Surgical approach with Er:YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT)

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Abstract Osteonecrosis of the jaw (ONJ) in patients on long-term bisphosphonate Therapy (BPT) has been reported with increasing frequency in literature over the past 4 years. Therapy for this condition is still a dilemma. Temporary suspension of BPT offers no short-term benefits; hyperbaric oxygen has no proven efficacy and therefore is not recommended. Intermittent or continuous antibiotic therapy with surgical debridement can be beneficial to palliate the symptoms. Er:YAG laser can be used to eliminate necrotic bone portions by partial or total resection as an alternative to conventional rotary devices. In our study, 91 patients affected by ONJ-BP lesion, for a total of 115 ONJ sites were observed between January 2004 and May 2008 (Department of Odontostomatology, University of Parma).

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Fifty-five ONJ sites were considered for this study in four different groups, retrospectively identified on the basis of treatment performed (G1–G4). G1: 13 ONJ-BP sites were treated with medical therapy (amoxicillin 1gr x 3/*die per os* with metronidazole 250 mg x 2/*die per os*) for at least 2 weeks; G2: 17 ONJ-BP sites received medical treatment in association with cycles of low-level laser therapy (LLLT) applications performed using an Nd:YAG laser (1,064 nm) once a week for 2 months; G3: 13 ONJ-BP sites were surgically treated (sequestrectomy of necrotic bone, debridement, corticotomy/surgical removal of alveolar and/or cortical bone); G4: 12 ONJ-BP sites were treated with surgical therapy performed using an Er:YAG laser (2,940 nm) in association with LLLT. Clinical success has been defined for each treatment performed as: (a) complete mucosal healing free from signs and symptoms (classified as stage "0") or (b) transition from a higher to a lower stage (Ruggiero staging) for at least 3 months. All the ONJ-BP sites treated with Er:YAG laser (G4 group) had a clinical improvement (100%) and 87.5% of sites had a complete mucosal healing with a mean follow-up of 13 months. The result obtained in the G4 is extremely significant in comparison with those obtained by medical treatment alone or in a traditional surgical approach. Thanks to the high degree of affinity of this wavelength for water and hydroxyapatite, both soft and bone tissues can be easily treated. This technique can also be used for conservative operations whereby necrotic bone is vaporized until healthy bone is reached. In addition, an additional advantage of the Er:YAG laser is its bactericidal and possible biostimulatory action, accelerating the healing of both soft tissues and bone tissues, in comparison to conventional treatments. In conclusion, from our experience, it is possible to observe that an early conservative surgical approach with Er:YAG

laser associated with LLLT, for BP-induced ONJ could be considered as more efficient in comparison with medical therapy or other conventional techniques.

Keywords Osteonecrosis of the jaws · Bisphosphonates · ONJ · ONJ treatment · Er:YAG laser · Surgical approach · Biostimulation · LLLT (Low-level laser therapy)

Introduction

Osteonecrosis (ON) is a natural consequence of numerous local or systemic factors capable of impairing blood flow to the bone marrow. Some cases of ON have been reported in long bones and even in the jaw related to local invasive cancer, human immunodeficiency virus, systemic lupus erythematosus, and thrombophilia or hypofibrinolysis [1]. Most cases of osteonecrosis of the jaw (ONJ) in immune-compromised patients are related to a microbial infection reaching the bone through non-vital teeth, periodontal lesions, or traumatic injuries related to surgical procedures such as tooth extractions. In some cases, bone necrosis is associated with corticosteroid therapy or radiotherapy. Osteoradionecrosis of the jaw occurs in approximately 20% of patients who have undergone local irradiation for head and neck malignancies. Cancer and its treatment have been associated with an increase in the risk of ON, a result of an impaired blood supply. A series of recent reports that have appeared over the last 4 years in the international literature suggests that long-term bisphosphonate therapy (BPT), most commonly administered intravenously (IV) as adjunctive therapy to bone metastasis and multiple myeloma, is associated with ONJ. Bisphosphonates (BPs) are structural analogues to inorganic pyrophosphate, a substance present in biological liquids able to inhibit the aggregation and dissolving of calcium phosphate crystals in vitro and ectopic calcification in vivo. Bone is a tissue with high metabolic activity continually subject to the replacement mechanism called "remodelling", comprising a phase of resorption followed by one of new formation [1]. All the BPs used today in clinical practice have several pharmacological properties: they are deposited mainly on skeleton tissue, bind strongly to hydroxyapatite crystals, suppress (even if with varying power and efficacy) osteoclast-mediated bone resorption, remain lengthily bonded to the skeleton and, finally, are excreted in urine without metabolic structural alteration. Their action is mainly directed to the osteoclasts where apoptosis is induced, shortening the time period these cells have for bone resorption. The half-life of BP is lengthened considerably and the portion of BPs retained by the bone is long-term eliminated: with alendronate, for example, it is more than 10 years. After carrying out their action on the skeleton,

BPs are deposited in the bone, where they remain for a lengthy period, even where remodelling is not involved. The in vitro activity of various BPs on the inhibition of bone resorption varies from 1 for etidronate, to > 10,000 for zoledronate [2]. Antiangiogenetic and antitumoral action has also been identified for zoledronate, through the inhibition of vascular endothelial growth factor, involved in the spread of secondary lesions in neoplasia [3].

BPs have been used for about 30 years for the prevention and treatment of osteoporosis, and since 1995 intravenously for the treatment of patients with multiple myeloma and bone metastasis.

