Clinical Study

Surgical Approach and Laser Applications in BRONJ Osteoporotic and Cancer Patients

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Bisphosphonates-related Osteonecrosis of the Jaw (BRONJ) management is controversial: there are no evidence-based guidelines in the literature associated with good results for a long-term follow-up, in particular regarding surgical procedures [1]. The main purposes of each treatment are to reduce pain and to control infection and slow the progression of the disease, taking into account as main target the eradication of BRONJ promoting the complete healing. Most of the authors privilege a noninvasive approach especially for asymptomatic stages of BRONJ (Stage I in Ruggiero’s staging) [2] but also different surgical approaches have been proposed, with variable types of surgical techniques and with or without discontinuation of bisphosphonates protocols [3–12].

Migliorati and colleagues reported percentages of healing variable from 17.3–17.6% for medical therapy or surgical debridement to 46.3% for free flap or surgical resection procedures [13].

Clinicians should always carefully consider the possibility of extensive surgery in oncological patients because of general status and life expectancy. One of the exclusion criteria was contraindications for surgery under general anaesthesia: this element appears to be an important limit to surgical procedure and confirms the choice for early minimal invasive surgical therapy in stages I and II of BRONJ.

The widespread variant of BRONJ (stage III), in particular those with mandibular fractures, requires bone resection with extension to apparently healthy margins such as bleeding points and normal colour of bone surfaces. On the basis of BRONJ pathogenesis, many authors recommend a large resection because an insufficient elimination of necrotic material may result in a recurrence of bone exposure.

The aim of this retrospective study is to present our experience in a wide number of patients treated with...
different kinds of surgical and nonsurgical approaches based or not on the use of laser-assisted techniques: the rationale to use laser with low dosages is the biostimulating effect reported in literature on both bone and soft tissues.

2. Material and Methods

One hundred and ninety patients (52 males, 138 females; 62 with multiple myeloma (MM), 85 with bone metastasis (BM), and 43 with osteoporosis (OP), mean age 67.3 ± 10 years) affected by BRONJ were evaluated at the Unit of Oral Pathology and Medicine and Laser-Assisted Surgery of the University of Parma, Italy, between January 2004 and November 2011 (Table 1).

At the time of BRONJ diagnosis, mean duration of BPT was 26 ± 20 months (ranging between 3 and 72 months) for cancer patients and 90 ± 40 months (ranging between 24 and 144 months) for noncancer patients. Thirty-nine patients (20.5%) were smokers, 22 (11.5%) had diabetes, and 125 patients (65.7%) received long-term corticosteroid treatments (Table 2).

Among the 43 “osteoporotic patients,” 2 were treated for rheumatoid arthritis, 39 for osteoporosis, and 2 for both rheumatoid arthritis and osteoporotic disease; corticosteroids were used in both the patients with rheumatoid arthritis, in 15 out of 39 osteoporotic patients and in 1 out of 2 patients with osteoporosis an rheumatoid arthritis.

One hundred twenty out of 190 patients (63.2%) had mandibular involvement, 53 out of 190 (27.9%) had BRONJ in the maxilla, and 17 out of 190 patients (8.9%) had the involvement of both the jawbones. All these patients were subclassified according to the staging system proposed by the AAOMS in the following groups: Stage I (34/190), Stage II (126/190), and Stage III (30/190) (Table 1).

Treated sites were 166, 38 in noncancer patients and 128 in cancer patients.

Inclusion criteria for treatment were presence of exposed or unexposed symptomatic BRONJ.

Incisional biopsy was performed independently from surgical procedure for BRONJ for lesions suspected to be manifestations of primary disease: specimen of every BRONJ lesions were extracted for histological evaluation.

Patients satisfying inclusion criteria but presenting a very poor health condition or mandibular fracture or diffused Stage III BRONJ not treatable under local anaesthesia were not included in the present evaluation; lack of consent to surgery was also an exclusion criteria for these patients.

An orthopantomography (OPT) and a CT scan of the lesion were obtained in all cases.

