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A Randomized, Double-Blind, Comparison of Denosumab versus Zoledronic Acid on Prolonging Bone Metastasis-Free Survival in Men with Hormone-Refractory Prostate Cancer

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Abstract: Bone metastases represent a critical factor contributing to illness and mortality among men diagnosed with prostate cancer. This study evaluates the therapeutic effectiveness of denosumab, a fully human monoclonal antibody targeting RANKL, in comparison to zoledronic acid for reducing the occurrence of such metastases or mortality in these patients. The investigation utilized a Cox proportional hazards model to assess bone-metastasis-free survival, factoring in variables such as chemotherapy use. Kaplan-Meier survival curves and hazard ratios (HRs) were employed to evaluate treatment differences. Results indicated that the antibody extended survival by a median of 29.97 months over its comparator. Moreover, it postponed the initial onset of metastases and improved survival outcomes. It outperformed the alternative treatment in minimizing skeletal complications and holds potential as an innovative option for men in this condition.

Keywords: Bone metastasis, Denosumab, Zoledronic acid, Prostate cancer, Randomized trial.

1. Introduction

Prostate cancer ranks as the most prevalent non-skin malignant disease affecting men in Western countries. In 2017, the American Cancer Society documented around 161,360 new instances of prostate cancer, alongside 26,730 fatalities attributed to the disease [1]. Bone metastases significantly contribute to the morbidity and mortality associated with prostate cancer, imposing a considerable burden on patients and healthcare systems, both in terms of disease impact and economic costs [2,3].

Managing prostate cancer often requires dealing with issues stemming from bone metastases, which significantly reduce patients' quality of life and can increase healthcare costs. Therefore, preventing these metastases is crucial for better outcomes in those with prostate cancer [4]. Two main treatments for this include denosumab, a fully human monoclonal antibody that targets and neutralizes RANKL, and zoledronic acid, a bisphosphonate that inhibits bone resorption by osteoclasts [5,6].

Denosumab was authorized in the USA due to its ability to decrease skeletal complications in patients with bone metastases arising from solid tumors. This approval stemmed from its demonstrated superiority over zoledronic acid in previous clinical trials, particularly those involving breast and prostate cancers [6]. However, additional studies are required to directly compare these two treatments, specifically regarding their effects on prolonging bone-metastasis-free survival in

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men with castration-resistant prostate cancer [7]. The current investigation seeks to fill this gap by assessing the effectiveness of both agents in extending bone-metastasis-free survival for patients with this condition.

The aim of this research is to guide clinicians in selecting the most effective therapeutic approach, thereby optimizing treatment strategies for prostate cancer. The subsequent sections outline the study design and statistical methodologies, detailing endpoint definitions and participant eligibility. Results are presented with a focus on bone-metastasis-free survival and overall survival. This is followed by an analysis of the findings in relation to existing research, addressing both the strengths and limitations of the study. The paper concludes with suggestions for future research, particularly regarding the long-term advantages of denosumab and the exploration of combination therapies.

2. Methods

2.1. Study Design and Participants

This phase 3 investigation was conducted from May 2006 to October 2009, involving men diagnosed with prostate cancer across 342 centers in 39 countries and 319 centers in an additional 30 countries. The participants were assigned to two distinct groups: one receiving zoledronic acid (control group) and the other denosumab (treatment group). Eligible participants were men aged 18 or older with a confirmed history of the disease.

In the control group, radioisotope bone scans were carried out during screening when required to exclude the presence of bone metastases. Conversely, the treatment group included individuals diagnosed with bone metastases linked to hormone-refractory prostate cancer. Eligibility also mandated the existence of documented clinical evidence and radiographic confirmation of at least one bone metastasis, whether present or previously observed.

To ensure robust and unbiased results, the randomization process was carefully conducted and verified, with both treatment and control groups undergoing similar follow-up schedules.

2.2. Endpoints and Statistical Analysis

The primary endpoint was bone-metastasis-free survival, defined as the duration until the initial appearance of bone metastasis (either symptomatic or asymptomatic) or mortality from any cause [8]. Secondary outcomes encompassed the interval to the first bone metastasis and overall survival. Other exploratory measures included progression-free survival and prostate-specific antigen (PSA) levels. Safety outcomes were assessed based on the frequency of adverse events related to treatment.