The number of cases of ONJ reported in literature is small given the widespread use of these drugs. In 2003, alendronate was the 19th most commonly used drug in the world, and risedronate was the 72nd. In the last 3 years, 190 million prescriptions of oral BPs have been given worldwide. The percentage risk of ONJ varies greatly according to the patient's disease, type of BP, treatment duration, other comorbidities, and the drugs taken for them [4–6]. The range is from 0.01% for orally administered BPs to about 10% for intravenous administration of compounds containing an amino terminal (pamidronate) group or lateral chain containing nitrogen (zoledronic acid) [7, 8].

The literature does not always clarify the clinical parameters relating to the presumed etiology and pathogenetic mechanisms of ONJ. Patients treated with injected bisphosphonates have an average risk of ONJ that is seven times higher if they undergo invasive dental surgery [9, 10]. ONJ has a spontaneous onset in about 40% of cases [11, 12].

ONJ can cause infection, halitosis, intense pain, extensive sequestration of bone, oral and cutaneous fistula, lower lip paresthesia, loose or mobile teeth, and mandibular fracture. Ruggiero proposed a staging of ONJ-BPT consisting of three levels of disease connected by severity of symptoms [5] (Table 1).

ONJ therapy

Interrupting BPT is a controversial option: the drugs accumulate at high levels inside the bone matrix. However, cessation of BPT can have severe consequences, such as hypercalcemia associated with tumors or an increase of skeletal events in the patients affected by metastasis, multiple myeloma, or osteoporosis. In general, until the end of 2005, all the guidelines related to the management of patients under BP treatment for ONJ recommended a non-surgical approach consisting of a mix of medical therapies (antibiotics, antimycotics, antivirals, and antiseptics) protracted ad libitum over numerous cycles. Hyperbaric oxygen therapy (HBO2) is described as ineffective by most authors, and useful only in rare cases [13]. More or less

Table 1 Clinical classification of ONJ by Ruggiero

STAGE I	No-symptomatic lesions with bone exposure in absence of infection's signs
STAGE II	Bone exposure with pain, infection and swelling in the lesion's area
STAGE III	Bone exposure, pain, inflammation, secondary infections, cutaneous fistulas, and pathological fractures

(Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Oct;102(4):433–41.)

aggressive surgery is recommended only in advanced, non-responsive cases, ONJ extension being supposed to be linked to surgical trauma. Surgical treatment, in accordance to AAOMS position paper, is reserved to patients affected by ONJ-BP lesions and classified as stage III (pain, clinical evidence of infection and extra-oral fistula, serious osteolyses extending to the inferior border of mandible or pathological fractures) [9]. Aggressive surgical treatment may occasionally results in even larger areas of exposed and painful infected bone. Certainly, with this disease, surgical outcomes are hard to predict, but the same result could be obtained by conventional treatment. Often patients who have lived for some time with an area of exposed bone in the oral cavity are subject to almost continuous symptomatic infection, treated with antimicrobial rinses in combination with oral systemic antibiotic therapy, further compromising their mental and physical health. Consequently, various authors reviewed the guidelines that are still controversial even if positive surgical outcomes are reported [14, 15]. From our experience on the management of 91 patients and the results obtained on 55 sites affected by ONJ-BF, it is our belief that surgery is suitable even in the early stage of the disease, such as stage I. The management of initial lesions enables better preservation, less invasive surgery, requires only local anesthesia (without hospitalization) and has a higher patient compliance [16].

Management of ONJ with Er:YAG laser

The surgical technique involves Er:YAG, a solid-state laser where the active medium is a crystal of yttrium-aluminium-garnet doped with erbium. The radiation wavelength is 2.94 μm and produces excellent absorption of hydroxyapatite and water.

The major components of bone, such as organic matrix and inorganic calcium salts, have very high absorption for the Er:YAG laser beam. The machine initially produces water vapor that expands and builds up pressure until micro-explosions occur and tissue is removed. This process of explosive ablation is called thermally induced mechanical ablation. The ablated fragments ejected from the tissue surfaces carry most of the energy with them, leaving only little thermal energy to damage the surrounding tissues.

The equipment can be used on soft tissues after intense hydration, and on mineralized tissues such as bone, enamel

and dentine, and is comparable in terms of cutting efficiency with conventional rotary tools [17]. The laser works by pulses with a repetition rate ranging from 4 to 50 Hz; the pulse duration may vary from 100 μs (VSP mode) to 1,000 μs (VLP mode). The shorter the pulse the lesser is the thermal effect. The erbium laser causes "cold ablation", working on soft tissues without causing coagulation or carbonization and induces a much lower increase in temperature in the bone and intrapulpal area than conventional rotary tools. The laser penetrates only very slightly (0.1 mm) in tissues, providing safety guarantees and allowing for precise, minimally invasive, work [18].

One undoubted advantage of this technique is the bactericidal and biostimulatory action of the laser beam, as reported frequently in literature. Currently, laser biostimulation (or biomodulation) has been investigated for a wide range of applications related mainly to healing processes and pain management [19]. Low-level laser therapy (LLLT) is used extensively in medicine and dentistry to treat both hard- and soft-tissue injuries.

For bone as well as for other tissues, the mechanism of LLLT is probably photochemical: the energy absorbed by the intracellular, particularly mitochondrial, chromophores is converted into metabolic energy by action at the level of the mitochondrial respiratory chain [20–22].

LLLT of the bone tissue causes a rise in the quantity of mRNA used to synthesize type I collagen and thereby stimulates the formation and repair of bone tissue [23, 24]. For ONJ-BPT management, the use of LLLT, in combination with medical or surgical treatment, appears to provide good results in terms of vascularization of the coating mucous membrane, regeneration of the bone, reduction of pain and signs of phlogosis [25–28]. It has been suggested that healing processes (bone, soft tissues) is accelerated when surgery is performed with an Er:YAG laser versus rotary instruments. This could be linked to different factors: biomodulation or tissue attachment to erbium treated surfaces. Moreover, the bactericidal effect of these wavelengths could help in ONJ-BP treatment by reducing secondary infection by agents such as *Actinomyces, Candida* spp. and anaerobes [29, 30].

