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Research Article

Efficacy and tolerability of medical ozone gas insufflations in patients with osteonecrosis of the jaw treated with bisphosphonates—Preliminary data ☆
Medical ozone gas insufflation in treating ONJ lesions

C.I. Ripamonti [a,*], M. Maniezzo [b], S. Boldini [a], M.A. Pessi [a], L. Mariani [c], E. Cislaghi [b]

[a] Supportive Care in Cancer Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Italy
[b] Dental Team, Fondazione IRCCS, Istituto Nazionale dei Tumori, Italy
[c] Medical Statistic and Biometry Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Italy

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ABSTRACT

Osteonecrosis of the Jaw (ONJ) is an adverse event reported especially in patients receiving cancer treatments regimen, bisphosphonates (BPs), and denosumab. We performed an open-label, prospective study in patients treated with zoledronic acid who developed ONJ lesions >2.5 cm, and had no benefit after the treatment with the standard therapy, to evaluate the efficacy and tolerability of medical ozone (O_3) treatment delivered as gas insufflations on each ONJ lesions.

Twenty-four patients (mean age 62.5, range 41–80; 12 female) with bone metastases due to breast (11), prostate (4)and lung (4)cancers, myeloma (2), or osteoporosis (3), previously treated with zoledronic acid and not underwent dental preventive measures and with ONJ lesions >2.5 cm, were observed and treated with topical O_3 gas insufflation every third day for a minimum of 10 for each pathological area or till necrotic bone sequestrum or surgery. We used a special insufflation bell-shaped device adjusted to the specific characteristics of the patient, capable of eliminating any residue of O_3 diffusion by degrading it and releasing O_2 into the air. Azithromicin 500 mg/day was administered for 10 days in all patients before the first three gas insufflation although they had previously received various cycles of antibiotics. Ten patients required more than 10 O_3 gas insufflations due to multiple lesions and/or purulent sovrainfections; one patient received two further O_3 insufflations while waiting the day of surgery. Six of 24 patients interrupted the O_3 gas therapy for oncological disease progression (five patients) and for fear of an experimental therapy (one patient). Six patients had the sequestrum and complete or partial (one patient) spontaneous expulsion of the necrotic bone followed by oral mucosa re-epithelization after a range of 4–27 of O_3 gas insufflations. No patient reported adverse events. In 12 patients with the largest and deeper ONJ lesions, O_3 gas therapy produced the sequestrum of the necrotic bone after 10 to 38 insufflations; surgery was necessary to remove it (11 patients). Of interest, removal was possible without the resection of healthy mandible edge because of the presence of bone sequestrum.

All together the response rate was 75.0% (95% CI, 53.3–90.2%) in ITT analysis and 100% (95% CI, 81.5–100%) in the PP analysis.

In all patients treated with O_3 gas $\pm$ surgery, no ONJ relapse appeared (follow-up mean 18 months, range 1–3 years). Medical O_3 gas insufflations is an effective and safe treatment for patients treated with BPs who developed ONJ lesions >2.5 cm.

Short abstract: ONJ is an adverse event reported in patients receiving cancer treatments regimen, bisphosphonates and denosumab. We performed an open-label, prospective study in 24 patients with solid tumours, myeloma or osteoporosis due to hormonal therapy, treated with zoledronic acid without previuos preventive dental screening, who developed ONJ lesions >2.5 cm, and had no benefit after standard therapy, to evaluate the efficacy and tolerability of medical ozone (O_3) treatment delivered as gas insufflations on each ONJ lesions.

The patients were treated with O_3 every third day for a minimum of 10 for each pathological area or till necrotic bone sequestrum or surgery. Eleven patients required more than ten O_3 gas insufflations.

☆The procedures followed in this study were reviewed and approved by the Ethics Committee of National Cancer Institute of Milan and are in accordance with the ethical standards of the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996 and 2000) of the World Medical Association.

* Corresponding author. Tel.: +39 02 2390 3644/3383; fax: +39 02 23904847.
E-mail address: carla.ripamonti@istitutotumori.mi.it (C.I. Ripamonti).

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1. Introduction

Osteonecrosis of the jaw (ONJ) is an adverse event reported in patients receiving BPs and RANKL inhibitors such as denosumab [1–9].

ONJ is defined as the persistence of exposed bone in the oral cavity, despite an adequate treatment for six weeks, without local evidence of malignancy and no prior radiotherapy to the affected region [10]. However, ONJ may present with the non-exposed variant of ONJ.

