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REVIEW ARTICLE

Osteonecrosis of the jaw related to non-antiresorptive medications: a systematic review

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Abstract

Introduction The reporting of osteonecrosis of the jaw (ONJ) related to anticancer agents without known antiresorptive properties (non-antiresorptives), such as antiangiogenics, tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, immune checkpoint inhibitors, and cytotoxic chemotherapy is increasing.

Objective To review characteristics of ONJ in cancer patients receiving non-antiresorptives.

Methods A systematic review of the literature between 2009 and 2017 was conducted by the Bone Study Group of MASCC/ISOO.

Results Of 6249 articles reviewed and from personal communication, 42 ONJ cases related to non-antiresorptives were identified. No gender predilection was noted. Median age was 60 years and ONJ stage 2 was most common, with predilection for posterior mandible. Exposed bone, pain, and infection were common at diagnosis. In comparison to bone targeting agents (BTAs), radiology, histology, and management were similar, with medication often discontinued. Delayed diagnosis (median 8 weeks) was noted.

Important differences included earlier time to ONJ onset (median 20 weeks), absence of trigger event (40%), and greater likelihood of healing and shorter healing time (median 8 weeks) as compared to BTA-related ONJ. Gastrointestinal cancers predominated, followed by renal cell carcinomas compared to breast, followed by prostate cancers in BTA-related ONJ, reflecting different medications.

Conclusions Data about non-antiresorptive-related ONJ is sparse. This type of ONJ may have better prognosis compared to the BTA-related ONJ, suggested by greater likelihood of healing and shorter healing time. However, the delay in diagnosis highlights the need for more education. This is the first attempt to characterize ONJ associated with different non-antiresorptives, including BRAF and immune checkpoint inhibitors.

Keywords Bone resorption · Cytotoxic chemotherapy · Immune checkpoint inhibitors · Inhibitors of angiogenesis · mTOR inhibitors · Tyrosine kinase inhibitors · BRAF inhibitors · Osteonecrosis of the jaw

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Introduction

Osteonecrosis of the jaw (ONJ) related to medications is an uncommon complication of the jaw bones that may develop after exposure to drugs with antiresorptive effects. These agents target bones (bone targeting agents (BTAs)), and they are used in oncology to prevent skeleton-related adverse events and to prevent complications of bone metastases. They include bisphosphonates, essentially administered by the intravenous route in oncology patients, and denosumab [1–3]. The concurrent administration of BTAs and other biological medications that have no antiresorptive properties, such as inhibitors of angiogenesis, tyrosine kinase inhibitors, inhibitors of mammalian target of rapamycin (mTORi), and cytotoxic chemotherapy may significantly increase the risk of BTA-related ONJ [4]. A shorter time to ONJ onset was reported when inhibitors of angiogenesis were administered concurrently with BTAs, while concurrent chemotherapy has been recognized as an important risk factor for ONJ development [5–8]. Recently, some ONJ cases have been observed following treatment of cancer patients with inhibitors of angiogenesis or tyrosine kinase inhibitors, inhibitors of mammalian target of rapamycin, immune checkpoint inhibitors, and cytotoxic chemotherapy, without concurrent BTAs [1, 3]. Thus, larger cancer populations are at increased risk for ONJ [9]. Therefore, improving the definition of ONJ-related to non-antiresorptive medications and distinguishing features in diagnosis, prevention, and therapy are of importance [9, 10]. Education of patients and oncologists about this oral complication will lead to early diagnosis and differentiation from other oral complications of cancer therapy such as stomatitis associated with targeted chemotherapy [10].

Dentoalveolar surgery, including dental extractions, has been considered a key local risk factor for the development of ONJ in cancer patients who receive BTAs [2, 5, 11, 12]. ONJ clinically appears, most often, as exposed necrotic bone in the jaws, although non-exposed disease has also been recognized [1, 5, 13–15].

Recent evidence has suggested that local dental/periodontal infections may precede the appearance of necrotic bone in patients receiving BTAs [16].

However, much less is known about the risk factors and mechanisms involved in the development of ONJ in patient exposed to non-antiresorptive agents [10, 17].

With the objective of evaluating the literature on this subject, a systematic review was initiated by the Bone Study Group (BSG) of MASCC/ISOO in June 2015 during the Annual MASCC/ISOO Symposium in Copenhagen, Denmark.

