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Dental Implants in A Patient with History of Zoledronate Therapy: A Challenging Case

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ABSTRACT

Implant placement in patient with history of bisphosphonate therapy is still controversial due to the risks of osteointegration failure and Biphosphonate related osteonecrosis of the jaws. Very few cases are reported. This paper aimed to report the success at 3 years follow up of 4 implants placed in a female patient with history of breast cancer and zoledronate infu-sions (twice yearly for 2 years).

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Introduction

Bisphosponates (BPs) are effective drugs in the treatment of diseases affecting bone me-tabolism such as hypercalcemia, osteoporosis and Paget's disease, as well as some cancer related conditions such as breast, lung and prostate cancers, due to their ability to inhibit bone resorption [1]. In fact, these drugs are pyrophosphate analogues with high affinity for bone hydroxyapatite which bind preferentially to bones that have high turnover rates. They are divided into three generations according to their nitrogen containing. The third generation (alendronate, risedronate, ibandronate and zoledronate) is character-ized by a very tight adhesion to hydroxyapatite mineral bone which makes them most ef-fective and often prescribed in oncology to metastasis. Besides, Zoledronate (ZOL) is a new-generation intravenous BPS with the greatest affinity and longest retention for bone mineral, and it has been largely utilized these last years in the treatment of osteoporosis and metastatic bone diseases [2].

While oral BPs are poorly absorbed and present a very small bioavailability due to their poor lipophilicity, Intra venous BPs are completely bioavailable and both of them have a very long half- life in bone, ranging among different species from 1 to 10 years, depend-ing largely on the rate of the bone turnover [3].

Despite the fact that BPs greatly increase the patient's quality of life, a severe complica-tion related to their use is now well documented. In fact, BPs related osteonecrosis of the jaws (BRONJ) is one of the most serious complication of BPs therapy characterized by the exposure of a necrotic bone in the maxillofacial region that has persisted for more than 8 weeks in patients who have current or previous treatment with antiresorptive or antian-giogenic agents and no history of radiation therapy to the jaws or metastatic disease to the jaws [4].

Most reported risk factors of BRONJ are periodontal surgery, tooth extractions, poor dental condition, chronic mechanical trauma of the jaw bone and implant placement [4].

Thus, dental implants placement in patients with a medical history of BPs therapy re-mains controversial especially in patient undertaking intravenous BPs [5].

In fact, few cases of dental implants placement in patients treated with Zoledronate were reported in the literature. Besides, implants were generally avoided or contraindicated in these patients due to the estimated risk of implant loss or failure as well as BRONJ on-set. However, many authors reported good results of osteointegration and minimal inci-dence of implant loss in patient taking either oral or intravenous BPs and concluded that dental implants in patients undergoing BPs therapy can osseointegrate and remain func-tionally stable. Moreover, the risk of BRONJ -though existing- could be controlled es-pecially in the absence of other risk factors such as chemotherapy, steroids therapy or lo-cal trauma [6,7].

With this regards, this paper aimed to report the successful outcome at 3 years follow up of dental implants placed in a female patient, with a history of a stage 1 breast cancer and a previous 2years_long Zoledronate therapy.

Case Report

A 52 years-old female patient consulted at the department of oral surgery during the summer of 2017, for the mobility of teeth 22.21.11.12.

The patient reported a history of breast cancer (T1N0M0) operated in 2010 and treated with com-bined chemotherapy and radiotherapy with no recurrence or metastasis till that date. She also had vitamin D supplementation in addition to prophylactic infusions of zoledronate (Zometa 4 mg IV) twice -yearly for 2 years.

Intra oral examination revealed good oral hygiene (Figure 1). However, all the maxillary incisors presented a second degree mobility and a severe alveolar bone loss revealed by the panoramic radiograph (Figure 2) that were attributed to chronic periodontitis and occlusal trauma. The pa-tient had no pain or other symptoms but was very concerned about the esthetic problem and the potential implications for her social and professional life. Conservative approach was impossible and the extraction was indicated. However, the patient refused to have removable prosthesis. Regarding dental implants, the patient was informed of the risks of the implants loss as well as the risk of developing a BRONJ due her medical history of BPS therapy. In this regards an informed consent was obtained before any medical intervention.

Figure 1: Intraoral photography showing malposition of the maxillary incisors and the egression of 21.

