	**54.1%**	**45.9%**

* **SRE** *Skeletal Related Events*
*__Fragility__ *Pathological fractures*

DISCUSSION

Pamidronate and Zoledronic acid have the same activity with some pharmacological and therapeutic differences [6]. There was a strong need to estimate and report the therapeutic efficacy of different drugs for the same indication in myeloma patients. Zoledronic acid was expensive than Pamidronate but the total therapy time was very less, which reduced the patient's stay in the hospital and more compliance to the patient [12].

During this study, different parameters were used to assess the therapeutic effectiveness

and safety of both study drugs. Both drugs were comparable as far as therapeutic efficacy is concerned. There was no statistically significant difference observed in baseline diagnostic parameters of the eligible patients. The resolution of hypercalcemia was comparable in both arms, however, with Pamidronate resolution of hypercalcemia in 3 -7 days was 54.3% than 46% with Zoledronic acid. Zoledronic acid reduced the overall proportion of skeletal related events (45.9%) as compared to Pamidronate (54.1%) over six months of treatment.

The Quality of life questionnaire provides a comprehensive assessment of the quality of life of cancer patients participating in clinical trial [13]. According to this questionnaire, global health status improved significantly over the course of the study, as did physical, social, and emotional functioning. In all cases, these improvements were >5% and considered clinically significant. Reasons cited for this preference included the elimination of travel, reduced treatment anxiety, reduced caregiver burden, and the ability to continue other duties. Cost benefit analysis was done by comparing the total mean cost of the treatment for six months with benefits in both groups [14].The total cost with Pamidronate showed a significant decreased trend as compared to Zoledronic acid, though both drugs were comparable as far as therapeutic efficacy and patient compliance was concerned but individual cost of Zoledronic acid was significantly higher than Pamidronate, which ultimately increased the net cost of treatment with Zoledronic acid.

Complete blood counts were comparable in both treatment groups without any significant variations; however, serum creatinine was higher in Pamidronate treatment group at fourth month of treatment as compared to Zoledronic acid. Compared with Pamidronate,

Zoledronic acid reduced the overall risk of developing skeletal complications including hypercalcemia (41.7% with Zoledronic acid, 58.3% with Pamidronate.) in multiple myeloma patients. Mild adverse events were observed in treatment groups including vomiting, loose motions, headache, chest pain, leg pain and hypocalcaemia without any significant difference.

CONCLUSION

Zoledronic acid was safe and more effective in reducing the risk of skeletal complications in patients with bone metastases, whereas Pamidronate is more effective in resolution of hypercalcemia in multiple myeloma patients. Infusion of Zoledronic acid significantly improved pain and quality of life of patients with better compliance. Additionally, the short infusion time of Zoledronic acid including patient benefits reveals that Zoledronic acid is a drug of choice. It is suggested that the cost of treatment and patient out-of-pocket expenses needs to be conducted to assess complete economic benefits for patients and the healthcare system.

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