Impact of Different Interval Dosing of Zoledronic Acid on Skeletal Events …. Mansoura Experience

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Abstract:

Background: Zoledronic acid was accepted as a line of management of cases with bone metastasis from solid tumors and cases of multiple myloma. It's generally a safe drug, but sometimes it is associated with toxic effects like flu like symptoms, renal impairment and osteonecrosis of the jaw. Dose interval of giving the treatment varies between short (3-4) weeks and long (12) weeks.

Aim: to determine the incidence of skeletal related events (SREs), which includes pain, cord compression or pathological fracture and duration of SREs free survival. Also, to assess the incidence of toxicity between different time intervals of giving the treatment.

Methods: This is a retrospective study done on cases of breast and prostate cancer with bone metastasis and cases of multiple myeloma who received zoledronic acid for at least 1.5 years. Cases were divided according to time interval of receiving treatment to 3 groups; group 1 received treatment every 4 weeks, group 2 every 6 to 8 weeks and group 3 every 10 to 12 weeks.

Results: after a follow up period ranging between 26 and 36 months, it was noticed that as the time interval of receiving zoledronic acid increased, the number of cases developed SREs increased, with non-significant P value (0.071). Regarding the incidence of toxicity, it decreased as the time interval increased with non-significant P value for flu like symptoms (0.12), nephrotoxicity (0.28) but it was significant regarding development of osteonecrosis of the jaw (0.029). Comparing the SREs free survival, it was better in short time interval with significant P value (0.027).

Conclusion: short time interval of giving zoledronic acid is preferred as its associated with significant SREs free survival. Longer time interval is a good option for cases who can't tolerate the toxicity.

Key words: zoledronic acid, dose interval, SREs.

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Introduction:

Bone metastasis is a common problem associated with many cancer types. Zoledronic acid was accepted as a line of treatment for cases of bone metastasis associated with solid tumors like breast and prostate cancer and for cases of multiple myloma [1]. Zoledronic acid is usually given every 3 to 4 weeks but sometimes in longer time interval. The aim of giving the drug is to palliate pain and decrease the incidence of other SREs, specially cord compression and bone fracture [2].

Zoledronic acid is a well-tolerated drug, but sometimes is associated with adverse effects which include renal impairment, flu like symptoms and osteonecrosis of the jaw [3]. osteonecrosis of the jaw is more manifest with cumulative doses (1.5% documented for cases treated for one year and 7.7% for cases treated for 3 years) [4] renal impairment associated with zoledronic acid is manifested as gradual increase in serum creatinine. flu like symptoms sometimes happen from 1st time giving the drug [5]. The time interval for giving zoledronic acid is a matter of debate. Giving the drug every 4 weeks was done empirically rather than to be based on confirmed studies specially when considering pharmacodynamic aspect [6]. Due to financial problems as regarding availability of the drug, many patients are not regular on the time interval between doses of treatment. However, the impact of these different time interval is not well assessed although some researches recommend that zoledronic acid could be given in longer time interval without negative effect on the clinical outcome [7]. In this study we tried to show our experience at clinical oncology and nuclear medicine department, Mansoura university hospital about cases of metastatic breast and

prostate cancer to bone and cases of multiple myeloma who received zoledronic acid. We noticed that many cases were not regular on the treatment so we could not put them on comparative study. So, we included only cases who were regular on treatment either every 4 weeks or 6 to 8 weeks or 10 to 12 weeks. The idea of choosing this specific time interval is that most of previous studies compared short (4 weeks) versus long (12 weeks) intervals. So, we try to show our experience at Mansoura university comparing short and long interval and also to see if there will be different results with a median interval (6-8 weeks).

The primary endpoints of the study were to determine the incidence of SREs including pain, bone fracture or cord compression and the duration of SREs free survival between the 3 groups. The secondary endpoint was to assess the development of toxicity in the form of flu like symptoms, osteonecrosis of the jaw, and kidney dysfunction.