In each case the first therapeutic approach was chosen on the basis of the most updated guidelines available at the time of treatment. Surgical approach was taken into account after three consecutive antibiotic cycles not leading to a stable improvement of BRONJ. Each surgical intervention was performed under local anaesthesia and planned according to the extension of the lesion: limited or extensive treatments have been performed with the same kind of approach for both laser-assisted and nonlaser-assisted protocols. In all surgical cases, mucoperiosteal flaps were elevated to visualize and remove the necrotic bone. Surgical instruments included conventional bone burs or Er:YAG laser. A complete closure of the surgical wound was performed through conventional sutures.

In addition to antibiotic or surgical treatment in two separate groups we performed LLIT applications using Nd:YAG laser. According to the ethical standards of the Academic Hospital of Parma, we obtained a specific informed consensus for each patient.

Each patient was treated according a specific protocol (Table 3) as follows.

G1: BRONJ sites treated only with antibiotic therapy (oral amoxicillin 1 gr 2 times/day with oral metronidazole 250 mg 2 times/day) for two weeks. Mouthwashes with chlorhexidine (0.20%) and hydrogen peroxide (3%) were also prescribed two/three times a day, sometimes with antymycotic rinses.

G2: BRONJ sites treated with antibiotic therapy (oral amoxicillin 1 gr 2 times/day with oral metronidazole 250 mg 2 times/day) for two weeks. Mouthwashes with chlorhexidine (0.20%) and hydrogen peroxide (3%) were also prescribed two/three times a day, sometimes with antymycotic rinses.

G3: BRONJ sites treated with antibiotic and traditional surgical therapy. In this group antibiotic treatment

Table 1: Baseline data of patients: BRONJ stage according to Ruggero’s classification, gender distribution, age, and primary disease; BM: bone metastasis, MM: multiple myeloma, OP: osteoporosis and/or rheumatoid arthritis.

| BRONJ Stage | Patients number | Gender   | Mean age ± SD | Primary disease |
|-------------|----------------|----------|---------------|----------------|
|             |                | Female   | Male          | BM            | MM       | OP       |
| Stage I     | 34             | 26       | 8             | 66.3 ± 11.4   | 15       | 9        | 10       |
| Stage II    | 126            | 92       | 34            | 67.9 ± 9.1    | 57       | 43       | 26       |
| Stage III   | 30             | 20       | 10            | 65.5 ± 12.2   | 13       | 10       | 7        |
Table 2: Risk factors: smoking habits, diabetes, hypertension, heart disease comprehending coagulation disorders, liver disease, and corticosteroids administration; BM: bone metastasis, MM: multiple myeloma, OP: osteoporosis and/or rheumatoid arthritis.

| Primary disease | Patients number | Smoking habits | Diabetes | Hypertension | Heart disease | Liver disease | Corticosteroids |
|-----------------|-----------------|----------------|----------|--------------|---------------|---------------|-----------------|
| BM              | 85              | 25             | 10       | 24           | 21            | 2             | 69              |
| MM              | 7               | 6              | 17       | 10           | 2             | 38            | 38              |
| OP              | 43              | 7              | 6        | 18           | 6             | 1             | 18              |

Table 3: Protocols used for different therapeutical approaches.

| Treatment                  | Protocols                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| G1 Medical therapy        | Antibiotic therapy (oral amoxicillin 1 gr 2 times/day with oral metronidazole 250 mg 2 times/day) for two weeks. Mouthwashes with chlorhexidine (0.20%) and hydrogen peroxide (3%) two/three times a day. |
| G2 Medical therapy + LLLT | G1 protocol + LLLT applications once a week for two months with Nd:YAG Laser (1.25 W, 15 Hz, VSP, 320 µm) of fibre diameter, nonfocused way with scanning method, 2 mm from tissue, for 1 minute and repeated 5 times. |
| G3 Traditional surgery    | Antibiotic treatment prescribed beginning three days prior to the operation and ending 10 days after it. Conservative surgical treatments using traditional surgical instruments consisted in sequestrectomy of necrotic bone or superficial debridement/curettage or corticotome/surgical removal of alveolar and/or cortical bone. |
| G4 Traditional surgery + LLLT | G3 protocol + LLLT applications once a week for two months with Nd:YAG Laser (1.25 W, 15 Hz, VSP, 320 µm) of fibre diameter, nonfocused way with scanning method, 2 mm from tissue, for 1 minute and repeated 5 times. |
| G5 Er:YAG laser surgery   | Antibiotic treatment prescribed beginning three days prior to the operation and ending 10 days after it. Bone resection or vaporization of the necrotic areas was obtained with Er:YAG laser 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. |

