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Resource Utilization in Patients with Bisphosphonate - Associated Osteonecrosis of the Jaw

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Abstract

Bisphosphonate-associated osteonecrosis of the jaw (BONJ) is an emerging oral complication that occur secondary to cancer therapy in approximately 5% of cancer patients that are treated with high dosages of intravenous (IV) bisphosphonates and can be associated with significant health-care associated costs.

A retrospective electronic medical record based on review of ninety-four cancer patients with BONJ. All health care related resources were abstracted using a structured chart abstraction tool, including medications, imaging, pathology, procedures, and visits. Standardized references were used to assign costs.

The median cost of a case of BONJ in our cohort was $1,546 (interquartile range from $869-$3,166). Medication costs comprise 48%, visits 23%, procedures 16%, imaging 10% and pathology 2%. The major contributing factors that affect BONJ treatment cost were long term medication and follow up visits

Long term medication, sequestrectomy and debridement are a bit expensive but could be a part of evidence-based successful clinical outcome. The cost of BONJ treatment is modest compared with the cost of cancer care.

Key Words: Osteonecrosis, Bisphosphonates, BONJ, cancer, cost.

Introduction

Osteonecrosis of the jaw (ONJ) is a bone disease that affects the maxilla and the mandible. Jaw bone (osteo-) damage and death (-necrosis) occurs largely as a result of reduced local blood supply (ischemia). In recent years, an increased incidence of ONJ has been associated with the use of high dosages of BPs given intravenously for the management of cancer patients with destructive bone lesions. This condition is referred to as Bisphosphonate-associated Osteonecrosis of the Jaw (BONJ) [(1)].

It is postulated that BPs accumulate in human jaws at higher levels than the skeleton generally, as bone turnover in the jaws has been demonstrated to be higher. The consequent over-suppression of bone turnover may compromise jaw healing, both in response to injury and the normal physiological micro-damage from occlusion [(2)].

Osteonecrosis of the jaw has also been associated with invasive-dental

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procedures during BP treatment [3,4]. Dental trauma increases the demand for bone remodeling/ repair, and theoretically increases the number of potential binding sites for BPs that would result in local accumulation of the drugs[5].

Early reports of BONJ came from the USA [6,7,8] but the number of cases reported worldwide continues to grow [9,10,11]. Cases are particularly prevalent in patients with multiple myeloma, breast, lung and prostate cancer who are being treated with IV bisphosphonates[6,7].

Bisphosphonate-associated Osteonecrosis of the Jaw is characterized by exposed necrotic bone in the oral cavity and is often associated with pain. Pain is most commonly the result of secondary bacterial infection of the local surrounding soft tissue; however other causes include sharp bony sequestra, pathologic fracture, and neuropathy. In many cases the diagnostic work-up includes jaw imaging studies to evaluate the extent of bony changes [12].

Medical management of BONJ focuses on treatment and prevention of infections and symptom management; it is typically initiated with nonsurgical treatments which include the removal of bony sequestrum when mobile, debridement of rough/sharp areas of bone, and medical management of infections with topical and systemic antibiotics and neuropathic symptoms with appropriate pharmacologic agents. It is not uncommon for patients to require long-term therapy with antibiotics and/or anticonvulsants (in the case of neuropathic dysesthesias and neuralgias) [13]. In cases where teeth become symptomatic or progressively loose within the field of osteonecrosis, dental extractions are necessary [14].

Bisphosphonate-associated Osteonecrosis of the Jaw may become a chronic source of pain, infection, reduced function, and their corresponding costs. While a number of reports have characterized BONJ clinically and epidemiologically and provided important information on treatment outcomes, to date there has been no analysis of the associated costs of managing ONJ have been published [15].

Patients and Methods

This was a retrospective electronic medical record based review of cancer patients with BONJ that were evaluated and managed at the Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, Boston, MA.USA. All patients were clinically evaluated by an expert group of oral health care specialists.

Eligibility criteria in this study were included in patients with multiple myeloma and solid tumors with bone metastases with BONJ secondary to IV aminobisphosphonate therapy that were evaluated and managed at the Division of Oral Medicine and Dentistry, Brigham and Women's Hospital, between 2002 and 2010.