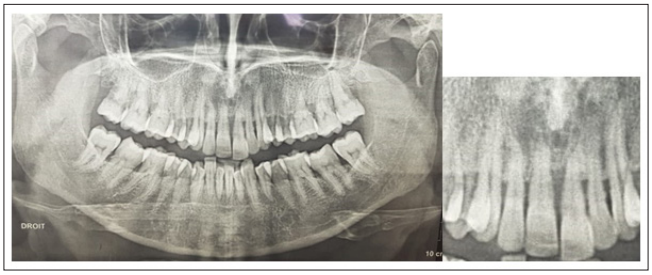

Figure 2: Panoramic radiograph showing severe bone resportion of the maxillary incisors (11.12.21.22) extended to the apical third.

Atraumatic extraction of the maxillary incisors was performed under local anesthesia and antibiotic prophylaxis (amoxicillin 2g/day ,2 days before the surgery extended until mucosal healing) immediately followed by the placement of a removable partial prothesis replacing the teeth 11.12.21.22 (Figures 3 (a) and (b)).

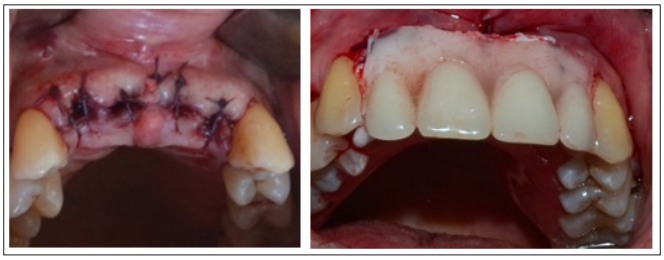

Figure 3: (a) Atraumatic extraction of the maxillary incisors. (b) Immediate placement of an atraumatic partial prosthesis replacing the missing teeth.

The patient was asked to wear this prosthesis as few as possible in order to avoid any possible traumatic lesion. Healing was uneventful and without complaints.

Six weeks later, a CBCT was performed, the decision to place 4 implants replacing each tooth with one by one was made. (Figure 4). The surgery was performed under local anesthesia and antibiotic prophylaxis, 2g of amoxicillin starting 2 days before the implant surgery extended until mucosal healing. A midcrestal incision in the area of the maxillary incisors, with a minor release incision, was performed. After reflection of a mucoperiostal flap, 4 implants (3.75/11.5 mm ,4.2 × 11.5 mm, 4.2/11.5 and 3.75/11.5. Implant master S easy implant by easy prod) were placed. Cover screw were placed, and the implant were fully submerged for a healing period of 5 months. Six months later, the final prosthesis were sealed (Figure 5).

Figure 4: Panoramic radiograph taken immediately after the implant placement showing good orientation of the fixtures

Figure 5: Intra oral photography showing good aesthetic and functional integration of the prosthesis.

Follow up sessions were scheduled every 3 months during the first year , then every six months the next years.

At 3 Years follow up , the panoramic x-ray showed very good osteointegration of the implants with no signs of local infection or

crestal bone resorption (Figure 5). The patient had no subjective complaint and was satisfied with the aesthetic outcome. Further follow up sessions were needed as the risk of complications especially of delayed BRONJ could not be excluded.

Discussion

Bisphosphonates BPs have now been used for decades in both benign and malignant bone diseases and the number of patients using them is expected to increase in the coming years. Zoledronate has recently been used frequently in patient with breast cancer. In fact Earlier research suggested that Zometa might help stop breast cancer from spreading to the bone and might help reduce the risk of the cancer recurrence in women diagnosed with early-stage breast cancer. Furthermore, preliminary data suggest that Zoledronate may have antitumour effects, which may reduce the risk of overall disease progression [7].

In the other hand, dental implants remain the best way to replace teeth in both partial and complete edentulism and are now largely used worldwide. With this regards, implant placement in patient treated by, or with history of BPs therapy remains controversial due to two kinds of potential risks: first, the risk of osteointegration failure given the effect of BPs on bone renewal and second the risk of the onset of biphosphonate related necrosis of the bone where the implant is placed both at the short or the long term.

In the case we report, the patient have had 4 prophylactic infusions of Zoledronate, twice a year (from 2011 to 2013) as part of her stage 1 breast cancer therapy. Thus, deciding to replace her extracted teeth with implants was based on a thorough reflection with regards to her risks of implant failure and BRONJ onset. In fact bisphosphonates, specially intravenous BPS, interfere with the bone turnover process provoking a reduction of bone resorption followed by a reduction in bone forming activity that can lead to microdamages that might jeopardize the implant osteointegration. Furthermore, BPs are known to inhibit angiogenesis which may also have a negative impact on the healing process [8].