Patients and Methods:

This study is a retrospective one, was done at Mansoura university hospital, clinical oncology and nuclear medicine department on cases of bone metastasis of breast and prostate origin and cases of multiple myeloma who received zoledronic acid for at least 1.5 years. Cases were divided according to time interval of receiving treatment into 3 groups; group 1 received treatment every 4 weeks, group 2 every 6 to 8 weeks and group 3 every 10 to 12 weeks. Cases who were not regular on one of those interval times were excluded. cases with visceral metastasis were excluded as they were on different protocols of chemotherapy and had many complications which could affect the toxicity profile of the cases. Cases older than 70 years were excluded because most of them had morbid diseases which could also mask the effect of the drug and toxicity profile of the cases. Study was started at Oct 2020 and ended at Sep 2023. Cases who lost follow up were excluded. Cases who completed the whole duration of follow up were examined clinically every month and assessed radiologically every 3 months for development of SREs including pain, bone fracture and cord compression and for development of toxicity including flu like symptoms, nephrotoxicity and osteonecrosis of the jaw.

Statistical analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). The normality of data was first tested with one-sample Kolmogorov-Smirnov test.

Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves was determined by Log-Rank test. The results were considered significant when the $p \leq 0.05$.

Results:

At the end of the study, 517 cases were identified. All cases received zoledronic acid for 1.5 year at least. The duration of follow up ranged between 26 and 36 months (median follow up period = 31 months). Cases were divided into 3 groups according to time interval of receiving the treatment. G1 including 172 cases received zoledronic acid every 4 weeks, G2 including 175 cases with time interval 6 to 8 weeks and G 3 including 170 cases with time interval 10 to 12 weeks.

Table 1 compares the 1ry tumor site between the three groups. Breast cancer was the 1ry tumor site in 90 cases in group 1, 93 cases in group 2 and 89 cases in group 3. The 1ry tumor site was the prostate in 60 cases in group 1, 61 cases in group 2 and 59 cases in group 3. There were 22 cases of multiple myloma in group 1, 21 cases in group 2 and 22 cases in group 3. The 3 groups were matched regarding the 1ry tumor site without significant P value (0.99).

Table 2 compares the incidence of SREs between the 3 groups. 24 (14%) cases developed SREs in group 1 compared to 36 (20.6%) cases in group 2 and 40 (23.5%) cases in group 3. Although its noticed that the number of cases developed SREs increases as the time interval of receiving zoledronic acid increased, but the P value was not significant (0.071). When studying every event alone we found that 10 cases developed pain in group 1 compared to 15 cases in group 2 and 18 cases in group 3. Regarding bone fracture, there were 8 cases in group 1 compared to 11 cases in group 2 and 11 cases in group 3. When comparing cases developed cord compression, it was 6 cases in group 1, 10 cases in group 2 and 11 cases in group 3. Again, the incidence of every single event increased as the time interval increased but also still without significant P value. It was (0.27) comparing pain, (0.73) comparing bone fracture and (0.43) comparing cord compression. Figure 1 shows the SREs between the 3 groups and it confirms that the number of cases developed SREs increases as the time interval of receiving zoledronic acid increased.

Table 3 shows the incidence of toxicity between the 3 groups. it was found that 21 (12.2%) cases in group 1 complained of flue like symptoms compared to 15 (8.6%) cases in group 2 and 10 (5.9%) cases in group 3. As regards nephrotoxicity, 11 (6.4%) cases in group 1 showed elevated serum creatinine compared to 7 (4%) cases in group 2 and 5 (2.9%) cases in group 3. Osteonecrosis of the jaw was reported in 5 (2.9%) cases in group 1 compared to only 1 (0.6%) case in group 2 and 0 cases in group 3. It was obvious that the incidence of toxicity was decreased as the time interval of receiving treatment increased. But when assessing those values with Chi square test of significance, the P value was not significant as regarding development of flu like symptoms (0.12) and development of nephrotoxicity (0.28). the only significant P value was detected when comparing the development of osteonecrosis of the jaw between the 3 groups as it was (0.029). and that was expected result as no cases in group 3 developed this complication. Figure 2 shows the incidence of toxicity

between the 3 groups and the significant P value when comparing the osteonecrosis of the jaw.

The duration of SREs free survival between the 3 groups was 1ry end point in our study. At the end of our research, it was found that the mean SREs free survival was 33.779 months in group 1 compared to 32.343 months in group 2 and 31.359 months in group 3. Using the log rank test, the P value was significant between the 3 groups (0.027) as shown in table 4.

Figure 3 showed the Kaplan-Meier curve for survival functions between the 3 groups. And from the curve we can noticed that the 18 months SREs free survival was 98% in group 1 compared to 88% in group 2 and dropped to 76% in group 3.