Clinical staging (0-3) was determined according to the guidelines published by AAOMS[16,17]. Exclusion criteria were 1) non-cancer patients with BONJ secondary to IV bisphosphonate therapy, 2) patients that developed BONJ following oral BP therapy, 3) single visit patients.

Dental, medical and pharmacy utilization data were abstracted from the patients' electronic medical records. Clinical and demographic information, BONJ features (e.g. staging, number and location of lesions); diagnostic tests/imaging studies, medications prescribed, number of office visits, and type and

number of procedures/interventions were collected using a standardized collection form. The costs of these services were calculated using standard cost references (Medicare allowable charges and Red Book of Drug Facts) [18].

All data collection and primary analyses was completed over a period of 3 months. We reviewed 94 case-records for this study (forty five woman and forty nine men, median age 60 years at initial visit).

The Institutional Review Board (IRB) and Dana-Farber/Harvard Cancer Center's Office for Human Research Subjects approved the study protocol; a waiver of consent has been obtained from the IRB after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

Statistical Analyses

Data were analyzed through the use of SPSS (Statistical Process for Social Sciences) version 10.0 application Statistical analysis system and Excel (Statistical package).

Statistical and economic analyses were conducted in collaboration with the Division of Pharmacoepidemiology, Brigham and Women's Hospital. Descriptive statistics included the baseline characteristics of the study cohort, including sociodemographics, comorbid conditions, and BONJ features. Unit costs were assigned to each health care resource identified in the chart review using standard references, such as Medicare Allowable Charges and the Average Wholesale Price. Median costs and interquartile ranges were calculated for the total cohort and relevant subgroups (Table 2).

Results

Ninety-four cancer patients diagnosed with BONJ were included in this study. The majority of patients were white, and (52%) were male. All of them were under IV bisphosphonate medication. Fifty percent (50%) were under zoledronic acid, (11.7%) under pamidronate, with median duration therapy of 36 months. Patient's age at initial visit ranged from thirty eight to eighty years, with median age of sixty years as can be seen in (Table 1).

The median onset of symptoms was 6 months; Follow up duration of patients ranged from two to sixty two months with median duration of eleven and a half months. The most frequent underlying cancer diagnoses were multiple myeloma (63.8%), breast cancer (19.1%), prostate cancer (4.3%), lung cancer (3.2%), osteoporosis (2.1%), and other medical diagnosis with a (7.5%). At the initial visit, (50%) had Stage 2 BONJ which was the highest (58.5%) among BONJ stages and most (72.3%) presented with a single quadrant of involvement. The non-surgical treatments in combination with pharmacologic management resulted in more than (75%) healed/improved cases as illustrated in (Table 1).

The highest median cost of treatment was for the prostate cancer patients (4.3%) at $3177.00, followed by breast cancer (19.1%) at $1916.00 which included the patient with the maximum cost of treatment of the total study cohort that raised breast cancer group to rank second, lung cancer $1601.00, osteoporosis $1568.00. while the lowest median cost of treatment was for the most frequent cancer diagnosis, multiple myeloma (63.8%) at $1186.00. We also found that the incidence of BONJ in patients with multiple myeloma seems to be higher than in patients with breast cancer as shown in (Table 2).

We found that the median cost of treatment increased with the advanced BONJ stage, stage 3 is the utmost cost of $3803.00, followed by stage 2 at $1949.00, stage 1 at $1070.00 and the least cost was stage 0 at $ 962.00 as seen in (Table 2).

We found that the median cost of treatment of two quadrants involved BONJ patients ($3506.00) were higher than three ($2689.00) and four ($3141.00) quadrants. The nonsurgical management in BONJ patients treated (75.5%) of the total number of study participants and had the best treatment results. The median cost is not much different in healed/improved cases and progressive ones. The healed/improved cases were the most expensive conditions regardless of their medical diagnosis, while the median cost of treatment for the stable cases of BONJ patients was less than the progressive ones as demonstrated in (Table 2).

Medication-associated costs accounted for (47.8%) of total costs. Different doses of Augmentin cost (67%) of total medication costs. Levofloxacin 500 mg (11%), Clindamycin 300 mg (10%), Chlorhexidine gluconate (4%), Azithromycin 250 mg (3%), other medications including Clindamycin 150 mg, Penicillin 500 mg, Gabapentin 600 mg, Oxcarbazepine 300 mg sum up to a total of (4%) of the total medication cost, While the remaining medications didn't reflect more than (1%) impact on the total medication cost.