Pourzarandian et al. [31, 32] report both bone-coating tissues and quicker healing following surgery with an erbium laser. The areas of tissue next to the perforations in rat calvaria show a fibroblastic reaction and more marked

revascularization after laser treatment compared to tungsten carbide tools. Fourteen days after surgery the group treated by laser had greater bone regeneration. Takasaki et al. [33] carried out research on periimplantitis induced in Beagles, removing intraosseous and periimplant granulation tissue with decontamination of the implant surfaces by Er: YAG (10 J/cm², 20 Hz). Histological examination 2 weeks later showed new bone formation in comparison to the plastic curette-treated sites.

In a study based on experimental osteotomies of rat tibia, de Mello et al. [34] used Er: YAG laser (500 mJ, 10 Hz) reporting good results compared to conventional rotary tools. In addition, minimal intra-surgical production of smear layer and creation of clean surgical surfaces, histological examination 14 days after surgery showed improved healing compared to the other side treated with conventional tools.

Surgical technique with Er:YAG laser

Erbium laser technique allows partial or total resection of the jaw without using conventional rotary cutting tools. In addition to exploiting the direct action of the beam and the affinity of this wavelength for water and hydroxyapatite, the aggressive photo-acoustic effect is also useful. Preservative surgery can also be performed by gradual vaporization of necrotic bone at increasing depths close to the healthy bone. Surgery does not harm the tissues insofar as the penetration of the radiation is very limited. Surgical ablation of bone tissue takes place reducing the thermal damage to the adjacent tissue, which heals more quickly. The Er:YAG wavelength does not cause coagulation or carbonization and enables avascular portions of the bone to be clearly distinguished from those that are still vascularized.

Conservation surgery, maintaining the overall integrity of the jawbone, is chosen on the basis of the specific features of individual cases, ranging from simple curettage to debridement of the necrotic area, from sequestrectomy to resection of larger bone portions. Two types of handpieces may be used for the surgery: mirror and sapphire tip. There is a risk to break down the sapphire tip when cutting and bumping it against the bone walls. To avoid this risk, the sapphire tip has to be maintained in the hand following strictly the incision lines. This should be very difficult to respect with mirror handpiece (problem of focal distance).

The mini-invasive technique of ablation of the necrotic bone resurfaces and causes bleeding from healthy bone that could help in the future re-vascularization [35].

Patients and methods

From January 2004 to May 2008, 91 patients (25 males, 66 females; mean age 67 years, range 35–80) affected by ONJ-BP were examined at the Department of Odontostomatol-ogy, University of Parma, Italy, collecting these observation conformed to a protocol that satisfied the ethical standard as described by the Azienda Ospedaliero-Universitaria di Parma. Thirty-nine patients were diagnosed with multiple myeloma, 33 with bone cancer metastasis, 16 with osteoporosis, and one received BPT to treat bilateral femur bone necrosis after long-term chemotherapy but also developed an oral squamous cell carcinoma and was then treated with radiotherapy. The mean duration of BPT until occurrence of osteonecrosis was 25 months (min-max interval 2–120). All these patients were classified as affected by ONJ-BP according to AAOMS guidelines [9]. In particular, 62/91 patients presented exposure and necrosis of the mandible, 21/91 necrosis of the maxilla, while 8/91 patients had both maxilla and mandibular bone involvement. ONJ occurred spontaneously in 41/91 patients (45.1%) and in 50/91 patients (54.9 %) after dental extractions or other oral surgical procedures. In agreement with Ruggiero et al., ONJ-BP staging classification, ONJ lesions were classified as stage 1 (8/91), stage 2 (66/91), and stage 3 (17/91) at the time of first examination. Treatment of each ONJ-BP lesion was planned in accordance with the AAOMS therapeutic guidelines (2006 edition) and taking in consideration systemic and local conditions of each patient and of each site affected by ONJ (i.e., age of the patient, status of pathology, extension of the lesions, presence and recurrence of infection, reported pain, quality of life of each patient, and patient compliance). In addition to the proposed treatment strategies, we added the use of low-level laser therapy (LLLT), in order to improve the healing process of these lesions [12, 26, 27].

We observed 91 patients affected by ONJ-BP lesion, for a total of 115 ONJ-sites. Of these 115 sites, 92 were treated between January 2004 and May 2008: 88 were followed at the Sezione di Odontostomatologia, and four were referred to Oral Maxillo-Facial Surgery Department, University of Parma, for extensive osteotomy performed under general anesthesia and were not included in this study.

Each strategy treatment was performed in accordance with the "available guidelines" present at the time of the first examination of each lesion, as well as systemic conditions of each patient and compliance, as previously described. The characteristics of each lesion and its response to antibiotics were also registered.

A placebo group was not introduced in this study for ethic reasons: ONJ is a serious pathology often affecting oncologic patients. Medical treatment alone (consisting in repeated cycles of antibiotic therapy) could be considered as a control group.