Methods

An invitation letter was sent to the BSG members to participate in the review [18]. A search strategy was developed by combining medical subject headings and/or keywords from four categories: (1) cancer patients, (2) medications related to ONJ, (3) questions of interest for the review (dental extractions, other dental surgery), and (4) ONJ. Searches were limited to human studies published in English. Reviews, editorials, and letters were excluded. Unpublished cases of ONJ related to non-antiresorptives, fulfilling the same criteria as the published cases, would also be included following communication with expert clinicians. The detailed inclusion criteria and exclusion criteria are as follows:

Inclusion criteria Articles which reported patients who received ONJ-related medications for cancer, articles which reported on both cancer patients and patients who received ONJ-related medications for benign conditions, if the cancer group had been assessed separately (only the cancer group was then included in this review), clinical research papers testing the "specific questions," as they were set upon the initiation of the project and included (1) dental extractions and ONJ, (2) ONJ management, and (3) ONJ related to agents without bone antiresorptive action, articles published in a peer-reviewed journal, articles indexed in Medline between 1 January 2009 to 31 December 2016, adult patients.

Exclusion criteria Articles, which reported patients who received ONJ-related medications for osteoporosis or other benign disease only, articles which included patients with cancer and patients with benign conditions assessed as one group, articles that did not report testing the "specific questions" described above, animal or in vitro studies, literature reviews (literature reviews were checked for relevant citations), articles published in a language other than English, abstracts presented in meetings-not full article published.

PubMed and Embase were searched. A manual search of the bibliography of identified published articles was also performed. Personal communication with relevant experts was conducted. Literature searches were completed based on the key words listed below:

Cancer, cancer therapy, drug holiday, adverse drug reaction, drug discontinuation, adverse events, osteonecrosis, osteonecrosis of the jaw, dental extraction, dental surgery, oral surgery, periodontal disease, management, management of osteonecrosis, healing, healing time, healing of osteonecrosis, treatment of osteonecrosis, treatment outcome of osteonecrosis, drug discomfort, treatment, drug holiday, drug discontinuation, antiresorptive, zoledronic acid, zometa, ibandronate, alendronate, clodronate, bisphosphonate, denosumab, antiangiogenic, angiogenesis inhibitor, bevacizumab, sunitinib, chemotherapy, everolimus, temsirolimus, aflibercept, pazopanib, and ipilimumab.

The published literature was critically evaluated and graded based on quality of evidence. All assessments were made by two reviewers, who were calibrated as described in the article

by Bowen et al. and using the Hadorn et al. and Somerfield et al. criteria for clinical practice guidelines [18–20]. An Excel form for data extraction, kindly provided by the MASCC Mucositis Study Group, was modified according to the needs of our review. All reviewers were calibrated. The calibration consisted of blinded review of the paper by Owosho et al. [21]. An agreement between reviewers was obtained.

Results

We retrieved 6249 titles; of those, 579 were selected by the title. Abstracts of 144 articles were selected from those 579 titles. One hundred and six full articles were selected and of those 60 articles were finally selected to be included in the review. The 60 articles were divided in 3 groups, depending on their relation to a specific question, as stated earlier, and were assigned to the 3 groups of collaborators. Four articles were related to the question about "dental extractions," 38 were related to "ONJ management," and 18 were case reports related to non-antiresorptive targeted therapies.

After the literature was evaluated, 18 articles that reported cases of ONJ related to non-antiresorptive medications alone were selected for the review. Furthermore, additional eleven articles were retrieved after the literature search was extended to December 2017. Two articles that were published in 2008 were also added in the review due to the paucity of literature on this important issue of ONJ-related medications. In total, 31 articles, case reports and a case series, describing 39 cases of ONJ were reviewed. Three unpublished cases from the author's medical files were also included.

Forty-two cases of ONJ related to non-antiresorptives were identified. Thirty-eight cases of ONJ were related to targeted therapies, such as inhibitors of angiogenesis, tyrosine kinase inhibitors, inhibitors of mammalian target of rapamycin, BRAF inhibitors and immune checkpoint inhibitors, and 4 ONJ cases were related to cytotoxic chemotherapy [21–51]. Table 1 shows the list of non-antiresorptive agents that were found related to ONJ, either as monotherapies or in combinations or in sequence. The BTA agents that were administered before or concurrent with the non-antiresorptives are also shown in this table.

