

Medical Ozone (O₃) Oil or Gas Applications Heal Osteonecrosis of the Jaw (ONJ) in Patients Treated with Bisphosphonates (BPs): Preliminary Results of a Single Arm Study

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INTRODUCTION

- Bisphosphonates (BPs) are well established and a recommended therapy to reduce the frequency and severity of skeletal-related events (SREs) due to bone metastases in patients of solid tumors or multiple myeloma.¹
- Osteonecrosis of the jaw (ONJ) is an uncommon condition which has been reported in patients receiving complex cancer treatment regimens, including BPs.²
- The exact frequency and etiology of ONJ is still unclear, however putative risk factors include concurrent disease, diabetes, tooth extractions or invasive dental surgery during the course of BP therapy, duration of administration and type of BP, poor oral hygiene and use of concomitant cancer drugs such as chemotherapy, thalidomide and corticosteroids.^{3,4}
- Prevention and therapeutic management of ONJ is essential in view of the considerable benefits of BPs, in the prevention of bone metastases-related SREs.
- The application of simple preventive measures such as proper dental hygiene, avoidance of dental procedures during BP treatment, and frequent dental examinations have been shown to effectively reduce ONJ incidence up to 75%.^{5,6}
- There are however few current options to treat ONJ lesions, and recent recommendations for the treatment of ONJ include prophylactic antibiotics, the use of oral antimicrobial rinses, and debridement (Table 1).
- Ozone therapy (O₃) has previously been shown to enhance the benefits of surgical and pharmacologic treatments of ONJ when administered before and after treatment procedures.^{7,8}
- In a pilot study with ten patients, we had previously reported that the application of topical medical O₃ oil suspension rapidly and completely resolves ONJ lesions ≤ 2.5 cm.⁹
- The present study continues to assess the therapeutic efficacy of the localized application of medical O₃ as an oil suspension or gas form in healing ONJ lesions in conjunction with prior antibiotic treatment.

Table 1. Staging and Treatment of ONJ (AAOMS 2009).¹⁰

ONJ stage	Treatment recommendations
At risk: No exposed necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates	No treatment indicated Patient education
Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms	Systemic management, including the use of pain medication and antibiotics
Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse Clinical follow-up and a quarterly basic Patient education and review of indications for continued bisphosphonate therapy
Stage 2: Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Symptomatic treatment with systemic antibiotics Oral antibacterial mouth rinse Pain control Surgical debridement to relieve soft tissue irritation
Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: radiographic evidence of additional foci of osteolysis extending to the inferior border	Antibacterial mouth rinse Antibiotic therapy Surgical debridement/resection for longer-term palliation of infection and pain

¹⁰From: American Association of Oral and Maxillofacial Surgeons-Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw—2009 Update
AAOMS: American Association of Oral and Maxillofacial Surgeons; ONJ: Osteonecrosis of the jaw

METHODS

- This clinical trial is based on a Simon stage-two design of which the second stage is on-going.
- All the patients had received various cycles of antibiotic therapies from the diagnosis of ONJ until the initiation of treatment with medical O₃. Some of them underwent hyperbaric oxygen therapy without ONJ healing.
- Patient sample size was calculated assuming a probability of the null and alternative hypothesis of 5% and 25%, respectively, and a probability of type I and II errors of 10%.
- Eligibility criteria
- Cancer patients who previously received N-BP treatment in the absence of odontologic preventive measures, and who developed stage 2 (AAOMS 2009 guidelines) ONJ lesions were included in the study.

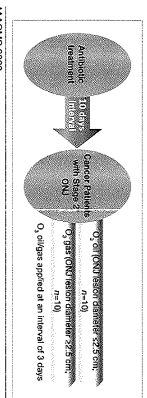
Diagnosis of ONJ

- ONJ was defined by the presence of exposed bone in the maxillofacial region with no evidence of healing after 6 weeks with appropriate dental care.¹⁰
- A differential diagnostic methodology was followed to distinguish ONJ lesions from metastatic disease of the jaw or osteoradionecrosis.¹⁰

Study scheme

- Patients were treated with antibiotic therapy (azithromycin [Zithromax], 500 mg/day for 10 days) 10 days prior to the initiation of the investigational treatment with the aim to reduce the gum infection.
- The experimental treatment consisted of localized application of O₃ oil (for lesion size ≤ 2.5 cm) or O₃ gas (for lesion size > 2.5 cm) on the ONJ lesions, at 3-day intervals until complete healing of ONJ (Figure 1).

Figure 1. Study Scheme



*AAOMS 2009

Primary end-point

- The goal of the study was to evaluate the level of healing response, and radiological lesion disappearance with complete reconstitution of oral tissue.

RESULTS

- The present report discusses the findings from the primary phase in which 10 patients were treated with medical O₃ oil with a median follow-up of 8 months, and 10 patients were treated with medical gas O₃. The patients treated with O₃ gas do not have a longer follow-up time to rule out relapse.
- A total of 20 patients (breast cancer (n=11), prostate cancer (n=1), non-Hodgkin lymphoma (n=2), lung cancer (n=2) and multiple myeloma (n=4) were enrolled in the study. All the patients had stable disease without progression.

