

BRONJ expert panel recommendation of the Italian Societies for Maxillofacial Surgery (SICMF) and Oral Pathology and Medicine (SIPMO) on Bisphosphonate-Related Osteonecrosis of the Jaws: risk assessment, preventive strategies and dental management

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an adverse drug reaction that negatively impacts on the quality of life of afflicted patients. To date, the pathogenesis of this disease is still controversial and the most effective treatment protocols are still not established. In this scenario, the construction of a preventive strategy for BRONJ and, above all, the identification of efficient dental strategies to manage patients taking aminobisphosphonates (NBP) have become a clear need for physicians and dentists. The Board of the Italian Societies for Maxillofacial Surgery (SICMF) and Oral Pathology and Medicine (SIPMO) appointed a Panel of experts for the study of bisphosphonate-related osteonecrosis of the jaws with the following aims: 1) to provide updated perspectives on categories of patients at risk for BRONJ and give a thorough description of the most recognized risk factors; 2) to supply clinicians with updated strategies for prevention of BRONJ; 3) to provide clinicians with a schematic approach to the routine dental management of patients at risk for BRONJ. The BRONJ pertinent literature was collected and studied. On the basis of available evidence and after discussion among panelists, the main local and systemic risk factors as well as prevention strategies have been reviewed, discussed and presented; in addition, flow charts with clinical recommendations for the dental

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management in patients affected by malignancies or osteometabolic disorders, who are about to start or have already started NBP intake, are provided.

KEY WORDS: Osteonecrosis, prevention and control - Jaw - Practice management, dental.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an adverse drug reaction that negatively impacts on the quality of life of afflicted patients. Since the first report of BRONJ in 2003, hundreds studies have focused on this topic; nonetheless, the pathogenesis of this disease is still controversial and effective treatment protocols are away from being recognized. In this view, the construction of a preventive strategy for BRONJ and, above all, the

identification of efficient dental strategies to manage patients taking aminobisphosphonates (NBP) have become a clear need for physicians and dentists.

In recent years, the fear of precipitating BRONJ in patients undergoing NBP therapy, especially those treated for cancer dissemination, has led to the diffusion of very prudent recommendations, where surgical procedures and dental extraction in particular were thought responsible for BRONJ occurrence in a substantial number of cases and therefore mainly contraindicated.¹ On the opposite, limited consideration was given to dental and periodontal infection foci as possible triggers for BRONJ.²⁻⁵ The growing body of knowledge is changing the common idea that surgery is contraindicated in patients taking NBPs,⁶⁻⁸ and made obvious the need for improved and updated preventive strategies and protocols for routine dental management of these patients.

For these reasons, the Board of the Italian Societies for Maxillofacial Surgery (SICMF) and Oral Pathology and Medicine (SIPMO) appointed a Panel of experts for the study of Bisphosphonate-Related Osteonecrosis of the Jaws, composed of clinicians with proved experience in caring for these patients and basic science researchers.

The present paper, which is an essential part of an entire document on BRONJ, contains the official position of the Italian Societies for Maxillofacial Surgery (SICMF) and Oral Pathology and Medicine (SIPMO) on the strategies for prevention of BRONJ and routine dental management of patients at risk for BRONJ.

Both SICMF and SIPMO believe it essential that this information be largely disseminated among dental practitioners, Maxillofacial Surgeons and other medical specialties.

It is understood that the strategies and treatment algorithms outlined in this paper are based on the current understanding of BRONJ and future modifications and refinements will be possibly required.

Purpose

The aims of this paper are:

- 1) to provide updated perspectives on subjects categories at risk for BRONJ occurrence and give a thorough description of the most recognised risk factors;
- 2) to supply clinicians with updated strategies for prevention of BRONJ;

- 3) to provide clinicians with a schematic approach to the routine dental management of patients at risk for BRONJ, specifically designed for each category of risk.

Risk factors for BRONJ

Local risk factors

The main local risk factors reported in the literature are listed below in order of importance and summarized in Table I.⁹⁻¹⁴

This Panel Commission considers useful to point out that at the time of this writing, most of the available data in the literature on risk factors for the development of BRONJ refers to subjects with oncologic/hematologic diseases and only a small part to patients with osteometabolic disorders. In the light of the different frequency of BRONJ in the two categories of subjects, it is likely that each specific risk factor will contribute to disease onset in a different way in patients with cancer and osteoporosis. This explains why strategic choices of prevention and dental behaviours differentiated for the two groups of subjects are necessary (see chapter on dental prevention and management).

Dento-alveolar surgery

The relationship between the performance of surgical procedures in the oral cavity (e.g. avulsion of erupt-

TABLE I.—*Local risk factors.*

Dento-alveolar surgery	<ul style="list-style-type: none"> – Tooth extraction – Bone surgery – Periapical surgery – Periodontal surgery
Dental implant surgery	
Dental/periodontal inflammation and peri-implant disease	<ul style="list-style-type: none"> – Chronic periodontitis – Odontogenic infections <ul style="list-style-type: none"> – endodontic abscess – periodontal abscess – Endoperiodontal lesion – Perimplantitis – Poor oral hygiene
Removable incongruous dentures	
Anatomical conditions	<ul style="list-style-type: none"> – Palatine torus – Lingual tori – Exostosis – Pronounced mylohyoid ridge

ed or impacted teeth, periapical surgery, periodontal surgery) and the onset of BRONJ in subjects treated with NBP is certainly the most studied, although still not supported by definitive evidence. Among the thousands of cases of BRONJ nowadays reported in the literature, the event “dento-alveolar surgical procedure” has been reported as the most ‘common factor temporally associated with BRONJ, with a risk of developing up to 44 times higher¹⁴ as compared to patients not subjected to any surgical procedure.

We report a general consensus, even among different scientific societies such as the Italian AIOM (Italian Association of Medical Oncology) [<http://www.aiom.it>], the SIF (Italian Society of Pharmacology) [<http://www.sifweb.com/>], the SIOMMMS [<http://www.siommmms.it>] in considering the dental-alveolar surgery an important risk factor for the development of BRONJ, if not the most relevant, even in subjects undergoing NBP treatment (currently or previously) for osteoporosis. In fact, the rate of BRONJ following dento-alveolar surgical procedures ranges from 50 - 100% in the published case series.^{2, 4, 11, 15-19}

Dental implant surgery

The placement of osseointegrated implants is considered a potentially risky surgical procedure, like the dento-alveolar surgical procedures, especially in patients treated with intravenous NBP for oncological diseases. It is not known what is the real risk of BRONJ resulting from implantation in cancer patients undergoing NBP therapy, but it is important to consider the fact that most of the published cases of osteonecrosis occurred at implant sites that had been rehabilitated before initiation of NBP therapy.^{11, 19}

The majority of recent clinical studies aiming to assess the risk of BRONJ linked to the insertion of dental implants were conducted in subjects treated with NBP for osteoporosis.^{12, 21, 22} In these subjects, the risk of developing BRONJ was low and partly related to the cumulative dose and the duration of NBP treatment.^{20, 23, 31} Of course, this risk was much lower than the same implant procedures performed in patients with cancer treated with intravenous NBP.

It is the opinion of this Commission that implant surgery definitely poses a risk for BRONJ development during NBP treatment (previous or current), like all invasive dento-alveolar surgical procedures, both in cancer and in the osteoporotic patients. Nevertheless, it has to be stressed out that the risk of

BRONJ occurrence highly differs between the two categories, being much less for the osteoporotic patient. The data offered in the literature suggest that the NBP orally administered for a period not exceeding three years, in patients without co-morbid factors (chronic metabolic diseases, or corticosteroid therapy) does not appear to produce significant effects on the success of implant procedures.²⁴⁻³³

Beyond the risk of BRONJ due to the surgical procedure itself, patients receiving osseointegrated implants will be exposed to an increased risk of BRONJ occurrence year after year, in case of peri-implantitis, due to the gradual accumulation of the drug.