In particular, we have retrospectively subdivided the treatments performed on the 55 ONJ-BP sites (on 48 patients) into four different groups:

– G1: ONJ-BP sites treated only with medical therapy;

– G2: ONJ-BP sites treated with medical therapy and LLLT;
– G3: ONJ-BP sites treated with surgical therapy;
– G4: ONJ-BP sites treated with surgical therapy performed with Er:YAG laser and LLLT;

(1) G1: 13 ONJ-BP sites were treated with medical therapy with antibiotics (amoxicillin 1 g x 3/*die per os* with metronidazole 250 mg x 2/*die per os*) for at least two weeks. Mouthwashes with chlorexidine and hydrogen peroxide were also prescribed two/three times a day, sometimes with antimycotic rinses. Clinical examination of the lesions was performed 2 weeks after therapy and 3 weeks after antibiotics suspension as well. Of these 13 ONJ-BP sites, 1/13 (7.6%) was classified at the time of first clinical evaluation as stage I, 9/13 (69.3%) as stage II and 3/13 (23%) as stage III

(2) G2: 17 ONJ-BP sites received medical treatment (as described in G1) in association with cycles of LLLT. In particular, each lesion received LLLT applications once a week for 2 months. Each LLLT application was performed with an Nd:YAG laser (1,064 nm, Fidelis Plus, Fotona, Slovenia) used at 1.25 W power, 15 Hz frequency, and 320 μm of fiber diameter. The laser light was used in a non-focused way, 2 mm from tissue, for 1 min and repeated five times (power density: 268.57 W/ cm^2 - fluence: 2.0175 J/cm^2). The usefulness of the ONJ-BP laser treatment is connected with two different considerations:

(a) Usually, bone exposure is not a real indicator of extension of disease because frequently the apparent healthy mucosa covers some part of the involved bone;
(b) ONJ is a condition connected to both bone and surrounding soft-tissue involvement.

For this reason, laser application (LLLT) could not be restricted to exposed bone but also extended to peripheral anatomic area. In all cases, LLLT was applied in a sweeping motion in emimaxilla or emimandibula, in vestibular or palatal side, independently of the size of bone exposure.

Table 3 Analysis of different variables that may interfere with ONJ-BPT healing improvement

	*Healing improvement	No healing improvement	p-value
BP-therapy discontinuation	10	15	0.78
No BP-therapy discontinuation	14	16	
Maxilla	4	6	1.00
Mandible	20	25	
Multiple myeloma	13	14	0.39
Cancer metastasis	6	13	
Osteoporosis	5	4	
Stage1	4	4	0.0873
Stage 2	19	22	
Stage 3	0	6	

Statistical analysis was performed with Fisher's exact test (2 x 2 and rxc tables)

*Healing improvement: ONJ-BP sites after medical or surgical treatments (with or without LLLT) that underwent to "clinical success":

a) Stage 0 or b) pass from higher stage to a lower one (for at least 3 months)

Out of 17 ONJ-BP lesions, 3/17 (17.6%) were classified at the time of first clinical evaluation as stage I, 12/17 (70.5%) as stage II and 2/17 (11.7%) as stage III.

(3) G3: 13 ONJ-BP sites were treated with surgical therapy. Conservative surgical treatments consisting in sequestrectomy of necrotic bone, superficial debridement/curettage, corticotomy/surgical removal of alveolar and/or cortical bone. Each operation was planned according to the extension of the lesion (visualized with ortopanthomography and CAT evaluations) in association with medical therapy (antibiotic treatment was usually prescribed beginning 3 days prior to the operation and 10 days after) and performed under local anesthesia at Department of Odontostomatology, University of Parma, Italy. Incision of oral soft tissues may be performed by conventional tools or by quantum molecular resonance (QMR) device set to the "cutting" mode.

Table 2 Parameter of "clinical success" of ONJ-BP therapy evaluation by Vescovi: level -a- transition from a higher stage to stage 0, level -b- transition from a higher to a lower stages. Maintenance of results for over at least 3 months

STAGE III	Persistence of bone exposure, pain, inflammation, secondary infections, cutaneous fistulas, and pathological fractures
STAGE II	Presence of bone exposure with pain, infection and swelling in the lesion's area. Disappearance of cutaneous fistulas
STAGE I	Presence of bone exposure , regression of infection's signs, regression of symptoms
STAGE 0	Complete mucosal healing, absence of symptoms, absence of infections signs

(Vescovi P: *JOMS* 2006; 64: 1460–146)

Table 4 Characteristics of patients. 4a: G1 group; 4b: G2 group; 4c: G3 group; 4d: G4 group

Patient	Sex	Age	Primary Disease	Localization	Stage before treatment	Stage after treatment
G1						
AA	F	61	Multiple myeloma	Mandible	I	I
BB	F	78	Multiple myeloma	Mandible	III	III
CF	F	67	Osteoporosis	Mandible	II	II
CM	F	57	Bone metastasis	Mandible	II	II
CM	F	56	Multiple myeloma	Mandible	II	II
CB	F	63	Osteoporosis	Mandible	II	II
FD	F	60	Multiple myeloma	Mandible	III	III
GL	F	56	Osteoporosis	Mandible	II	II
LV	M	66	Multiple myeloma	Mandible	II	II
MC	F	74	Multiple myeloma	Maxilla	II	II
PMA	F	86	Multiple myeloma	Maxilla	II	II
SD	F	70	Multiple myeloma	Mandible	III	III
VL	F	85	Bone metastasis	Mandible	II	II
G2						
BJ	F	79	Multiple myeloma	Mandible	II	0
BGF	M	70	Multiple myeloma	Mandible	II	II
BFM	M	62	Bone metastasis	Maxilla	III	III
BFM	M	62	Bone metastasis	Mandible	III	III
CI	F	55	Bone metastasis	Maxilla	I	0
CR	F	73	Bone metastasis	Mandible	II	III
CI	F	80	Osteoporosis	Mandible	II	II
FP	F	70	Osteoporosis	Mandible	II	0
OF	M	67	Multiple myeloma	Mandible	II	II
PA	F	46	Bone metastasis	Mandible	I	I
PA	F	67	Multiple myeloma	Mandible	II	0
PMA	F	70	Osteoporosis	Mandible	II	0
RI	F	67	Bone metastasis	Mandible	II	II
SBI	F	61	Osteoporosis	Mandible	II	0
SG	M	72	Bone metastasis	Maxilla	I	I
USE	F	69	Osteoporosis	Maxilla	II	0
ZG	F	69	Bone metastasis	Mandible	II	II
G3						
BL	F	65	Bone metastasis	Mandible	II	II
BL	F	65	Bone metastasis	Mandible	II	II
BL	F	65	Bone metastasis	Mandible	II	II
CL	F	76	Osteoporosis	Mandible	II	0
DK	F	54	Osteoporosis	Maxilla	I	0
FL	F	84	Bone metastasis	Mandible	II	0
GR	M	71	Multiple myeloma	Mandible	II	0
GV	M	80	Multiple myeloma	Mandible	III	III
MA	M	68	Multiple myeloma	Mandible	II	0
RC	F	60	Bone metastasis	Maxilla	II	II
SC	F	79	Bone metastasis	Mandible	II	0
TS	M	65	Multiple myeloma	Mandible	II	II
TS	M	65	Multiple myeloma	Mandible	II	II
G4						
AL	F	80	Multiple myeloma	Mandible	II	0
BF	F	66	Bone metastasis	Mandible	II	I