Microbiological and histopathological investigations-associated costs accounted for (1%) of total costs.

The overall median treatment cost for the total study cohort with different BONJ stages was $1,546. Treatment cost of more than 60% of study participants didn't exceed $2,000, while 25% of study participants' treatment cost ranged $2,000 - $4,000. As for the remaining 15%, the treatment cost increased gradually to a maximum of $10,000 per patient, except for one patient at $20,000 due to prolonged usage of medication and long visit follow up as demonstrated in (Figure 1).

The greatest factors contributing to the costs of treatment of BONJ included in long term medication and clinical visits with relatively equal median cost which were $467.40 (38%) and $436.52 (35%) respectively, while the median costs of interventions and imaging tests were $226.46 (18%) and $109.90 (9%) respectively as seen on (Figure 2).

Imaging studies accounted for 10% of total costs, with the periapical imaging tests ranked the highest in cost among all imaging tests done for the study participants.

Procedure-associated costs accounted for (16.4%) of total costs, with sequestrectomy and debridement accounting for the majority (63.14%) of the total cost of interventions at ($23,098.92), followed by extraction of symptomatic teeth (15.33%) equal to ($5,610.00).

Cost of appliances (10.36%) at ($3,792.00), root canal treatment (7.24%) at ($2,652), while the remaining interventions did not exceed (5%) of the total cost of interventions.

Discussion

In the United States, medical care is not free compared to Iraq, therefore the cost of medical interventions is considered a very important issue and becomes the first priority when making a treatment plan.

The present investigation represents the first study specifically evaluating the economic consequences of BP osteonecrosis, with respect to the required office visits, dental and

surgical procedures, medications and how these measures were related to disease severity/staging.

According to our results (52%) of the study participants were male. Sex was not statistically associated with BONJ [19,20].

We also found that the median age of patients at initial visit diagnosed with BONJ was 60. In a study done by Marx, (2003) the vast majority of patients receiving BPs are over the age of 50. In consideration of certain accepted age changes within the jaws that include the reduction in blood circulation and ability to respond to trauma, it would seem reasonable to consider old age as a risk factor for this condition.

Age and gender had been reported as prognostic factors for treatment needs for conservative dental treatment, tooth extractions, and prostheses. Younger and female patients may have better motivation or manual abilities needed for oral hygiene. Thus, better oral hygiene may suggest fewer possible trigger factors for the development of BONJ in younger women, resulting in a lower prevalence of BONJ [21].

The majority of our patients were white (96.8%), this might suggest that this race at higher risk for developing BONJ than others. Race was reported in one study to be a risk factor, with Caucasians having an increased risk for BONJ compared with blacks [22].

The BPs that are related to BONJ development in other studies were nitrogen-containing bisphosphonates such as zoledronate, pamidronate, and ibandronate [23]. This observation was also true in our cohort. Most of the patients had been administered zoledronate (50%), the most potent BP. However, our trial was not designed to compare among different BPs, and conclusions should be withheld until prospective comparisons have been performed [24].

In BONJ patients the most common pathogens, based on culture and sensitivity tests, are considered to be Actinomyces, Eikenella and Moraxella species [25]. Therefore penicillin V (phenoxymethylpenicillin) 500 mg four times per day is a suitable antibacterial drug. In penicillin allergic patients, doxycycline 100 mg once daily is suitable. Metronidazole 200 mg three times per day has proven effective in patients' refractory to the above antibiotics. This result agrees with a previous study conducted by Khosla, (2007) considering the target pathogens, who noted that amoxicillin and clindamycin are not first line drugs for prophylaxis in this condition [26].

The highest median cost of treatment was for the prostate cancer patients, a possible explanation might be that the prostate patients in our cohort who were treated with BPs have a higher stage of BONJ at presentation and had received long-term antibiotics which necessitate prolonged follow-up [27].

