EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 5
73-79
Year: 2016

ANTI-ANGIOGENIC AGENTS AND OSTEONECROSIS OF JAW

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Article Received on 29/02/2016 **Article Revised on 20/03/2016** **Article Accepted on 11/04/2016**

ABSTRACT
Anti angiogenic agents is a highly promising therapeutic approach for the management of cancer. However one of the serious side effects associated with these drugs is Osteonecrosis of the Jaw. This review aims at understanding the association of anti angiogenic agents with occurrence, prevention and management of osteonecrosis of the jaw (ONJ). A PubMed search of the literature for relevant articles using the Medical Subject Heading (MeSH) terms "Anti-angiogenic agents", "Bevacizumab", "Sunitinib", "Trastuzumab"," Everolimus", "Cabozantinib", "Sorafenib", " Tyrosine Kinase Inhibitors", "Mammalian Target Of Rapamycin (Mtor) Inhibitors", "Osteonecrosis of jaw", was performed in various combinations. Additional articles were assessed in the reference lists of the retrieved articles.

KEYWORDS: Anti angiogenic agents, Ostoenecrosis of jaw, Bevacizumab, Sunitinib, ONJ.

INTRODUCTION

With the advent of cancer therapy protocols, focus is now given to the development of more precise therapies that target tumor tissue and reduce damage to non-neoplastic (normal) tissues.[1] Since angiogenesis is critical for tumor growth and metastasis, anti-angiogenic treatment has a very promising therapeutic approach.[2] However in conjunction with its promising anti-neoplastic activity, a series of side effects have been seen in patients undergoing anti angiogenic therapy.[3] One of the serious side effects is Osteonecrosis of the Jaw.

Hence a PubMed search of the literature for relevant articles using the Medical Subject Heading (MeSH) terms "Anti-angiogenic agents", "Bevacizumab", "Sunitinib", "Trastuzumab"," Everolimus", "Cabozantinib", "Sorafenib", " Tyrosine Kinase Inhibitors", "Mammalian Target Of Rapamycin (Mtor) Inhibitors", "Osteonecrosis of jaw", was performed in various combinations. Additional articles were assessed in the reference lists of the retrieved articles.

HISTORY

Judah Folkman in 1970 found that in the absence of neovascularization, tumors cannot grow more than 2 to 3 millimeters [4]; this gave rise to the field of angiogenesis and laid the foundation for antiangiogenic cancer therapy. [5] It was not until 2004 that the first antiangiogenic drug, bevacizumab was approved by the first FDA for the management of advanced colon cancer.[6]

ANGIOGENESIS

The phenomenon of formation of new blood vessels from pre-existing ones is termed as angiogenesis. In normal physiology, angiogenesis is the basis for repair and healing of tissues.[7] However, from the cancer growth perspective, the development of new blood vessels not only serves to supply the tumor tissue with nutrients, but they can also serve as a means for cancer cells to metastasize.[8] Angiogenesis involves various mediators, but a common agreement puts vascular endothelial growth factor (VEGF) and its signaling as the rate-limiting step of this process. Anti-angiogenic therapies target angiogenesis by two major mechanisms: blocking the receptor tyrosine kinases intracellularly or neutralizing angiogenic factors such as VEGF or its receptors.[9] These newerl medications have demonstrated efficacy in the treatment of gastrointestinal tumors, renal cell carcinomas, neuroendocrine tumors and others.[10]

OSTEONECROSIS OF JAW (ONJ)

Osteonecrosis of the jaw (ONJ) is a rare but serious disease of the jaw namely the maxilla and mandible.[11] The current definition proposed by AAOMS comprises the following criteria.[10]

1. Current or previous treatment with antiresorptive or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula (e) in the maxillofacial region that has persisted for more than eight weeks; and
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

PROPOSED MECHANISMS OF ANTI ANGIOGENIC AGENTS INDUCED ONJ

Several studies have shown that VEGF plays an essential or crucial role in bone repair. Consequently, inhibition of the physiological effects of VEGF through use of VEGF antagonists which are also referred to as ''anti-VEGF agents'' could theoretically predispose patients to ONJ.[11]

From a mechanistic stand point, anti-VEGF therapies are broadly classified into categories: monoclonal antibodies that bind to VEGF and thereby neutralize its biological activity and small molecule tyrosine kinase inhibitors (TKIs) that block the VEGF receptor and its preceeding signaling pathways.

