Effectiveness of Initial Denosumab Versus Sequential Bisphosphonate-to-Denosumab Therapy in Preventing Skeletal-Related Events in Breast Cancer Patients with Bone Metastases: A Retrospective Single-Center Study

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Background

- Bone metastasis is highly prevalent in advanced breast cancer, affecting approximately 70% of patients and frequently resulting in skeletal-related events (SREs) such as such as pathological fractures, spinal cord compression, bone radiotherapy, and bone surgery[1,2].
- Bone-targeting agents (BTAs)—including bisphosphonates and denosumab—play a crucial role in preventing SREs[3]. Denosumab, a subcutaneous and non–renally cleared RANKL inhibitor, has been shown to delay first and subsequent SREs more effectively than zoledronic acid, supporting its recommendation as a bone-modifying agent in metastatic breast cancer[4].
- An increasing number of patients in real-world practice transition from bisphosphonates to denosumab, yet the comparative effectiveness and safety of this sequential strategy versus upfront denosumab for SRE prevention remain unclear[5,6].

Objective

To clarify this issue, we analyzed 165 Chinese breast cancer patients with bone metastases, comparing SRE outcomes and safety between upfront denosumab and sequential bisphosphonate-to-denosumab therapy.

Methods

- This retrospective single-center cohort study included 165 breast cancer patients with radiologically confirmed bone metastases treated between January 2019 and April 2024. Patients were categorized according to their BTA strategy: upfront denosumab (Up-Den, n=67) or sequential bisphosphonate-to-denosumab therapy (Seq-BP-D, n=98). Patients treated before 2019, prior to national approval of denosumab, were excluded.
- The primary endpoint was the 1-year SRE rate, defined as the time to first on-treatment SRE, while secondary endpoints included cumulative SRE incidence and treatment-related safety outcomes.

Results

- Baseline characteristics, including age, tumor stage, molecular subtype, visceral involvement, bone lesion burden, and SREs at bone metastasis diagnosis, were broadly comparable between treatment groups.
- The interval from bone metastasis diagnosis to BTA initiation was short and comparable between groups, with a median of 0.9 months. The time from breast cancer diagnosis to bone metastasis showed similar stage-stratified distributions, with medians of 30.9 months in stage I, 50.2 months in stage II, 44.8 months in stage III, and 29.8 months in stage IV disease ***(Table 1)***.

Baseline characteristics are well balanced between treatment groups

Table 1. Clinical and pathological characteristics

Characteristic	Overall (n=165)	Seq-BP-D (n=98)	Up-Den (n=67)
Age at breast cancer diagnosis, years			
Median (IQR)	49.0 (42.0,58.0)	50.0 (42.0,58.0)	48.0 (39.0,58.0)
Age at bone metastasis diagnosis, years			
Median (IQR)	54.7 (45.7,62.1)	55.0 (46.0,62.3)	54.6 (42.0,60.8)
Stage, n (%)			
I	5(3.2)	2(2.2)	3(4.7)
II	14(9.0)	10(11.0)	4(6.3)
III	11(7.1)	8(8.8)	3(4.7)
IV	125(80.6)	71(78.0)	54(84.4)
Unknown	10(6.1)	7(7.1)	3(4.5)
Histological grade, n (%)			
I	2(1.9)	2(3.4)	0
II	52(50.0)	31(52.5)	21(46.7)
III	50(48.1)	26(44.1)	24(53.3)
Unknown	61(37.0)	39(39.8)	24(35.8)
Molecular subtype, n (%)			
HR+HER2-	115(72.3)	71(76.3)	44(66.7)
HR+HER2+	15(9.4)	7(7.5)	8(12.1)
HR-HER2+	11(6.9)	6(6.5)	5(7.6)
TNBC	11(6.9)	3(3.2)	8(12.1)
Unknown	13(7.9)	11(11.2)	2(3.0)
Bone metastasis at diagnosis, n (%)			
Yes	56(33.9)	36(36.7)	20(29.9)
No	109(66.1)	62(63.3)	47(70.1)
Visceral metastasis, n (%)			
Yes	85(51.5)	51(52.0)	34(50.7)
Lung	54(32.7)	32(32.7)	22(32.8)
Liver	38(23.0)	20(20.4)	18(26.9)
Stomach	1(0.6)	1(1.0)	0
No	80(48.5)	47(48.0)	33(49.3)
Number of bone metastases, n (%)			
<3	72(43.6)	37(37.8)	35(52.2)
3-4	34(20.6)	25(25.5)	9(13.4)
≥5	59(35.8)	36(36.7)	23(34.3)
Incidence of SREs at Bone Metastasis Diagnosis，n (%)			
Yes	46(27.9)	21(21.4)	25(37.3)
No	119(72.1)	77(78.6)	42(62.7)
Time from bone metastasis diagnosis to BTA initiation, months			
Median (IQR)	0.9(0.3,1.8)	0.9(0.3,1.7)	0.9(0.3,2.3)
Time from breast cancer diagnosis to bone metastasis, months，Median (range)，months			
Stage I	30.9(0.3,56.4)	28.4(0.3,56.4)	30.9(4.3,40.5)
Stage II	50.2(1.4,178.6)	35.8(1.4,178.6)	79.4(17.7,140.8)
Stage III	44.8(14.2,197.9)	39.4(17.0,197.9)	44.8(14.2,64.4)
Stage IV	29.8(0,217.3)	17.8(0,217.3)	40.5(0,199.4)

Upfront denosumab shows a lower on-treatment SRE incidence than the sequential approach

- On-treatment SREs occurred in 17.0% of patients overall, with a markedly lower incidence in the Up-Den group (4.7%) compared with Seq-BP-D (25.5%). Most were single events, and ≥2 events remained uncommon across groups.
- The 1-year cumulative incidence of first on-treatment SREs was 15.7% in Seq-BP-D versus 5.9% in Up-Den, indicating a numerically lower early SRE risk with upfront denosumab ***(Table 2).***
- Notably, malignancy-associated hypercalcemia was most frequent with bisphosphonates (11.6%, Seq-BP-D), dropping to 5.8% post-denosumab switch and 0% in upfront denosumab.