Imaging studies, usually obtained after the onset of clinical symptoms, show involvement of the affected jaw extending beyond what is clinically evident. In the current study imaging studies accounted for (10 %) of total costs, the periapical imaging tests ranked the highest in cost among all imaging tests done for the study participants; this is due to the fact that the periapical imaging tests are usually done more frequently than all other imaging tests [28].Computerized Tomography imaging tests routinely used in the diagnosis and management of metastatic cancer, contrast enhanced and non-contrast enhanced ranked the second highest in cost among all imaging tests done with total number of 27 CT imaging tests only.

Panoramic imaging test is routinely used to image the hard tissues of the maxillofacial region and is a modality readily accessible to the majority of oral healthcare specialists. Nevertheless, it ranked third in cost impact compared to other tests and second in number of tests done for the whole group. Compared with CT, both the radiation exposure and financial cost are substantially lower [(29)].

Occlusal imaging tests were the lowest in total cost among other tests performed, but not the lowest price one. Magnetic resonance imaging was the least test performed while ranking third from the bottom cost wise. All remaining imaging tests were not used extensively and didn't reflect more than 10% impact on the total cost of imaging test performed for the entire study participants [(30)].

We found that the median cost of treatment of two quadrants involved BONJ patients were higher than three and four quadrants. This was probably due to the fact that most of the patients in the last two categories were at stage 1 BONJ. The rate of healing of BONJ in the studied group was significantly associated with the stage of BONJ at presentation, with higher stages linked with lower healing rates. This result suggests that the proposed staging system, which is based on reported symptoms and clinical findings, is not only valid to guide the treatment but can also be used to predict the clinical outcome [(31)].

Medication-associated costs accounted for (47.8%) of total costs. Different doses of Augmentin cost (67%) of total medication costs, so Augmentin of different doses is much more expensive than other medications, it has the highest cost impact followed by Levofloxacin 500 mg, we suggest the prescription of other medications including Clindamycin 150 mg, Clindamycin 300 mg or Penicillin 500 mg as an alternative antibiotic to overcome the cost problem, while the remaining medications were within reasonable prices and can be prescribed as long term treatment to achieve maximum benefits for patients.

The conservative nonsurgical management of patients with BONJ was based on removal of the necrotic bone, minor debridement to smooth sharp bone edges, antibiotics, antibacterial agents for active infections and periodic follow-ups. These are determined by the severity of each individual case. Nonsurgical management in BONJ patients treated (75.5%) of the total number of study participants and had the best treatment results. Our findings are consistent with Montefusco, (2007) who suggested that prophylactic antibiotics before and during dental procedures may reduce the risk of developing ONJ.

Conclusions

Cost of BONJ treatment was modest compared with other metastases, as BONJ progress the median cost of treatment will increase. Medications were highly effective in treatment of BONJ, more than 75% of patients getting healed/improved with this treatment modality.

We found that the removal of the alveolar bone and a correct antimicrobial prophylaxis (antibiotics and mouthwash) can reduce the risk of osteonecrosis in patients taking bisphosphonates.Medications have the greatest effect on the total cost of treatment especially the Amoxicillin/clavulanate potassium which was effective in treatment of BONJ but rather expensive. Although long term medication, sequestrectomy and debridement are a bit expensive

but is part of evidence-based positive clinical outcome.