Patient characteristics

Gender, age, cancer types, and medications are shown in Table 1.

No gender predilection was noted. The median age of the patients was 60 years (range 33–79). Advanced gastrointestinal cancers were the predominant cancer diagnoses, followed by metastatic renal cell, lung, and breast cancers. Six patients had hematological malignancies.

ONJ was associated with a wide variety of biological therapies, with inhibitors of angiogenesis being the most common association.

Characteristics of ONJ

ONJ stage, type and location, time from initiation of medication to ONJ diagnosis, time from initiation of symptoms to diagnosis of ONJ, clinical signs and symptoms at diagnosis, radiological findings, and histology are shown in Table 2.

ONJ stage and type, exposed, or non-exposed, were reported by the authors in one article with a series of 4 cases and by the authors in the three unpublished cases; 6 were exposed type ONJ and one was non-exposed [22, Nicolatou-Galitis personal file] (Fig. 1). The other 35 cases were classified based on each case description and according to the criteria of the American Association of Oral Maxillofacial Surgeons (AAOMS) updated ONJ classification 2014 and the article by Schiodt et al. 2014 [1, 15]. Thirty-three cases were classified as exposed type and 2 as non-exposed, based on the presence of fistula and purulence, combined with radiological findings consistent with ONJ, as reported by the authors.

The time to onset of ONJ (the time from the initiation of medication to the development of ONJ) was difficult to define due to the varying frequency of administration protocols. Some medications are administered daily (imatinib, cabozantinib, sorafenib, axitinib, pazopanib, dasatinib, everolimus, dabrafenib, trametinib), others weekly (rituximab), others every 2 weeks (aflibercept, nivolumab), others every 3 weeks (bevacizumab, ipilimumab), others daily for 3 weeks with 1-week break (regorafenib), or daily for 4 weeks followed by 2-week break (sunitinib), while cytotoxic chemotherapy is usually given in cycles of 15 to 21 days.

Approximately, half of the patients developed ONJ after 20 or more weeks (range 2–180 weeks) from the initiation of medication. According to the description of each case, patients reported having symptoms prior to diagnosis of ONJ, ranging from 1 to 72 weeks (median 8 weeks).

Pain was the dominant symptom

Exposed bone, purulence, swelling, fistula, inflammation, and trismus were the most commonly reported clinical signs at diagnosis.

The radiological findings of ONJ were described in 34 cases, mainly using cone beam computed tomography (CBCT) and orthopantomograph (OPG), while a wide variation of terms were applied to describe the radiological picture. Hyper-dense bone, cortical bone changes, opaque areas, radiolucency, radiolucency associated with non-healing socket, osteolysis (Fig. 2), bone loss, fragmented cancellous bone, necrotic bone, and maxillary sinusitis were among the terms used to describe the radiological findings.