Figure 1: Stage III BRONJ in a female patient treated with alendronate for osteoporosis.

G4: BRONJ sites treated with antibiotic, traditional surgical therapy, and LLLT. Sites were treated with medical and surgical therapy in association with LLLT (Nd:YAG laser) applications. Surgical operations were performed as described in G3 in association with laser Nd:YAG biostimulation (1.25 W power, 15 Hz frequency, fibre of 320 µm). The laser light was used as described in G2. The first application of LLLT was performed during the surgical intervention. The operated site was then treated every week with LLLT applications (same protocol described for G2) for 2 months.

G5: BRONJ sites treated with antibiotic, Er:YAG laser surgical therapy, and LLLT. Surgical removal of necrotic and peripheral bone was achieved with Er:YAG laser. Bone resection or vaporization 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 (Figures 1, 2, 3, 4, 5, 6, 7, and 8) [16].

Results were evaluated by comparing the performed treatments in cancer and non cancer groups; statistical analysis was performed using Fisher test, and results were considered statistically significant for P < 0.05.
3. Results

Nonsurgical approach adopted on 69 sites induced an improvement in 35 sites (50.7%) and complete healing in 19 sites (27.5%), while surgical approach performed on 97 sites induced an improvement in 84 sites (86.6%), of which, 78 completely healed (80.41% of the total).

Improvement was recorded in 31 out of the 38 (81.5%) BRONJ sites treated in non cancer patients and in 88 out of 128 (68.75%) sites in cancer patients. Complete healing was recorded in 27 out of 38 (71.5%) BRONJ sites treated in non cancer patients and in 69 out of 128 (53.9%) sites in cancer patients.

Results in terms of clinical improvement and complete healing are reported in Tables 4, 5, 6, and 7 for both groups of patients. The mean follow-up was $16.44 \pm 10.95$ months (ranging from 6 to 54).

For non cancer patients, a statistically significant result in terms of improvement was recorded from the comparison between BRONJ sites treated with antibiotic therapy alone (G1) and sites treated with local LLLT applications (G2) ($P = 0.0031$). Moreover, in this group of patients, the comparison between non surgical (G1 + G2) and surgical (G3 + G4 + G5) approach confirmed a statistically significant result in terms of both clinical improvement ($P = 0.0080$) and healing ($P < 0.0001$) (Table 4).
Table 4: Clinical results and statistical analysis in noncancer patients in terms of clinical improvement and complete healing. Statistical analysis in cancer patients: comparison between nonsurgical nonlaser-assisted approach (G1) and nonsurgical laser-assisted approach (G2) and comparison between nonsurgical approach (G1 + G2) and surgical approach (G3 + G4 + G5).

| Treatment          | Sites | Improvement | % | Healing | % |
|--------------------|-------|-------------|---|---------|---|
| G1 Medical therapy | 10    | 3           | 30| 2       | 20|
| G2 Medical therapy + LLLT | 9      | 9           | 100| 5       | 55.5|
| G3 Traditional surgery | 4      | 4           | 100| 4       | 100|
| G4 Traditional surgery + LLLT | 5      | 5           | 100| 5       | 100|
| G5 Er:YAG laser surgery | 10    | 10          | 100| 10      | 100|