References

1- Woo, S.; Hellstein, J. and Kalmar, J. (2006). Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 144 (10): pp. (753-761).
2- Cheng, A.; Daly, C.G.; Logan, R.M.; Stein, B. and Goss, A.N. (2009). Alveolar bone and the bisphosphonates. Aust Dent J . 54(Suppl1): pp. (S51–861).
3- Bilezikian, J.P. (2006). "Osteonecrosis of the jaw--do bisphosphonates pose a risk?" N Engl J Med. 355(22): pp. (2278-2281).
4- Khosla, S.; Burr, D.; Cauley, J. (2007). Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 22(10): pp. (1479-1491).
5- Dixon, R.B.; Tricker , N.D. and Garetto, L.P. (1997). "Bone turnover in elderly canine mandibles and tibia". J. Dent. Res. 76(IADR Abstracts): 2579.
6- Marx, R.E. (2003). "Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic". J Oral Maxillofac Surg; 61: pp. (1115-1117).
7- Migliorati, C.A. (2003). "Bisphosphonates and oral cavity avascular bone necrosis". J Clin Oncol; 21: pp. (4253-4254).
8- Ruggiero, S.L.; Mehrotra, B.; Rosenberg, T.J. and Engroff, S.L. (2004). "Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases". J Oral Maxillofac Surg;62: pp. (527-534).
9- Thumbigere-Math, V.; Sabino, M.C.; Gopalakrishnan, R. (2009). Bisphosphonate related osteonecrosis of the jaw: clinical features, risk factors, management, and treatment outcomes of 26 patients. J. Oral Maxillofac. Surg. 67, pp. (1904–1913).
10- Hong, J. W.; Nam, W.; Cha, I.H.; Chung, S.W.; Choi, H.S.; Kim, K.M.; Kim, K.J.; Rhee, Y. and Lim, S.K. (2009). Oral bisphosphonate-related osteonecrosis of the jaw: the first report in Asia. Osteoporos. Int. 21, pp. (847–853) .
11- Saussez, S.; Javadian, R.; Hupin, C.; Magremanne, M.; Chantrain, G.; Loeb, I. and Decaestecker, C. (2009). Bisphosphonate-related osteonecrosis of the jaw and its associated risk factors: a Belgian case series. Laryngoscope 119: pp. (323–329).
12- Treister, N.S.; Richardson, P.; Schlossman ,R.; Miller, K. and Woo, S.B. (2008). Painful tongue ulcerations in patients with bisphosphonate-associated osteonecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 105(6):e1-4.
13- Bjartell, A. (2006). Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Retrieved from Urosource: http://www.urosource.com/diseases/prostatecancer/view/article/ bisphosphonate associated-osteonecrosis-a-long-term-complication-of-bisphosphonate-treatment. 7(6): pp. (508-516).
14- Khan, A.A.; Sándor, G.K.B.; Dore, E.; Morrison, A.D.; Alsahli, M.; Amin, F. et al. (2008). "Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw". J Rheumatol; 35: pp. (1391–1397).
15- Migliorati, C.A.; Siegel, M.A. and Elting, L.S. (2006). Bisphosphonate – associated osteonecrosis: a long term-complication of bisphosphonate treatment . Lancet Oncol . 7(6): pp. (508-514).
16- Ruggiero, S.L.; Fantasia, J. and Carlson, E. (2006). Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Path Oral Radiol Endod 102:433.
17- American Association of Oral and Maxillofacial Surgeons Position Paper on "Bisphosphonate-Related Osteonecrosis of the Jaws". (2007). Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. J.Oral Maxillofac. Surg. 65:369.
18- Thomson Health Care. (2008). The Red Book of Medicines. Newark: Thomson Health Care.
19- Jadu, F.; Lee, L.; Pharoah, M.; Reece, D. and Wang, L. (2007). A retrospective study assessing the incidence, risk factors and comorbidities of pamidronate-related necrosis of the jaws in multiple myeloma patients. Ann Oncol 18: pp. (2015–2019).
20- Hoff, A.O.; Toth, B.B.; Altundag, K. (2008). "Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates". J Bone Miner Res 23: (826-836).
21- Montal, S.; Tramini, P.; Triay, J.A.; and Valcarcel, J. (2006). Oral hygiene and the need for treatment of the dependent

institutionalized elderly. Gerodontology. 23:67-72.
22- Badros, A.; Weikel, D.; Salama, A. (2006). "Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors". J Clin Oncol 24:pp. (945-952).
23- Walter, C.; Grotz, K.A.; Kunkel, M. and Al-Nawas, B. (2007). Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. Support Care Cancer. 15:197-202.
24- Pavlakis, N.; Schmidt, R. and Stockler, M. (2005). Bisphosphonates for breast cancer. Cochrane Database Syst Rev. CD003474.
25- Marx, R.E. (2007). "Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment". J Oral Maxillofac Surg. 65: 2397-2410.
26- Khosla, S.; Burr, D.; Cauley, J. (2007). Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 22(10): pp. (1479-1491).
27- Walter, C.; Al-Nawas, B.; du Bois, A.; Buch, L.; Harter, P. and Gro¨tz, K.A. (2009). Incidence of bisphosphonate-associated osteonecrosis of the jaws in breast cancer patients. Cancer 115:1631–1637.
28- Chiandussi, S.; Biasotto, M. and Dore, F. (2006). Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. Dentomaxillofac Radiol 35:236.
29- Brenner, D.J.; Hall, E.J. (2007). "Computed tomography – an increasing source of radiation exposure". N Engl J Med .357: 2277–2284.
30- Phal, P.M.; Myall, R.W. and Assael, L.A. (2007). "Imaging findings of bisphosphonate-associated osteonecrosis of the jaws". AJNR Am J Neuroradiol 28:1139.
31- Walter, C.; Klein, M.O.; Pabst, A.; Al-Nawas, B.; Duschner, H. and Ziebart, T.(2010). Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. Clin Oral Investig 14:35–4.