Cases of BRONJ arisen on implant sites in osteoporotic patients during treatment with NBP reported in the literature show that the elapsed time between implant placement and BRONJ occurrence varies from a few months to several years¹⁹. This seems to confirm that not only the surgical procedure itself but also and more often the repeated occurrence of peri-implant inflammation would start the disease process.

The reduced immune defences of the bone caused by chronic therapy with NBP and the absence of a barrier at the bone-implant interface promote the risk of peri-implantitis and the spread of infection to the surrounding bone structure conveyed by the implant.

This Commission believes that the incremental risk of developing BRONJ following dental implant placement should be clearly discussed with the patient who takes NBPs, especially if the patient is likely to continue the treatment lifelong. The final indication to implant surgery should be subjected to the acquisition of a large and detailed informed consent.

Dental-periodontal inflammation and peri-implant disease (chronic periodontitis, odontogenic infections, endo-periodontal lesions, peri-implantitis, poor oral hygiene)

Poor management of dento-periodontal health and lack of control of plaque in a patient treated with NBP significantly increase the risk of developing BRONJ during treatment and provide a factor of aggravation of the clinical picture in case of already diagnosed BRONJ.^{9, 24-28} Infact, periodontal disease was diagnosed in 84% of cases in a large sample of patients with BRONJ.¹¹ Patients with a history of inflammatory dental disease, periodontal and dental

abscesses, when exposed to high-dose intravenous NBP, are seven times more likely to develop BRONJ compared to individuals with the same dental-periodontal problems but not in treatment with NBP.¹⁴ Like the periodontal disease, peri-implantitis may increase the risk of BRONJ.

Removable dentures

The removable prosthetic devices are considered risk factors for the development of BRONJ in that they can damage the mechanical barrier of the oral mucosa, facilitating penetration of microbes within the bone, if not well adapted to the mucosal surfaces. It has been documented a significant correlation between the use of removable dentures and the development of BRONJ in a population of metastatic cancer patients treated with high-dose iv NBP,^{29, 30} a result which was not confirmed by other studies. Dental malocclusion is not a risk of BRONJ at this stage.

Anatomical conditions

The presence of anatomical anomalies (e.g. mandibular tori and/or palatal exostosis, especially prominent mylohyoid crest) can be a risk factor for the development of BRONJ, especially in patients wearing total removable dentures in the maxilla and partial or total in the jaw.¹

In conclusion, tooth extraction and incongruous removable dentures are the most frequently cited local risk factors in the international literature,^{29, 34} while, anatomical anomalies, implant surgery and elective dento-alveolar surgery are under reported, likely because of the limited number of elective surgical operations performed to date in patients at risk for BRONJ.

Drug-related and systemic risk factors

In a multifactorial and relatively infrequent disease as it is BRONJ, it would be useful to identify risk factors of the disease that could help to distinguish patients at high and low risk, with consequent impact in terms of prevention and early detection. To obtain statistically relevant data there should be the need for the following:

a) cohort data on numerous samples of patients

treated with NBP, with and without BRONJ, to study (multivariate analysis) the characteristics in question;

b) statistically appropriate case-control studies, comparing cases of BRONJ and selected “controls”;

c) comparison of characteristics between groups of patients with BRONJ (e.g. records of cases) and case studies of populations treated (e.g. patients referred by insurance systems, epidemiological data on the general population).

Unfortunately, there are currently no definitive data on risk factors.³⁵ Indeed, the paucity and heterogeneity of cohorts of BRONJ published,^{14, 30, 36, 37} the small number of case-control studies^{29, 38} as well as the scarcity of sufficiently large database for phase III clinical trials^{39, 40} mean that it is impossible to draw conclusive remarks. Therefore, the Commission decided to summarize in Table II the risk factors so far reported in the literature, identifying for each level of “strength” without considering the merits of scientific evidence of the level or degree of recommendation.

TABLE II.—*Drug-related and systemic risk factors.*

Drug (NBP):	
- Molecule (zoledronate versus other)	+++
- Route of administration (intravenous versus oral)	++
- Cumulative dose	+++
- Duration of treatment	+++
Underlying disease (for which treatment with NBP is indicated):	
- Solid tumors	++
- Multiple myeloma	++
- Non- cancer disease (metabolic)	+/-
Supportive care:	
- Chemotherapy	-/+
- Steroids in cancer patients	-/+
- Steroids in patients with non- cancer disease (dismetabolic)	+
- Antiangiogenic cancer patients	++
- Thalidomide	+/-
- Erythropoietic stimulation factors	+/-
Lifestyles:	
- Smoke	+/-
- Alcohol	-/+
- Obesity	+/-
Personal characteristics	
- Sex	+/-
- Age	+/-
- Genetic factors	+/-
Concomitant disease (comorbidity):	
- Diabetes	+/-
- Rheumatoid arthritis	+
- Hypocalcemia, hyperparathyroidism	+
- Renal dialysis	+
- Anemia	+/-

We analyze in detail the following risk factors:

1) molecule: in hematologic and oncologic patients, zoledronic acid (used in most patients with BRONJ but also the drug most commonly used, at least after 2002) seems to result in a statistically higher risk of BRONJ^{14, 30, 36, 38, 41} compared with pamidronate, despite the absence of randomized studies; insufficient data do not allow a definitive comparison with ibandronate, even if it appears to be at lower risk.²⁹ In non-cancer patients, there are currently no data comparing alendronate and risedronate (the two most widely used drugs).

2) Route of administration (intravenous vs. oral): the risk is much higher for NBP administered intravenously, but this is closely connected to their prevalent use in cancer patients (at total doses and durations significantly higher).^{38, 42, 43}

3) Total dose of NBP intravenously administered (cumulative dose): data are essentially unique in indicating an increased risk with an increase of total dose of NBP intravenously administered to cancer and haematological patients, both for the zoledronate and for pamidronate.^{14, 30, 36} As previously reported, there are no follow-up data sufficient for zoledronate and ibandronate intravenous with doses every 3-12 months in non-cancer patients. Cumulative dose and duration of treatment with oral NBP: the majority of cases of BRONJ were observed in patients treated for years (usually more than 2-3 years) with an average of 4.6 years, according to the review by Palaska *et al.*⁴⁴

4) Duration of treatment with intravenous NBP: on average BRONJ patients were treated for longer periods than those without BRONJ. In fact, the duration of intravenous treatment with NBP is correlated with the total dose of drug administered, given the type of monthly administration, continuous and indefinite in time recommended by major guidelines until 2007.^{13, 36, 37} In a recent review of the literature,⁴⁴ the minimum average time for the appearance of BRONJ turned out to be respectively 1.8 years and 10 months for zoledronate, 2.8 years and 1.5 years for pamidronate. Finally, despite the lack of studies that analyze separately the factor "survival time" by the "duration of treatment with NBP", the increased survival in cancer and hematological patients, understood as the time between the diagnosis of cancer and the exitus, could represent in the future^{13, 14, 37, 40, 45} an additional risk factor as responsible of prolonged exposure to other risk factors already known.

5) Underlying disease: patients with malignancy are usually defined at a higher risk, even if it seems to come from different types of treatment with NBP⁴² Among hematologic and oncologic patients, seems to infer that patients with multiple myeloma are at increased risk of BRONJ than those with prostate or breast cancer in the metastatic phase; this would be deductible based on the highest data rate/incidence (6-12% *vs.* 1-5%) and it is also based on the relative lower frequency of myeloma disease,^{40, 46} but some authors have not confirmed this increased risk and tend to explain the higher frequencies with a higher average exposure to the NBP.³⁶

6) Chemotherapy treatments: there are no statistically robust data combining BRONJ to an increased risk of "chemotherapy" or individual chemotherapy drugs,^{38, 47} but these aspects have not been adequately studied.