Table 2. Incidence of SREs After BTA Initiation

SREs After Bone BTA Initiation	Overall (n=165)	Seq-BP-D (n=98)	Up-Den (n=67)	*P value*
Incidence of SREs，n (%)				<0.001
Yes	28(17.0)	25(25.5)	3(4.7)	
No	137(83.0)	73(74.5)	64(95.3)	
Cumulative number of SREs，n (%);	n=28	n=25	n=3	0.005
1 event	25(89.3)	22(88.0)	3(100.0)	
≥2 events	3(10.7)	3(12.0)	0	
1-year first on-treatment incidence of SREs %，95% CI	12.5(6.8-17.7)	15.7(8.1-22.7)	5.9(0-12.3)	

p<0.05 indicates statistical significance

- The cumulative SRE curve remains nearly flat in Up-Den, whereas Seq-BP-D demonstrates a steady rise in events over time. The RR for on-treatment SREs is 0.364 (95% CI 0.085–1.028; p=0.096), indicating a non-significant trend favoring upfront denosumab.
- With limited follow-up and few mature events, statistical power remains low, yet the clear early separation of curves suggests a clinically meaningful trend that may strengthen over time ***(Figure 1).***

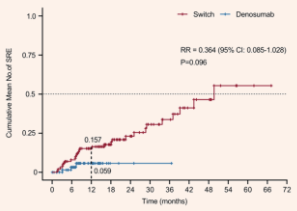


Figure 1. Risk Ratio for On-Treatment SREs between treatment groups

Table 3. Univariate Analysis of Risk Factors for SREs

Characteristic	No SRE (n=134)	SRE (n=31)	HR (95%CI)	*P value*
Stage, n (%)				
I	2(1.6)	3(10.0)	Ref	-
II	12(9.6)	2(6.7)	0.227(0.038-1.361)	0.105
III	7(5.6)	4(13.3)	0.542(0.121-2.435)	0.424
IV	104(83.2)	21(70.0)	0.192(0.056-0.657)	0.009
N, missing	134,9	31,1		
Line of therapy, n (%)				
1st-line	91(67.9)	12(38.7)	Ref	-
2nd-line	21(15.7)	11(35.5)	2.651(1.160-6.057)	0.021
≥3rd-line	22(16.4)	8(25.8)	1.539(0.621-3.814)	0.352

Stage and line of therapy are the characteristics showing significant associations with SRE occurrence

- Stage demonstrates a significant association with SRE risk. Patients with stage IV disease show a markedly lower hazard of SREs compared with early-stage disease (HR 0.192; p=0.009), reflecting lower event rates within this predominantly stage IV cohort.
- Line of therapy also influences SRE risk. Second-line treatment is associated with a higher likelihood of SREs (HR 2.651; p=0.021), whereas ≥3rd-line therapy does not show a significant effect ***(Table 3).***

Key Adverse Events of Interest are infrequent across treatment groups

- Hypocalcemia was observed at low rates (5.8–14.3%) and mostly Grade 1. Osteonecrosis of the jaw (ONJ) were rare, with only isolated Grade 1 events reported in the Seq-BP-D group and none in Up-Den. No Grade 2 toxicities were observed, indicating a favorable and comparable safety profile across treatments ***(Table 4).***

Table 4. Analysis of Adverse Events

Adverse Event	Seq-BP-D						Up-Den n=28		
	During Bisphosphonate Treatment n=86			During Denosumab Treatment n=86					
	Any Grade	Grade 1	Grade 2	Any Grade	Grade 1	Grade 2	Any Grade	Grade 1	Grade 2
Hypocalcemia	8(9.3)	6(7.0)	1(2.3)	5(5.8)	4(4.7)	1(1.2)	4(14.3)	3(10.7)	1(3.6)
ONJ	1(1.2)	--	--	1(1.2)	--	--	0	0	0

Conclusions

- Upfront denosumab is associated with a numerically lower incidence of on-treatment SREs than sequential bisphosphonate-to-denosumab therapy. The cumulative SRE curves demonstrate early and sustained separation in favor of upfront denosumab, although limited follow-up and few mature events reduce statistical power. Notably, no hypercalcemia occurred in the Up-Den group, reflecting its effective control of tumor-related calcium dysregulation.
- Stage and line of therapy emerge as the principal clinical factors associated with SRE risk, reflecting underlying disease biology and treatment intensity.
- Adverse events remain infrequent and comparable across treatment strategies, with hypocalcemia occurring at low rates and ONJ being rare, supporting the favorable safety profiles of both approaches.
- Follow-up is ongoing, and additional mature events will provide more definitive estimates of treatment effect. With longer observation, clearer insights into SRE risk dynamics and the potential clinical advantage of upfront denosumab are anticipated.

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