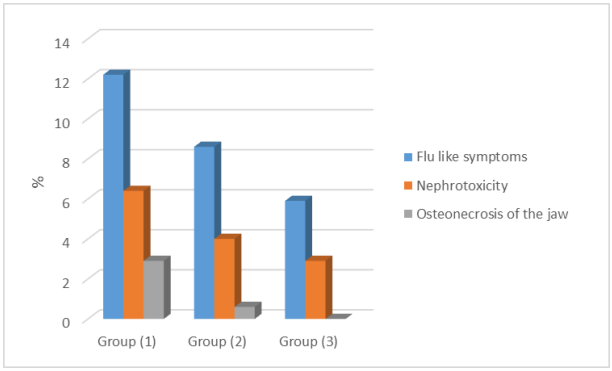

Figure 2: incidence of toxicity between the 3 groups

The P value was non-significant except for osteonecrosis of the jaw (0.029)

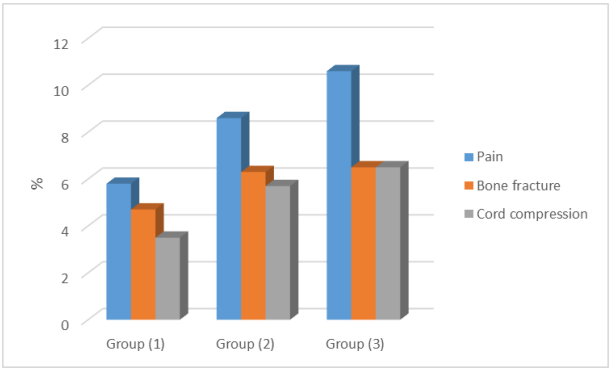

Figure 1: SREs between the 3 groups

The P value was non-significant

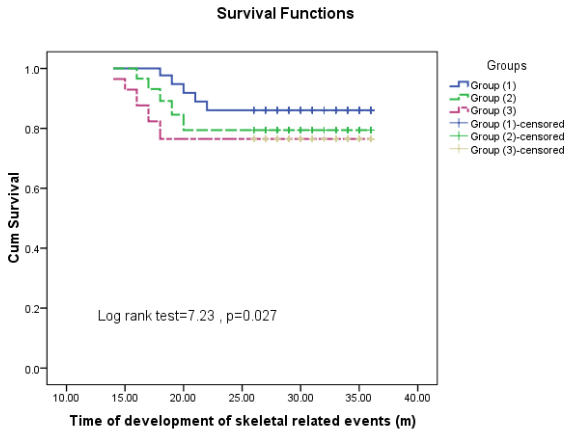

Figure 3: The Kaplan-Meier curve for SREs events free survival either pain, bone fracture or cord compression.

18 months SREs free survival was 98% in group 1 compared to 88% in group 2 and dropped to 76% in group 3.

Table (1): Primary tumor site between 3 groups

Primary tumor site	Group (1) (n=172)	Group (2) (n=175)	Group (3) (n=170)	Test of significance	P value
1ry tumor site					
Breast	90 (52.3%)	93 (53.1%)	89 (52.4%)	χ^2 =0.086	0.99
Prostate	60 (34.9%)	61 (34.9%)	59 (34.7%)		
Multiple myloma	22 (12.8%)	21 (12.0%)	22 (12.9%)		

The 3 groups were matched regarding the 1ry tumor site without significant P value (0.99).

Table (2): Compare incidence of SREs between 3 groups

	Group (1) (n=172)	Group (2) (n=175)	Group (3) (n=170)	Test of significance	P value
Development of skeletal related events					
Yes	24 (14.0%)	36 (20.6%)	40 (23.5%)	χ^2 =5.28	0.071
No	148 (86.0%)	139 (79.4%)	130 (76.5%)		
Skeletal related events					
Pain	10 (5.8%)	15 (8.6%)	18 (10.6%)	χ^2 =2.57	0.27
Bone fracture	8 (4.7%)	11 (6.3%)	11 (6.5%)	χ^2 =0.63	0.73
Cord compression	6 (3.5%)	10 (5.7%)	11 (6.5%)	χ^2 =1.67	0.43

the number of cases developed SREs increases as the time interval of receiving zoledronic acid increased, but the P value was not significant (0.071).
The incidence of every single event increased as the time interval increased without significant P value. (0.27) comparing pain, (0.73) comparing bone fracture and (0.43) comparing cord compression.

