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Review

Risk-reductive dental strategies for medication related osteonecrosis of the jaw among cancer patients: A systematic review with meta-analyses

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ABSTRACT

The purpose of this systematic review with meta-analysis was to assess the effectiveness of dental interventions in preventing or reducing the incidence of medication-related osteonecrosis of the jaw (MRONJ) in cancer patients receiving antiresorptive therapy, compared to similar control groups receiving no intervention. Randomized controlled trials (RCT), case-controls and cohorts on cancer patients with primary outcome being the prevalence of MRONJ were included. Four electronic databases were searched (Cochrane Library, PubMed, EMBASE and Web of Science) up to February 12, 2018. A total of 409 abstracts were assessed and one case-control, one RCT and four cohort studies with 2332 cancer patients met our inclusion criteria. Risk of bias analysis followed Cochrane's handbook. Risk of bias was unclear for the case-control study and high risk for the RCT and all cohort studies. Five studies utilized preventive measures consisting of an initial examination and performing all necessary dental treatment before patients initiated antiresorptive therapy; one study used specialized post-extraction protocols utilizing plasma-rich in growth factors (PRGF) on cancer patients receiving antiresorptive therapy. Though dental preventive measures decreased MRONJ incidence by 77.3% in six studies with 2332 cancer patients (95% CI = 47.4–90.2%; p = .001) compared to control groups, quality of the evidence was low due to high or unclear risk of bias and the observational nature of five of the included studies. In conclusion, high-quality long-term prospective large sample size studies are needed to confirm these results due to high risk of bias and heterogeneous interventions. No funding.

Introduction

Osteonecrosis of the jaw (ONJ) is described as an intraoral complication and defined as an unexpected development of necrotic bone in the oral cavity [1] which is commonly associated with administration of bisphosphonates (BPs) (i.e. pamidronate and zoledronate), and other antiresorptive medications such as receptor activator of nuclear factor Kappa-B ligand (RANKL) inhibitors and angiogenesis inhibitors [2]. Cases of non-healing exposed bone in the maxillofacial area in patients treated with intravenous (IV) BPs were first described in 2003 [3,4]. Oral BPs are associated with this complication but at a much lower incidence range (0.001–4%) when compared to IV BPs (4.1–18.6%) [5]. Tooth extraction is considered the intervention responsible for most cases of medication-related osteonecrosis of the jaw (MRONJ) with some authors reporting that it is seen in up to 69% of cases [6] while others reporting as high as 86% [7]. As the number of reported cases increased, in 2007 the American Association of Oral and Maxillofacial Surgeons (AAOMS) released their position paper on bisphosphonate-related osteonecrosis of the jaw (BRONJ) in which the AAOMS adopted a working definition for BRONJ and proposed staging categories with corresponding treatment strategies [8]. In 2009, the AAOMS revised their position paper with revisions to diagnosis (exposed necrotic bone was revised to exposed bone) and staging (a patient with BRONJ stage 0 with its corresponding treatment strategy was added) [9]. Most recently, case reports of ONJ have been reported in patients being treated with other types of antiresorptive medications such as denosumab (Prolia and Xgeva) and with antiangiogenic agents [10,11]. In 2014, the AAOMS released another update to their previous position paper in

Abbreviations: MRONJ, medication-related osteonecrosis of the jaw; ONJ, osteonecrosis of the jaw; RCT, randomized controlled trial; BPs, bisphosphonates; RANKL inhibitors, receptor activator of nuclear factor Kappa-B ligand inhibitor; IV, intravenous; AAOMS, American association of oral and maxillofacial surgeons; BRONJ, bisphosphonate-related osteonecrosis of the jaw; PRGF, plasma-rich in growth factors; RR, risk ratio; CI, confidence interval; SRE, skeletal related events; EDTA, ethylenediaminetetraacetic acid; CAR, chimeric antigen receptor

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which it was recommended that the term BRONJ be changed to MRONJ. Although the pathophysiology of MRONJ has not been fully explained, several hypotheses have been proposed: altered bone remodeling or over suppression of bone resorption, angiogenesis inhibition, constant microtrauma, suppression of innate or acquired immunity, vitamin D deficiency, soft tissue toxicity by BPs, and inflammation or infection [12]. Also, several studies have described IV route of administration and dento-alveolar procedures as the main risk factors for the development of MRONJ [13].

Preventive interventions to reduce the incidence of MRONJ are: Comprehensive oral examination with appropriate radiographs/photographs; Oral hygiene instructions; Maintenance of good oral health (education, frequent recalls, prophylaxis cleanings, periodontal maintenance); Completion of necessary dental treatment before commencing antiresorptive therapy; Use of antimicrobial mouth rinses; Use of antibiotics before and after extraction; Use of plasma-rich in growth factors (PRGF) during extraction of teeth on patients already subjected to antiresorptive therapy.