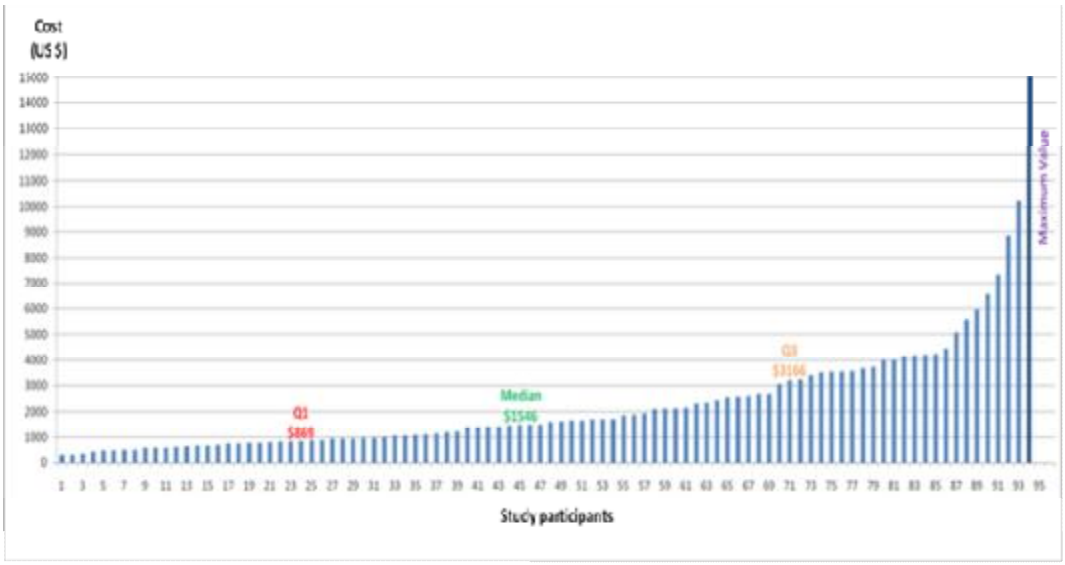

Figure (1): The distribution of each patient's treatment cost with a total study cohort (n=94), showing Median cost = $1546, 25th percentile cost (Q1) = $869, 75th percentile cost (Q3) = $3166, Maximum value exceeding $15,000.