7) Steroid treatments: low and high doses of steroids were not risk factors in cancer patients in one study,³⁸ while positive data have been reported in patients with myeloma.⁴⁷ Prolonged use of oral steroids associated with oral NBP may be a cofactor in the onset of BRONJ.⁴⁸⁻⁵⁰

8) Antiangiogenic treatments: the use of latest-generation biological drugs, with anti-angiogenic function (*i.e.* bevacizumab, sunitinib, sorafenib) in association with NBP in patients with bone metastases from solid tumors seem to increase the incidence of BRONJ,^{3, 41, 43, 51} but there are no data on sufficiently large series, with the partial exception of bevacizumab.⁵² Conflicting data have been published on the role of thalidomide in patients with multiple myeloma, due to methodological difficulties of the early studies and probably for the almost systematic use of the drug (in the various lines of therapy) in the last year.^{36, 38, 53}

9) Erythropoietic factors: they are reported as a risk factors in a study of patients with myeloma.⁴⁷

10) Smoking: predictive value asserted by some authors,^{38, 54, 55} but denied in other studies.^{29, 30}

11) Alcohol: It often cited as a possible risk factor, but without statistical data in favor.

12) Obesity: a significant achievement in one study.³⁸

13) Gender: not available unique data at present to a preference in the male or the female (often unbalanced series on the basis of the underlying disease).

14) Age: although in some series data are in favor

of a correlation between age and risk of BRONJ,^{13, 47, 56} the higher prevalence of cases in older age groups seems likely linked to normal age distribution of metastatic cancer patients.

15) Diabetes: claimed by some authors (Khamaisi 2007; Urad 2009) but not confirmed by others.^{19, 54, 57}

16) Rheumatoid arthritis: patients with rheumatoid arthritis treated with steroids as well as immunological drugs, seem to have a higher risk of oral BRONJ related to NBP.^{15, 50, 58}

17) Hypocalcemia and hyperparathyroidism: a single study it seems positive and is awaiting confirmation. There are insufficient studies that evaluate a possible role of hypovitaminosis D, demonstrated in animal models.⁵⁹

18) Dialysis: in a single trial was recorded a positive association between dialysis and BRONJ.⁴⁷

19) Anemia: low serum hemoglobin levels were reported in the same Canadian study.⁴⁷

20) Genetic factors: in a preliminary study, some variants of the CYP2C8 gene were predictive of BRONJ in patients with myeloma,⁵⁶ but this result was not confirmed in patients with prostate cancer⁶⁰ or in another work on patients with myeloma.⁵⁴ In the latter study, however, other gene determinations were predictive of BRONJ.⁵⁴ In an Italian study,⁶¹ variants of another gene (FPDS) seem to be correlate with the risk of BRONJ. Pharmacogenetics is a field of research therefore, still open.

Other conditions (*e.g.*, immunosuppression, hypertension, vascular disease, dyslipidemia, hyperviscosity syndrome) have been suggested as possible risk factors assuming the etiopathogenetic hypothesis of an ischemic necrosis of BRONJ and / or similarity to the femoral necrosis,^{42, 62} but there are no data to confirm or deny this hypothesis.

Dental management of the patient

Prevention remains the most significant approach in order to protect the health of the patient requiring NBP therapy. However, the incomplete understanding of the etiopathogenetic bases of BRONJ, limits the possibility and the effectiveness of the preventive control of risk factors. Among the latter, as is known, the most significant are surgical procedures involving the maxillary bones (*e.g.* tooth extraction), periodontal infections and incongruous removable dentures. It seems evident that they are

the absolute responsibility of dental professionals, which have a major role in prevention strategies of BRONJ. This requires filling gaps in knowledge and management of the problem by the prescribing physician and the dentist,⁶³ as well as deficiencies in information the patient.⁶⁴ All this undoubtedly makes it very difficult to isolate the risk factors and patients and therefore, complicates the preventive approach and its effectiveness. In this regard, a number of recommendations for dental professionals, have been reported in the literature but their effectiveness in reducing the risk of BRONJ is often controversial and still don't have adequate scientific evidence. Given the current recommendations, the Commission in this section presents a guide for the dental management of the patient before, during and after treatment with NBP as a means of easy consultation and immediate clinical applicability.

A rational preventive approach must take into account the following parameters:

- type of bisphosphonate (BP): aminobisphosphonates (NBP) *versus* non-aminobisphosphonates;
- indication to aminobisphosphonate therapy (NBP) (oncologic disease *versus* osteo metabolic disease);
- timing of administration of the NBP (immediately before *versus* during treatment with NBP);
- dental procedures (therapeutic *versus* rehabilitation).

Type of bisphosphonate

NON-AMINOBISPHOSPHONATES

To date, for bisphosphonates not containing amino groups, there was no evidence of association with BRONJ, unless in individual and sporadic case reports, so the relevant medical history on the taking of this class of drugs does not change the behavior of the dentist, and the standard management protocols of oral health.¹

AMINOBISPHOSPHONATES

NBP are, to date, the only class of bisphosphonates that have been associated with the development of BRONJ. Therefore, the following recommendations are applicable only to them.

Indication for aminobisphosphonate therapy

ONCOLOGIC DISEASE

The available epidemiological data indicate a close association between the occurrence of BRONJ and high- power NBP administered intravenously in cancer patients,¹ the cancer patient who needs NBP requires a precautionary approach that begins even before the administration of NBP and continues regularly throughout the duration of treatment and also at the end of it. This is obtained through the coordinate action of various professionals, including dentists (management of oral problems and their prevention), the oncologist (management of cancer disease) and the physician and/or other specialists (management of comorbid conditions).

OSTEOMETABOLIC DISEASE

The analysis of the literature shows a less robust relationship between BRONJ and NBP administered orally⁶⁵⁻⁷³ for guidance on the prevention and/or treatment of osteometabolic diseases (*e.g.*, osteopenia, osteoporosis). In these subjects, the incidence of BRONJ turns out to be very low, and it was estimated to 0.7/100000 person-years of exposure.⁷⁰ These data, obtained by dividing the number of reported cases of BRONJ and the number of doses of alendronate from the date of its placing on the market, could potentially underestimate the problem. In fact, data from clinical studies indicate an incidence of BRONJ in patients taking weekly oral alendronate equal to 0.01% to 0.04%.⁷⁴ Overall to date, the risk would seem clinically not significant, however, not enough to justify the refusal by the dentist to refer to dental treatment the patient receiving NBP, in the absence of other specific contraindications. Indeed, the lack of treatment could prolong or precipitate inflammatory conditions / infections that may increase the risk of BRONJ. Regarding, however, osteoporosis treatment with a single annual dose of zoledronic acid intravenously, a large prospective study showed no significantly increased risk of BRONJ with this regimen.^{75, 76}

Therefore, the cancer patient who is about to start therapy with NBP, requires a preventive approach compared to the previous, fewer restrictive BRONJ category, which consists in the diagnosis and treatment of periodontal and dental disease,

like the general population of similar age and sex. This approach must begin within 6 months after the first administration of NBP and continue regularly throughout the duration of treatment and also at the end of it, through the coordinated action of several professionals, including dentists (oral management of problems and their prevention) and the physician and / or other specialists (management of comorbid conditions).