Table (3): Compare incidence of toxicity between 3 groups

Toxicity	Group (1) (n=172)	Group (2) (n=175)	Group (3) (n=170)	Test of significance	P value
Flu like symptoms	21 (12.2%)	15 (8.6%)	10 (5.9%)	χ^2 =4.25	0.12
Nephrotoxicity	11 (6.4%)	7 (4.0%)	5 (2.9%)	χ^2 =2.52	0.28
Osteonecrosis of the jaw	5 (2.9%)	1 (0.6%)	0 (0%)	χ^2 =7.09	0.029*

χ^2 : Chi square test, *significant p≤0.05

the P value was not significant regarding development of flu like symptoms (0.12) and development of nephrotoxicity (0.28).
the only significant P value was detected when comparing the development of osteonecrosis of the jaw (0.029). it was better in long interval group.

Table (4): Kaplan-Meier for SREs free survival between 3 groups

	Disease free survival				
	Mean Survival time	Std. Error	95% CI	Log Rank test	P – value
Groups					
I	33.779	0.422	32.95-34.60		
II	32.343	0.545	31.27-33.41	7.25	0.027*
III	31.359	0.644	30.09-32.62		
SREs free survival	32.497	0.317	31.87-33.12	-	-

Log Rank (Mantel-Cox) was used, CI: confidence interval
the P value was significant between the 3 groups (0.027) with better survival in short interval compared to more longer intervals.

Discussion:

Zoledronic acid is usually given in short interval (every 3–4 weeks) but either due to unavailability of the drug or developed toxicity, many patients received the drug at longer time intervals [8]. Specialists are interested in determining the better time interval that ensures efficacy and reduces the side effects [9].

In this retrospective study involving cases of bone metastasis of breast and prostate origin and cases of multiple myeloma who received zoledronic acid for at least 1.5 years, we tried to compare the effect of short versus median and long intervals of receiving the treatment. Our results showed as the time interval of receiving zoledronic acid increased, the number of cases developed SREs increased, but the incidence of toxicity decreased with non-significant P value except

for development of osteonecrosis of the jaw. When comparing the SREs free survival, it was better in short time interval with significant P value.

Most of previous studies compared only short to long intervals of receiving zoledronic acid. In a prospective clinical randomized trial of 4 versus 12 weekly administrations of zoledronic acid in cases with bone metastases from breast and prostate done by Clemons et al, the trial included 263 patients, the one-year cumulative incidence of symptomatic skeletal event was 7.6% in every 4 weeks interval with 95% CI (4.3, 10.9) versus 16.6 % for every 12 weeks interval with 95% CI (12.0, 21.2) with a non-significant P value of 0.27. that was matched with our results. However, the symptomatic skeletal event free survival was 79.1% in 4weeks group (95% CI: 71.0 to 85.2) versus 72.4% in 12 weeks group (95% CI: 63.5 to 79.5) at 1-year with a non-significant P value 0.31[10] that was not matched with our results. This could be explained by the short time of follow up (12 months) compared to median follow up of 31 months at our study

In another clinical randomized study done by Himelstein et al to assess effect of longer-interval vs standard 3-4 weeks' time interval of zoledronic acid on skeletal events in cases with bone metastases, an open-label trial done at academic and community sites. 1822 cases with bone metastasis of breast and prostate cancer, or multiple myeloma. The percent of patients who had at least 1 SRE within 2 years of study was 29.5% for patients who received the drug every 4 weeks compared to 28.6% in longer interval (12weeks) group with a noninferiority P value [11]. That was matched with our study as regards the nonsignificant P value although the total number of cases developed SREs were more in short interval group compared to the long one in contrast to our study.

The OPTIMIZE-2 clinical randomized trial that included 416 women with only metastatic breast cancer to bone. After follow-up period of 1 year, SREs was reported in 44 cases (22.0%) in every 4 weeks group and 47 cases (23.2%) in every 12 weeks group also with noninferiority P = .02). Regarding the SRE free survival, there was no statistically significant difference (P value was 0.84) [12]. Again, this result matched with our results as regards the incidence of SREs but not the SREs free survival and like Clemons study this could be explained by the shorter duration of follow up (only 12 months). Also, this study compared cases of metastatic breast cancer only and did not include metastatic prostate or myloma cases which could also explain the difference with our study.

