Original Article

MedInform

DOI: 10.18044/MEDINFORM.2024111.1753

ISSUE 1, 2024

The period of time from the surgical intervention as a predictive factor on the outcome of the treatment of bisphosphonate – associated osteonecrosis of the jaws

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Abstract

Bisphosphonates are highly effective antiresorptive drugs that are used in the treatment of bone metastases in malignancies, Paget's disease, fibrous dysplasia, osteogenesis imperfecta, osteoporosis. Their usage unfortunately leads to development of avascular osteonecrosis of the jaw which has been recognized as a complication of bisphosphonate use. BAONJ is a multifactorial disease and there are several factors that can affect the development and the outcome of the BAONJ treatment. The **aim** of the present study is to establish the influence of one of the risk factors - the period of time from of the surgical intervention on the outcome of the treatment of BAONJ

Materials and methods: In the present study, we included 44 patients diagnosed with Bisphosphonate-associated osteonecrosis of the jaw (BAONJ). The treatment methods applied to the patients we studied are surgical, conservative and surgical-conservative methods. The statistical method used is one-dimensional logistic regression which is from the direction of regression analysis.

Results: Our study shows that with the increase of the he period of time from the surgical intervention, the likelihood of disease progression also increases, found in the examination of the patient on the first and on the sixth month after the treatment of BAONJ.

Conclusion: The factor period of time from the surgical intervention can be used as a predictor of the outcome of BAONJ treatment, and with increasing of its value, the likelihood of disease progression increases.

Keywords: osteonecrosis, bisphosphonates, jaw bones

Introduction

Bisphosphonates are highly effective antiresorptive drugs that are used in the treatment of bone metastases in malignancies (1-3), Multiple myeloma (4-8), Paget's disease (9), fibrous dysplasia (10), osteogenesis imperfecta (11,12). Bisphosphonates are the most widely prescribed drugs for osteoporosis (13-16).
"Painful bone exposure" of the upper and lower jaws in patients taking pamidronate (Aredia; Novartis Pharmaceuticals, EastHanover, NJ) and zoledronate (Zometa; No-vartis Pharmaceuticals) was first described by Marx in 2003 (17). Subsequently, avascular osteonecrosis of the jaw has been recognized as a complication of bisphosphonate use and a number of authors have published their cases (4, 18, 19- 23).
Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is defined as: current or previous treatment with antiresorptive or antiangiogenic agents, resulting in exposed bone or bone that can be probed through an intra- or extraoral fistula in the maxillofacial region which persists for more than 8 weeks in the absence of evidence of radiotherapy of the jaw bones or overt metastatic jawbone disease (24).
BAONJ is a multifactorial disease, with risk factors for the development of the disease divided into risk factors related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors (25). There are insufficient systematic data in the literature on the influence of risk factors for the development of BAONJ on the outcome of BAONJ treatment.

Aim

The aim of the present study is to establish the influence of one of the risk factors - the period of time from of the surgical intervention on the outcome of the treatment of BAONJ by using the statistical method one-dimensional logistic regression which is from the direction of regression analysis.

Materials And Methods

In the present study we included 44 patients diagnosed with Bisphosphonate-associated osteonecrosis of the jaw (BAONJ). For each patient included in the study, information on the anamnesis, general and local status and results of clinical and paraclinical studies is recorded in an individual card. 20 (45.5%) of the patients included in our survey were women and 24 (54.5%) were men, minimum age 36 years, maximum age 88 years, mean 62 years. The present study shows that in 40 (90, 9%) of the patients the main diagnosis was malignant disease, and in 4 patients (9.1%) the intake of BF was indicated by osteoporosis. In 32 (72.7%) patients the introduced BF was Zoledronic acid, in 1 patient (2.2%) it was Pamidronic acid, in 2 (4.5%) Ibandronic acid, in 5 (11.4%) - Zoledronic acid and Pamidronic acid, in 1 patient (2.2%) - Zoledronic and Alendronic acid, in 2 (4.5%) Alendronic and Ibandronic acid and 1 patient (2.2%) received Zoledronic,

Ibandronic and Pamidronic acid. In 4 of the patients (9.1%) BF was taken orally, and in 40 patients (90.1%) it was administered intravenously. Our study showed a maximum value of the duration of BF 108 (in months), a minimum of 8 months, an average of 41.75 months.
The treatment methods that we used were surgical, conservative and surgical-conservative methods. The performed surgical interventions can be summarized in two surgical approaches: surgical debridement and sequestrectomy. The applied drug treatment can be divided into: Antibiotic treatment - the choice of antibiotic is in accordance with the recommendations of AAOMS: Amoxicillin, in combination with Metronidazole; in patients with allergy to penicillin, the use of clindamycin or azithromycin is recommended (24); Antimicrobial agents - Flagyl and use of antiseptic solutions - oral rinses with 2% chlorhexidine solution (Eludril).
We used the period of time from the surgical intervention (TPSI) to denote the time from the surgical intervention (tooth extraction, dental implant placement) to the time of diagnosis of BAONJ, measured in months. The results of the treatment are reported on the 30th day and on the 6th month. Periodic follow-up examinations were performed with a frequency determined by clinical symptoms and indications for treatment.