G1 versus G2
P = 0.0031
P = 0.1698

G1 + G2 versus G3 + G4 + G5
P = 0.0080
P < 0.0001

Table 5: Clinical results and statistical analysis in cancer patients in terms of clinical improvement and complete healing. Statistical analysis in cancer patients: comparison between nonsurgical nonlaser-assisted approach (G1) and nonsurgical laser-assisted approach (G2) and comparison between nonsurgical approach (G1 + G2) and surgical approach (G3 + G4 + G5).

| Treatment          | Sites | Improvement | % | Healing | % |
|--------------------|-------|-------------|---|---------|---|
| G1 Medical therapy | 22    | 5           | 22.7| 4       | 18.2|
| G2 Medical therapy + LLLT | 28      | 18          | 64.3| 6       | 21.4|
| G3 Traditional surgery | 13      | 7           | 53.8| 7       | 53.8|
| G4 Traditional surgery + LLLT | 34      | 28          | 82.3| 24      | 70.6|
| G5 Er:YAG laser surgery | 31    | 30          | 96.8| 28      | 90.3|

G1 versus G2
P = 0.0046
P = 1

G1 + G2 versus G3 + G4 + G5
P < 0.0001
P < 0.0001

G3 versus G4 + G5
P = 0.0061
P = 0.0726

For cancer patients a statistically significant difference in terms of improvement was recorded when the BRONJ sites treated with antibiotic therapy alone (G1) were compared to those treated with local LLLT applications (G2) (P = 0.0046). Moreover, in this group of patients, the comparison between non surgical (G1 + G2) and surgical (G3 + G4 + G5) approach reported a statistically significant difference in terms of both clinical improvement (P < 0.0001) and healing (P < 0.0001). The comparison between surgical group without LLLT (G3) and surgical groups with LLLT (G4 + G5) highlighted a statistically significant results in terms of clinical improvement (P = 0.0061) (Table 5).

The comparison between the performed treatment in cancer and non cancer patients showed a significant difference in terms of complete healing for surgical approach (G3 + G4 + G5) (P = 0.200).
Table 6: Improvement and healing in relation with primary disease and BRONJ stage independently by the therapy (BM: bone metastasis, MM: multiple myeloma, OP: osteoporosis and/or rheumatoid arthritis).

| Primary disease | Stage | Number of sites | Improvement (%) | Healing (%) |
|-----------------|-------|-----------------|-----------------|------------|
| BM              | I     | 18              | 14 (77%)        | 14 (77%)   |
|                 | II    | 48              | 37 (77%)        | 25 (52%)   |
|                 | III   | 3               | 0 (0%)          | 0 (0%)     |
| MM              | I     | 12              | 9 (75%)         | 8 (66.6%)  |
|                 | II    | 44              | 28 (63.6%)      | 22 (50%)   |
|                 | III   | 3               | 0 (0%)          | 0 (0%)     |
| OP              | I     | 6               | 5 (83.3%)       | 5 (83.3%)  |
|                 | II    | 26              | 22 (84.6%)      | 17 (65.4%) |
|                 | III   | 6               | 4 (66.6%)       | 4 (66.6%)  |

Table 7: Improvement and healing in relation with BRONJ stage independently by the primary disease.

| BRONJ stage | Treatment | Sites | Improvement (%) | Healing (%) |
|-------------|-----------|-------|-----------------|-------------|
| Stage I     | G1        | 4     | 1 (25%)         | 1 (25%)     |
|             | G2        | 6     | 3 (50%)         | 3 (50%)     |
|             | G3        | 3     | 3 (100%)        | 3 (100%)    |
|             | G4        | 7     | 5 (71.4%)       | 4 (57.2%)   |
|             | G5        | 16    | 16 (100%)       | 16 (100%)   |
| Stage II    | G1        | 22    | 7 (31.8%)       | 5 (22.7%)   |
|             | G2        | 30    | 24 (80%)        | 8 (26.6%)   |
|             | G3        | 13    | 8 (61.5%)       | 8 (61.5%)   |
|             | G4        | 32    | 28 (87.5%)      | 25 (78.12%) |
|             | G5        | 21    | 20 (95.2%)      | 18 (85.7%)  |
| Stage III   | G1        | 6     | 0 (0%)          | 0 (0%)      |
|             | G2        | 1     | 0 (0%)          | 0 (0%)      |
|             | G3        | 1     | 0 (0%)          | 0 (0%)      |
|             | G4        | —     | —               | —           |
|             | G5        | 4     | 4 (100%)        | 4 (100%)    |

