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Early and Late Severe and Rare Adverse Events Associated with Zoledronic Acid in Cancer Patients: A Seven-Case Series and Literature Review

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Abstract **Case Series**

Zoledronic acid (ZA) is a third-generation nitrogen-containing bisphosphonate widely used in oncology for the prevention of skeletal-related events (SREs) in patients with bone metastases, the treatment of hypercalcemia of malignancy, and the prevention of cancer treatment-induced bone loss (CTIBL). Although ZA has demonstrated substantial efficacy and an overall favorable safety profile, uncommon but potentially severe adverse events may occur, ranging from acute metabolic and immune-mediated reactions to delayed complications such as medication-related osteonecrosis of the jaw (MRONJ). We report a seven-case series of clinically significant early and late ZA-related adverse events observed in routine oncology practice and compare our findings with the available literature to emphasize their clinical presentation, management, and preventive strategies.

Keywords: Zoledronic acid, medication related osteonecrosis of the jaw, allergic reaction, tetany, carpopedal spasm.

INTRODUCTION

Zoledronic acid (ZA) is a third-generation nitrogen-containing bisphosphonate that potently inhibits osteoclast-mediated bone resorption through inhibition of farnesyl pyrophosphate synthase in the mevalonate pathway, ultimately inducing osteoclast apoptosis and suppressing bone turnover. Owing to its high affinity for mineralized bone and prolonged skeletal retention, ZA is one of the most widely used bone-modifying agents in oncology [1-3].

In clinical oncology, ZA is recommended for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors and multiple myeloma, for the treatment of hypercalcemia of malignancy, and for the prevention of cancer treatment-induced bone loss (CTIBL). Multiple randomized clinical trials have demonstrated that ZA significantly reduces the risk of pathological fractures, spinal cord compression, and the need for radiotherapy or surgery to bone, thereby improving patients' quality of life. Current international guidelines from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) endorse its use in appropriately selected patients [3-6].

Although ZA is generally well tolerated, its administration may be associated with a broad spectrum of adverse events ranging from mild, self-limiting acute-phase reactions to uncommon but potentially severe complications. Frequently reported toxicities include fever, myalgia, arthralgia, fatigue, and transient flu-like symptoms, particularly after the first infusion. More serious adverse events include symptomatic hypocalcemia, renal impairment, hypersensitivity reactions, and medication-related osteonecrosis of the jaw (MRONJ), all of which may compromise quality of life, require treatment interruption or discontinuation, and necessitate multidisciplinary management [2,7-10].

While individual case reports have described severe ZA-induced hypocalcemia, allergic reactions, or MRONJ, reports illustrating the full spectrum of these uncommon toxicities within the same cohort of oncology patients remain scarce. We therefore present a retrospective case series of seven patients who developed clinically significant early and late adverse events

following ZA administration in routine oncology practice and compare our findings with the current literature to highlight their clinical presentation, management, and preventive strategies.

PATIENTS AND METHODS

1) Study Design

We conducted a retrospective descriptive case series at the Day Care Hospital, Department of Medical Oncology, National Institute of Oncology, Rabat, Morocco**.** The study included seven consecutive cancer patients who developed clinically significant adverse events following intravenous administration of zoledronic acid (ZA) between 04/11/2023 to 03/06/2026. The objective was to characterize the spectrum of early and late severe toxicities associated with ZA in routine oncology practice.

2) Data Collection

Clinical data were retrospectively extracted from patients' medical records using a standardized data collection form. The following variables were collected:

- Demographic characteristics (age and sex);
- Primary cancer type and disease stage;
- Indication for zoledronic acid therapy;
- Zoledronic acid regimen (dose, frequency, cumulative exposure, and treatment duration);
- Time from ZA administration to the onset of adverse events;
- Clinical presentation and relevant laboratory findings;
- Diagnostic investigations performed;
- Therapeutic interventions and supportive management;
- Clinical outcomes and follow-up.

3) Statistical Analysis

Given the descriptive nature of this case series and the small sample size, data were summarized using descriptive statistics. Continuous variables are presented a median age of 64 years (range: 42–80 years) while categorical variables are reported as frequencies and percentages. No comparative statistical analyses were performed.

4) Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki**.** Patient confidentiality was strictly maintained by anonymizing all clinical data. Written informed consent for publication was obtained from all patients (or their legal representatives), including consent for the publication of clinical photographs where applicable. The study protocol was approved by the Institutional Review Board/Ethics Committee of the National Institute of Oncology, Rabat.

Table 1: Baseline Characteristics of the Study Population

Patient	Sex	Primary Cancer	Disease Stage	Indication for ZA	Comorbidities
1	F	Small-cell neuroendocrine breast carcinoma	Metastatic	Bone metastases	None
2	F	HR+/HER2− breast cancer	Early	CTIBL prevention	None
3	F	Breast cancer	Metastatic	Bone metastases	—
4	M/F	Prostate/Breast cancer	Metastatic	Bone metastases	—
5	M	Prostate cancer	Metastatic	Bone metastases	Diabetes
6	F	Breast cancer	Metastatic	Bone metastases	—
7	M	Prostate cancer	Metastatic	Bone metastases	Hypertension

Abbreviations: ZA, zoledronic acid; CTIBL, cancer treatment-induced bone loss; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

DISCUSSION

Zoledronic acid (ZA) is the most potent nitrogen-containing bisphosphonate currently used in oncology and represents a cornerstone in the prevention of skeletal-related events (SREs) associated with bone metastases from solid tumors and multiple myeloma. Beyond reducing the incidence of pathological fractures, spinal cord compression, and the need for surgery or radiotherapy to bone, ZA also plays an important role in the management of hypercalcemia of malignancy and in the prevention of cancer treatment-induced bone loss (CTIBL). Although its efficacy has been consistently demonstrated in randomized clinical trials and it is generally well tolerated, severe adverse reactions may occur and occasionally require hospitalization, treatment discontinuation, or multidisciplinary management. Our seven-case series illustrate the broad clinical spectrum of uncommon but clinically significant ZA-related toxicities, including severe symptomatic hypocalcemia, hypersensitivity reactions, and medication-related osteonecrosis of the jaw (MRONJ), emphasizing the importance of early recognition and preventive strategies in routine oncology practice.

1) Mechanism of Action of Zoledronic Acid

ZA is a third-generation nitrogen-containing bisphosphonate characterized by a high affinity for hydroxyapatite crystals in mineralized bone. Following intravenous administration, the drug accumulates preferentially at sites of active bone remodeling, where it is internalized by osteoclasts during bone resorption. Its

principal mechanism of action involves inhibition of farnesyl pyrophosphate synthase (FPPS) within the mevalonate pathway, preventing the synthesis of isoprenoid lipids required for the prenylation of small guanosine triphosphate-binding proteins (GTPases), including Ras, Rho, and Rac. These proteins are essential for osteoclast cytoskeletal organization, membrane trafficking, and survival. Their inhibition ultimately results in osteoclast dysfunction, apoptosis, and suppression of bone resorption [1].

While these pharmacological effects account for the clinical efficacy of ZA, profound inhibition of bone turnover also underlies several of its adverse events. Reduced osteoclastic activity decreases calcium release from the skeleton, predisposing susceptible individuals to hypocalcemia. Similarly, prolonged suppression of bone remodeling may impair physiological repair of microdamage within the jawbones, contributing to the development of MRONJ [2].

2) Severe Symptomatic Hypocalcemia

Hypocalcemia is a recognized adverse effect of intravenous bisphosphonates and is usually asymptomatic or transient. However, severe symptomatic hypocalcemia requiring hospitalization remains uncommon. In our series, one patient developed acute tetany with painful carpopedal spasms shortly after the first ZA infusion, requiring intravenous calcium replacement and permanent discontinuation of therapy.

Several mechanisms contribute to ZA-induced hypocalcemia. Potent inhibition of osteoclast-mediated bone resorption markedly reduces calcium mobilization from bone. Normally, this reduction is compensated by increased parathyroid hormone secretion and enhanced intestinal calcium absorption mediated by vitamin D. Patients with vitamin D deficiency, hypoparathyroidism, renal impairment, hypomagnesemia, or extensive osteoblastic bone metastases may be unable to compensate adequately, resulting in clinically significant hypocalcemia [12].

