Hans Journal of Surgery 外科, 2014, 3, 1-5
http://dx.doi.org/10.12677/hjs.2014.31001 Published Online January 2014 (http://www.hanspub.org/journal/hjs.html)

Denosumab, a RANKL Inhibitor, Induced Osteonecrosis of the Jaw*

Longwei Hu[1], Liqun Xu[2#]

[1]College of Stomatology, School of Medicine, Shanghai Jiao Tong University, Shanghai
[2]Department of Oral and Maxillofacial Surgery, The Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
Email: handsomelong@163.com, #maxilla@sina.com

Received: Nov. 4th, 2013; revised: Nov. 7th, 2013; accepted: Nov. 8th, 2013

Abstract: The two main kinds of drugs that induced osteonecrosis of the jaw are bisphosphonates and anti-RANKL. Anti-RANKL is a fully human monoclonal antibody. It is effective to prevent skeletal-related complications in cancer patients with bone metastasis and to increase bone mineral density in patients with osteoporosis. This article summarizes the mechanism of action, clinical use, adverse effects of denosumab and its comparison with bisphosphonates as well as osteonecrosis of the jaw induced by it.

Keywords: Denosumab; Bisphosphonates; Osteonecrosis of the Jaw

RANKL 抑制剂地诺塞麦所致颌骨坏死*

胡龙威[1]，徐立群[2#]

[1]上海交通大学医学院，口腔医学院，上海
[2]上海交通大学医学院附属第九人民医院口腔颌面外科，上海
Email: handsomelong@163.com, #maxilla@sina.com

收稿日期：2013 年 11 月 4 日；修回日期：2013 年 11 月 7 日；录用日期：2013 年 11 月 8 日

摘　要：引起药物性颌骨坏死的主要两大类药物包括双磷酸盐及 RANKL 抑制剂。RANKL 抑制剂地诺塞麦是一种完全人化单克隆抗体，临床上主要用于预防实体肿瘤发生骨转移患者骨相关事件的发生以及用于增加骨质疏松患者的骨密度。本文就地诺塞麦的作用机制、临床应用、副作用，与双磷酸盐比较及所致的颌骨坏死做一综述。

关键词：地诺塞麦；双磷酸盐；颌骨坏死

1. 引言

颌骨坏死临床上较为常见，是颌骨发生的一种严重病变。与用于治疗骨转移性疾病及骨质疏松的药物密切相关。双磷酸盐已广泛用于治疗影响骨改建的相关疾病，如前列腺癌，乳腺癌，多发性骨髓瘤等[1,2]。目前发现临床上大剂量应用尤其是静脉注射双磷酸盐类药物可致颌骨坏死，可能是由于双磷酸盐类药物能抑制骨更新及血管形成等原因[3-5]，但其确切病理机制仍未明确。RANKL 抑制剂地诺塞麦是一类与双磷酸盐具有相似作用的药物，自 K.H.等[6]2009 年首次报道其治疗过程中可导致颌骨坏死，随后相关病例报道

*项目基金：上海市科委(编号：12441901802)。
#通讯作者。

相继增多，地诺塞麦这一副作用逐渐受到关注。本文就 RANKL 抑制剂地诺塞麦的作用机制，临床应用，副作用，与双磷酸盐比较及所致的颌骨坏死做一综述。

2. RANKL 抑制剂地诺塞麦

2.1. RANKL 抑制剂地诺塞麦作用机制

RANK 是一类与 TNF 受体相似的受体，该受体在破骨细胞发育过程中存在表达，其配体与 TNF 相似，称为 RANKL[7]。RANKL 产自肿瘤细胞和成骨细胞，能与 RANK 高度特异性结合，诱导破骨细胞分化，促进其活化，最终导致骨溶解。而后释放一些骨源性生长因子，包括胰岛素样生长因子(insulin-like growth factor, IGF)，β 转化生长因子(transforming growth factor-β, TGF-β)。这些生长因子能与肿瘤表面相应受体结合，然后激活胞质内的 TGF-β 介质和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)。这一信号转导通路能促使癌细胞增殖以及甲状旁腺激素相关蛋白的产生，最终钙离子重吸收，而发生高钙血症[8,9]。