STAGING AND TREATMENT STRATEGIES[10]

Table 1: Staging and treatment strategies for ONJ

ONJ† Staging	Treatment Strategies‡
At risk category No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates	• No treatment indicated • Patient education
Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms	• Systemic management, including the use of pain medication and antibiotics
Stage 1 Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	• Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and ery-thema in the region of the exposed bone with or without purulent drainage	• Symptomatic treatment with oral antibiotics • Oral antibacterial mouth rinse • Pain control • Debridement to relieve soft tissue irritation and infection control
Stage 3 Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the fol-lowing: exposed and necrotic bone extending beyond the region of alveolar bone,(i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor	• Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

† Exposed or probable bone in the maxillofacial region without resolution for greater than 8 weeks in patients treated with an antire-sorptive and/or an antiangiogenic agent who have not received radiation therapy to the jaws.

‡ Regardless of the disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. The extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process.

ANTI-ANGIOGENIC AGENTS ASSOCIATED WITH OCCURENCE OF ONJ

Table 2: Various anti-angiogenic agents[11]

Drug	Mode of action	Half life	Dose	Route	Approved indication
Bevacizumab	Inhibition of angiogenesis byblocking action of VEGF	11–50 days	5–10 mg every 2 weeks 15 mg every 3 weeks	IV	Metastatic colorectal carcinoma Glioblastoma Metastatic NSCLC Metastatic renal carcinoma
Sunitinib	Inhibition of tyrosine kinase ofVEGFR, PDGFR, FLT3, c-kit	40–60 h	50 mg daily for 4 weeks of a 6 week cycle	Oral	GIST Metastatic renal cell carcinoma Neuroendocrine tumors
Sorafenib	Inhibition of tyrosine kinase ofVEGFR, PDGFR, FLT3, c-kit, BRAF	25–48 h	400 mg twice daily	Oral	Metastatic hepatic carcinoma Metastatic renal cell carcinoma
Everolimus	Inhibition of mTOR	30 h	0.75–1 mg twice daily Oral Kidney and liver	Oral	Kidney and liver transplant Hormone receptor positive

			transplant 10 mg daily		breast cancer Metastatic renal cell carcinoma
Temsirolimus	Inhibition of mTOR	17 h	25 mg weekly	IV	Metastatic renal cell carcinoma
Cabozantinib	Inhibition of tyrosine kinase of VEGFR, MET, RET	55 h	140 mg daily	Oral	Metastatic medullary thyroid cancer

BEVACIZUMAB AND ONJ

Bevacizumab is a recombinant, humanized monoclonal antibody that binds to VEGF, thus inhibiting angiogenesis. It was approved by the US Food and Drug Administration in 2004 for the treatment of metastatic colorectal cancer. Bevacizumab, in combination with other agents, has also demonstrated clinical efficacy in many other cancers, including breast and lung cancer.[12,13]

Table 3 Shows various case reports published in pubmed on cases of ONJ associated with the use of bevacizumab. Table 4 shows incidence of ONJ with Bevacizumab.

Table 3: Case Reports of ONJ associated with the use of Bevacizumab

Study	Age (years) /Gender	Indication	Treatment	Site of ONJ	Other risk factors	Ref
Estilo et al.	33/F	Glioblastoma multiforme	Radiation (not including oral cavity and jaw) + temozolamide + bevacizumab 10 mg/kg every 2 weeks	Right Mandible	None	14
Estilo et al.	52/F	Metastatic breast cancer	Capecitabine 1000 mg twice daily (2 weeks on and 1 week off) + bevacizumab 15 mg/kg every 3 weeks	Posterior Mandible	None	14
Greuter et al.	63/F	Metastatic breast cancer	Liposomal doxorubicin + bevacizumab	Left Maxilla	Tooth extraction	15
Hopp et al	58/M	Retinal vascular Thrombosis	Intravitreal bevacizumab 2.5 mg every month	Left Mandible	None	16
Diesel et al	51/M	Metastatic sigmoid colon	FOLFOX+ bevacizumab 5 mg/kg every 2 weeks	Posterior mandible	None	17
Katsensos et al.	57/M	Metastatic NSCLC	Cistplatin IV 75 mg/m2 + paclitaxel IV 75 mg/m2 + bevacizumab 15 mg/kg every 3 weeks	Right Posterior mandible	Denture use + IV zoledronicacid 4 mg every month	18
Magremanne et al.	49/M	Glioblastoma multiforme	Bevacizumab	Left Posterior mandible	Corticosteroid	19
Giordana et al	57/F	Bilateral non-small-cell lung cancer (NSCLC)	Gemcitabine +cisplatin + 945 mg of intravenous bevacizumab every 21 days	Left mandible	Corticosteroid	20
Sato et al	67/M	Metastatic sigmoid colon cancer	mFOLFOX6+ bevacizumab			21
Santos-Silva et al.	61/M	Metastatic renal cell carcinoma	Bevacizumab IV 10 mg/kg every 2 weeks & temsirolimus 25 mg IV weekly	Left mandible	Smoking , temsirolimus	22