Statistical evaluation aimed to estimate the hazard ratio between denosumab and zoledronic acid, employing a Cox proportional hazards model, with the treatment group serving as the independent variable. Stratification was performed according to chemotherapy status as a randomization factor. The initial assumption was a hazard ratio of 0.8 for denosumab relative to zoledronic acid, with an objective of achieving 80% statistical power and a significance threshold of 0.025, equivalent to 0.05 in a two-sided test utilizing a one-sided maximum likelihood approach. All p-values were computed as two-sided. R Studio (version 4.3.2) was utilized for all statistical computations.

3. Results and discussion

3.1. Results

Table 1: Baseline demographics and disease characteristics.

	Zoledronic acid n (%)	Denosumab n (%)	Total n (%)
Subjects in population	756	576	1332

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Table 1: (continued).

Age			
< 65	175(23.1)	83(14.4)	258(19.4)
≥ 65	581(76.9)	493(85.6)	1074(80.6)
Mean	70.97	73.62	
Median	71	74	
Race			
White or Caucasian	645(85.3)	492(85.4)	1137(85.4)
Black or African American	24(3.2)	35(6.4)	59(4.4)
Hispanic or Latino	46(6.1)	23(3.9)	69(5.2)
Asian	21(2.8)	13(2.2)	34(2.6)
Other	20(2.6)	12(2.0)	32(2.4)
Missing†	0(0.0)	1(0.1)	1(0.75)
Geographic Region			
Europe	392(51.8)	240(41.6)	632(47.4)
Latin America	163(21.5)	66(11.4)	229(17.1)
North America	143(18.9)	194(33.6)	337(25.3)
Others	58(7.6)	76(13.1)	134(10.2)
ECOG			
Grade 0	339(44.8)	410(71.1)	749(56.23)
Grade 1	368(48.7)	165(28.6)	533(40.01)
Grade 2	49(6.5)	1(0.1)	50(3.75)
Prior Chemotherapy Regimens			
Y	174(23)	46(8)	220(16.5)
N	582(77)	530(92)	1112(83.5)
Gleason Score			
Grade 2-6	149(19.7)	164(28.3)	313(23.5)
Grade 7	280(37)	173(30)	453(34)
Grade 8-10	327(43.3)	183(31.6)	510(38.3)
Missing†	0	56(9.7)	56(4.2)
(Database Cutoff Date: 30/12/2023)			

The primary outcome of this study was to evaluate bone-metastasis-free survival in patients treated with either denosumab or zoledronic acid. Table 1 provides an overview of the baseline demographic and clinical characteristics of the study population. A total of 1332 patients were enrolled, with 576 receiving denosumab and 756 receiving zoledronic acid. The median age was comparable between groups, with the majority of patients aged 65 or older. Additionally, geographic region, race, prior chemotherapy regimens, ECOG performance status, and Gleason score were recorded to assess the comparability of the groups at baseline. This descriptive statistical analysis indicates that the treatment and control groups were well-balanced across key demographic and clinical features, supporting the validity of subsequent outcome comparisons.