Based on the BAONJ staging of AAOMS according to clinical manifestations, we divided the patients as follows:
At risk—no apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates
Stage 0—no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms
Stage 1—exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection
Stage 2—exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage
Stage 3—exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and 1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor (26).

The analysis of clinical data shows that one patient (2.3%) was diagnosed in stage 0, 4 patients (9.1%) in stage I, 33 patients (75%) in stage II and 6 (13.6 %) are in stage III. In the present study the results were reported according to the following criteria:
- progression - transition to a more advanced stage of BAONJ;
- stationing - the patient is in the same stage of BAONJ at different intervals of documentation
- clinical improvement - transition to a lower stage of BAONJ
- remission - complete coverage of the exposed bone with intact oral mucosa, without clinical and paraclinical signs of inflammation.

After analyzing the data on the development of BAONJ in a follow-up examination after 1 month, we found the following distribution: in 15 (34.1%) patients there was a clinical improvement in the disease, in 2 (4.5%) there was progression of the disease, 26 (43%) of the patients have the disease stationing and in 1 patient (2.3%) - remission.
Regarding the development of the disease after 6 months, we found the distribution as follows: clinical improvement was observed in 11 (25%) patients, remission in 6 (13.6%), stationing in 20 (45.5%) and progression in 7 (15.9%) patients.
Statistical method: The statistical method univariate logistic regression is used, which is from the direction of regression analysis. Regression analysis is a branch of mathematical statistics in which possible functional dependencies between two or more random variables are studied and evaluated. The main questions are whether there is a functional relationship between two dependent random variables and if so - to find a function that describes it accurately enough.

The variable which variations we want to explain or predict is called dependent - this is the consequence, and the variable for which influence on the consequence is sought is called the independent variable /predictor, factor, regressor/. The objectives of regression analysis are to determine how and to what extent the dependent variable varies or changes as a function of changes in the independent variable (s) that are the cause. For this purpose, the regression coefficients Bi (i = 1, 2, ...) are estimated before the independent variables in the functional dependence. If an independent variable is considered, the regression is called one-dimensional. The estimated coefficient B1> 0 is interpreted as follows: increasing the values of the independent variable leads to increasing the value of the dependent (27).
When the values of the dependent variable are real numbers, i.e. it is quantitative to model the dependence applied linear or nonlinear regression analysis. When the dependent variable is dichotomous qualitative /two outputs: state A or state B/, logistic regression is used for modeling, and the independent variables /predictors/ can be both quantitative and qualitative. If an independent variable is considered, the regression is called one-dimensional.
The aim is to detect prognostic factors, i.e. statistically significant among the independent variables for which the null hypothesis is rejected that the state of the dependent is not affected by their change. To test the null hypothesis, the level of statistical significance p = 0.05 is most often chosen. This is the probability of making a error of the first kind, namely to reject the null hypothesis (the factor is not predicative) when it is true.
Obtaining values of p <0.05 for the coefficient B1 from Wald's Chi-square statistics, the null hypothesis is rejected and the hypothesis that the factor is statistically significant is confirmed, i.e. predicative. The method also gives a classification of false-positive and false-negative cases and the percentage of cases correctly predicted by the logistics model.
For statistical analysis of the data, a specialized statistical analysis package STATISTICA 11 (28) was used. In our study, the dependent variable was the result of treatment of BAONJ, which assumes a state of "stationing" and "progression".

Two cases were considered for the dependence of the "period of time from the surgical intervention" (TPSI):
1. The result of the treatment of BAONJ was reported 1 month after treatment
and
2. The result of the treatment of BAONJ was reported 6 months after treatment.

The parameters of the constructed univariate logistics models for the dependence of BAONJ and the predictor "period of time from the surgical intervention" (TPSI) were evaluated.
Two cases were considered for the dependence of the duration of BF: 1. when the result of the treatment of BAONJ was reported 1 month after treatment and 2. when it was reported 6 months after treatment.
The parameters of the constructed univariate logistics models for the dependence of BAONJ progression and the predictor "period of time from the surgical intervention" (TPSI) were evaluated. The p=0.05 was chosen as the significance level.