Similar cases have been reported in the literature, particularly among patients with vitamin D deficiency or impaired renal function. While the incidence of severe symptomatic hypocalcemia remains low, its consequences may be life-threatening, including seizures, cardiac arrhythmias, prolonged QT interval, bronchospasm, and tetany [9,12]. Prompt recognition, intravenous calcium gluconate administration, correction of electrolyte abnormalities, and vitamin D supplementation remain the cornerstone of management.

Our observation reinforces current ASCO and ESMO recommendations advocating systematic assessment of serum calcium, phosphate, magnesium, renal function, and vitamin D status before initiating ZA therapy, together with appropriate supplementation when deficiencies are identified [3,13].

3) Hypersensitivity Reactions

Acute-phase reactions are among the most frequent adverse events associated with ZA and typically manifest as fever, myalgia, arthralgia, and influenza-like symptoms within 24–72 hours after the first infusion. These reactions are believed to result from transient activation of γδ T lymphocytes with subsequent release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ [1].

In contrast, true hypersensitivity reactions are rare. Our series included three patients who developed severe allergic manifestations after the first ZA infusion, including delayed erythematous rash, generalized grade III pruritic rash, and acute angioedema. All required treatment interruption, systemic corticosteroids, antihistamines, and permanent discontinuation of ZA.

The exact immunological mechanisms remain incompletely understood. Proposed mechanisms include delayed T-cell-mediated hypersensitivity reactions as well as immediate IgE-independent mast-cell activation. Individual case reports have described urticaria, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS), although these events are exceptionally uncommon [14].

Because hypersensitivity generally occurs after the initial infusion, patients should be informed about warning symptoms and monitored closely during and shortly after administration. Immediate discontinuation of ZA is recommended in severe reactions, and re-exposure should generally be avoided because of the risk of recurrence.

4) Medication-Related Osteonecrosis of the Jaw

MRONJ remains the most feared long-term complication of bisphosphonate therapy. According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), MRONJ is defined by the presence of exposed bone or bone that can be probed through an intraoral or extraoral fistula persisting for more than eight weeks in patients receiving antiresorptive or antiangiogenic agents without a history of radiation therapy to the jaws [7].

Three patients in our series developed MRONJ after prolonged ZA exposure. Clinical manifestations ranged from localized mandibular pain with radiological abnormalities to extensive mandibular and bilateral maxillary osteonecrosis. Management included discontinuation of ZA, prolonged antibiotic therapy, antiseptic mouth rinses, and referral to specialized oral and maxillofacial surgery services.

The pathogenesis of MRONJ is multifactorial. Proposed mechanisms include profound suppression of bone remodeling, inhibition of angiogenesis, chronic inflammation, bacterial biofilm formation, altered immune function, and repeated microtrauma to the jaws. Unlike other skeletal sites, the jaws are continuously exposed to mechanical stress and oral microorganisms, rendering them particularly susceptible to impaired healing following dental extractions or trauma [7,12].

Several risk factors have been consistently identified, including prolonged cumulative exposure to intravenous bisphosphonates, invasive dental procedures, poor oral hygiene, periodontal disease, diabetes mellitus, corticosteroid therapy, smoking, advanced age, and concomitant antiangiogenic therapies. Our MRONJ patients had prolonged ZA exposure, consistent with previous studies demonstrating that cumulative treatment duration is among the strongest predictors of disease development [8].

AAOMS classifies MRONJ into stages based on clinical severity, ranging from Stage 0 (non-specific symptoms without exposed bone) to Stage 3 (extensive necrotic bone with pathologic fracture, extraoral fistula, or extension beyond the alveolar bone). This staging system guides therapeutic decision-making, ranging from conservative management with antimicrobial mouth rinses and analgesics to surgical debridement or resection in advanced disease [7].

Computed tomography plays an important role in evaluating the extent of osseous destruction, sequestration, cortical disruption, and maxillary sinus involvement. In our patients, maxillofacial CT findings correlated closely with the clinical presentation and facilitated multidisciplinary treatment planning.

5) Clinical Implications

The spectrum of toxicities observed in our study highlights several practical measures that may substantially reduce the risk of severe ZA-related complications.