This systematic review is focused on studies comparing patients receiving dental preventive measures to a control group including studies published up to February 2018. A recent systematic review on the prevention of MRONJ found no consensus on all the recommendations of the evaluated clinical practice guidelines [14]. The objective of this systematic review with meta-analysis was to determine the efficacy of preventive dental measures in the prevention of osteonecrosis of the jaw in patients with cancer receiving anti-resorptive therapy.

Materials and methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses PRISMA checklist [15].

Criteria for considering studies for this review. Types of studies

Controlled clinical trials of patients undergoing treatment with BPs and/or other antiresorptive medications with reported outcomes of incidence and/or prevalence of MRONJ in patients with and without preventive dental measures were included. Case-control studies, RCTs and cohort studies were also included.

Search methods for identification of studies

Four electronic databases were searched on 3/15/2017 using the strategies presented in eTable 1. Search was updated on 2/12/2018 with no relevant clinical trials found, however three systematic reviews were found [14,16,17] which have been included in the discussion.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.oraloncology.2018.08.003.

Data collection and risk of bias analysis

Three author reviewers (H.K., J.G. and H.S.R.) individually assessed abstracts resultant of the search strategy to determine eligibility and

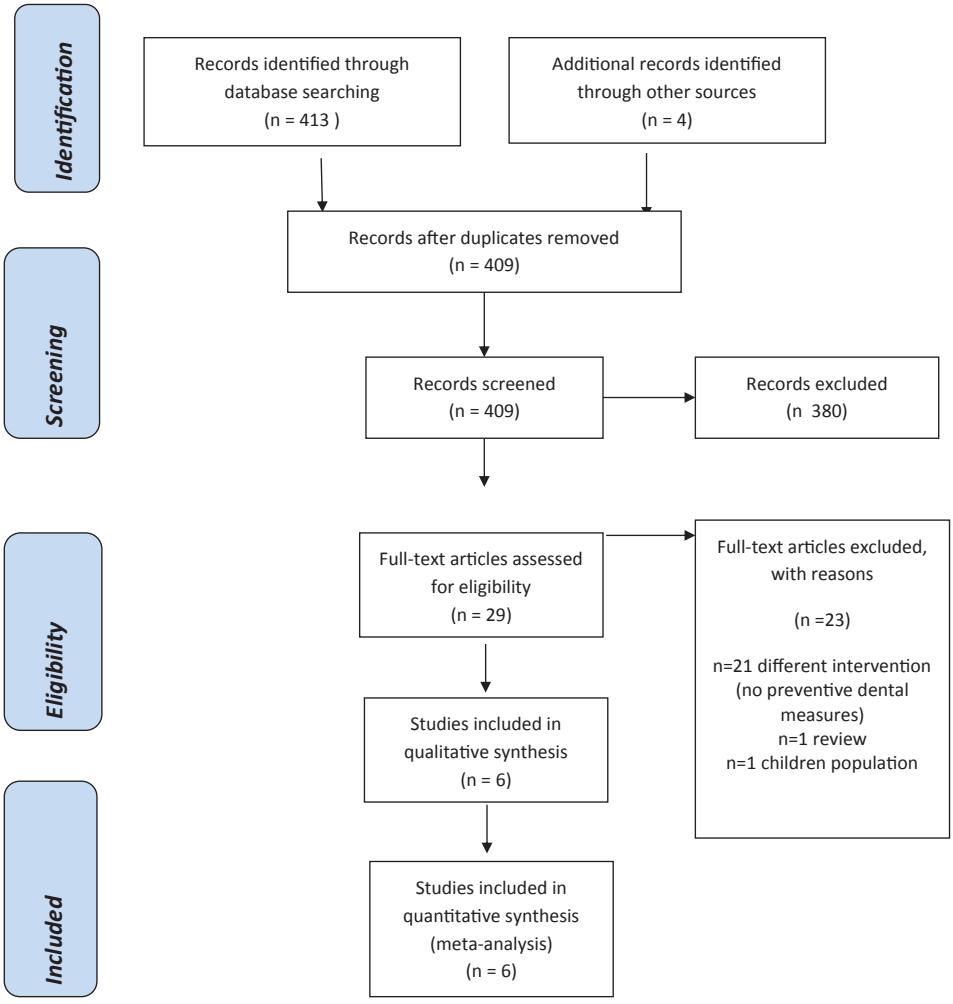

Fig. 1. PRISMA flow diagram [15].