Table 4: Studies on incidence of ONJ with Bevacizumab

STUDY	ONJ OCCURENCE	REF.
Bevacizumab related ONJ in patients with osseous metastases from various tumors	Incidence of ONJ among bevacizumab recipients was lower (1.1%, 1/91) as compared with those who received bevacizumab and bisphosphonates.	23
Bevacizumab related ONJ in patients with locally recurrent or metastatic breast cancer	Incidence of ONJ in patients treated with bevacizumab in AVADO, RIBBON-1 and ATHENA was 0.3–0.4% and in those patients receiving bevacizumab and bisphosphonate therapy the incidence was slightly higher at 0.9–2.4%.	24
Bevacizumab related ONJ in patients with cancer	Incidence of ONJ in patients treated with bevacizumab without bisphosphonate was 0.1% and in those treated with bevacizumab and bisphosphonate was higher at 2%.	25

SUNITINIB AND ONJ

Sunitinib is an orally administrated small molecule that inhibits tyrosine kinase and multiple other targets, including vascular endothelial growth factor receptors (VEGFR1, VEGFR2, VEGFR3), platelet-derived growth factor receptors (PDGFR, PDGFR), stem cell factor receptor (KIT), Fms-like tyrosine kinase 3 (FLT3), colony-stimulating factor type 1 (CSF-1R), and glial cell– derived neurotrophic factor receptor (RET). On January 26, 2006, the FDA approved sunitinib for the treatment of patients with imatinib refractory or intolerant GIST. Accelerated permission was granted for the treatment of advanced renal cell carcinoma.[26]

Table 5 Shows various case reports published in pubmed on cases of ONJ associated with the use of sunitinib. Table 6 shows Studies on incidence of ONJ with Sunitinib.

Table 5: Case reports on occurence of ONJ with the use of sunitinib.

Study	Age (years) /Gender	Indication	Treatment	Site of ONJ	Other risk factors	Ref
Brunello et al.	59/M	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Left mandible	Previous treatment with IV zoledronate	27
Kock et al.	59/M	Renal cell carcinoma	Sunitinib	Left posterior mandible	Tooth extraction, previous treatment with sorafenib	28
Hoefert et al.	62/NA	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Left Madible	Smoking Tooth extraction IV zoledronate 4 mg every month	29
Hoefert et al.	56/NA	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Right Mandible	Tooth extraction (right molar) IV zoledronate 4 mg every month started 1 month	29
Hoefert et al.	55/NA	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Mandible	IV ibandronate 6 mg every month	29
Galitis et al.	64/M	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Mandible	Denture use	30
Balmor et al.	63/M	Metastatic renal cell carcinoma	Sunitinib	Maxilla, Palate	IV pamidronate, Tooth extraction	31
Fleissig et al.	58/F	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Right mandible	Tooth extraction	32
Agrillo et al	62/M	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off+ temsirolimus	Left mandible	IV zoledronate 4 mg every month	33
Agrillo et al	65/M	Metastatic renal cell carcinoma	Sunitinib 50 mg 4 weeks on and 2 weeks off	Right mandible	IV zoledronate	33