First, biochemical assessment before treatment initiation is essential. Serum calcium, phosphate, magnesium, creatinine, and vitamin D levels should be evaluated and corrected before the first infusion. Calcium and vitamin D supplementation should be prescribed according to international guidelines unless contraindicated [3,13].

Second, comprehensive dental evaluation remains the most effective preventive strategy against MRONJ. Existing dental infections should be treated, teeth with poor prognosis extracted before initiating therapy, and patients educated regarding meticulous oral hygiene and regular dental follow-up. Elective invasive dental procedures should preferably be completed before the first ZA infusion whenever feasible [10, 13].

Third, renal function should be monitored before each infusion because impaired renal clearance increases the risk of metabolic complications. Dose adjustments or treatment postponement may be necessary in patients with deteriorating kidney function [4].

Finally, clinicians should maintain a high index of suspicion for both early and late adverse events. Patient education regarding symptoms such as muscle cramps, paresthesia, facial swelling, skin rash, oral pain, or exposed bone may facilitate earlier diagnosis and prompt intervention.

6) Strengths and Limitations

The principal strength of our study lies in the simultaneous description of three distinct categories of severe ZA-related toxicities within a single real-world oncology cohort. Unlike most published reports that focus on a single complication, our case series illustrates the broad spectrum of clinically significant adverse events encountered in daily practice, ranging from acute metabolic disturbances and hypersensitivity reactions to delayed skeletal complications. Furthermore, the inclusion of clinical photographs and radiological imaging enhances the educational value of the report.

Nevertheless, several limitations should be acknowledged. The retrospective design may have introduced information bias, and the small sample size precludes estimation of incidence or identification of independent risk factors. As a single-center study, our findings may not be generalizable to other populations. In addition, laboratory investigations such as baseline vitamin D concentrations were not consistently available for all patients, limiting assessment of predisposing factors for hypocalcemia.

Table 2: Comparison with Published Literature

Author	Year	Number of Patients	Toxicity	Time to Onset	Management	Outcome
Peter *et al.,*	2016	1	Severe hypocalcemia	First infusion	IV calcium	Recovery
Jamil *et al.,*	2023	1	Systemic inflammatory response	First infusion	Supportive care	Recovery
Ruggiero *et al.,*	2022	Guideline	MRONJ	Long-term exposure	Stage-based	Variable
Present study	2026	7	Hypocalcemia, hypersensitivity, MRONJ	Early and late	Multidisciplinary	Favorable

Table 3: Characteristics of Zoledronic Acid-Related Adverse Events

Patient	Adverse Event	Time to Onset	CTCAE Grade	Diagnostic Findings	Management	Outcome
1	Symptomatic hypocalcemia	After first infusion	Grade 3	Corrected calcium ↓	IV calcium gluconate, potassium replacement	Complete recovery
2	Delayed erythematous rash	4 days	Grade 2	Clinical	Corticosteroids + antihistamines	Recovery
3	Generalized pruritic rash	Iimmediate	Grade 3	Clinical	Steroids	Recovery
4	Angioedema	Immediate	Grade 3	Clinical	Steroids + antihistamines	Recovery
5	MRONJ	Months	Stage 2/3	CT + clinical examination	Antibiotics + ZA withdrawal	Improved
6	MRONJ	Months	Stage 2	CT + clinical examination	Conservative treatment	Stable
7	MRONJ	Months	Stage 3	CT + clinical examination	Surgery referral	Ongoing follow-up

RESULTS

Seven patients who developed clinically significant adverse events following intravenous zoledronic acid (ZA) administration were included in this retrospective case series. The cohort comprised five women and two men, with a median age of 64 years (range, 42–80 years). Breast cancer was the most common underlying malignancy (n = 5), followed by prostate cancer (n = 2). ZA was administered for the prevention of skeletal-related events in patients with bone metastases (n = 5) and for the prevention of cancer treatment-induced bone loss in patients with early-stage breast cancer (n = 2). Baseline patient characteristics are summarized in Table 1.

Four patients (57.1%) experienced early adverse events**,** all occurring after the first ZA infusion. One patient developed severe symptomatic hypocalcemia characterized by tetany and painful carpopedal spasms, requiring hospitalization and intravenous calcium gluconate replacement. Three patients developed severe hypersensitivity reactions, including a delayed erythematous rash, a grade 3 generalized pruritic rash, and acute angioedema. All hypersensitivity reactions were managed with systemic corticosteroids and antihistamines, and ZA was permanently discontinued in each case Table 4.