RANKL 抑制剂地诺塞麦是完全人化单克隆抗体，通过与 RANKL 结合从而阻断 RANKL 与 RANK 的作用，使破骨细胞活化受抑制，促使破骨细胞凋亡，维持骨吸收与形成间的平衡，抑制癌细胞增殖。

2.2. RANKL 抑制剂地诺塞麦临床应用

2010 年 10 月，美国 FDA 批准地诺塞麦用于预防实体肿瘤发生骨转移患者骨相关事件(病理性骨折，压迫脊髓，骨接受放疗或手术治疗)的发生。2011 年 9 月，美国 FDA 批准地诺塞麦用于增加高风险骨折患者骨量，包括用于非转移性前列腺癌去势治疗的患者。对于预防骨相关事件发生，地诺塞麦(Xgeva®; Amgen, Thousand Oaks, CA)于上臂,大腿或腹部皮下每次注射 120 mg，每四周一次。而当地诺塞麦(Prolia®; Amgen)用于增加骨量时[10]，则皮下每次注射 60 mg，每六个月一次[11]。

健康自愿者(n = 73)单次皮下注射 60 mg 地诺塞麦，第十天(从 3~21 天)达到最大血清浓度，平均值为 6.75 mg/mL[12]。该药能很快被机体吸收，单次皮下注射 1.0 mg/kg 至 3.0 mg/kg，一小时后能测出的血清浓度分别大于 1 μg/mL 和 5 μg/mL。这一浓度水平一直维持 84 天[13]。

2.3. RANKL 抑制剂地诺塞麦副作用

地诺塞麦在临床应用过程中使患者受益颇多，但其相关的副作用值得引起关注。其所致的低钙血症较为常见，有文献报道皮下注射地诺塞麦约有 13%患者出现低钙血症，血钙水平降低常发生在首次治疗后前六个月内[14]。因此在接受治疗前应补足血钙，并且治疗过程中应严密随访，尤其是在治疗开始后前几个月内。骨质疏松指南提出超过 50 岁患者在接受地诺塞麦治疗时每日应补充 1200~1500 mg 钙以及每日 800~1000 国际单位维生素 D[15]。

地诺塞麦导致另一严重的并发症为颌骨坏死。对 1432 名去势非转移前列腺癌患者第三期临床试验中，地诺塞麦组颌骨坏死的发生率为 5%，而安慰剂对照组为零[16]。发生颌骨坏死的患者中大部分口腔卫生条件较差，有近期拔牙史。因此，在接受地诺塞麦治疗前，应对口腔进行彻底检查。如治疗过程中出现颌骨坏死的前期症状，患者应进行严密随访。

其它一些不常见但较严重的并发症包括感染，继发恶性肿瘤等。由于 RANKL 在 T 细胞及 B 细胞上均有表达，因此就地诺塞麦是否会导致严重感染及是否会促进肿瘤的发生及发展目前存在争议。相关研究发现，在试验组中，有一小部分接受地诺塞麦治疗的患者出现呼吸道感染及蜂窝织炎等感染症状[17]。

2.4. 地诺塞麦与双磷酸盐比较

致颌骨坏死两大类药物目前主要为 RANKL 抑制剂与双磷酸盐，RANKL 抑制剂地诺塞麦在应用过程中有许多双磷酸盐类药物不可比拟的优势。

双磷酸盐类药物需经过肾脏代谢，静脉注射双磷酸盐药物如唑来膦酸可导致肾功能不全。有研究表明，其所致肾毒性与用药剂量呈明显相关性，接受唑来膦酸治疗组与安慰剂组对照显示，唑来膦酸组肾功能不全发生率为 11%~12.2%，而安慰剂组为 7%~10.3%[18,19]。地诺塞麦一般经皮下注射，其半衰期约为 26 天。与其它单克隆抗体类似，其主要依靠内皮网状系统清除，而不经过肾脏[20]。因此地诺塞麦一般不引起肾功能不全，这一结果提示对于慢性肾炎患者，应用地诺塞麦较唑来膦酸更为安全。