Table 6: Studies on incidence of ONJ with Sunitinib

STUDY	ONJ OCCURENCE	REF.
Sunitinib related ONJ in patients with metastatic renal carcinoma	Incidence of ONJ among patients treated with sunitinib was 29%. The excessively high incidence of ONJ noted in this study (29%) could only be ascribed to the co-administration of zoledronate to all sunitinib treated patients.	34
Sunitinib related ONJ in patients with renal cell carcinoma or gastrointestinal stromal tumor (GIST)	No cases of ONJ among reported in sunitinib recipients.	26

ONJ WITH OTHER TYROSINE KINASE INHIBITORS (TKIS)

Other TKIs available for use in clinical practice which are similar to sunitinib from a mechanistic stand point include: axitinib, pazopanib and cabozantinib. Besides VEGFR receptor inhibition, these drugs block the biological activities of other receptor tyrosine kinases. To our knowledge, case reports describing ONJ with the use of sorafenib, axitinib and pazopanib are currently lacking.

CABOZANTINIB AND ONJ

Marino R et al reported a case report of a 51 year old woman who received cabozantinib for medullary thyroid cancer. She underwent a tooth extraction, two months after which, bone necrosis was seen. The clinical, radiographic and histologic picture of a chronic nonhealing extraction socket was consistent with drug-induced osteonecrosis of the jaw.[35]

Elisei R et al conducted a double-blind, phase III trial comparing cabozantinib with placebo in 330 patients with metastatic Medullary Thyroid cancer. Patients were

randomly assigned (2:1) to cabozantinib (140 mg per day) or placebo. Onj was noticed in 3 of the 219 (1.4%) patients who were receiving cabozantinib with1 patient having a grade-3 ONJ.[36]

INCIDENCE OF ONJ WITH MAMMALIAN TARGET OF RAPAMYCIN (MTOR) INHIBITORS

Rapamycin and related mTOR inhibitors prevent endothelial cell VEGF expression, as well as VEGF induce endothelial cell proliferation.[37] Inhibitors of mTOR are an important class of anti-angiogenic agents. These include: deforolimus, everolimus, rapamycin (sirolimus), and temsirolimus.[38,39] Because mTOR signaling is controlled by the VEGF pathway, it is also reasonable to expect some reported cases of ONJ with the use of these agents.

Two case reports of occurence of ONJ with everolimus have been documented.

F. Giancola et al reported a case report of a 64-year-old male patient with clear-cell renal carcinoma. He was treated with zoledronic acid 4 mg IV every 4 weeks for 2 years. Later he developed recurrence and lung metastasis for which he was treated with everolimus 10 mg/die for 6 months. 6 months after the introduction of everolimus the patient presented with ONJ.[40]

In the other case report by Kim and colleagues, ONJ developed after treatment with everolimus. However the patient gave a history of treatment with IV zoledronate 6 years back.[41]

PREVENTION OF ONJ

Critical for ONJ prevention is early screening and implementation of appropriate dental measures before initiation of anti angiogenic agents, since most reported ONJ cases occurred after invasive dental procedures.[11] A multi-disciplinary approach should be taken for the treatment of patients who benefit from anti angiogenic agents. This approach should include councelling with an appropriate dental professional. Thorough clinical and radiographic assessment should be done. Patient should be motivated and educated regarding dental care. Dental prophylaxis, caries control and conservative restorative dentistry should be done.

Dentures should be examined for areas of mucosal trauma. Extraction of non-restorable teeth and those with a poor prognosis should be done prior to initiation of drug.[10,42,43] The antiangiogenic therapy should be delayed, if systemic conditions permit, until the extraction site has mucosalized (14-21 days) or until there is adequate osseous healing.

For patients who are already on anti angiogenic agents, dental extraction, placement of dental implants or any other invasive dental surgery should be avoided. However there is no data regarding the risk of ONJ associated with implant placement in patients receiving antiangiogenic medications.[10] The crown of a severly carious tooth must be removed and root canal treatment of the root must be done. Thorough history should be noted of the drugs that the patient is on especially bisphosphonates, corticosteroids since they may increase the risk of developing MRONJ.

CONCLUSION

Osteonecrosis of the jaw is a serious side effect that severely affects the quality of life of the patient. Since one of the side effects seen with antiangiogenic agents includes osteonecrosis of the jaw, care must be taken to prevent it. Further studies are needed to completely understand the reason for its occurence and management.