Timing of NBP administration (immediately before versus during treatment with NBP)

The primary prevention of BRONJ, as far as limited to the control of known risk factors, is done in patients who are about to start NBP therapy or already take it. In both cases, the goal of prevention is to maintain and/or re-establish the dental-periodontal health of the patient to reduce the chance that inflammatory/infectious events occur. This would require invasive procedures, which together are the main local risk factors for BRONJ. In addition, the patient, in both situations, must be informed of the risk of BRONJ and made aware of its manifestations in order to alert promptly the physician/dental care allowing an early diagnosis⁶⁴. More specifically, the following is the recommended behavior in the two occurrences.

ADMINISTRATION OF AMINOBISPHOSPHONATES PLANNED BUT NOT YET STARTED

In patients who have to start taking NBP must be carefully evaluated the dento-periodontal status and previous prosthetic rehabilitation, both by clinical examination performed by a dentist with a radiographic evaluation, so that any outstanding issues or conditions of uncertainty (*e.g.* teeth with questionable prognosis), can be readily and properly resolved, preferably before the start of treatment with NBP, especially if this requires intravenous NBP for oncology indications. Initiation of therapy should be delayed until the complete biological healing of the oral tissues,⁷⁷⁻⁷⁹ consistent with the underlying disease that determines the indication for administration of NBP and critical assessment of the clinical who prescribes them. In other words, according to the ministerial recommendations,⁸⁰ prior to administration of the NBP for the oncological patient should be referred to a dentist, the latter, provides for the

assessment of oral status, the treatment of local diseases and establishment of an adequate program of prevention and maintenance of oral health.

The opinion of this Commission is that this behavior is desirable and even necessary for the administration of NBP for non-oncological indications, in which case the evaluation and eventual dental rehabilitation should be conducted, ideally, before the administration of the BP or otherwise in the next few months after it (within 6 months), given that the duration of treatment with NBP is a significant risk factor for BRONJ.

CURRENT ADMINISTRATION OF AMINOBISPHOSPHONATES

Patients already taking NBP must be included in a rigorous program of dental-periodontal prevention and/or supportive periodontal therapy in order to minimize the risk of tooth decay or periodontal/peri-implant problems, and supervision of those in place. In this regard, patients must perform periodic inspections at a rate not less than that normally used in protocols of oral and periodontal maintenance in the general population. This, according to dental-periodontal status and age of the patient, involves conducting the re-evaluation of the patient every four or six months⁸¹. The prosthetic rehabilitation should be included methodically in the periodic reevaluation, in particular, the detachable type must be monitored to check for and remove any trauma to the mucosa (especially in the posterior and lingual region of the jaw). It is necessary to keep in mind that a positive correlation between duration of exposure to NBP and risk of BRONJ has been documented in the literature⁸². In this respect, it was shown that, for the oral NBP, the risk increases significantly when the duration of NBP exposure exceeds three years.³⁴

The rather long half-life of NBP causes a long lasting inhibition of osteoclast function. The effects of NBP on bone may be very prolonged in time, even after a single administration. It has been shown that these molecules are present in the bone even after many years from the date of their assumption. It seems intuitive that the more prolonged is the time that elapses between the end of drug exposure and invasive dental treatment, the greater will be the potential metabolic and vascular recovery of the bone and coating tissues,⁸³ with potential reduction of risk.

Dental procedures versus therapeutic rehabilitation

Compared to the oral health of a patient about to begin therapy or already assumes NBP, two possible scenarios can be realized:

1. maintained oral health, for which are required only preventive dental-periodontal procedures or elective rehabilitative procedures;
2. Presence of dental- periodontal or peri-implant disease and / or mucosal lesions, for which it is necessary an appropriate treatment.

MAINTAINED ORAL HEALTH

Whether treatment with NBP is in progress or planned, the primary objective will be to maintain the status of oral health through the normal procedures of prevention (periodic checks, application of topical fluoride, maintaining hygiene and / or support periodontal treatment, screening for mucosal lesions) to reduce the risk of BRONJ connected to inflammatory/infectious odontogenic phenomena and related surgical procedures.^{79, 80, 84} Any elective procedures (prosthesis, orthodontics) will still be possible, while elective invasive procedures (e.g., dental implant surgery, preimplant bone surgery), will be carefully considered depending on the underlying disease, the type and amount of NBP changed over time. In particular, whether the administration of NBP has not yet started, the therapies of choice can, theoretically, be carried out according to common protocols. In case of invasive procedures, they will be completed before the start of treatment with NBP, always bearing in mind the real utility of the procedure for the patient and its priorities, especially for the cancer patient. If the therapy with NBP for oncology indications had already started, elective-invasive therapies are contraindicated and should be avoided.^{79, 80}

For this reason, the Commission confirms that in cancer patients are always to be considered contraindicated preimplant osseous surgery and dental implant surgery, whether treatment with NBP is in progress or planned. This approach is less stringent in the case of therapy with NBP for osteometabolic diseases, during which the invasive procedures (dental implant surgery and preimplant bone surgery) may be performed if the therapy is started for less than three years and there are no other risk factors; if specific risk fac-

tors are present and / or treatment with NBP has persisted for more than three years, should be assessed case by case.

Some authors^{1, 8} indicate the possibility of suspending the administration of the bisphosphonate 3 months before the elective invasive procedure, consistent with the underlying disease and prior arrangement with the doctor, (so-called “drug holiday”) and take it again once the biological process of tissue healing. The Commission underlines the fact that there is currently no scientific evidence to support the real utility of the “drug holiday”.

PRESENCE OF DENTOPERIODONTAL OR PERI-IMPLANT DISEASE AND/OR MUCOSAL LESIONS OF TRAUMATIC NATURE

These should be managed before the start of treatment with NBP, consistent with the pathology that requires the administration of the bisphosphonate. If the administration of NBP has already started, as a criterion of general guidance, the elimination of the inflammatory/infectious hotbed should not be delayed. The therapeutic procedures aimed at the treatment of inflammatory/infectious diseases in place are always indicated, by application of specific protocols, if required.⁷⁷⁻⁷⁹

Any elective procedures (prosthesis, orthodontics), also and especially if invasive (e.g., implant surgery, preimplant bone surgery), will be carefully considered and will be possible, unless contraindicated, once resolved inflammatory/ infectious processes.

Here are analyzed the various dental procedures with recommendations for clinical management of patients.

The different therapeutic procedures will be considered in the two risk categories: patients treated with NBP for oncology indications and for osteometabolic diseases. Individual procedures will be analyzed at two different stages: before the assumption of the NBP, and while taking the NBP. In this last phase is assimilated also the occurrence in which the patient has terminated or discontinued therapy with NBP.

The levels of risk and the feasibility or otherwise of different dental procedures will be provided (Figure 1, 2).

Therefore, in this chapter will be used the following notations:

- low risk: BRONJ eventuality is unlikely;

- high risk: probability of BRONJ is significantly concrete;

- risk is not defined: there is no evidence to allow even an approximate measure of the risk of BRONJ related to a procedure in itself and/or possible complications of the procedure. Especially when these are risk factors and are able to actualize even from a distance of time, can be added to the increase of the total amount of NBP and their period of administration.

In view of the connotation of risk, dental procedures are classified as:

- indicated: no or low risk, and / or there is a need to perform the same procedures as the benefit derived from them far exceeds the possible risk of BRONJ

- possible: pretty low risk, if any, in the absence of specific contraindications, there is no need to perform them that characterizes the procedures “indicated”;

- not indicated: the risk is not defined so caution is recommended in planning treatment by careful consideration of all risk factors, comorbidities, the details of the specific procedure to be carried out strictly on a case by case basis;

- contraindicated: the risk of BRONJ subsequent procedure is high, and / or benefits are insubstantial.