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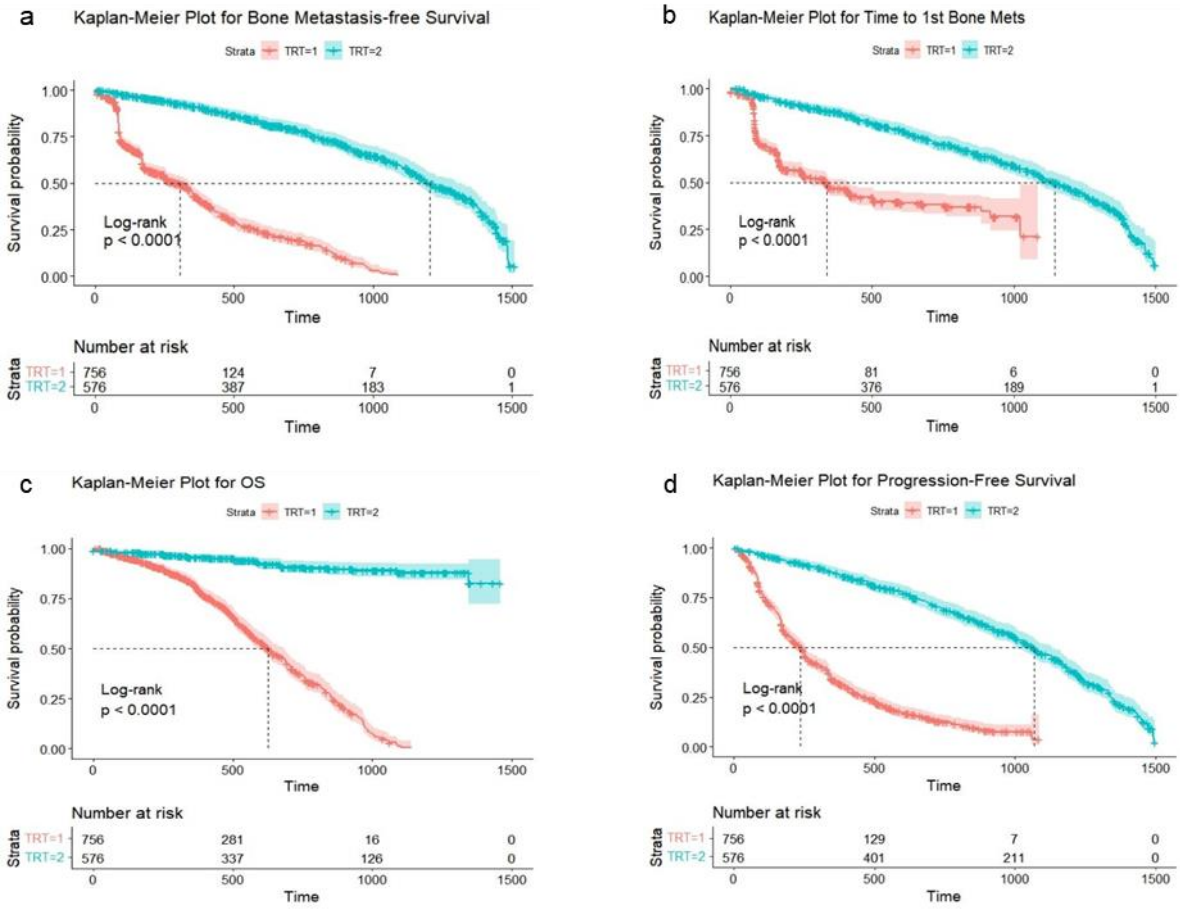

Figure 1: Kaplan-Meier curves showing bone-metastasis-free survival (a), time to first bone metastasis (b), overall survival (c), and progression-free survival (d) in patients receiving denosumab vs. zoledronic acid.

The comparative assessment of bone-metastasis-free survival, time to the initial bone metastasis, overall survival, and progression-free survival revealed marked differences between the two therapeutic groups. The outcomes are illustrated in Figure 1, which offers Kaplan-Meier survival curves for both interventions. Specifically, Figure 1a highlights that the median bone-metastasis-free survival was considerably extended in the denosumab cohort (40.17 months) compared to the zoledronic acid cohort (10.2 months) (HR 0.122, 95% CI 0.0998-0.148, p<0.001). Figure 1b shows that the first incidence of bone metastasis was markedly postponed in those treated with denosumab (median 38.1 months), in contrast to those receiving zoledronic acid (median 11.37 months; HR 0.262, 95% CI 0.210-0.326, p<0.001). Figures 1c and 1d present overall survival and progression-free survival, respectively, with notable advancements seen in the denosumab group. All survival metrics revealed statistically significant differences according to the log-rank test ($p < 0.001$).

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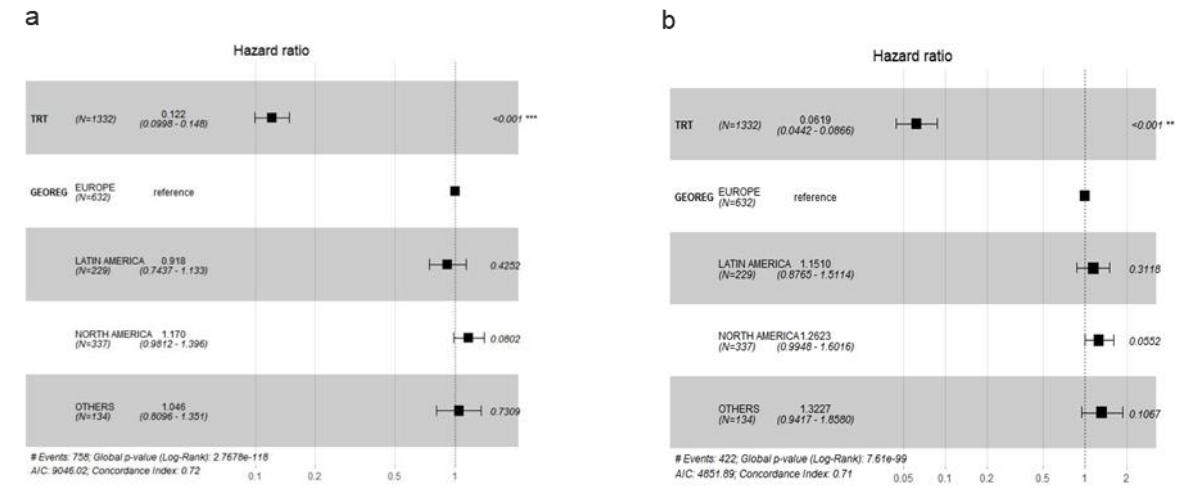