Table 1 Patient, disease, and medication characteristics, $n = 42$

			n	%
Gender				
	M		23	54.7
	F		19	45.2
Age				
	Mean (SD)	59.19 (9.55)		
	Median	60		
	Range	33–79		
Type of cancer				
	Metastatic			
		GI tract	12	28.5
		Renal cell	7	16.6
		Lung	5	11.9
		Breast	5	11.9
		Thyroid	2	4.7
		Parotid	1	2.3
		Melanoma	1	2.3
	Non-resectable			
		Glioblastoma	2	4.7
		Pancreatic	1	2.3
	Hematological			
		Acute lymphoid leukemia	3	7.1
		Lymphoma	2	4.7
		Chronic myeloid leukemia	1	2.3
Targeted therapy				
	Angiogenesis inhibitors alone or in combinations			
		Bevacizumab	11	26.1
		Aflibercept	5	11.9
		Sunitinib	4	9.5
		Imatinib	3	7.1
		Cabozantinib	1	2.3
		Sorafenib	1	2.3
		Regorafenib	1	2.3
		Axitinib	1	2.3
		Pazopanib	1	2.3
		Dasatinib	1	2.3
		Bevacizumab/sorafenib	1	2.3
		Bevacizumab/temsirolimus	1	2.3
	mTOR inhibitors alone			
		Everolimus	3	7.1
	BRAF inhibitors in combinations			
		Dabrafenib/trametinib	1	2.3
Targeted therapies prior to				
	Sorafenib prior to sunitinib		1	2.3
	Sunitinib and everolimus prior to pazopanib		1	2.3
	Pazopanib and nivolumab prior to axitinib		1	2.3
	Erlotinib prior to sorafenib/bevacizumab		1	2.3
	Bevacizumab prior to nivolumab		1	2.3
Immunotherapy				
		Ipilimumab	1	2.3
		Rituximab	1	2.3
		Nivolumab	1	2.3
Concurrent chemotherapy			14	33.3
Bone targeted agents				
	6 years prior to everolimus	Zoledronic acid	1	2.3
	4 years prior to imatinib	Zoledronic 1 iv and alendronate 2 years per os	1	2.3
	2 years prior to imatinib	Denosumab (prolia) 4 inj and zoledronic acid (aclasta) 2 inj	1	2.3
	1 infusion concurrent with everolimus	Zoledronic acid	1	2.3
	2 injections concurrent with dabrafenib trametinib	Denosumab	1	2.3
Classical chemotherapy alone			4	9.5
Comorbidities/smoking				
	Hypertension		6	12.1
	Hypothyroidism		4	9.7
	Osteoporosis		3	7.1
	Diabetes		1	2.3
	Prostate hyperplasia		1	2.3
	Smoking		3	7.1
Medications	Steroids		10	23.8
	Vascular coagulation		1	2.3
	problems/anticoagulants cardiac arrhythmia		1	2.3

Table 2 Osteonecrosis characteristics at diagnosis, $n = 42$

		n	%
ONJ stage			
	1	6	14.2
	2	29	69.0
	3	7	16.6
Type			
	Exposed	39	92.8
	Non-exposed	3	7.1
Location			
	Mandible (when location was reported: posterior mandible 22/31 and posterior lingual mandible 9/22)	34	80.9
	Maxilla	8	19.0
Time from initiation of medication to diagnosis of ONJ (weeks) ($n = 41$)			
Mean (SD)	42.09 (45.74)		
Median	20		
Range	2–180		
Time from initiation of symptoms to diagnosis of ONJ, (weeks) ($n = 25$)			
Mean (SD)	15.24 (18.20)		
Median	8		
Range	1–72		
Clinical signs			
	Exposed bone	39	92.8
	Purulence	1	26.1
	Swelling	11	26.1
	Fistula	6	14.2
	Inflammation	7	16.6
	Trismus/difficulty chewing	5	11.9
	Non-healing socket	3	7.1
	Periodontal disease, tooth mobility	3	7.1
	Other: halitosis, bleeding, erythema, ulcer	6	14.2
Clinical symptoms			
	Pain, discomfort/tenderness/roughness	25	58.5
	Asymptomatic	7	17.0
	Paresthesia/anesthesia/neuralgia	4	9.7
	Not clear/not reported	1	2.4
Radiology, $n = 34$			
Techniques used			
	CBCT	22	64.7
	OPG	1	61.7
	Periapical	5	14.7
	Other: scintigraphy, MRI, CT scan	4	11.7
Findings			
	Hyper-dense bone, thickening of periosteum	8	23.5
	Cortical bone lesion, erosion, irregularity	8	23.5
	Not significant	5	14.7
	Maxillary sinusitis	5	14.7
	Radiolucency non-healing socket	7	17.9
	Osteolysis	5	14.7
	Bone sequestrum	3	8.8
	Fragmented cancellous bone	3	8.8
	Necrotic bone	3	8.8
	Bone loss	2	5.8
	"Signs of ONJ"	2	5.8
	"Hypercaptation"	2	5.8
	Other: radiolucent/opaque areas, periapical Radiolucency, low signal intensity, PDL widening	4	11.7
Histology/findings, $n = 18$			
	Necrotic bone	11	
	Consistent with ONJ	3	16.6
	Osteomyelitis	4	22.2
	Inflammatory cells	5	27.7
	Bacteria consistent with actinomyces	5	27.7
	Bacteria	2	11.1

CBCT, cone beam computed tomography; *OPG*, orthopantomograph; *MRI*, magnetic resonance image; *CT*, computed tomography. Hypercaptation, increased uptake shown by scintigraphy