Routine dental management for patients at risk for BRONJ

Dento-alveolar and preimplant surgery

Generally, before the start of therapy with NBP for oncology or osteometabolic indications, dento-alveolar surgical therapies (see invasive therapeutic procedures) are indicated in order to eliminate inflammatory and infectious foci, or any dental elements with a dubious unchangeable prognosis.

If treatment with NBP has already begun, in patients with osteometabolic diseases, invasive therapeutic procedures (tooth extraction) are not generally contraindicated.¹ However, for patients treated with intravenous NBP for oncology indications the risk of developing BRONJ following tooth extraction is increased up to 53 times.²⁹ For this reason, in most publications of the last years, oral surgery procedures interesting bone and especially dental extractions were considered contraindicated in these

TABLE III.—*Clinical recommendations for the dental management of patients about to start NBP therapy or already NBP users.*

	Malignancies		Osteometabolic disorders	
	NBP therapy about to start	NBP therapy already started	NBP therapy about to start, or started (<3 years)	NBP therapy already started (>3 years) +/- risk factors
Dento-alveolar surgery and preimplant bone surgery	Indicated: dental extractions* Contraindicated: GBR preimplant bone surgery Necessary await until complete wound healing before starting NBP therapy (4-6 weeks) * If NBP administration cannot be delayed, use prevention protocols with mucoperiosteal flap surgery for primary wound closure	Indicated: dental surgery* Contraindicated: GBR preimplant bone surgery Advisable: suspend NBP therapy for the period between the surgical procedure and wound healing (4-6 weeks), if compatible with malignant disease stability and in accordance with the physician prescribing the NBP * Use prevention protocols with mucoperiosteal flap surgery for primary wound closure	Indicated: dental extractions Possible: GBR and bone preimplant surgery	Indicated: dental surgery* Possible: GBR and bone preimplant surgery * Use prevention protocols with mucoperiosteal flap surgery for primary closure of the wound
Restorative dentistry	Indicated	Indicated	Indicated	Indicated
Endodontics	Indicated	Indicated	Indicated	Indicated
Dental implant surgery	Contraindicated	Contraindicated	Possible* *exhaustive information of the patient for potential long-term risk of BRONJ	Possible* * exhaustive information of the patient for potential short- and long-term risk of BRONJ
Ortodontics	Possible	Possible (use carefully controlled forces)	Possible	Possible
Periodontology: Hygiene and non surgical therapy	Indicated	Indicated with a 4 month frequency	Indicated	Indicated with a 4-6 month frequency
Periodontology and endodontic surgery	Indicated* *Only if aimed at treating significant ongoing inflammatory-infective processes not treatable by means of non invasive approaches. If NBP administration cannot be delayed, consider dental extraction. Necessary: await until complete wound healing before starting NBP therapy (4-6 weeks)	Indicated* *Only if aimed at treating significant ongoing inflammatory-infective processes not treatable by means of non invasive approaches. Use prevention protocols with mucoperiosteal flap surgery for primary wound closure; it is mandatory to obtain a stable wound closure.	Indicated	Indicated* *Only if aimed at treating significant ongoing inflammatory-infective processes not treatable by means of non invasive approaches. Use prevention protocols with mucoperiosteal flap surgery for primary wound closure; it is mandatory to obtain a stable wound closure. Possible** **elective procedures (e.g. for aesthetic reasons)
Fixed dental prosthesis	Possible	Possible Mandatory: do not invade "biologic width" (check precision of cervical marginal fit; consider supragingival finish line)	Possible	Possible Mandatory: do not invade "biologic width" (check precision of cervical marginal fit; consider supragingival finish line)
Removable dental prosthesis	Possible	Possible Mandatory: check for and avoid mucosal traumas; consider soft relining; 4 months frequency of follow up.	Possible	Possible Mandatory: check for and avoid mucosal traumas; consider soft relining; 4-6 months frequency

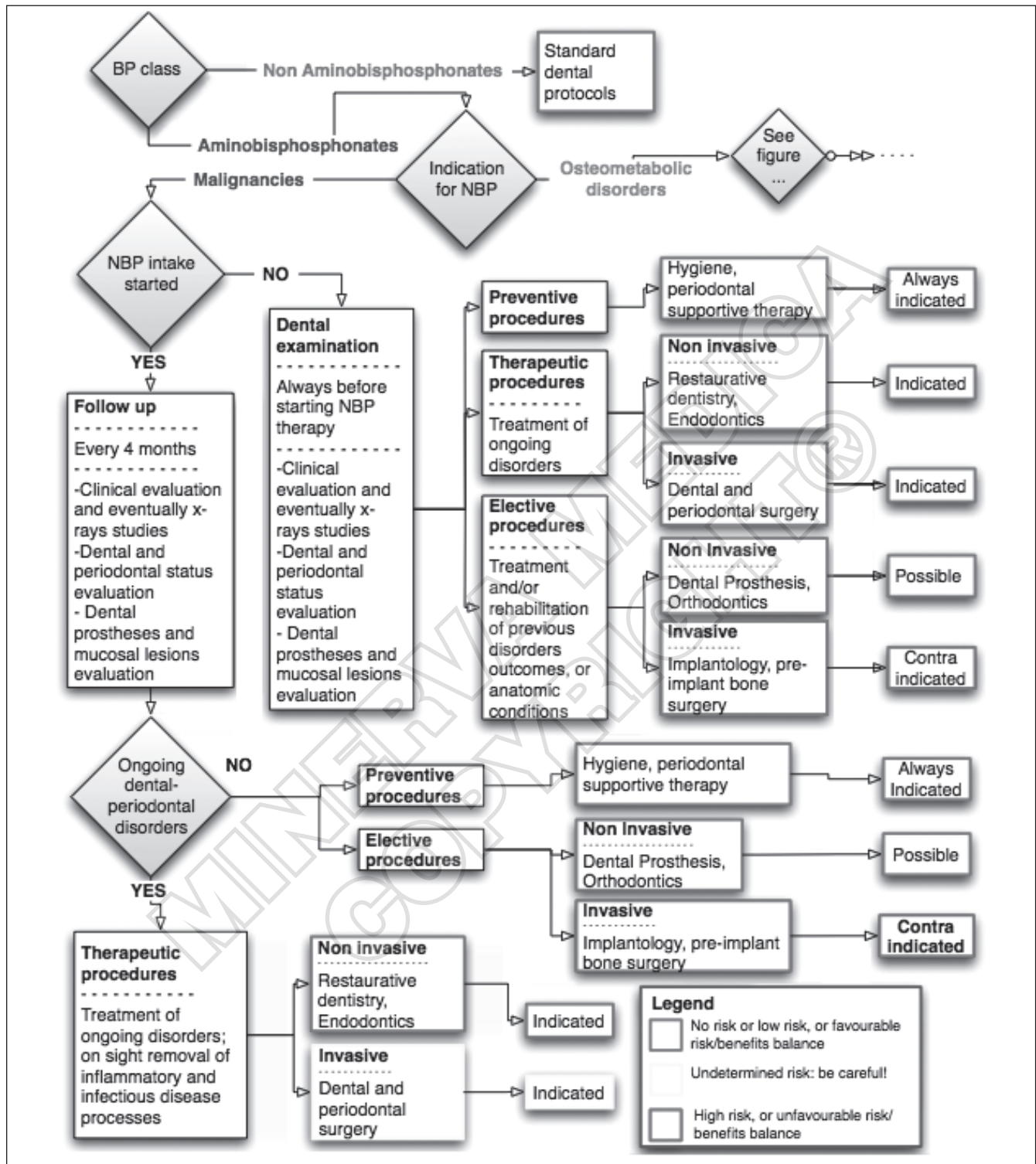


Figure 1.—Schematic diagram of the appropriate dental management of patients at risk for BRONJ-malignancies.

patients. However, in this regard should be made a few comments: having regard to the involvement of infectious-inflammatory mechanisms in the genesis of BRONJ, in the light of the significant decline in BRONJ incidence observed after the introduction of specific protocols of oral prevention in patients with NBP⁸⁴, failure to perform invasive therapeutic procedures when they represent the ultimate solution to inflammation/infection in the jaw bones (*e.g.* those associated with impaired or non-recoverable dental elements), maintaining these processes active, may increase the risk of BRONJ more than the performance of the therapy.