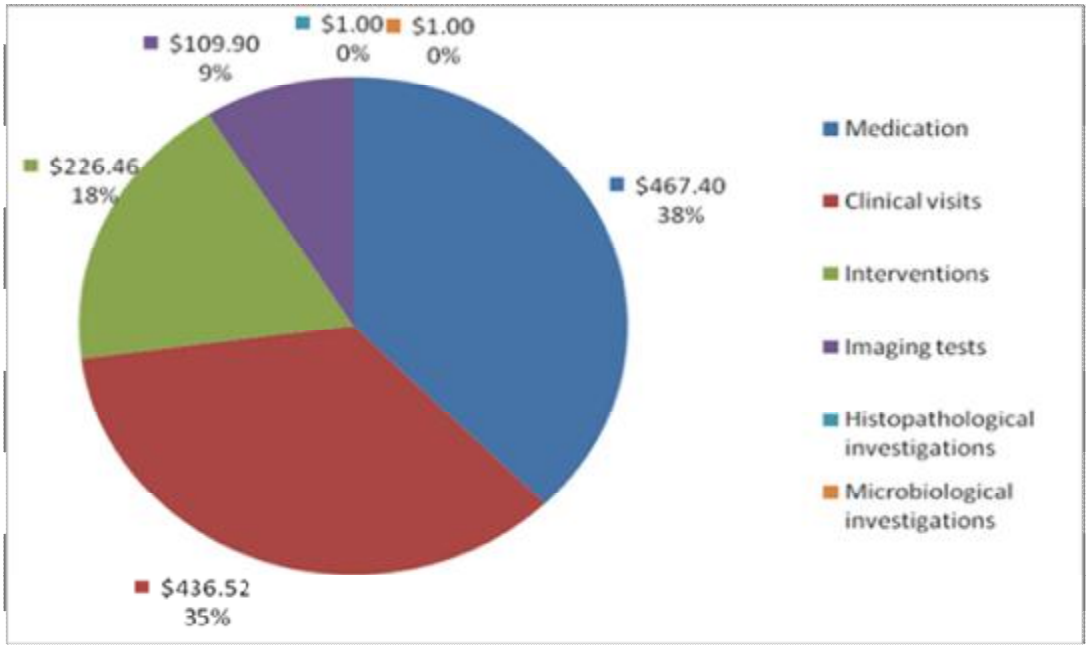

Figure (2): Median cost for each category. Medication with the highest median cost impact at $467.40 (38%), followed by clinical visits which cost $436.52 (35%), interventions cost $226.46 (18%), and imaging test which cost $109.90 (9%). As for the median cost of histopathological and microbiological investigations we assumed to be $1.00 (0%) each.

Table 1. Characteristics of the Study Cohort (n = 94)

Characteristics	
	N (%) or median (IQR)
Gender	
Male	49 (52.1)
Female	45 (47.9)
Race/ethnicity	
White	91 (96.8)
Black	2 (2.1)
Asian	1 (1.1)
Median age at initial visit (years)	60.6 (38.0-80.5)
Medical diagnosis	
Multiple myeloma	60 (63.8)
Breast cancer	18 (19.1)
Prostate cancer	4 (4.3)
Lung cancer	3 (3.2)
Osteoporosis	2 (2.1)
Others	7 (7.5)
Type of bisphosphonate	
Pamidronate	11 (11.7)
Zoledronic acid	47 (50.0)
Pamidronate and zoledronic acid	30 (31.9)
Ibandronate	1 (1.1)
Not available	5 (5.3)
Median duration of biphosphonates therapy (months)	36 (5.0- 156)
Quadrants involved	
1 quadrant	68 (72.3)
2 quadrants	21 (22.3)
3 quadrants	3 (3.2)
4 quadrants	2 (2.1)
Stage of BONJ at initial visit	
Stage 0	8 (8.5)
Stage 1	37 (39.4)
Stage 2	47 (50.0)
Stage 3	2 (2.1)
Highest BONJ score	
Stage 0	2 (2.1)
Stage 1	32 (34.1)
Stage 2	55 (58.5)
Stage 3	5 (5.3)
Median duration of onset of symptoms(months)	6 (1.0- 48.0)
Median duration of follow up (months)	11.5 (0.19-62.0)
Clinical outcome	
Improved/ healed	71 (75.5)
Stable	20 (21.3)
Progressive	3 (3.2)

Table 2. Cost of Care by Relevant Sub-groups

Medical diagnosis	**No. of patients**	**Median**	**25th percentile**	**75th percentile**
		US dollars		
Multiple myeloma	60	1186	738	2778
Breast cancer	18	1916	1153	3276
Prostate cancer	4	3177	1977	5718
Lung cancer	3	1601	1173	3017
Osteoporosis	2	1568	1492	1643
Others	7	2317	1434	3074
BONJ Stage				
Stage 0	8	962	719	1612
Stage 1	37	1070	701	2558
Stage 2	47	1949	1179	3533
Stage 3	2	3803	2712	4894
Quadrants				
One quadrant	68	1399	749	2179
Two quadrants	21	3506	1160	4163
Three quadrants	3	2689	1791	5771
Four quadrants	2	3141	3094	3188
Clinical Outcome				
Healed/ Improved	71	1699	852	3533
Stable	20	1069	917	1986
Progressive	3	1641	1196	1881