静脉注射双磷酸盐类药物常见的副作用为急性期反应，表现为短暂发热，寒颤，肌痛以及关节痛[21]。在一项临床对照试验中，唑来膦酸用来治疗绝经后妇女所致骨质疏松，31.6%的患者在静脉注射唑来膦酸后 3 天或更短时间内出现短暂发热，肌痛，流感样症状，头疼或关节痛，而安慰剂对照组为 6.2%[22]。而皮下注射地诺塞麦所致的急性期反应较为罕见，有临床试验比较骨转移患者地诺塞麦治疗组与唑来膦酸治疗组急性期反应发生率，结果表明，地诺塞麦组急性期反应发生率明显较唑来膦酸组低[23]。另有研究指出，骨质疏松患者接受地诺塞麦治疗，其所致急性期反应与安慰剂组没有明显差别[24,25]。

骨转移的晚期癌症患者易发生骨相关事件(skeletal-related events, SRE)，地诺塞麦在减少 SRE 发生及延缓 SRE 首次发生时间上比双磷酸盐更具有优势。相关研究报道，乳腺癌患者接受地诺塞麦治疗组未发生骨相关事件，而接受唑来膦酸组发生骨相关事件的平均时间为 26.4 个月[26]。前列腺癌患者接受地诺塞麦治疗组发生骨相关事件的平均时间为 20.7 个月，而唑来膦酸组为 17.1 个月[27]。

双磷酸盐致颌骨坏死发生在静脉用药后平均 33 个月，口服用药后平均 48 个月[28,29]。然而在目前所有报道的病例当中 RANKL 抑制剂地诺塞麦所致的颌骨坏死发生在用药后早期阶段。由于双磷酸盐能与骨共价结合并在停药数年后仍影响骨转换指标[30]，当撤除用药后，颌骨坏死症状不能马上缓解，影像学检查显示，拔牙创在数月甚至是数年内骨改建都不能完成[31]。而停用地诺塞麦几个月后骨转换指标能趋于正常，因此有假说认为随着 RANKL 抑制剂用量减少，颌骨发生坏死的几率也逐渐下降，但目前仍缺乏证据支持这一假说。影像学表明，在停用地诺塞麦后拔牙创内骨改建随之发生[32]。

3. RANKL 抑制剂所致颌骨坏死

目前研究表明导致颌骨坏死病因包括：颅面部放疗，化疗，颌骨创伤，感染，局部恶变，自发性颌骨坏死以及一些药物治疗(双磷酸盐，RANKL 抑制剂，长效糖皮质激素)等。颌骨坏死与骨重建受抑制有关，尤其是抑制破骨细胞活动导致创伤骨聚集，因此颌骨坏死可发生于所有针对抑制破骨细胞治疗中。RANKL 抑制剂地诺塞麦能强烈抑制破骨细胞活动，减少骨的吸收。目前报道指出地诺塞麦治疗过程中能导致颌骨坏死，且其所致颌骨坏死总发生率与双磷酸盐无明显差异，但由于地诺塞麦作用的药理学机制与双磷酸盐不同，故其相关颌骨坏死较双磷酸盐致颌骨坏死能更快恢复。

3.1. 颌骨坏死的诊断与分期

目前国内外尚未对 RANKL 抑制剂所致颌骨坏死提出确切诊断依据以及临床分期，现已报道相关文献主要参照双磷酸盐致颌骨坏死的诊断和分类标准。美国口腔颌面外科协会(American Association of Oral and Maxillofacial Surgeons, AAOMS) 2009 年对双磷酸盐所致的颌骨坏死的定义为：颌面部出现死骨暴露时间持续 8 周以上，有双膦酸盐类药物治疗史，颅面部未接受过放射治疗。若死骨暴露时间短于 8 周，其他条件都符合，仅能列为疑似病例[33,34]。双磷酸盐所致颌骨坏死临床分为四期：0 期：口服或静脉注射双磷酸盐治疗的患者，出现非特异性临床表现和症状，如下颌疼痛或骨硬化，但无骨外露的临床证据；Ⅰ期：有暴露/坏死骨，病人无症状，无感染表现；Ⅱ期：暴露/坏死骨与感染有关，如骨外露区域疼痛和红斑，伴或不伴口内瘘管形成；Ⅲ期：暴露/坏死骨疼痛，感染，并至少有 1 种下述表现，如病理性骨折、口腔外的瘘管，或骨质溶解破坏延伸至下颌骨下缘或上颌窦[34-37]。

颌骨坏死临床表现为上下颌骨死骨暴露至少持续 8 周，同时可伴有疼痛、感觉异常，黏膜肿胀、瘘管、红斑、溃疡，牙齿松动等。牙槽创伤是导致颌骨坏死最普遍的危险因素[38,39]，伴有牙科炎性疾病(如牙周炎、牙脓肿)的患者在一定程度上又增加了颌骨坏死的风险性。