In fact, it has been shown that after tooth extraction, BRONJ occurs in those cases where the alveolar bone is already affected by alterations in osteomyelitis highlighted histologically,⁶ probably triggered by the contribution of inflammation/infection that indicated the extraction. Therefore, surgery not only is not, in itself, a risk factor, but it may reduce the risk of BRONJ by early eliminating inflammatory/infectious outbreaks.

In this sense, encouraging results following invasive therapeutic procedures in cancer patients treated with intravenous NBP, in appropriate prevention protocols, have been recently reported.^{6, 85} These protocols provide for the administration of systemic antibiotics and oral antiseptic pre and/or post-surgery, performing atraumatic extraction procedures and as common to all protocols, the mobilization of mucoperiosteal flaps for primary closure of the surgical site.

Regarding the type of antibiotic and duration of its administration, the different protocols are not unique. In general, broad-spectrum antibiotics have been used, particularly amoxicillin (1 g, 3 times/day) with or without clavulanic acid, even in combination with metronidazole (500 mg, 2 times/day) or, in case of allergy to penicillin, erythromycin (600 mg, 3 times/day), clindamycin (600 mg, 2 times/day) or ciprofloxacin (500mg, 2 times/day). In relation to the duration of preoperative administration, some reports indicate the best results in case of prolonged pre-operative antibiotic therapy (3-4 weeks),⁸⁶ while others show good results with short preoperative antibiotics (started three days,⁸⁷ or 1 day⁸⁸ prior to extraction) or with treatment started the same day of extraction.⁶ The execution of professional oral hygiene procedures performed two or three weeks before surgery associated with the daily use of chlo-

rexidine mouthwash appears to increase further the level of effectiveness of therapeutic invasive procedures.^{87, 88}

The continuation of postoperative antibiotic therapy in the protocols mentioned has been reported in a range from 5 days^{88, 89} to 17 days.⁸⁷ In this regard, an opinion cannot be expressed about the optimal choice that is, ultimately, left to the clinician's opinion with regard to the specific case, since the protocols reported are not comparable and their effectiveness is based on currently insufficient scientific evidence.

Some protocols proposed to perform the extractions with minimally invasiveness of the bone,⁸⁷ to reduce which the use of ultrasonic surgical equipment to perform any ostectomy/osteoplasty was also proposed.⁸⁸ The proposed surgical extraction protocols with the use of conventional dental instruments,^{6, 89} compared to more invasiveness, however, does not appear to increase the risk of BRONJ over the use of ultrasonic instruments, at least based on current evidence.

The removal of granulation tissue inside of the alveolus and the primary closure of the extraction site obtained with the mobilization of mucoperiosteal flaps are recommended in all major protocols published and are probably the decisive factors in the risk of BRONJ reduction after tooth extraction.

The role of factors potentially capable of improving bone healing such as platelet-derived growth factors⁸⁸ has yet to be validated.

It is the opinion of this Commission that the dentoalveolar surgery (see invasive therapeutic procedures) is indicated and can be performed without modification of the normal protocols before starting the administration of NBP, not only in people suffering from osteometabolic disease, but also cancer, provided that, especially in the latter case, it is possible to wait for the complete biological healing of the extraction site (usually 4-6 weeks). Otherwise, the extraction techniques must be similar to those recommended during treatment with NBP.

When treatment with NBP began, in the case of oral NBP for less than 3 years for osteometabolic disease, the risk is very low, so surgical dentoalveolar procedures can be performed according to standard protocols, because the risk-benefit balance is to total advantage of the benefits obtained by the elimination of diseases that pose an indication for surgery. If the therapy for osteometabolic diseases NBP be-

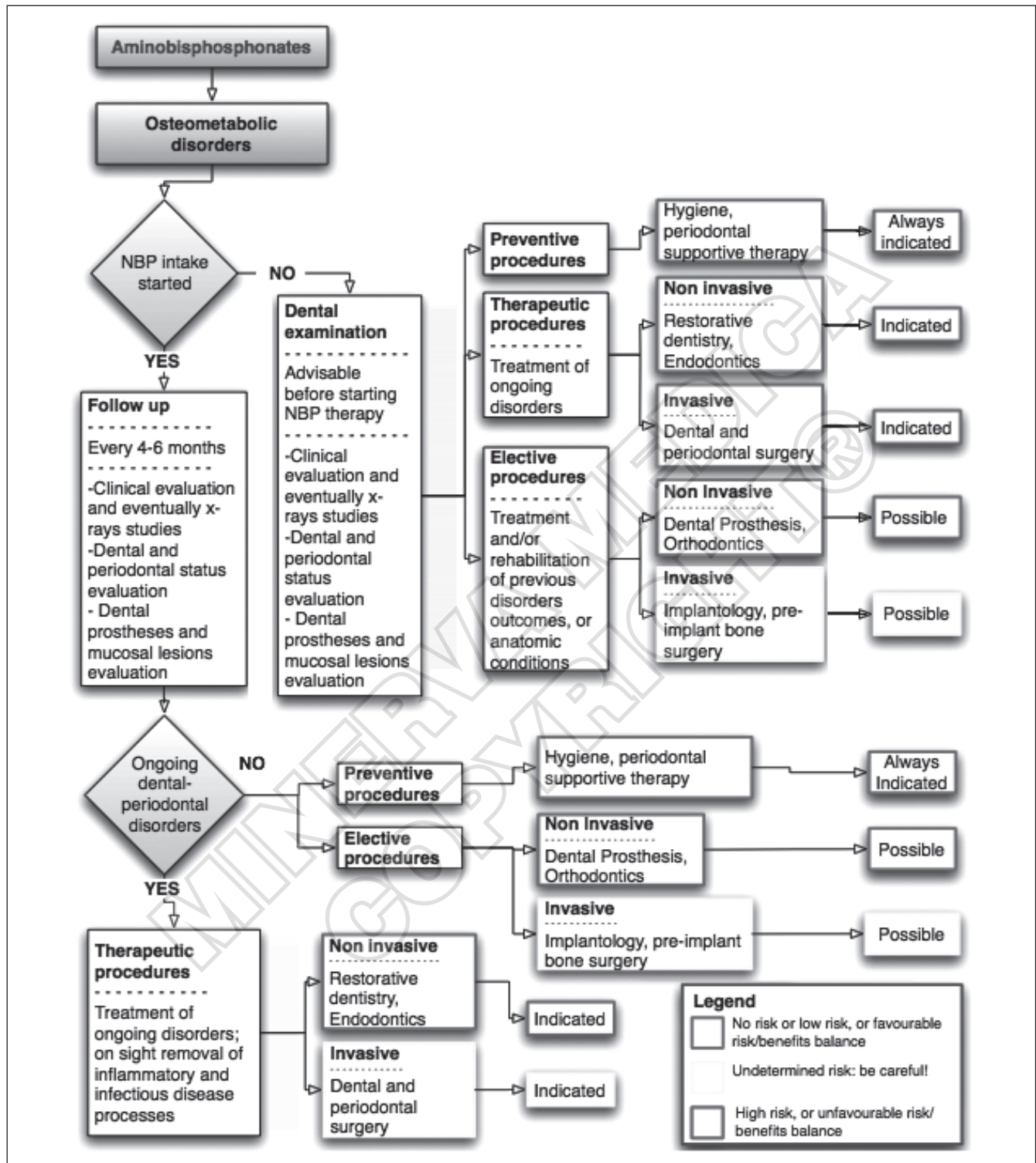


Figure 2.—Schematic diagram of dental management of patients at risk for BRONJ - Osteometabolic disorders.

gan more than 3 years, or in the presence of other risk factors, it should be considered the possibility of using dental extraction protocols involving surgical removal of granulation tissue inside the alveolus and primary closure of the extraction site obtained with the mobilization of mucoperiosteal flaps. It is highly recommended and indicated the use of the abovementioned extractive protocol in cancer patients already treated with intravenous NBP. It is also advisable in these subjects a temporary suspension of NBP since the extraction until the full biological healing of the extraction site (4-6 weeks), if the patient's condition allows it, and if the suspension does not have deleterious effects on the underlying disease.