Table 4 (continued)

Patient	Sex	Age	Primary Disease	Localization	Stage before treatment	Stage after treatment
CO	F	85	Bone metastasis	Mandible	II	0
FV	M	77	Multiple myeloma	Maxilla	II	0
FV	M	77	Multiple myeloma	Mandible	II	0
GR	M	71	Multiple myeloma	Mandible	II	0
MR	M	74	Multiple myeloma	Mandible	II	0
NS	F	67	Multiple myeloma	Mandible	I	0
NS	F	67	Multiple myeloma	Maxilla	I	0
PA	F	78	Multiple myeloma	Mandible	II	0
PA	F	78	Multiple myeloma	Mandible	I	0
TM	F	77	Multiple myeloma	Mandible	II	I

The necrotic and surrounding bone were eliminated using traditional rotary cutting instruments. Of these treated 13 ONJ-BP lesions, 1/13 (7.6%) was classified at the time of the first clinical evaluation as stage I, 11/13 (84.6%) as stage II and 1/13 (7.6%) as stage III.

(4) G4: 12 ONJ-BP sites were treated with surgical therapy performed with Er:YAG laser (2,940 nm) Fidelis Plus® equipment (Fotona - Slovenia) used to incise soft tissues and remove or vaporize necrotic bone or surrounding bone involved. Within these 12 treated bone lesions, 11 where localized in the mandible and 1 in the maxilla. Two are connected to BPT for cancer metastasis and 10 with multiple myeloma. The initial stage was I for 3/12 sites and II for 9/12. Bone resection or evaporation of the necrotic areas was obtained with variable parameters, from 250 mJ 20 Hz (VSP) with a fluence of 50 J/cm² up to 300 mJ, 30 Hz and fluence of 60 J/cm2. During the surgical intervention we used as irrigation a iodopovidone solution; Er:YAG laser device has been used with a distilled water irrigation system.

The use, the type, and the dosage of analgesics for each patient were recorded in clinical dossiers.

The identification of elements to define favorable result in the surgical and or medical treatment of ONJ-BP in the literature is still unclear. Because it is impossible to verify, and probably to obtain, a complete histological or radiological *restitutio ad integrum* of these lesions, the clinical features is the unique parameter of evaluation of therapy effects. In order to define a clinical parameter that could be used to evaluate the results obtained with the different strategies of ONJ management reported above, we have already introduced [28] what we call "clinical success", identified as a treatment able to give a positive result (at least in terms of patient quality of life):

(a) Complete mucosal healing free from signs and symptoms (classified as stage "0")

(b) Transition from a higher to a lower stages (healing improvement) (passage from III stage to II stage or I stage).

ONJ is a chronic disease characterized by frequent relapses even after possible treatment (medical, surgical, or laser). Thus the evaluation of clinical results must be observed not only after 1 week and/or by a single examination, but during a longer period of follow-up. For this reason, when we define "positive" or "negative" results (as described in Tables 1 and 2) we mean a global analysis of the selected parameters (presence/absence of pain, mucosal healing, signs of infection) during the 3 months after each treatment performed. Therefore it is difficult to maintain a single blind examiner for such a long period of time and for several control examinations.

To define "clinical success" the positive results of each therapy must be maintained over at least 3 months (Table 2).

These two levels of clinical success have then been used in this study to identify the results obtained from the four treatment groups retrospectively evaluated. In addition, discontinuation of BP therapy (over at least 3 months) prior to the beginning of each treatment was also recorded.

Clinical signs (swelling, pus drainage, dimension of bone exposition) and symptoms (pain, halitosis, paresthesia) as well as consequent stage on the basis of Ruggero's staging system were recorded for all patients in clinical records.

Before each treatment, pictures of intraoral and extraoral ONJ manifestations were taken. The same elements were recorded 1 week after treatment and every 2 weeks until the third month and then monthly in the following 6 months.

Statistical analysis was performed with the well-known Open Source Statistical software R ("R Development Core Team (2008)", version 2–7.1, using the routines chisq.test, fisher.test (exact test for 2×2 and rxc contingency tables) and pairwise.prop.test for multiple comparison of propor-

Table 5 Percentage of clinical success obtained in the ONJ-BPT sites treated with different therapy strategies

Therapy	Sites	Sites with healing improvement	Percentage of clinical success (%)
Medical (G1)	13	0	0
LLLT (G2)	17	7	41
Surgery (G3)	13	6	46
Er:YAG surgery + LLLT (G4)	12	12	100

*Healing improvement: ONJ-BP sites after medical or surgical treatments (with or without LLLT) that underwent to "**clinical success" a) Stage 0 or b) pass from higher stage to a lower one (for at least 3 months)

tions (Groups 1 to 4). This latter routine can use up to eight different methods to account for type I and type II errors in multiple comparisons. Four methods [36–42] are designed to give strong control of the familywise error rate (type I), and it is therefore more difficult to obtain a statistical significant result. Other available methods [43, 44] (BH: method of Benjamini and Hochberg, and BY: method of Benjamini and Yekutieli) are based on the "false discovery rate" that is less stringent than the familywise error rate, so these tests are more powerful than the others [45].