Three patients (42.9%) developed late adverse events Table 4, all of which were diagnosed as medication-related osteonecrosis of the jaw (MRONJ) following prolonged ZA exposure. Clinical manifestations ranged from persistent dental pain with radiological abnormalities to extensive mandibular osteonecrosis and bilateral maxillary osteonecrosis with fistula formation. Management consisted of permanent discontinuation of ZA, systemic antibiotic therapy, analgesic treatment, and referral to specialized oral and maxillofacial surgery services. Representative clinical and radiological findings are presented in Figure 1(A, B, C, D, E).

Overall, all patients with early adverse events achieved complete clinical recovery following prompt medical management. Patients with MRONJ required prolonged multidisciplinary follow-up, with stabilization of disease after conservative treatment and discontinuation of ZA. No deaths were directly attributable to ZA-related adverse events.

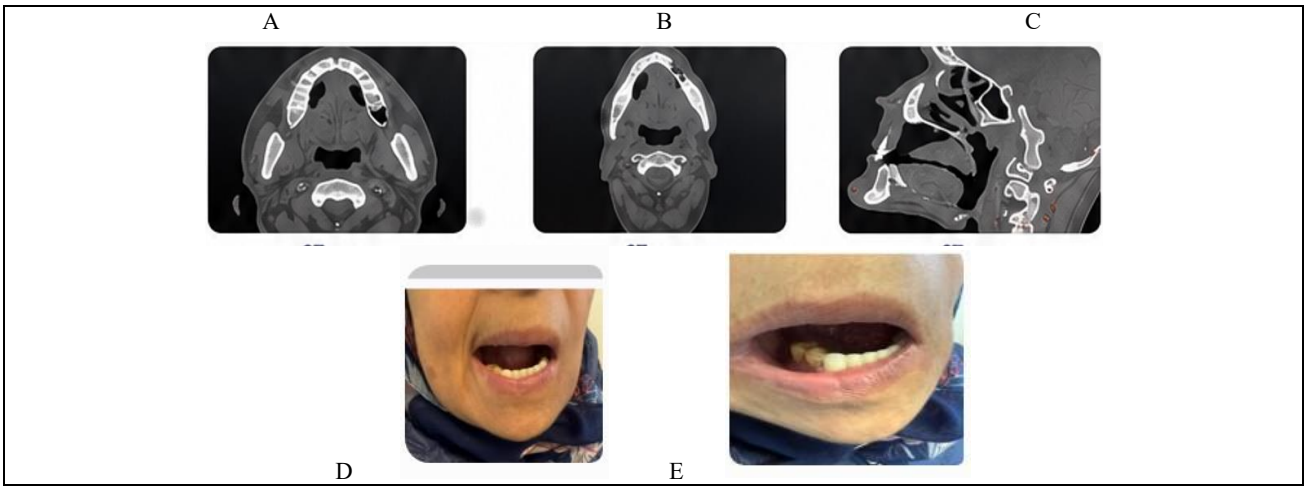

Fig. 1

Table 4: Timeline of Adverse Events

Patient	First ZA Infusion	Adverse Event	Treatment	Outcome
1	Day 0	Tetany	IV calcium	Recovered
2	Day 0	Rash (Day 4)	Corticosteroids	Recovered
3	Day 0	Generalized rash	Steroids	Recovered
4	Day 0	Angioedema	Emergency treatment	Recovered
5	Long-term	MRONJ	Antibiotics	Improved
6	Long-term	MRONJ	Conservative care	Stable
7	Long-term	MRONJ	Surgery referral	Follow-up

CONCLUSION

Our seven-case series demonstrate that although zoledronic acid remains an effective and generally safe bone-modifying agent, clinicians should remain vigilant for severe but uncommon complications, including symptomatic hypocalcemia, hypersensitivity reactions, and MRONJ. Careful patient selection, correction of metabolic abnormalities, baseline dental assessment, routine biochemical monitoring, and multidisciplinary management are fundamental to minimizing treatment-related morbidity and optimizing the safe use of ZA in routine oncology practice.

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