Results

1. Analysis of the relationship between the period of time from the surgical intervention (TPSI) and short-term treatment outcomes reported on day 30.
The obtained p-value of Wald for B1 is 0.03 <0.05 i.e. the null hypothesis for independence of BAONJ, reported for 1 month, was rejected after treatment with the period of time from the surgical intervention.
The constructed logistic regression model can predict the probability of BAONJ progression, reported in the first month after treatment, using the estimated coefficients B0=-1,0155, B1=0,1221. The probability is calculated by the formula y=exp(-1.0155+(0.122)x)/(1+exp(-1.0155+(0.122)x)), where the variable "x" is replaced by the value of the period of time from the surgical intervention.

The positive coefficient B1 before TPSI shows that with the increasing of the period of time from the surgical intervention, the likelihood of disease progression increases, established in the first month after treatment.

Model: Logistic regression (logit) N of 0's: 19 1's: 25 Dep. var: Development of BAONJ registered on the 1st month after the treatment Loss: Max likelihood (MS-err. scaled to 1) Final loss: 26,846259841
Chi2(1)=6,4837 p=,01089

	Const.B0	B1 (TPSI)
Estimate	-1,015557	0,1221467
Standard Error	0,630885	0,05635345
p Wald's Chi-square -value	0,1074659	0,03020324
Odds ratio (unit change)	0,3622007	1,12992
-95%CL	0,1013947	1,008456
+95%CL	1,293848	1,266013

Table 1. Estimated parameters of the logistic regression models for BAONJ and the period of time from the surgical intervention (TPSI), reported 1 month after the treatment.

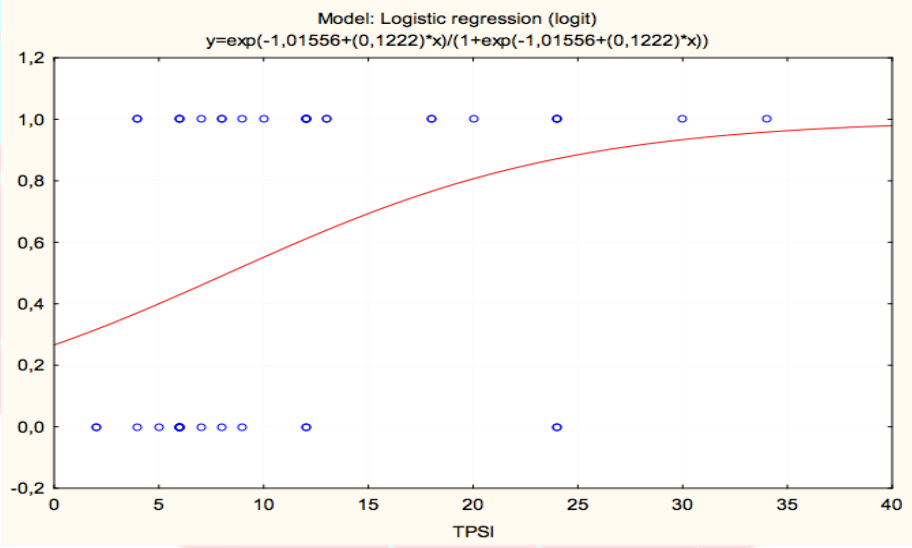

Figure 1. Estimated probability distribution for progression of BAONJ, reported in the first month of treatment, associated with the period of time from the surgical intervention (TPSI).

For example, for a value of x=4, there is a probability of progression of BAONJ in the first month of treatment equal to 0.3, i.e. 30%. It can be seen that the probability for TPSI 5 months is 0.35 and increases to 0.96 for TPSI of 35 months.

2. Analysis of the relationship between the period of time from the surgical intervention and the results of treatment of BAONJ, established in the sixth month.

Analogously to item 1, it was found that the factor duration of BF treatment is a prognostic factor for BAONJ, reported 6 months after treatment because the p-value was 0.02 <0.05. The coefficient B1 is positive (0.094). The estimated parameters are now shown in Table 2.

Model: Logistic regression (logit) N of 0's: 17 1's: 27Dep. var: Development of BAONJ registered on the 6th month after the treatment Loss: Max likelihood (MS-err. scaled to 1) Final loss: 26,195877511

Chi2(1)=6,3125 p=,01199

Table 2. Estimated parameters of the logistic regression models for BAONJ and the period of time from the surgical intervention (TPSI), reported 6 months after the treatment.