3.2. 颌骨坏死的治疗

关于 RANKL 抑制剂所致颌骨坏死的治疗目前尚无明确有效的方法，一般较保守的治疗包括广谱抗生素的运用，局部抗菌漱口液冲洗[6,40]，然而有报道提出这些治疗方法对于 60%的患者都是无效的[6,41]。较公认的还是分期对症治疗。0 期可不予治疗，或保守处理口腔各种局部刺激因素如龋坏、牙周病等；Ⅰ期应定期应用抗菌漱口剂并定期临床随访；Ⅱ期应用抗

菌漱口剂，同时联合全身应用广谱抗生素，控制疼痛，可进行表浅组织清创以减轻软组织刺激；III期应在II期的基础上进行外科手术干预(如清创术、部分或完全颌骨切除)，以减轻感染和疼痛[42,43]。

虽为分期治疗，但是无论在哪一期发现活动性死骨均应去除，并避免暴露未受累的骨；拔除暴露死骨内有症状的牙齿，不会加重已发生的骨坏死。由于高压氧可以增加颌骨坏死区域的伤口愈合，减少水肿和炎症，激活干细胞，同时可以缓和被抑制的骨更新[44]，因此高压氧也被用于治疗颌骨坏死。研究指出，早期激光辅助治疗颌骨坏死同样有较好的效果[45]。对于外科手术治疗颌骨坏死，其缺点是坏死骨边缘往往不能明确，因此要完全清除坏死骨较难。Sven Otto 等报道指出处理 RANKL 抑制剂所致颌骨坏死的患者，采用荧光介导下的骨切除技术在术中能明确坏死骨的边界。同时严密关闭创缘以及配合抗生素的使用能有效处理地诺塞麦所致的颌骨坏死[32]。并提出在对口内进行任何外科手术之前，最好停用 RANKL 抑制剂。

4. 小结

RANKL 抑制剂地诺塞麦因其在治疗骨转移性疾病以及抗骨吸收方面表现出较双磷酸盐更为有效的优势，将为患者带来更多的益处与方便，将来会有更广阔的应用前景。然而地诺塞麦在使用过程中导致的一些副作用，尤其是颌骨坏死这一严重副作用，是多因素共同作用的结果，它不仅严重影响患者的生活质量且对相关疾病的治疗也影响很大，而且目前很多临床医生对这一副作用并不了解。如何有效的使用地诺塞麦以及预防颌骨坏死的发生依然是临床和科学工作者的一大难题。同时，此病的发病机制，以及如何做到早期诊断，预防以及有效治疗等，也需要进一步研究。

参考文献 (References)

[1] Vescovi, P., Merigo, E., Meleti, M., et al. (2012) Bisphosphonatesrelated osteonecrosis of the jaws: A concise review of the literature and a report of a single-centre experience with 151 patients. *Journal of Oral Pathology & Medicine*, **41**, 214-221.

[2] Rustemeyer, J. and Bremerich, A. (2010) Bisphosphonate-associated osteonecrosis of the jaw: What do we currently know? A survey of knowledge given in the recent literature. *Clinical Oral Investigations*, **14**, 59-64.

[3] Allen, M.R. and Burr, D.B. (2009) The pathogenesis of bisphosphonaterelated osteonecrosis of the jaw: So many hypotheses, so few data. *Journal of Oral and Maxillofacial Surgery*, **67**, 61-70.

[4] Wehrhan, F., et al. (2010) Expression of Msx-1 is suppressed in bisphosphonate associated osteonecrosis related jaw tissue-etiopathology considerations respecting jaw developmental biology-related unique features. *Journal of Translational Medicine*, **8**, 96.

[5] Hoefert, S., Schmitz, I., Tannapfel, A. and Eufinger, H. (2010) Importance of microcracks in etiology of bisphosphonate-related osteonecrosis of the jaw: A possible pathogenetic model of symptom-matic and nonsymptomatic osteonecrosis of the jaw based on scanning electron microscopy findings. *Clinical Oral Investigations*, **14**, 271-284.