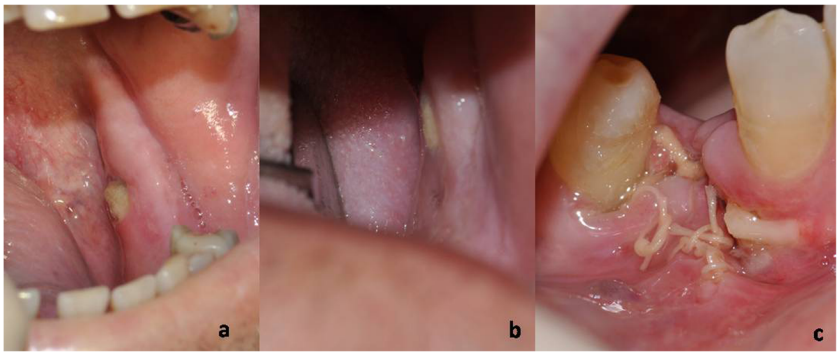

Fig. 1 **a** Necrotic exposed bone (ONJ) is observed on the left posterior lingual mandible. Patient was managed for lung cancer with dabrafenib and trametinib. **b** ONJ is observed on the left lingual mandible. The patient was managed for lung cancer with nivolumab. **c** ONJ extends on the buccal aspect, right mandible, after the dental extraction of the first premolar. Exposed bone was observed prior to dental extraction by the author, who provided this case. The patient was managed for gastrointestinal stromal tumor with imatinib

Histologic study was reported in 18 cases and included necrotic bone, lesion consistent with ONJ, and osteomyelitis. In 5 cases, associated bacteria were consistent with actinomyces, though not confirmed microbiologically (Table 2).

Trigger event characteristics, management, and clinical outcome

The trigger event, signs and symptoms and their duration prior to ONJ diagnosis, and management and clinical outcomes are shown in Table 3.

Dental extraction was reported as a trigger/preceding event in 14 patients, however, no trigger event was identified in another 17 cases. Instead, spontaneous mucosal breakdown, spontaneous tooth loss, swelling, pain, and bone exposure were reported.

The related medication was discontinued in 14 and continued in 10 of 24 patients, where information was available.

Of 39 patients, with available information, 29 were managed with medical (non-surgical) therapy alone and 3 with a combination of medical therapy and sequestrectomy. Seven patients were surgically managed.

Healing was achieved in 16 patients. Different terms were used to describe healing and included normal mucosa or mucosal coverage (9 cases), no exposed bone (2 cases), complete recovery (2 cases), fully resolved (2 cases), and free of lesion (1 case). Five patients had renal cell carcinoma, 4 had different types of leukemia, and the remainders were patients with different cancers. As shown in Table 3, about half of the patients with stage 2 and 3 healed. Only one of six patients with stage 1 achieved healing, while 5 remained stable.

Discussion

Forty-two cases of ONJ related to biological therapies without antiresorptive properties were reviewed. The non-antiresorptive medications which were found related to ONJ included bevacizumab, aflibercept, sunitinib, imatinib, cabozantinib, sorafenib, regorafenib, axitinib, pazopanib, dasatinib, everolimus, temsirolimus, ipilimumab, and rituximab. Novel cases of ONJ related with inhibitors of BRAF, dabrafenib, trametinib, and the immune checkpoint inhibitor, nivolumab, were added from our personal files. The cytotoxic medications which were found related to ONJ were combinations of (1) cytarabine, idarubicin, and daunorubicin; (2) gemcitabine, vinorelbine, and doxorubicin; (3) doxorubicin and cyclophosphamide; and (4) 5-azacitidine as monotherapy. As summarized below, similarities and differences with the ONJ related to BTAs were found.

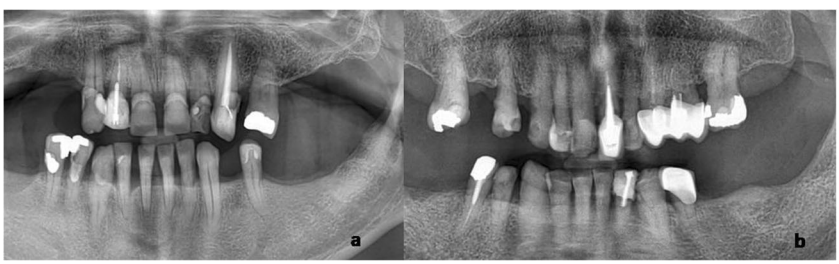

Fig. 2 **a** Orthopantomograph shows osteolysis on the left mandible of the patient from Fig. 1a at the area of the clinical necrotic, exposed bone. **b** Orthopantomograph shows osteolysis on the left mandible of the patient from Fig. 1b at the area of clinical necrotic exposed bone