It is the opinion of this Commission that the pre-implant surgery and mucogingival surgery is contraindicated in cancer patients who initiated treatment with NBP or is about to do so.

It is possible to perform instead, elective invasive therapy in a patient with invasive osteomtabolic disease, whether it has yet to begin (or has begun for less than 3 years) the assumption of NBP, or the therapy is initiated by more than 3 years or in the presence of other risk factors. The Commission also stresses the importance of adequate information on the risk to the patient, while low, to develop BRONJ in the years after completion of these procedures for the construction of an implant-prosthesis, in case the treatment with NBP should continue.

Discontinuation of NBP therapy before dento-alveolar and preimplant surgical procedures

There is no scientific evidence that supports the validity of withdrawal of treatment with NBP, whether intravenous or oral administration, before dento-alveolar surgical procedures. The rather long half-life of these molecules results in an effect on the inhibition of osteoclast function of unpredictable duration. The effects of BP on bone may be very prolonged over the time, even after a single administration.

It is assumed that the discontinuation of therapy may be associated with a reduction in anti-angiogenic effect exerted by the NBP on the periosteum and soft tissues which, in turn, might improve blood flow and lead to faster healing after surgical procedures. Other authors suggest discontinuation of the drug in the month following the extraction, in case

of therapy with intravenous NBP in cancer patients, to reduce the accumulation of NBP in the site of extraction, where the accumulation of NBP would be increased for the tropism of the drug for sites with a high bone turnover.⁶

However, any decision on the suspension of therapy should always be taken in accordance with the oncologist or internist after a thorough risk assessment of the patient's underlying condition. NBP discontinuation in cancer patients is a procedure that potentially poses at risk for progression of the underlying disease and for failure to control bone-related events. Guidelines of the American Society for Bone and Mineral Research (ASBMR) and the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended the suspension of NBP only if the systemic conditions permit.^{1, 70} The Myeloma Foundation of Australia (MFA) recommended the NBP discontinuation for at least three months following the onset of BRONJ except for patients with uncontrolled hypercalcemia. The resumption of therapy depends on the individual risk of skeletal-related events (SRE) and would still be recommended only after resolution of BRONJ.⁹⁰

In the case of a patient, candidate for the intravenous treatment with NBP and which must be subjected to oral surgery, if the conditions permit, medical therapy should be delayed until complete re-epithelialization of the extraction site (biological healing). It is rather questionable the risk-benefit balance in the case of suspension of the NBP in a patient already taking it: some authors recommend the suspension until a month after surgery, but there are no case-control studies that could confirm the real utility.

For all patients treated with oral NBP for more than three years or less than three years but in the presence of additional risk co-factors, the guidelines drawn up by AAOMS suggest to discontinue therapy with NBP three months before the surgery if the patient's systemic conditions permit, and to resume therapy after complete closure of the surgical site. This attitude, however, is based purely on expert opinion and has not been validated in any way in the literature. As the beneficial effects of NBP on the control of the underlying disease and its complications are known, while there are doubts about the results of their suspension in order to reduce the risk of BRONJ, it is necessary always inform the pa-

tient about the lack of predictability of the suspensive effect⁹¹ and the possible risk associated with worsening of metabolic bone balance.

Conservative and endodontic therapy

The term used in international literature “dental procedures”, which can be translated generically as “dental therapy”, may create confusion among specialists. It is necessary to distinguish conservative, endodontic and restorative care that are not considered as procedures at potential risk of osteonecrosis and the invasive surgical treatments. The conservative treatment of compromised teeth, if predictable, is recommended in both groups of patients (oncologic and not) treated with NBP, to avoid dental extractions.⁹² It should be considered that current cases of osteonecrosis occurred in coincidence with root canal therapy are few and of dubious interpretation,^{24, 93} but the risk of BRONJ could be higher as a result of complications or procedural errors during the execution of endodontic therapy in a patient treated with NBP.⁹⁴⁻⁹⁶ It is, therefore, encouraged in all the recommendations, orthograde endodontic treatment rather than invasive surgical procedures, identifying in this therapeutic solution a preventive action against the onset of osteonecrosis.^{97, 98} The only question is represented by debilitated patients with cancer, multiple myeloma or bone metastases to the spine: the extreme difficulty of maintaining sitting or declivis position for a long time and the obstruction to apply the dam for the presence of nausea and vomiting, represent a serious threat to the proper endodontic procedure.

They are then marked differences in “sensitivity” in considering the potential recovery of the dental element between specialists in endodontics and oral surgeons.⁹⁹

Recently, it has been suggested that a risk factor for the onset of osteonecrosis can be represented by the application of rubber dam during endodontic or conservative treatment.¹⁰⁰ The trauma exerted on the mucosa and alveolar bone could be a phenomenon triggering the osteonecrotic process.

The recommendations on the desirability of limiting the performance of conservative care prior to the administration of NBP are still very weak in both categories of patients; in fact, there is no evidence that the conservative or endodontic therapy involving a substantial increase in risk of BRONJ in any

category of patients (cancer or not cancer) during treatment with NBP or once suspended the intake of these drugs. Therefore, it is the opinion of this Commission that the conservative and endodontic therapies can be performed without restriction during treatment with NBP.

Dental implant surgery

The relationship between dental implants and the use of NBP is quite complex and controversial: while it is still trying to define the risk of BRONJ for a dental implant surgery in a patient treated with these drugs, in the past bisphosphonates were tested in order to improve the process of osseointegration. The number of retrospective studies that report the effects of implant placement in patients with NBP has grown over the past 4 years. The majority of studies focused on the definition of implant success in patients with NBP (particularly patients with non-oncologic diseases), the risk of BRONJ in relation to implant procedures has received much less attention.

It is still difficult to determine whether the implant surgery itself and/or implant-supported prosthesis, may represent a priori a real risk of BRONJ. The doubt is that local or systemic conditions of the patient (especially cancer patient) may favour the occurrence of a peri-implantitis, an easy way of spreading the infection process to the bone, and thus constitute the factor precipitating BRONJ. The clinical recommendations are agreed to define that the assumption of NBP intravenously for cancer indications is an absolute contraindication in implantology during the therapy or after it. This Commission fully agrees on this point. This contraindication should be considered valid even after cessation of therapy with NBP, although for a period of time still undefined.

The administration of NBP intravenously with different doses and indications other than cancer is still too limited to provide accurate and recent indications.