4. Discussion

Minimally invasive surgical approach with Er:YAG laser and the use of LLLT represent a good choice for BRONJ treatment especially for antibacterial and biostimulant properties. Surgery performed with Er:YAG and followed by laser biosimulation (LLLT) may determine complete mucosal healing and reduce the microbial component, thus decreasing patient symptoms and providing a higher level of quality of life.

Moreover, Er:YAG laser surgery allows partial or total resection of the jaw without using conventional rotary cutting tools. Preservative surgery can also be performed by gradual vaporization of necrotic bone at increasing depths. Surgical ablation of bone tissue is performed reducing the thermal damage to the adjacent tissue with a quicker healing. The Er:YAG wavelength does not cause coagulation or carbonization. It is therefore possible to clearly distinguish avascular portions of the bone from those that are still vascularised. The Er:YAG laser has great potential for hard tissue treatment due to its high absorption by both water and hydroxyapatite. Such a device provides a clean and precise cut with minimal injury to the adjacent hard and soft tissues while producing an ablated surface favorable for cell attachment.

Conservative surgery, maintaining the overall integrity of the jawbone, is chosen on the basis of specific features in individual cases, ranging from simple curettage to debridement of the necrotic area, from sequestrectomy to resection of larger bone portions. The mini-invasive technique of ablation of the necrotic bone usually induces resurface and causes bleeding from healthy bone which could help in the future revascularization.

As already reported in literature [17, 18], medical therapy alone induces only little improvement of BRONJ lesions in both cancer and non cancer patients.

In nonsurgical-treated patients in both evaluated groups, LLLT applications induced a higher improvement of BRONJ suggesting that the application of LLLT can be useful, especially for patients that cannot be treated surgically.

A statistically significant difference was observed for surgical approach, both for a complete mucosal healing and for a clinical improvement.

The evaluation of the percentage of the sites, with clinical healing achieved with the different treatments, clearly
showed how the combination of antibiotic therapy, conservative surgery, and LLLT applications gives better results in both groups of patients.

From our experience, medical approach alone (antibiotic therapy) does not provide permanent clinical outcomes. Symptoms improvement and complete mucosal healing were obtained in 22.7% and 18.2% in cancer patients and in 30% and 20% in osteoporotic patients. Surgical approach performed in early stages of BRONJ induces better results between 53.8% and 100%.

Osteoporotic patients obtained higher levels of improvement with every approach; surgical therapy with or without laser induced complete mucosal healing in all cases (100%).

For cancer patients Er:YAG laser surgery induced complete remission of BRONJ in a statistically significant number of cases (90.3% versus 53.8% obtained with traditional surgery) (Tables 4 and 5); as reported in literature [19–21], this technique allows a miniminvasive surgery probably related to the good results of this approach in BRONJ treatment.

Angier et al. [19], Scoletta et al. [22], and Romeo et al. [23] reported the usefulness of laser biostimulation in BRONJ. Our experience confirms that LLLT in both categories cancer and osteoporotic patients can offer great results in terms of reduction of inflammation and pain control as we already reported [24, 25].

Independently by the performed therapy, the percentage of complete BRONJ healing was related to the stage of disease (Table 7): 75% Stage I, 54.24% Stage II, and 33.3% Stage III.

In conclusion an early conservative surgical approach with Er:YAG laser combined with LLLT, for BRONJ, could be considered as more efficient in comparison to medical therapy alone for the management and quality of life of these patients.

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