Predictors of Medication-related Osteonecrosis of the Jaw in HR+/HER2- Metastatic Breast Cancer Patients Treated with CDK4/6 Inhibitors

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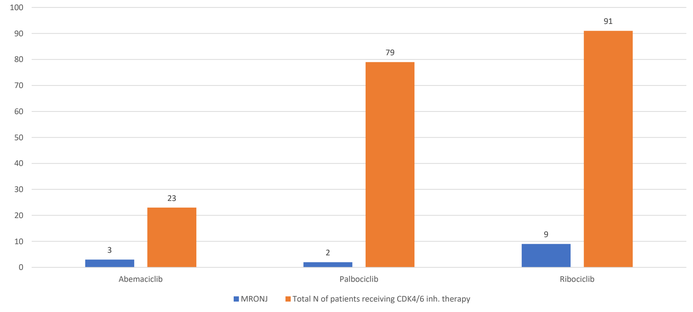
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Background

Hormone receptor positive, human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (mBC) represents 60-70% of all mBC, with bones being the most common site of metastases in ~60% of cases. Combination of endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) is the standard treatment in HR+/HER2- mBC with addition of antiresorptive therapy (ART) in cases of bone metastases. ART implies application of parenteral or peroral bisphosphonates as well as denosumab. Medication-related osteonecrosis of the jaw (MRONJ) is a known side effect of all ART. This study aimed to assess the incidence and predictors of MRONJ in HR+/HER2−mBC patients receiving CDK4/6 inhibitors and ART, with emphasis on treatment type, duration, and cumulative dose.

Methods

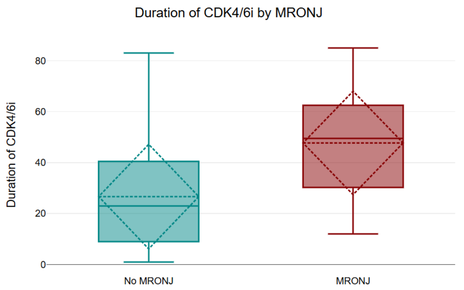
A retrospective cohort of 193 female patients with HR+/HER2− mBC treated with CDK4/6i (ribociclib, palbociclib, abemaciclib) and ART (zoledronate, ibandronate, denosumab, clodronate and pamidronate) in the University Hospital Center Zagreb was analyzed with prior Ethics Committee approval. Descriptive statistics, group comparisons, and logistic regression models were used to identify clinical and treatment-related predictors of MRONJ.

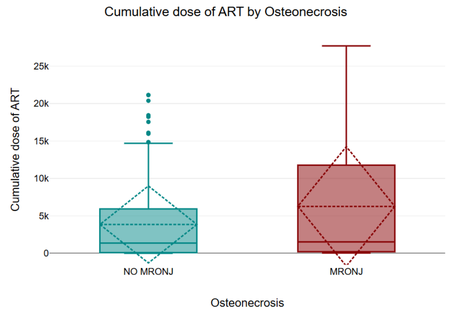


Results

MRONJ was developed in 14 out of 193 patients (7.3%), who were significantly older (71.6 ± 8.0 vs. 63.8 ± 13.8 years; p = 0.0039) and had longer CDK4/6i exposure (median 48.0 vs. 22.0 months; p = 0.047). MRONJ incidence was higher in patients treated with abemaciclib (13.0%) and ribociclib (9.9%) than with palbociclib (2.5%), though this difference did not reach statistical significance (p = 0.0952). Among 193 patients receiving ART, most commonly used ART agents were zoledronic acid in 104 patients (53.9%), followed by ibandronate in 71 patients (36.8%) and denosumab in 18 patients (9.3%). Among the 14 patients who developed MRONJ, 8 (57.1%) had received zoledronic acid, 4 (28.6%) ibandronate, and 2 (14.3%) denosumab. Adjusted cumulative ART doses were calculated, and higher doses were observed in MRONJ compared to the non-MRONJ group (6266,85 mg vs 3848,8 mg respectively), without reaching statistical significance (p = 0.47). Total ART duration was significantly longer in the MRONJ group (52.71 vs. 33.98 months), with a p-value of 0.033.







Conclusion

Older age and longer CDK4/6i exposure was associated with an increased risk of MRONJ in patients with HR+/HER2− mBC. Although MRONJ incidence appeared higher with abemaciclib and ribociclib compared to palbociclib, it did not reach statistical significance, possibly due to small numbers. These findings highlight the need for careful monitoring and risk assessment in patients undergoing long-term CDK4/6i therapy in combination with ART.

References

1. Öner İ, Anık H, Kurt İnci B, et al. A Comparison of the Efficacy and Safety of Denosumab and Zoledronic Acid in Patients with Bone Metastatic Breast Cancer Receiving CDK4/6 Inhibitor Therapy. Medicina (Kaunas). 2025;61(2):360. Published 2025 Feb 19. doi:10.3390/medicina61020360
2. Scafetta R, Donato M, Gullotta C, et al. Comparative analysis of Denosumab and Zoledronic acid in advanced breast cancer patients receiving CDK4/6 inhibitors. Breast. 2025;82:104502. doi:10.1016/j.breast.2025.104502
3. Marcianò A, Ingrasciotta Y, Isgrò V, et al. Cancer Patients at Risk for Medication-Related Osteonecrosis of the Jaw. A Case and Control Study Analyzing Predictors of MRONJ Onset. J Clin Med. 2021;10(20):4762. Published 2021 Oct 17. doi:10.3390/jcm10204762