ZOOM trial also included patients with only metastatic breast cancer to bone. The study assessed 425 patients. At 12 months, the estimated skeletal-related events were 18·3% in the 4-week group, and 22·1% in the 12-week group with no significant P value (log-rank p=0·912) [13].

These data was almost similar when the effect of longer- interval time of zoledronic acid administration was studied in patients with bone metastasis from only bronchogenic carcinoma by Tam,A.H., ET AL. they found that Incidence of SRE at 1 year was 23.9% in 4 weeks interval versus 23.5% in12 weeks interval with a non-significant P value of 0.968 (P = 0.530;) [14].

It is noticed that the results of our study agree with the previous studies except when assess the SREs free survival. Most of studies show no significant P value between short and long interval time of treatment, but our study confirmed a significant P value. As we said, this could be explained by the long period of follow up at our study and because many of previous studies consider only cases of metastatic breast cancer. Also, exclusion of older cases than 70 years and cases with visceral metastasis could explain the significant results regarding SREs free survival at our study.

Regarding the development of side effects relative to dosing time interval, we noted that the rate of toxicity was decreased as the time interval of receiving treatment increased with a non-significant P value regarding the development of flu like symptoms (0.12) and development of nephrotoxicity (0.28). as regards the development of osteonecrosis of the jaw, there were no reported cases in long interval dosing (12 weeks) group and so the P value was significant (0.029)

The randomized study of short (4-weeks) versus long (12-week) administration of zoledronic done by Clemons et al showed that patients did not have severe side effects, the reported incidence of osteonecrosis of the jaw was one patient in each group, renal impairment was 4 patients in each group with a non-significant P value (P=1) [10]. The larger number of cases in our study (517) compared to smaller number of that study (263) may explain the significant P value that was documented in our study considering the development of osteonecrosis of the jaw.

These toxicity rates data were almost the same in the study done by Himelstein et al. either the rate of renal impairment or osteonecrosis of the jaw did not have significant P value between the 2 groups. The incidence of jaw osteonecrosis was 2.0% in the 4-week group compared to 1.0% in 12-week group (P=0.08). Kidney dysfunction occurred in 1.2% of cases in 4 weeks compared to 0.5% in 12 weeks (P = .10) [11]. Although the number of cases in that study was large (1822) but the relatively short period of follow up (2 year) could explain the non-significant P value of developing osteonecrosis of the jaw in contrast to our study.

The OPTIMIZE-2 trial reported that the renal adverse events occurred more in 4 weeks group 9.6% compared to 7.9% in 12-week interval with no significant P value. Two cases only developed osteonecrosis of the jaw were presented in the 4 weeks group [12]. Those results match completely with our results.

The ZOOM clinical trial showed that the overall toxicity rate was 0·26 in the long interval (12 weeks) group compared to 0·22 in the short interval (4weeks) group. Flu-like symptoms was the most common grade 3–4 toxic effect in both groups. It was documented in 27% of cases in the long interval group compared to 30 %in the short interval group. Osteonecrosis of the jaw was reported in both groups with non-significant difference [13] those results also matches with our

results but again except when considering the development of osteonecrosis of the jaw.

As noticed, nearly all studies compared short interval (3-4) weeks versus long interval (12 weeks) administration of zoledronic acid. Our study assessed another group of patients who received treatment at a median time interval (6-8) weeks. Our results showed that this group had better toxicity profile compared to short interval group but with lower efficacy and when compared with long interval group, it showed better efficacy but with slightly more incidence of toxicity. So, it may be a good choice for a category of patients with border line kidney function or who could not tolerate the treatment at every 4 weeks.

Conclusion:

We recommend giving zoledronic acid in short time interval is (3-4 weeks) rather than long time interval (10-12 weeks) as its associated with significant SREs free survival. We also recommend giving zoledronic acid at 6-8 weeks rather than 10-12 weeks interval for cases with border line kidney function and cases who could not tolerate the toxicity of treatment as its associated with better response compared to 10-12 weeks interval and better toxicity profile compared to 4 weeks interval specially regarding the development of osteonecrosis of the jaw which has significant P value when compared to short time interval.

Authors' contributions:

Dr Mohamed S. Zahi carried out the collection of data and preparing the tables. Dr Manal. M. Saleh carried out the statistical assessment and documented the results. Dr Nora A. Shaband carried out the design of the study and writing of the background and the discussion. All authors read and approved the final manuscript

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