REFERENCES

1. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: a narrative literature review. Oral Oncol, 2011; 47: 441-448.
2. Rajeev S. Samant and Lalita A.Shevde. Recent Advances in Anti-Angiogenic Therapy of Cancer Oncotarget, 2011; 2: 122–134.
3. Alan Roger Santos-Silva, Giuliano Augusto Belizário Rosa, Gilberto de Castro Júnio. Osteonecrosis of the mandible associated with bevacizumab therapy. Oral Surg Oral Med Oral Pathol Oral Radiol, 2013; 115: e32-e36.
4. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med., 1971; 285: 1182–6.
5. Hwang C, Heath EI. Angiogenesis inhibitors in the treatment of prostate cancer. J Hematol Oncol, 2010; 3: 26.
6. FDA. Avastin (bevacizumab) Information. May 25th. 2011 http://wwwfdagov/Drugs/DrugSafety/ Postmarket Drug Safety Information for Patients and Providers/ucm193900htm
7. Samant RS and Shevde LA. Recent Advances in Anti-Angiogenic Therapy of Cancer Oncotarget, 2011; 2: 122-134.
8. Weiss L, Orr FW, Honn KV: Interactions between cancer cells and the microvasculature: A rate-regulator for metastasis. Clin Exp Metastasis, 1989; 7: 127-67.
9. Al-Husein B, Abdalla M, Trepte M. Anti-angiogenic therapy for cancer: An update. Pharmacotherapy, 2012; 32(12): 1095–1111.
10. Ruggiero SL , Dodson TB, Fantasia J et al.American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg, 2014; 72(10): 1938-56.
11. Hamadeh IS, Ngwa BA, Gong Y. Drug induced osteonecrosis of the jaw. Cancer Treatment Reviews, 2015; 41: 455–464.
12. Miller KD, Chap LI, Holmes FA, et al: Randomized phase III trial of capecitabine compared with bevacizumab and capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol, 2005; 23: 792-799.