[6] Taylor, K.H., Middlefell, L.S., Mizen, K.D., *et al.* (2010) Osteonecrosis of the jaws induced by anti-RANK ligand therapy. *British Journal of Oral and Maxillofacial Surgery*, **48**, 221-223.

[7] Dougall, W.C. (2011) Molecular pathways: Osteoclast-dependent and osteoclast-independent roles of the RANKL/RANK/OPG pathway in tumorigenesis and metastasis. *Clinical Cancer Research*, **18**, 326-335.

[8] Lumachi, F., Brunello, A., Roma, A. and Basso, U. (2009) Cancer-induced hypercalcemia. *Anticancer Research*, **29**, 1551-1555.

[9] Sivolella, S., Lumachi, F. and Stellini, E. (2013) Denosumab and anti-angiogenetic drug-related osteonecrosis of the jaw: An uncommon but potentially severe disease. *Anticancer Research*, **33**, 1793-1798.

[10] Cummings, S.R., San, M.J., McClung, M.R., et al. (2009) for FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *The New England Journal of Medicine*, **361**, 756-765.

[11] Adler, R.A. and Gill, R.S. (2011) Clinical utility of denosumab for treatment of bone loss in men and women. *Clinical Interventions in Aging*, **6**, 119-124.

[12] Amgen Incorporated, “Prolia™ (Denosumab) injection, for subcutaneous use: US prescribing information,” TAmgen Inc., housand Oaks, 2010. http://pi.amgen.com/united_states/prolia/prolia_pi.pdf

[13] Body, J.J., Facon, T., Coleman, R.E., et al. (2006) A study of the biological recep-tor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. *Clinical Cancer Research*, **12**, 1221-1228.

[14] Smith, M.R., Kabbinavar, F., Saad, F., et al. (2005) Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *Journal of Clinical Oncology*, **23**, 2918-2925.

[15] National Osteoperosis Foundation (2010) Clinician’s guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington DC.

[16] Smith, M.R., Saad, F., Coleman, R., et al. (2012) Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: Results of a phase 3, randomised, placebo-controlled trial. *Lancet*, **379**, 39-46.

[17] Rothstein, A. (2009) Denosumab safety: Division of reproductive and uro-logic products, center of drug evaluation and research at the food and drug administration. http://courses.washington.edu/bonephys/denosumab/Rothstein%20FDA%20deno%20safety.pdf

[18] Ibrahim, A., Scher, N., Williams, G., et al. (2003) Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clinical Cancer Research*, **9**, 2394-2399.

[19] Chang, J.T., Green, L. and Beitz, J. (2003) Renal failure with the use of zoledronic acid. *The New England Journal of Medicine*, **349**, 1676-1679; Discussion 1676-1679.

[20] Baron, R., Ferrari, S. and Russell, R.G. (2011) Denosumab and bisphosphonates: Different mechanisms of action and effects. *Bone*, **48**, 677-692.

[21] Pazianas, M., Cooper, C., Ebetino, F.H. and Russell, R.G. (2010)

Long-term treatment with bisphosphonates and their safety in postmenopausal osteoporosis. *Therapeutics and Clinical Risk Management*, **6**, 325-343.

[22] Black, D.M., Delmas, P.D., Eastell, R., et al. (2007) Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *The New England Journal of Medicine*, **356**, 1809-1822.

[23] Henry, D.H., Costa, L., Goldwasser, F., et al. (2011) Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *Journal of Clinical Oncology*, **29**, 1125-1132.

[24] Ellis, G.K., Bone, H.G., Chlebowski, R., et al. (2008) Randomized trial of deno-sumab in patients receiving adjuvant aromatase inhibitors for nonmeta-static breast cancer. *Journal of Clinical Oncology*, **26**, 4875-4882.

[25] Smith, M.R., Egerdie, B., Hernandez, T.N., et al. (2009) Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *The New England Journal of Medicine*, **361**, 745-755.

[26] Stopeck, A.T., Lipton, A., Body, J.J., et al. (2010) Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *Journal of Clinical Oncology*, **28**, 5132-5139.

[27] Fizazi, K., Carducci, M., Smith, M., et al. (2011) Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant pros-tate cancer: A randomised, double-blind study. *Lancet*, **377**, 813-822.

[28] Otto, S., Abu-Id, M.H., Fedele, S., Warnke, P.H., Becker, S.T., Kolk, A., et al. (2011) Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: Not just a sporadic coincidence e a multi-centre study. *Journal of Cranio-Maxillofacial Surgery*, **39**, 272-277.