The pooled risk estimated incidence of ONJ, in BPs users, is 2,4% [11–14]. In RCTs comparing zoledronic acid and denosumab in 5677 patients who underwent screening dental procedure, 89 ONJ cases were reported of which 52 in the denosumab group [8,11–13].

Factors adversely influencing bone remodelling are considered to be pivotal in the pathophysiology of the ONJ and preclinical data shows that the bone turnover is higher in the jaws with respect to other skeletal areas [10,15–17]. The presence of chronic periodontal pathologies, the duration and type of BP therapy, tooth extractions, the use of dental appliances, denture traumatisms, invasive dental surgery during the course of BP therapy, poor oral hygiene, concurrent disease (e.g. diabetes, peripheral vasculopathy) and the concomitant use of chemotherapy, antiretroviral therapies, thalidomide, and corticosteroids or the presence of anaemia are considered putative additional risk factors [1–5,18,19]. In a retrospective analysis of 567 cases Vescovi et al. [20] studied the differences between the non surgery-triggered vs surgery-triggered variants bisphosphonate-related osteonecrosis of the jaws. In 205 cases (36.2%) of ONJ no surgery was performed as against 362 cases (63.8%) of post-local invasive procedure forms including tooth extraction in 361 cases and implant placement in one case only.

Bisphosphonates are a well-established, standard-of care treatment option to reduce the frequency and severity and time of onset of the skeletal related events (SREs) in patients with bone metastases due to either solid tumours or multiple myeloma [21–33]. From many years, BPs have been incorporated into clinical practice recommendations for these patients [33–39]and denosumab has been approved in many countries for the delay of onset of SREs due to bone metastasis in breast or prostatic cancer patients.

Preventive dental measures, after dental screening examination [1,40–44], are advocated to reduce the ONJ incidence [14,45,46]due to their efficacy in patients with bone metastases but not in oncological patients with osteoporosis yet. Recent recommendations for ONJ, include a conservative approach with intermittent prophylactic antibiotic therapy, rinses with oral chlorhexidine and debridement [44]; moreover a careful sequestrum removal is recommended [1,17,40–47].

In a previous study [47]we evaluated the efficacy and tolerability of localised topical application of an oil suspension enriched with medical O_3 gas, as treatment for ONJ lesions ≤ 2.5 cm in another sample of patients who failed to respond to various cycles of antibiotics. Unexpectedly, total sequestration of the necrotic bone, with spontaneous expulsion in eight patients and new bone formation around the necrotic area in two patients was observed. No patient required surgical intervention. In two patients with pre- and post-treatment X-rays, no residual bone lesions were observed after treatment.

Ozone is a gas naturally produced by atmospheric air; medical ozone is produced from oxygen. Its role in treating bone lesions has been previously reported [47]. Ozone has antimicrobical and wound-healing properties. The role of O_3 produced by air to treat ONJ has been evaluated in some pre-clinical and clinical studies because it was thought that O_3 could induce the repair of tissues by cleansing the osteonecrotic lesions, which leads to mucosal healing [47–53]. Ozone therapy has previously shown to enhance the benefits of surgical and pharmacologic treatments of ONJ when administered before and after treatment procedures [47,51,53].

The aim of this open-label, prospective study, was to investigate the efficacy and tolerability of medical O_3 gas (produced from pure oxygen and not from air) topical insufflations, as the treatment for ONJ lesions > 2.5 cm in patients treated with BPs whose ONJ lesion did not heal with prior conservative therapy or relapsed after surgery performed before the patients arrived to our hospital for the specific consultation and cure with the Dental Team and the Supportive Care in Cancer Team.

2. Patients and methods

2.1. Eligibility criteria

All adult patients with solid tumours and multiple myeloma on stable disease or patients with osteoporosis due to hormonal therapy, who previously received nitrogen-containing BP treatment in the absence of preventive screening carried out by a dentist and a dental care team and who developed stage two ONJ lesions [10,44], and had no benefit after the treatment with the standard therapy, were included in the study. The patients with lesions > 2.5 cm were considered for O_3 gas therapy after they gave the consensus.

No patient took part in the previous published study [47]. No patient with metastatic disease of the jaw or osteoradionecrosis or treated with radiotherapy to the jaws were included.

2.2. Efficacy criteria

The level of clinical response was: (1) bone sequestrum followed by spontaneous expulsion of the necrotic bone with re-epithelization of oral mucosa and with regenerated epithelial tissue or (2) bone sequestrum followed by surgery to remove necrotic bone.

2.3. Safety criteria

The treatment area was assessed for the presence or absence of oral mucosa redness around the lesion area, pain, progressive