Table 3 Trigger event, drug discontinued/continued, management, and clinical outcome, $n = 42$

			N	%
Trigger event				
	Not identified (spontaneous mucosal breakdown, swelling, pain, tooth loss, bone exposure)		17	40.4
	Not clear/not reported		2	4.7
	Dental extraction		14	33.3
	Denture wearer		4	9.5
	Mucosal trauma/stomatitis		2	4.7
	Compromised periodontal status		2	4.7
	Symptomatic tooth eruption		1	2.3
Drug discontinued/continued, $n = 24$				
	Discontinued		14	58.3
	Continued		10	41.6
Management, $n = 39$				
	Medical		29	74.3
		Antibiotics/rinses	19	48.7
		Laser, ozone, follow-up	5	12.8
		Conservative not specified	4	10.2
	Medical and sequestrectomy		3	7.6
	Surgery		7	17.9
Clinical outcome, $n = 37$				
	Healed		16	43.2
		ONJ 1	1 of 6	16.6
		ONJ 2	12 of 29*	41.3
		ONJ 3	4 of 7#	57.1
	Improved		12	32.4
	Worsened		1	2.7
	Patient died of underlying disease, with ONJ		7	18.9
Time to healing (weeks), $n = 11$				
	Mean (SD) 8.3636 (8.01589)			
	Median 8			
	Range 1–28			

*12 of 29 cases in which ONJ stage 2 could be defined, # 4 of 7 cases in which ONJ stage 3 could be defined

Similarities

Similarities were noted in gender, age, medical risk factors, type and stage of ONJ, jaw bone location, clinical signs and symptoms, radiological, histological findings, and management (Table 4).

1. No gender prevalence was reported and the median age of the cancer patients of the present review was similar to that reported by others in patients with cancer, who received BTAs [2, 3, 52].
2. About one third of patients received concomitant cytotoxic chemotherapy and about one fourth received steroids. These concurrent medications are known risk factors for BTA-related ONJ [3, 7, 8, 52].
3. Most ONJ cases were classified as stage 2 and exposed type, as it has been documented in BTA-related ONJ [3, 5, 11, 52]. No stage 0 cases were documented. The absence of cases with ONJ stage 0 is also noted in other publications of BTA-related ONJ in cancer [3, 52]. It should be noted that, in the present study, the stage for 35 cases was extrapolated by the authors, from the case description. The delay in the diagnosis of ONJ, which was noted in the present review, might, however, be a reason why most ONJ cases associated with non-antiresorptives were exposed type of ONJ. Earlier diagnosis could increase the number of ONJ cases without bone exposure. On the other hand, non-exposed ONJ is recently identified and its definition continues to be an issue for discussions among ONJ expert clinicians.

Table 4 ONJ related to non-antiresorptives compared to BTA-related ONJ

Similarities		
	No gender predilection	
	Middle-aged adults	
	Similar medical risk factors	
		Chemotherapy, corticosteroids
	Common ONJ stage	
		ONJ stage 2
	Common jaw affected	
		Mandible
	Common radiological features	
		Osteolysis, opacities
	Common symptoms	
		Pain and other infectious manifestations
	Histology	
		Necrotic bone, inflammatory cells, bacteria
	ONJ-related medication	
		Often discontinued
	Most common management	
		Conservative
Differences		
	More common cancers	
		Gastrointestinal and metastatic renal cell carcinomas
	Local risk factor	
		Often not identified
	Time to onset of ONJ	
		Shorter
	Better ONJ prognosis	
		More patients healed, earlier healing