Results

(Tables 3, 4, 5)

No site of the 13 ONJ-BP lesions treated with medical therapy only (G1) showed a transition to stage 0 or transition from a higher to a lower stage for at least 3 months. The mean follow-up was 4.1 months (range 3–9 months). In contrast, for seven out of the 17 (41%) lesions treated with medical therapy combined with LLLT (G2) an improvement was observed. Of note, all of the seven ONJ-BP sites had a transition to stage 0 with a mean follow-up of 7.5 months (range 3–18 months). For 13 lesions treated in G3, six (46%) had a transition to stage 0, with a mean follow-up of 8.8 months (range 3–30).

Table 6 Statistical analyses for multiple comparisons of proportions (Groups 1 to 4)

	G1 (Medical therapy)	G2 (LLLT)	G3 (Surgery)
G2 (LLLT)	0.033	-	-
G3 (Surgery)	0.030	1.000	-
G4 (Surgery + LLLT)	0.000025	0.012	0.043

Statistical analysis was performed using the "Benjamini and Hochberg" method, using Open Source Statistical software R ("R Development Core Team (2008)", version 2–7.1; results were considered statistically significant for $p \leq 0.05$
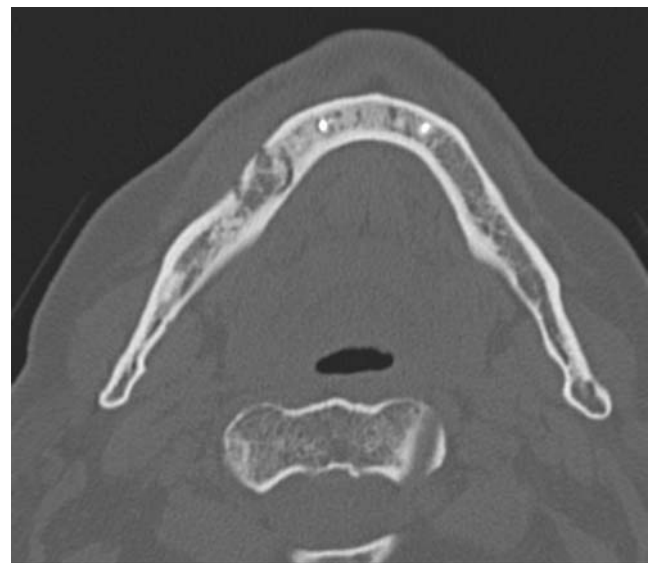
Fig. 1 Stage II ONJ in a 65-year-old male patient with multiple myeloma

Finally, in the G4 group all ONJ-BP sites treated with ER:YAG laser had an improvement (100%). In particular, 10/12 had a transition to stage 0 for a mean period of 16 months and are still maintaining this clinical result. For one patient affected by multiple myeloma, the intervention in the mandible produced a regression from stage II to stage 0 for 10 months and then an ONJ relapse. One patient, affected by breast cancer and bone metastasis, showed an improvement (regression of size and symptoms of ONJ) but did not shift to stage 0.
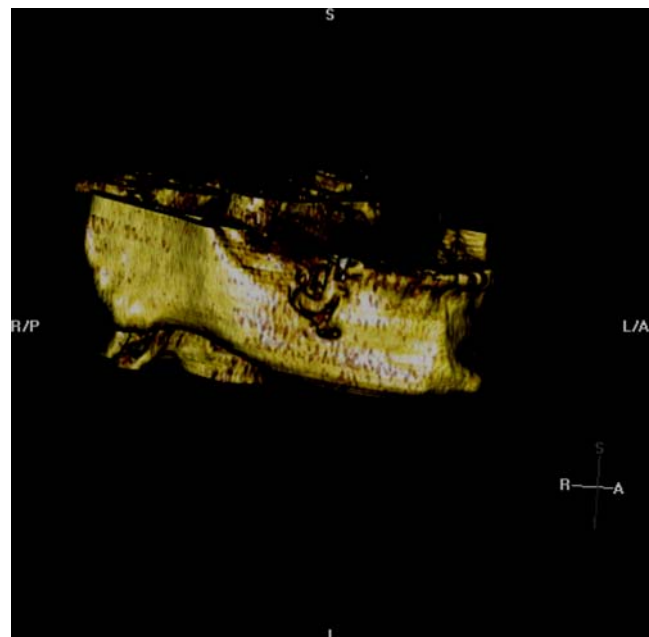
Fig. 2 Stage II ONJ in a 65-year-old male patient with multiple myeloma

Fig. 3 Stage II ONJ in a 65-year-old male patient with multiple myeloma

Fig. 5 Alveolar bone resection and corticotomy through Er:YAG laser

From the statistical analysis, applying the methods mentioned above, we found statistical significance comparing ONJ-BPT sites treated with medical therapy only (G1) and those where both surgery and LLLT applications were performed (G4) ($p<0.001$). In addition, a significance was also recorded for treatment performed with use of Er:YAG and LLLT (G4) ($p=0.02$) when compared to LLLT applications (G2) only. Finally, the use of Er:YAG and LLLT determine a significant improvement of ONJ-BP sites when compared with those treated with conventional surgical techniques ($p=0.03$) (G3). No other statistical significance ($\alpha=0.05$) was found for the other comparisons with the applied tests [36–38, 42].