[29] Otto, S., Schreyer, C., Hafner, S., Mast, G., Ehrenfeld, M., Sturzenbaum, S., et al. (2012) Bisphosphonate-related osteonecrosis of the jaws e characteristics, risk factors, clinical features, localization and impact on oncological treatment. *Journal of Cranio-Maxillofacial Surgery*, **40**, 303-309.

[30] Russell, R.G., Watts, N.B., Ebetino, F.H. and Rogers, M.J. (2008) Mechanisms of action of bisphosphonates: Similarities and differences and their potential influence on clinical efficacy. *Osteoporosis International*, **19**, 733-759.

[31] Groetz, K.A. and Al-Nawas, B. (2006) Persisting alveolar sockets: A radiologic symptom of BPONJ? *Journal of Oral and Maxillofacial Surgery*, **64**, 1571-1572.

[32] Otto, S., et al. (2013) Successful surgical management of osteonecrosis of the jaw due to RANK-ligand inhibitor treatment using fluorescence guided bone resection. *Journal of Cranio-Maxillo-Facial Surgery*, **41**, 694-698.

[33] Bonacina, R., Mariani, U., Villa, F., et al. (2011) Preventive strategies and clinical implications for bisphosphonaterelated osteonecrosis of the jaw: A review of 282 patients. *Journal of the Canadian Dental Association*, **77**, b147.

[34] Ruggiero, S.L., Dodson, T.B., Assael, L.A., Landesberg, R., Marx, R.E., Mehrotra, B. and American Association of Oral and Maxillofacial Surgeons (2009) American Association of Oral and Maxillofacial Surgeonsposition paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. *Journal of Oral and Maxillofacial Surgery*, **67**, 2-12.

[35] Shenker, N.G. and Jawad, A.S. (2007) Bisphosphonates and osteonecrosis of the jaw. *Rheumatology* (*Oxford*), **46**, 1049-1051.

[36] Dunford, J.E., Thompson, K., Coxon, F.P., et al. (2001) Structu-reactivity relationships for inhibition of farnesyl diphosphate synthase *in vitro* and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *Journal of Pharmacology and Experimental Therapeutics*, **296**, 235-242.

[37] Suleman, Y.F., Meer, S., Lurie, R., et al. (2007) Bisphosphonateinduced osteonecrosis of the jaws: Review, clinical implications and case report. *Head and Neck Pathology*, **1**, 156-164.

[38] Herbozo, P.J., Briones, D.L., Ferres, A.J., et al. (2007) Severe spontaneous cases of bisphosphonate-related osteonecrosis of the jaws. *Journal of Oral and Maxillofacial Surgery*, 2007, **65**, 1650-1654.

[39] Han, J.W. (2011) Bisphosphonate related osteonecrosis of the jaws: Report of two cases. *Imaging Science in Dentistry*, **41**, 129-134.

[40] Aghaloo, T.L., Felsenfeld, A.L. and Tetradis, S. (2010) Osteonecrosis of the jaw in a patient on denosumab. *Journal of Oral and Maxillofacial Surgery*, **68**, 959-963.

[41] Saad, F., Brown, J.E., Van Poznak, C., Ibrahim, T., Stemmer, S.M., Stopeck, A.T., et al. (2012) Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Annals of Oncology*, **23**, 1341-1347.

[42] Ficarra, G. and Beninati, F. (2007) Bisphosphonate-related osteonecrosis of the jaws: An update on clinical, pathological and management aspects. *Head and Neck Pathology*, **1**, 132-140.

[43] Kademani, D., Koka, S., Lacy, M.Q., et al. (2006) Primary surgical therapy for osteonecrosis of the jaw secondary to bisphosphonate therapy. *Mayo Clinic Proceedings*, **81**, 1100-1103.

[44] Freiberger, J.J. (2009) Utility of hype rbaric oxygen in treatment of bisphosphonate-related osteonecrosis of the jaws. *Journal of Oral and Maxillofacial Surgery*, **67**, 96-106.

[45] Romeo, U., Galanakis, A., Marias, C., et al. (2011) Observation of pain control in patients with bisphosphonate-induced osteonecrosis using low level laser therapy: Preliminary results. *Photomedicine and Laser Surgery*, **29**, 447-452.