The median time between the diagnosis of ONJ and the first O₃ oil application was 380 days.

- Patient demographics and baseline characteristics (Table 2).

Table 2. Patient Demographics and Baseline Characteristics

	O ₃ oil treatment (lesion size ≤ 2.5 cm) (n=10)	O ₃ gas treatment (lesion size ≥ 2.5 cm) (n=10)
Age range, years	46-74	53-77
Sex, n		
Female	8	4
Male	2	6
Primary tumor, n		
Breast	7	4
Prostate	1	0
Lung	0	2
Multiple Myeloma	1	3
Non-Hodgkin's lymphoma	1	1

- In the current analysis, a total of 16 patients (80%) showed complete response, in terms of radiological lesion disappearance with complete reconstitution of mucosal tissue. Lesion appearance before, during and after completion of successful treatment of a single patient is displayed in Figure 2.
- The mean recovery time was 26 days and 29 days for patients who received O₃ oil and O₃ gas therapy respectively.
- Currently six patients are still on treatment and displaying signs of improvement.
- Seventy percent of the patients treated with O₃ oil or gas experienced a complete response in 4 applications. Around 30% patients required 4-16 applications of O₃ oil or gas (probably depending on the severity of the lesion) (Table 3).
- 14 out of 20 patients developed spontaneous sequestrum with expulsion of the necrotic bone.
- Two patients required surgical intervention due to considerable severity and extent of necrotic lesion.
- No patients presented adverse events related to the use of O₃ treatments.

Figure 2. Response to O₃ Oil Treatment

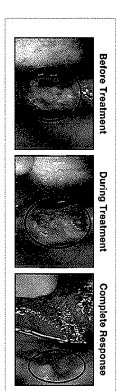


Table 3. Number of Applications of O₃ Oil/Gas Required for Complete Response

Number of applications required for complete response	O ₃ oil	O ₃ gas
3	3	3
4	4	4
≥ 10	3	3

CONCLUSIONS

- The results of this study demonstrate that application of medical O₃, either as an oil suspension or gaseous form enables a complete resolution of ONJ following antibiotic therapy without any adverse effects. While medical O₃ oil is more effective in treating minor ONJ lesions (≤ 2.5 cm), the application of O₃ gas appears to be very useful in patients with more severe lesions (> 2.5 cm).
- Previous investigations have demonstrated that the introduction of ONJ can be drastically reduced with the introduction of dental preventive measures before and during BP treatment.^{5,6} Emerging promising therapeutic options such as medical O₃ (oil/gas) investigated in this study, indicate that ONJ can also be treated, enabling patients to recover and heal from this debilitating condition.
- These results add to the evidence that cancer patients and clinicians should weigh the considerable benefits of BPs towards management of skeletal health as opposed to the possible risks posed by ONJ – an uncommon condition which can be preventable and also manageable. However, these results should be considered as preliminary requiring further investigation in a larger Phase III/IV trial.

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Treatment of bone metastasis with BP is aimed at preventing skeletal-related events (SREs) and rarely leads to ONJ (<1%) (Hoff, *JEM/R*. 2008). Preventive dental care is a simple and effective way to reduce the risk reduction of ONJ in 75% of the cases (Ripamonti, *Ann Oncol*. 2009). To date, there are still no standardized therapy for the treatment of ONJ. We report the effect of localized O₃ oil or gas application in cancer patients (breast cancer [n=11], prostate cancer [n=1], non-Hodgkin lymphoma [n=2], lung cancer [n=2] and multiple myeloma [n=4]) with ONJ observed in our institution. Patients had previously received nitrogen-BPs treatment in the absence of odontoiatric preventive measures. All the patients were in a stable disease without progression; 10 of them had ONJ lesions ≤ to 2.5 cm.

O₃ oil suspension applications on ONJ lesions ≤ 2.5 cm was carried out with localized applications directly on the lesions: pts with larger lesions (>2.5 cm) were treated with the O₃ gas locally applied. All the patients received treatment of O₃ oil every third day and all of them were treated with antibiotic therapy (azithromycin, 500 mg/day) 10 days prior the initiation of the treatment with O₃ oil.

The statistical analysis is based on a Simon two-stage design, the second stage is on-going. In this preliminary analysis we focus on 10 patients treated with O₃ oil with a median follow up of 8 months, and 10 patients on medical gas O₃.

80% of the patients (n=16) showed complete response in terms of radiological lesion disappearance with complete reconstruction of oral tissue. Among them, fourteen patients developed spontaneous sequestrum with expulsion of the necrotic bone whereas in 2 patients with large extent of bone involvement surgical intervention was necessary.

Seventy percent of the patients treated with O₃ oil experienced a complete response after 4 applications whereas patients treated with gas needed 4 to 16 applications (depending on the severity of the lesion). No patients presented adverse events related to the use of O₃ treatments. Six patients are still on treatment and are improving as well.

According to these results few application of O₃ oil suspension in patients with smaller lesions and gas medical O₃ for wider lesions following antibiotic therapy can rapidly lead to complete healing of ONJ. Further cases and complete follow-up data are required. These data indicate that ONJ is a manageable condition which can be not only prevented by means previous dental examination but also healed with medical O₃ applications.