4. The mandible was the most common jaw affected, with a predilection noted for the posterior lingual mandible. The mandible has also been the most common location for BTA-related ONJ in cancer patients [3, 11, 52].
5. Hyper-dense bone, thickening of periosteum, bone sequestrum, bone loss, trabecular changes, osteolysis, and radiolucency were the different terms used to describe the radiological findings. Similarly, high bone density, thickening of periosteum, opacities, radiolucencies, and osteolysis have been reported in relation to ONJ in patients receiving BTAs [1, 11, 53, 54].
6. Radiological findings were reported as non-significant in 5 (15%) of the cases in this study. No obvious radiological findings were also reported in 5 of 47 (7.95) of patients with BTA-related ONJ [11].
7. The various terms used to describe the radiological findings in both ONJ related to BTAs and to non-antiresorptives may be related to the need to better define the radiological findings in ONJ [10, 54].
8. Exposed bone and infectious manifestations were common clinical signs reported in patients with ONJ related to non-antiresorptives. Impaired wound healing, as an effect of inhibition of angiogenesis, cytotoxicity, and impaired immune response to infection have been discussed as common mechanisms for all those medications [10, 17, 21, 35]. Exposed bone and infectious conditions, such as inflammation, infection, abscess, and fistulas were also common clinical findings reported by others in BTA-related ONJ [1, 53].
9. Pain and discomfort were the most common symptoms, while paresthesia and neuralgia were also reported. Similarly, in patients with ONJ related to BTAs pain and altered neurosensory function were most often reported in patients with symptomatic ONJ [1, 53].
10. The histology included necrotic bone, inflammatory cells, and bacteria and was comparable to that described in BTA-related ONJ [16, 55–57].
11. More cancer patients discontinued the non-antiresorptive medication as it has been reported for cancer patients who developed BTA-related ONJ [3, 11]. The "drug-holiday" protocol was reported to promote healing of BTA-related ONJ [54].

12. Conservative medical (non-surgical) management was more common, as reported in cancer patients with BTA-related ONJ [1, 3, 11, 54, 58]. According to the AAOMS position paper, the common practice in BTA-ONJ is non-surgical approach, while surgical approach is reported in persistent stage 3 ONJ that has failed to respond to conservative treatment. In the present review, all four of the 7 cases with ONJ stage 3, which were managed surgically, healed and healing was not superior in ONJ stage 2 as compared to ONJ stage 3. Data about the post-surgical duration of the follow-up were not reported. The similar healing outcome of both ONJ stage 2 and 3 might be related to the surgical management, applied more often for ONJ stage 3 (4 of 7 cases). Other factors may also play a role in the healing outcomes, such as the underlying disease and general medical condition of the patients. In a recent safety study of long-term denosumab therapy, 42% of patients with breast cancer and 26% of patients with prostate cancer, who developed ONJ, healed. BTA-related ONJ healed earlier in breast cancer patients compared to patients with multiple myeloma and prostate cancer, although the time difference was not reported statistically significant [2]. The varying cancers in the present review, combined with the limited number of cases in each cancer, reported by different cancer centers at different follow-up times did not allow for further comparisons. Furthermore, the Eastern Cooperative Oncology Group (ECOG) performance status of each patient was not reported [59]. The different biology and shorter half-life of ONJ-related non-antiresorptive medications as compared to that of BTAs could have affected the shorter healing time. Half-lives of non-antiresorptive medications vary between 5 to 58 h for most targeted drugs (dasatinib, axitinib, dabrafenib, imatinib, everolimus, temsirolimus, sorafenib, sunitinib, pazopanib, cabozantinib, regorafenib) and from 4.8 to 32 days for trametinib, ipilimumab, rituximab, bevacizumab, and nivolumab. For comparison, the half-life is 360 days (in bone) for zoledronic acid and 25 days for denosumab.

Differences

Important differences were found in the prevalence of cancer diagnoses, time to diagnosis of ONJ after initiation of medication (time to onset of ONJ), local risk factors, time to healing, and number of patients who healed.