Furthermore, using the "BH" method, statistically significant results were also obtained from the comparison of ONJ-BPT sites treated with antibiotic therapy alone (G1) when compared to those treated with all the other methodologies used (G2: $p=0.03$, G3: p0.03; G4: $p<0.001$) (Table 6).
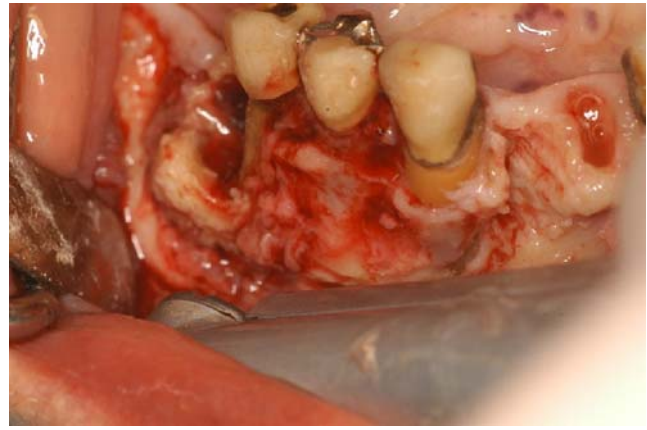
Discussion

Proper management of ONJ in long-term BPT patients is still unclear because no effective treatment has been found and interruption of BPT treatment does not seem to be beneficial. The treatment strategies of this condition are correlated to their classification in the three stages mentioned above, as reported in Table 1. The AAOMS guidelines are mainly based on the use of antibiotic therapy cycles that often need to be repeated in stage II patients (who represent the majority of patients affected by ONJ-BP) and those at stage III. Surgical treatment is reserved for stage III patients only, as long-term palliation of infection and pain. In contrast, different studies and reviews have reported that with the application of the AAOMS strategies, a progression of the disease from the initial to later stages could be observed, characterized by more severe complications. Local and general medical treatments only produce a temporary reduction of pain and local symptoms but have proved to be

Fig. 4 Stage II ONJ in a 65-year-old male patient with multiple myeloma
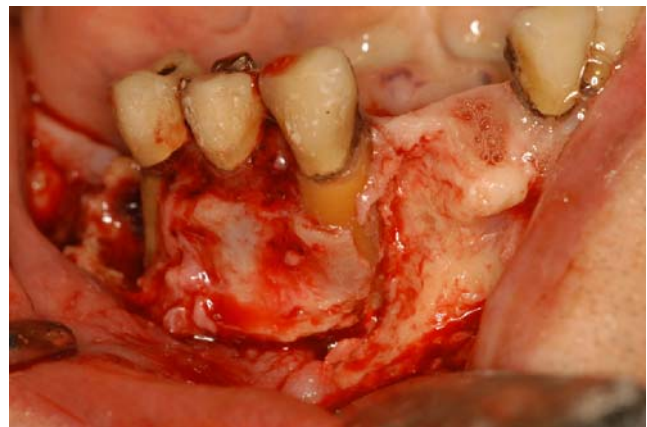
Fig. 6 Alveolar bone resection and corticotomy through Er:YAG laser

Fig. 7 Alveolar bone resection and corticotomy through Er:YAG laser

Fig. 9 Clinical image 1 week after surgery

ineffective in a long-term follow up. The persistence of symptomatic bone exposure frequently prompts the elimination of necrotic bone, but does not protect against newly exposed bone areas or recurrence of ONJ.

In our experience, performing conservative surgery on these lesions in the early stages of the disease was mainly based on the unsuccessful results obtained over a period of time with medical therapy. In addition, we hypothesized that the use of a low invasive surgery technique with Er:YAG laser and laser beam biostimulation (LLLT) may determine complete mucosal healing and reduce the microbial component, thus decreasing patient symptoms resulting in a higher level of quality of life.

Furthermore, the principal treatment goal for patients affected by ONJ-BP is to provide relief from signs and symptoms (sometimes difficult to control with drugs) caused by lesions that, if observed, often determine a worsening of their quality of life status, already influenced by their pathology.

From the retrospective analysis of the four groups evaluated in this study, it is possible to observe that medical

therapy alone did not determine any kind of improvement in these ONJ-BP lesions (0/13; 0%) for a reasonable period of time. A 3-month period was considered for this purpose as a reasonable timeframe in which suspension of antibiotic therapy can be regarded as successful. Antibiotic treatment can usually contain the acute process only for a short period of time (usually 3–4 weeks) with a subsequent relapse of signs and symptoms.
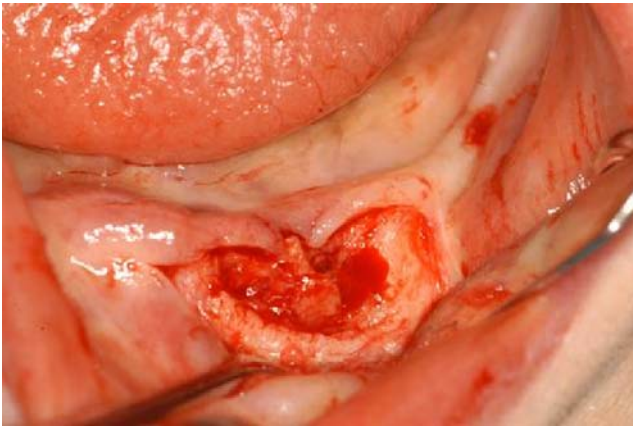
Furthermore, the use of both surgical approach performed with Er:YAG laser and LLLT applications together has shown the best mucosal healing ($p < 0.0001$) of the ONJ-BP sites, reaching complete mucosal healing (stage 0) in the 87.5% (or 100% considering the total ONJ-BP sites treated that had a transition from a higher to a lower stage) (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9).