Figure 2: Forest plot showing subgroup analysis of (a) bone-metastasis-free survival and (b) overall survival, comparing the treatment effects of denosumab versus zoledronic acid.

Figure 2 presents a comprehensive forest plot analysis for bone-metastasis-free survival and overall survival across different patient subgroups. The plots illustrate the hazard ratios for the subgroups, highlighting both the global treatment effect and variations among different geographic regions. For bone-metastasis-free survival (Figure 2a), the hazard ratio for denosumab compared to zoledronic acid was 0.122 (95% CI: 0.0998-0.148, $p < 0.001$), indicating a substantial reduction in the risk of bone metastasis with denosumab. Subgroup analysis shows that, while most regions benefited significantly from denosumab treatment, North America exhibited a hazard ratio of 1.170 (95% CI: 0.9812-1.396, $p = 0.0802$), suggesting no statistically significant difference compared to zoledronic acid.

For overall survival (Figure 2b), the hazard ratio for denosumab was 0.0619 (95% CI: 0.0442-0.0866, $p < 0.001$), demonstrating a considerable survival advantage over zoledronic acid. However, the analysis of specific regions shows that Latin America and North America have hazard ratios of 1.1510 and 1.2623, respectively, which did not reach statistical significance. This suggests variability in treatment response among regions, emphasizing the need for careful consideration of patient demographics in treatment planning. The overall results reinforce the efficacy of denosumab while highlighting specific population differences that may influence treatment outcomes.

3.2. Discussion

The results indicate that denosumab is more effective than zoledronic acid in preventing bone metastasis and extending bone-metastasis-free survival among men with castration-resistant prostate cancer. The findings from the subgroup analysis further demonstrate the robustness of denosumab across different patient groups, suggesting its broad applicability in clinical practice. The favorable safety profile of denosumab, with fewer Grade 3-4 adverse events and lower toxicity compared to zoledronic acid, strengthens its suitability as a preferred treatment option.

However, certain limitations must be acknowledged. Differences in baseline characteristics between the treatment groups may have introduced bias, which could have impacted the outcomes. A more balanced sampling method would reduce such potential confounding factors. Additionally, a longer follow-up period is required to fully assess the long-term effects on overall survival, as the current duration may not capture all relevant late outcomes.

These findings align with previous studies that have demonstrated the efficacy of denosumab in managing bone metastasis in advanced cancers [9]. Future research should focus on evaluating the

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long-term benefits of denosumab, including overall survival, and consider exploring combination treatments to optimize patient outcomes in castration-resistant prostate cancer.

4. Conclusion

This research focused on comparing the therapeutic performance of denosumab and zoledronic acid in managing skeletal-related complications in men with castration-resistant prostate cancer. The findings highlighted that denosumab exhibited a clear advantage over zoledronic acid by significantly extending bone-metastasis-free survival, reducing disease progression risk, and presenting a better safety profile. These results indicate that denosumab could be a preferable option for mitigating skeletal issues and easing the burden of the disease for affected individuals.

Although the outcomes are encouraging, the study does have some limitations, such as imbalances in baseline characteristics and the necessity for extended follow-up periods to assess long-term survival impacts comprehensively. Future research should aim to resolve these limitations by designing studies with more evenly distributed participant characteristics and longer observation durations. Moreover, exploring the synergistic potential of combination therapies involving denosumab could provide additional improvements in treatment efficacy for individuals with castration-resistant prostate cancer.

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