1. Gastrointestinal cancers (GI) were the most common, followed by metastatic renal cell carcinomas (mRCC), lung, and breast carcinomas. There were no patients with prostate carcinoma or multiple myeloma. In contrast, breast cancer, followed by prostate and multiple myeloma, is the most common diagnoses in patients with BTA-related ONJ [3, 5, 11, 52]. This difference seems to be related to the drugs, approved to manage GI, mRCC, and other cancers.
2. Dental extraction was the most common reported local risk factor (33.3%). This is lower than that reported in BTA-related ONJ in patients with cancer (49–77.4%) [2, 11, 12, 15, 52, 53]. Dental extraction was also identified as the most common local risk factor associated with ONJ in studies which included both cancer and non-cancer patients, who received BTAs, ranging between 45–61% [5, 8, 15]. Local ONJ factors were not identified or were not clear in 19 cases of the present review (45.1%). The differences in the prevalence of ONJ local factors may also indicate different pathways which are related to the non-antiresorptive-related ONJ. Wound healing inhibition may prevail in the development of ONJ related to the non-antiresorptive medications as opposed to the main osteoclastic bone remodeling effect and inhibition of the BTAs [17]. The reason for extraction, such as the presence of dental/periodontal disease prior to extraction which may be an important risk factor for ONJ, was not reported.
3. The time to onset (TTO) of ONJ was shorter, median 20 weeks and mean 38.8 weeks after initiation of the medication as opposed to that reported in BTA-related ONJ. In the recent multicenter cancer case registry study, the median and mean time to diagnosis of BTA-related ONJ were 108 weeks and 136 weeks respectively [3]. Other authors have also reported a long median time, 72 and 104 weeks, needed to develop BTA-related ONJ in cancer patients [5, 11]. The different drug properties, associated with the different pathogenic mechanisms to develop ONJ, may relate to the above difference in the time to onset of ONJ. Likewise, the frequency of dose administration (daily, weekly, monthly) may also contribute to the large range of onset time.
4. More patients with non-antiresorptive-related ONJ (43.2%) healed than those reported with BTA-related ONJ (25–35%) [3, 52]. This difference may be also related to the different pathobiology of non-antiresorptive medications and the related different mechanisms of ONJ development, as described earlier [17]. It is possible that "healing" may have been defined differently by articles reviewed, which may impact on these results. However, the most commonly accepted understanding of "healing" for ONJ is based on mucosal coverage of the formerly exposed bone area.
5. ONJ healed earlier in patients with ONJ related to the non-antiresorptives (median 8 weeks) than that reported in BTAs (median range between 29 and 72 weeks) [2, 3, 11]. Shorter healing time of ONJ related to

antiangiogenics alone was also reported in a recent review [9]. Twenty-two cases from that systematic review were included in the present review [9]. The shorter half-life of the non-antiresorptives, between 2.5 h to 32 days, as opposed to denosumab and zoledronic acid, with 26 days and 360 days in bone, respectively, could have affected the healing time. The shorter time to ONJ healing might indicate a better biological behavior and prognosis of non-antiresorptives-related ONJ. However, other factors that cannot be evaluated in the present retrospective review, such as underlying disease and comorbidities, may have affected the time to healing of ONJ.

In conclusion, increasing numbers of cancer patients are at risk of developing ONJ related to non-antiresorptive agents. ONJ related to BRAF inhibitors and nivolumab were reported for the first time.

Pain and infectious manifestations should alert the clinicians to early ONJ diagnosis in both BTA- and non-antiresorptive-related ONJ.

ONJ related to non-antiresorptives may have better prognosis compared to the BTA-related ONJ, suggested by greater likelihood of healing and shorter healing time.

The delay to diagnosis of ONJ highlights the need for increasing awareness of non-antiresorptive medications related ONJ, also pointed out for the BTA-related ONJ. [60–63].

This review is the first attempt to determine the characteristics, including the radiological and histological features, of ONJ related to the collective term of "non-antiresorptives" and this is the strength of the study. The agents, which were included, were angiogenesis inhibitors, cytotoxic chemotherapy, BRAF inhibitors, and immune checkpoint inhibitors. Immunotherapy is the great breakthrough in oncology for the present decade and the novel case of ONJ related to nivolumab further highlighted the need for awareness and education.

The low level of evidence of the articles reviewed (level V) represents a weakness of the study. Another weakness is missing information in the reports, which would be relevant to ONJ development, such as active or past oncology treatment, performance status, reason for dental extractions, and detailed description of clinical parameters. Prospective studies are urgently needed.

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Compliance with ethical standards

Conflict of interest Ourania Nicolatou-Galitis and Cesar Migliorati have received consultant fee from AMGEN. Maria Kouri, Erofili Papadopoulou, Emmanouil Vardas, Dimitra Galiti, Joel Epstein, Sharon Elad, Giuseppina Campisi, Nikolaos Tsoukalas, Kivanc Bektas-Kayhan, Winston Tan, Jean-Jacques Body, and Rajesh Lalla declare no conflict of interest.

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