13. Herbst RS, O'Neill VJ, Fehrenbacher L, et al: Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non–small-cell lung cancer. J Clin Oncol, 2007; 25: 4743-4750.
14. Estilo CL, Fornier M, Farooki A, Carlson D, Bohle 3rd G, Huryn JM. Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol, 2008; 26: 4037–8.
15. Greuter S, Schmid F, Ruhstaller T, Thuerlimann B. Bevacizumab-associated osteonecrosis of the jaw. Ann Oncol, 2008; 19: 2091–2.
16. Hopp RN, Pucci J, Santos-Silva AR, Jorge J. Osteonecrosis after administration of intravitreous bevacizumab. J Oral Maxillofac Surg, Mar, 2012; 70(3): 632-5.
17. Disel U, Besen AA, Ozyilkan O, Er E, Canpolat T. A case report of bevacizumab related osteonecrosis of the jaw: old problem, new culprit. Oral Oncol, 2012; 48: e2–3.
18. Katsenos S, Christophylakis C, Psathakis K. Osteonecrosis of the jaw in a patient with advanced non-small-cell lung cancer receiving bevacizumab. Arch Bronconeumol, 2012; 48: 218–9.
19. Magremanne M, Lahon M, De Ceulaer J, Reychler H. Unusual bevacizumab related complication of an oral infection. J Oral Maxillofac Surg, 2013; 71: 53–5.
20. Bettini G, Blandamura S, Saia G, Bedogni A. Bevacizumab-related osteonecrosis of the mandible is a self-limiting disease process. BMJ Case Reports, 2012; doi: 10.1136/bcr-2012-007284.
21. Sato M, Ono F, Yamamura A. Onochi S [A case of osteonecrosis of the jaw during treatment by bevacizumab for sigmoid colon cancer]. Nihon Shokakibyo Gakkai Zasshi, 2013; 110: 655–9.
22. Santos-Silva AR, Belizario Rosa GA, Castro Junior G, Dias RB, Prado Ribeiro AC, Brandao TB. Osteonecrosis of the mandible associated with bevacizumab therapy. Oral Surg Oral Med Oral Pathol Oral Radiol, 2013; 115: e32–36.
23. Christodoulou C, Pervena A, Klouvas G, Galani E et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology, 2009; 76(3): 209-11.
24. Guarneri V, Miles D, Robert N, Dieras V, Glaspy J, Smith I, et al. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat, 2010; 122: 181–8.
25. McArthur HL, Estilo C, Huryn J, Williams T, Fornier M, Traina TA, Howard J, Hudis CA, Dickler MN. Osteonecrosis of the jaw (ONJ) among intravenous (IV) bisphosphonate- and/or bevacizumab-treated patients (pts) at Memorial Sloan-Kettering Cancer Center (MSKCC) J Clin Oncol, 2008; 26:9588.
26. Goodman VL, Rock EP, Dagher R, Ramchandani RP et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res., Mar, 2007; 1; 13(5): 1367-73.
27. Brunello A, Saia G, Bedogni A, Scaglione D, Basso U. Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma. Bone, 2009; 44: 173–5.
28. Koch FP, Walter C, Hansen T, Jager E, Wagner W. Osteonecrosis of the jaw related to sunitinib. Oral Maxillofac Surg, 2011; 15: 63–6.
29. Hoefert S, Eufinger H. Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: presentation of three cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2010; 110: 463–9.
30. Nicolatou-Galitis O, Migkou M, Psyrri A, Bamias A, Pectasides D, Economopoulos T, et al. Gingival bleeding and jaw bone necrosis in patients with metastatic renal cell carcinoma receiving sunitinib: report of 2 cases with clinical implications. Oral Surg Oral Med Oral Pathol Oral Radiol, 2012; 113: 234–8.
31. Balmor GR, Yarom N, Weitzen R. Drug-induced palate osteonecrosis following nasal surgery. Isr Med Assoc J, 2012; 14: 193–4.
32. Fleissig Y, Regev E, Lehman H. Sunitinib related osteonecrosis of jaw: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol, 2012; 113: e1–3.
33. Agrillo A, Nastro Siniscalchi E, Facchini A, Filiaci F, Ungari C. Osteonecrosis of the jaws in patients assuming bisphosphonates and sunitinib: two case reports. Eur Rev Med Pharmacol Sci., 2012; 16: 952–7.
34. Smidt-Hansen T, Folkmar TB, Fode K, Agerbaek M, Donskov F. Combination of zoledronic acid and targeted therapy is active but may induce osteonecrosis of the jaw in patients with metastatic renal cell carcinoma. J Oral Maxillofac Surg, 2013; 71: 1532–40.
35. Marino R, Orlandi F, Arecco F, Gandolfo S, Pentenero M. Osteonecrosis of the jaw in a patient receiving cabozantinib. Aust Dent J, 2014.
36. Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, et al. Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol, 2013; 31: 3639–46.
37. Dormond O, Madsen JC, Briscoe DM: The effects of mtorakt interactions on anti-apoptotic signaling in vascular endothelial cells. J Biol Chem, 2007; 282: 23679-86.
38. Giles FJ, Albitar M: Mammalian target of rapamycin as a therapeutic target in leukemia. Curr Mol Med., 2005; 5: 653-61.
39. Martelli AM, Tazzari PL, Evangelisti C, Chiarini F, Blalock WL, Billi AM, Manzoli L, McCubrey JA, Cocco L: Targeting the phosphatidylinositol 3-kinase/ akt/mammalian target of rapamycin module for acute myelogenous leukemia therapy: From

bench to bedside. Curr Med Chem, 2007; 14: 2009-23.
40. Giancola F, Campisi G, Russo LL, Muzio LL, Di Fede O. Osteonecrosis of the jaw related to everolimus and bisphosphonate: a unique case report? Ann Stomatol (Roma), 2013; 4: 20–1.
41. Kim DW, Jung YS, Park HS, Jung HD. Osteonecrosis of the jaw related to everolimus: a case report. Br J Oral Maxillofac Surg, 2013; 51: e302–4.
42. Antiresorptives and Osteonecrosis of the Jaw. Yamashita J., McCauley L.K. J Evid Base Dent Pract, 2012; S1: 233-47.
43. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: Executive summary of recommendations from the American Dental Association Council on Scientific Affairs. Hellstein J.W., Adler R.A., Edwards B., Jacobsen P.L., Kalmar J.R., Koka S., Migliorati C.A., Ristic H. JADA, 2011; 142(11): 1243-51.