Of note, an evaluation of the percentage of sites where clinical healing was achieved with the different treatments clearly shows how the combination of conservative surgery, medical therapy (with or without Er:YAG laser) and LLLT applications may determine a greater improvement of the lesions for a longer period of time in comparison to the traditional medical approach. In addition, a slight difference

Fig. 8 Intraoperative laser biostimulation

Fig. 10 ONJ stage I in a 75-year-old female patient with multiple myeloma

Fig. 11 Debridement with Er:YAG laser (vaporization)

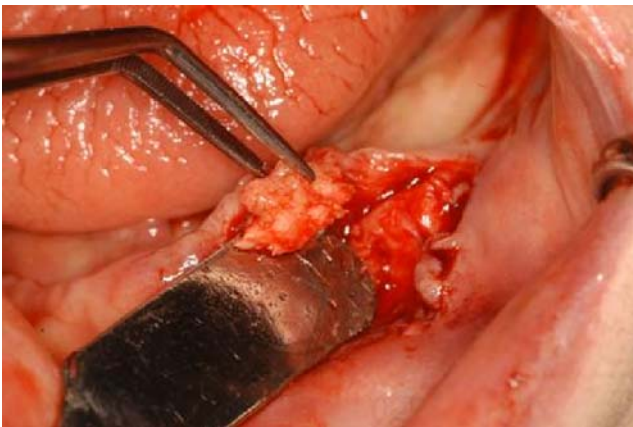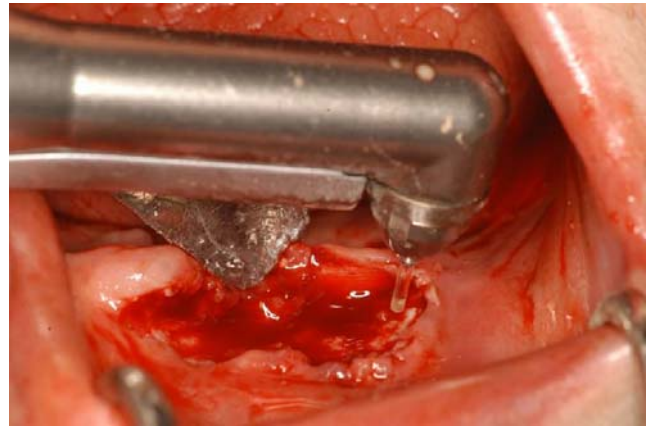
Fig. 13 Debridement with Er:YAG laser (vaporization)

can be noted between the results obtained with surgery (46% of clinical improvement) when compared with LLLT applications only (41% of clinical improvement). This result suggests that the simple application of LLLT may offer an aid in the treatment of ONJ-BP lesions, especially for patients that for different reasons cannot be treated with surgery.

Surgical operations proposed for stage III patients are invasive, extensive, and must be performed under general anesthesia: only a few patients affected by ONJ may undergo this type of surgery. On the contrary, less invasive surgery that can be performed under local anesthesia (day-hospital) may determine a complete mucosal healing containing the microbial secondary infection of soft tissues. Among our stage III patients, only one has been treated surgically and under local anesthesia because the medical balance did not permit an invasive treatment but only the elimination of bone sequestrum and antibiotic therapy of maintenance. Mandibulectomy and reconstruction are a very hard and heavy treatments and frequently the delicate balance of patients does not permit this extremely invasive option. Bone sequestrum removal under local anesthesia and/or medical therapy protracted ad libitum maybe a possible compromise. In addition, LLLT applications may stimulate the regeneration and angiogenesis of tissues increasing speeding up of the healing process [46].

In our experience, early mini invasive surgical removal of necrotic bone and local flap closure with minimal disturbance of overlying tissues and biostimulation of hard and soft tissues may be the treatment of choice at the moment (Figs. 10, 11, 12, 13, 14).

Oral soft tissues may be incised by conventional tools, different laser wavelengths or a quantum molecular resonance (QMR) device. The technique chosen should limit surgical trauma of mucosa, periost, and bone as far as possible. Conventional electro-surgery is not recommended, nor is the use of wavelengths that lead to marked carbonization, in order not to transfer thermal and electric shock to the soft coating tissues and bone, which could accentuate necrosis and complicate the covering of dehiscence. Vertical incision should be avoided or should be minimized in order to maximize the blood supply to the flap.

The Er:YAG laser has great potential for hard tissue treatment due to its high absorption by both water and hydroxyapatite. Several studies have documented the

Fig. 12 Debridement with Er:YAG laser (vaporization)

Fig. 14 Clinical image 7 months after surgery

ability of Er:YAG laser to ablate bone efficiently with limited collateral damages. The laser provides clean and precise cuts with minimal injury to the adjacent hard and soft tissues while producing an ablated surface favorable for cell attachment.

In conclusion, from our experience, it is possible to observe that an early conservative surgical approach with Er:YAG laser combined with LLLT, for BP-induced ONJ could be considered as more efficient in comparison to medical therapy alone or other techniques for the management and quality of life of these patients. Due to these special features plus the biostimulatory effects and bactericidal properties reported in literature concerning laser disinfection activity on *Candida* spp. and anaerobes, the Er:YAG laser is an important surgical instrument for the treatment of ONJ-BPT. It allows relatively mild surgery (sequestrectomy of necrotic bone, superficial debridement/curettage, corticotomy/surgical removal of alveolar, and/or cortical bone) and photoablation of the necrotic material.

The absence of vibration, the more rapid healing of soft and bone tissues and the relatively pain-free recovery improve patient compliance.

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