	Const.B0	B1 (TPSI)
Estimate	-0,8471821	0,09352041
Standard Error	0,6207451	0,04078372
Wald's Chi-square p-value	0,172331	0,02184974
Odds ratio (unit change)	0,4286211	1,098033
-95%CL	0,1224691	1,011279
+95%CL	1,500101	1,19223

Through the constructed logistic model, the probability of BAONJ progression can be predicted, reported 6 months after treatment, using the estimated coefficients B0=-0,847, B1=0,0935. The probability is calculated by the formula y=exp(-0,847+(0,0935)x)/(1+exp(-0,847+(0,0935)x)), where the variable "x" is replaced by the value of the period of time from the surgical intervention.

The distribution of the probability for the presence of "progress" of the BAONJ, reported 6 months after treatment, associated with the period of time from the surgical intervention is presented in Fig. 2.

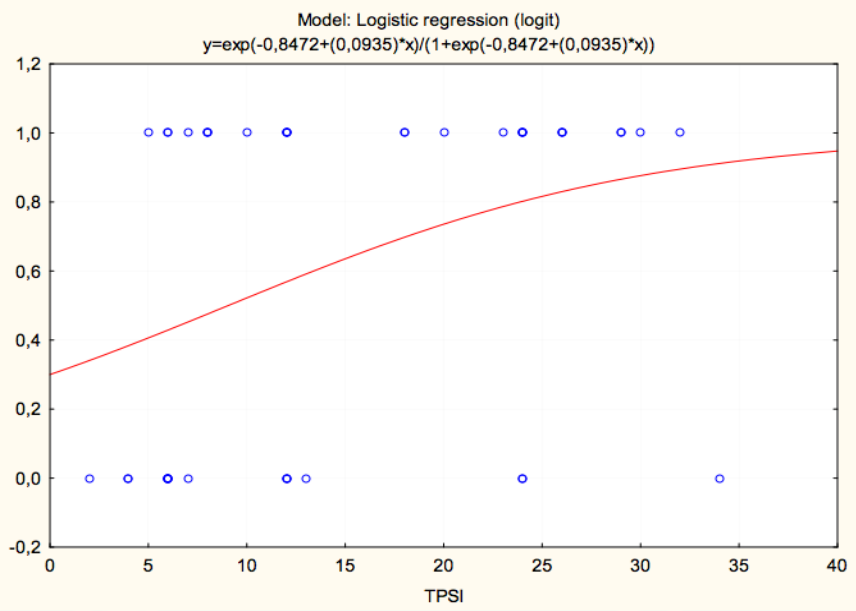

Figure 2. Estimated probability distribution for progression of BAONJ, reported in the sixth month of treatment, associated with the period of time from the surgical intervention (TPSI).

Discussion

When analyzing the results, we found a relationship between the factor period of time from the surgical intervention and treatment outcome established 1 month after it, as well as between period of time from the surgical intervention and treatment outcome established 6 months after it. As the time elapsed between surgery on the alveolar bone (extraction or placement of a dental implant) until the diagnosis of BAONJ increases, the likelihood of disease progression increases in the 1st and 6th month after diagnosis. We did not find results similar to our research in the literature.

There are data in the literature regarding the age of the patient as a risk factor for the development of BAONJ. A number of studies have linked old age to BAONJ (29-31), which is also shown in our study. According to Badros et al., the risk of developing BAONJ increases with each additional year of follow-up and with increasing age of patients (29). We did not find results showing a relationship between the patient's age and the outcome of BAONJ treatment. In our study, we found that the patient's age factor did not affect the outcome of the disease in the 1st and 6th month.

Conclusion

I. Our study shows that as the period of time from the surgical intervention increases, so does the likelihood of the progression of the disease, found in both the first and sixth months after treatment.

II. From the comparison of the graphs it can be concluded that the period of time from the surgical intervention is an important factor that can lead to unfavorable clinical results in outpatient treatment of BAONJ.

Our study shows that with the increase of the period of time from the surgical intervention, the likelihood of disease progression also increases, when examination of the patient on the first and on the sixth month

after the treatment of BAONJ is made. Therefore, we can conclude that the factor period of time from the surgical intervention can be used as a predictor of the outcome of BAONJ treatment, and with increasing of its value, the likelihood of disease progression increases.

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Ilieva B, Prodanova K, Svechtarov V. The period of time from the surgical intervention as a predictive factor on the outcome of the treatment of bisphosphonate – associated osteonecrosis of the jaws. Medinform 2024; 11(1):1753-1761.