However, many studies failed to prove a significant association between implant failure and BPs use. Javed et al showed that the incidence of implant failure was minimal in patients using either oral or intravenous BPs. Besides, Bell and Bell investigated the risk of dental implant failure in patients using BPs for a period varying for 6 months to 11 years and found that the implant success rate in patients using BPs was 95% which was very comparable to the normal success rate (96.6%) [8,9].

Furthermore, Shabestari et al found that neither being on oral bisphosphonate treatment before implant placement nor starting bisphosphonate therapy after implant installation in osteoporotic patients might compromise the successful osseointegration of the implant [10].

In the other hand, despite the fact that Zoledronate has the greatest affinity and longest retention for bone mineral and it is traditionally believed to be an antiresorptive agent, recent animal studies suggested that it could stimulate bone formation and even improve implant mechanical fixation [2]. Moreover, clinical studies revealed that ZOL was associated with decreased early implant migration and reduced peri-implant bone loss [9]. These results were confirmed by Ayan et al, who showed that ZOL did not affect the angiogenesis in bone around implant which might be explained by its inhibitory effects on osteoclasts and improving effects on osteoblasts proliferation, maturation and differentiation [11].

So based on this finding, the history of intravenous BPs was not considered as a major risk of implant failure. However, the risk of developing BRONJ remained plausible. with this regards, the latest systematic review and meta-analysis involving 13857 patients reported that the prevalence of BRONJ in cancer patients receiving zoledronic acid (Zol) ranged from 0.4% to 1.6%, 0.8% to 2.1%, and 1.0% to 2.3% after 1, 2, and 3 years of Zol exposure, respectively [12,13].

Moreover, Filiefel et al reported the triggering factors for BRONJ, regardless of administration routes. The most triggering factor was tooth extraction in 61.7% of the cases. However, spontaneous onset ocuured in 14.8% of the cases, while 7.4% of the cases were caused by prosthesis-induced trauma, 7.2% when history of dental surgery, 5.0% were related to periodontitis, and only 3.9% of BRONJ were triggered by dental implant-related treatment [14]. Thus we can conclude that tooth extraction and mechanical trauma could be considered as riskier than implant placement when it comes to BRONJ onset in this case. Consequently, good alveolar cicatrisation after tooth extraction in our patient, was a predictable factor of good prognosis regarding implant placement.

Additionally, It's well documented that BRONJ affects the mandible more often than the maxilla. In fact, the reported ratio of mandible to maxilla involvement found was 2:1. According to latest estimations, 65% of BRONJ cases were located in the mandible while less than 25% in the maxilla [15]. This could be attributed to the decreased vascularity of the mandible and to the local conditions of the mandible. In the other hand, it has been suggested that the development of BRONJ requires a long period of drug exposure. With this regards the risk of developing BRONJ is related to the duration of therapy and the risk appears to be higher after 3 years of treatment. Lo et al. reported a higher prevalence of BRONJ (0.21%) in patients treated with these drugs for more than 4 years, in comparison with those treated for less than 2.5 years. In the case we report, the patient has had a 2 years duration of Zoledronate therapy and at the time of the implant surgery, she had completed it 5 years earlier [16].

Besides the patient did not have any other risk factors such as tobacco consumption, chemotherapy or corticotherapy and had good oral hygiene.

Furthermore, replacing the missing teeth with a removable prothesis would have had a severe impact on the patient's psychological well-being without a real benefits regarding the risks mentioned above. Once the decision of placing implants has been made, the general precautions for an atraumatic procedure were strictly observed. prophylactic antibiotics has been performed on the basis of some limited retrospective findings [17]. Nevertheless, in such cases with increased risk and limited available evidence, there would be no harm in taking as many precautions as possible.

At 3 years follow up, the implants were both functionally and aesthetically well integrated, with no mobility and no signs of inflammation. On panoramic radiograph neither perimplant radiographic translucency nor crestal bone loss were noticed. With these considerations we can consider our results as a success according to Alberktsson criteria of implant success [18,19].

Author Contributions

All the authors have contributed to the manuscript elaboration. Dorsaf Touil and Rabeb ben Fraj did the writing of the original draft as well as the data gathering. it was reviewed by Ibtissem Grira. All the work was done under the supervision and then the

validation of Pr. Nabiha Douki Head of the department of dentistry at the university Hospital Sahloul, Tunisia. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: Nonoe

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