A major theme of discussion is represented by the oral or parenteral therapy in patients with osteometabolic diseases, for the very wide number of subjects included and for indication of implantology, typical of the age group affected by these diseases. Some authors had originally hypothesized that bisphosphonates represent in each case a contraindication

for implant surgery as they modify in a not predictable manner the response of the bone, the periosteum and soft tissue to the traumatic event.¹⁰¹⁻¹⁰³

Jeffcoat¹² reports the results of a study on the effects of alendronate versus placebo on the alveolar bone resorption and maintaining implants in 335 patients with moderate and severe periodontal disease and 50 patients treated with implant surgery. In over two years of follow-up is not reported any case of BRONJ and implant-prosthetic treatment success was 99% in both the group treated with alendronate than in the placebo. There also was a minor bone resorption in patients exposed to the drug. Fugaz-zotto²² in a study of post-extractive implants with immediate loading in 61 patients treated with oral NBP for a mean period of 3.3 years, reported a success in terms of maintaining the implant and absence of BRONJ in all subjects for a follow-up from 12 to 24 months.

Koka¹⁰⁴ reports the results of a case-control study of 137 postmenopausal women, including 55 treated with NBP. No cases of osteonecrosis occurred in the two groups and implants survival in patients in treatment and not, was comparable (98.19% *vs.* 99.17% respectively). No patient had stopped taking medication during the intervention.

Leonida¹⁰⁵ reports nine cases of patients treated with oral NBP successfully subjected to post-extraction implants with immediate loading of implants and full arch support of six implants. No patient has shown signs of soft tissue swelling or BRONJ for the entire period of follow-up. After two years of loading all the implants were stable and without any sign of inflammation or infection with an overall clinical survival of 100%. The solution of a prosthetics with the exclusive support of an implant, would completely minimize the risk of pressure sores and prosthetic trauma those are risk factors for the onset of BRONJ.

Grant³³ reports no cases of osteonecrosis in 468 implants applied in 115 patients receiving oral bisphosphonates. A review of the literature from 1995 to February 2010¹⁰⁶ identified 89 articles on the subject and states that the oral bisphosphonate therapy does not affect osseointegration and the function of implants.

However, some authors have reported individual cases of failure of implants and onset of BRONJ in patients treated with oral bisphosphonates.^{19, 107-109} The cases of post-implant BRONJ during treatment with NBP for osteometabolic diseases currently re-

ported in the literature are about a dozen. Cheng¹¹⁰ estimates a risk of implant loss in patients undergoing oral NBP, approximately of 0.88%.

If the results of these studies suggest that therapy with bisphosphonates in patients with cancer would not be a contraindication for dental implantology, comes from the same studies reported the need to consider more carefully the individual cases, especially in relation to any additional risk factors. In fact, it is reported that the concurrent treatment with oral NBPs for over three years and steroids, increases the risk of BRONJ, so that alternative therapies could be considered.¹¹¹ In addition, it should be noted that the number of cases studied prospectively is not statistically adequate to reach definitive conclusions and, on the other hand, the potential biological complications of the implant therapy (*i.e.*, peri-implantitis) can be configured as a risk factor for BRONJ. These complications can also occur after several months or years and if so their effect should be evaluated in combination with the increased risk of BRONJ caused by the progressive accumulation of the NBP with the time. This, in other words, it could mean that not the implant procedure itself, but its potential complications may exhibit an incremental risk of BRONJ. The Commission considers that it is the duty of the operator (dentist or maxillofacial surgeon) to inform the patient in therapy with NBP for osteometabolic diseases, during the planning of prosthetic implant rehabilitation, that there is a potential incremental risk of developing BRONJ in the implant site, linked to continuing in the years of the therapy and the possible onset of peri-implantitis. This, of course, makes it more likely when there is inadequate monitoring of the implant and oral health, even if it is linked to poor patient adherence to controls.¹⁰⁹ There is, therefore, the need to discuss and share with the patient the choice of implant and the necessary patient adherence to a strict program of professional oral hygiene.

The possible temporary suspension of the drug in patients treated with NBP with non-oncological indications is currently not sustainable with certainty (for a more detailed discussion see the section on the suspension in oral surgery procedures).

Orthodontic treatment

Since 2007 in the literature have started to appear

recommendations with regard to Orthodontics.^{112, 113} Although there are no studies that can be attributed a specific risk of increased osteonecrosis to this kind of therapy, or clinical cases of BRONJ arisen on sites treated orthodontically are described, it should be considered that the orthodontic movement causes a significant increase in bone turnover with a consequent local accumulation of drug. The decrease in osteoclastic activity in these patients will result in an intuitively difficult to move teeth and a plausible risk of periodontal disease, occlusal trauma, accumulation of plaque and tartar with gingival inflammation.^{114, 115} These may indeed be possible risk factors recognized for BRONJ. It is recommended, therefore, to consider with caution orthodontic treatment in patients undergoing at high doses and prolonged therapy, especially intravenously. Patients treated with oral bisphosphonates are considered, as for other non-invasive dental treatment, low risk. Orthodontic treatment must be planned to minimize the trauma exerted on the teeth and mucous membranes, using weak forces, selecting multiple anchors dental and avoiding as much as possible surgical therapies.^{116, 117} Surgical correction of mucous and muscular abnormalities (frenula and vestibular surgery) that do not specify the involvement of bone and tooth bases are preferable to more invasive interventions. There is, however, a medical and legal responsibility of the orthodontist: the patient being treated with bisphosphonate will be closely monitored, under radiographic and periodontal control, intercepting early tooth mobility or areas of radiolucency accompanied or not by subjective symptoms, possible early signs of osteonecrosis. Even in this case it has been suggested as a precaution to suspend NBP during orthodontic treatment, but there are doubts about its usefulness.

There is no clinical evidence that contraindicate orthodontic treatment in any of the categories of patients, oncologic and not, and in any of the stages of administration of the NBP. On the contrary, there are clinical experiences recommending orthodontic extrusion of roots or unrecoverable teeth up to their gradual exfoliation to remedy the most traumatic tooth extraction.¹¹⁸ The duration of this procedure depends on the morphology of each root, the state of periodontal tissues, the local anatomy and the cooperation of the patient. This solution is proposed as a treatment of choice when the ex-

traction is necessary in a patient who cannot suspend the NBP. This technique is, however, difficult to adapt in cancer elderly patients who show poor compliance for frequent dental visits and meetings, and it becomes impossible in case of partial edentulism in the areas around the element to be extracted, for the obvious impossibility of applying orthodontic traction ¹¹⁹.

Periodontal therapy and endodontic surgery

The periodontal disease is considered the main co-morbidity in cancer patients and not treated with NBP. The spread of bacteria through the periodontal pocket is the main factor of spreading infection to the bone structure ^{10, 42, 120, 121} and as such is considered a significant risk factor. Therefore, an appropriate protocol of home and professional oral hygiene is the prerequisite to the administration of NBP in cancer patients than in patients with osteometabolic diseases. It is also essential to maintain a strict control of hygiene/oral health with regular reminders that should be performed every four months in patients with cancer and every six in non-cancer.⁷⁹ Periodic rate will never be less than that normally used in oral and periodontal prevention programs, required by the dental-periodontal status and age of the patient.

Treatment of periodontal diseases in patients with oncologic or osteometabolic diseases, who are taking or have taken NBP, must be based on a careful causal therapy (no surgery) and an equally careful periodic reassessment; if from the latter should arise from residual problems and/or other needs and treatment goals, for stabilization of periodontal conditions and elimination of infectious-inflammatory foci, and these therapeutic goals are reachable only through surgical procedures, these must be practiced, but with particular caution.

It is the opinion of this Commission that the election procedures (see periodontal surgery with aesthetic purposes) are to be considered as contraindicated in cancer patients before, during and after treatment with NBP. Invasive therapeutic procedures are indicated (periodontal/endodontic surgery, that has as a goal the elimination of significant infectious-inflammatory processes taking place in the jaw) even during treatment. It should, however, always be preferred options and surgical techniques that minimize bone manipulation. If invasive thera-

peutic procedures are arranged before the start of treatment with NBP, the commission considers necessary waiting for the biological healing of the tissues before the start of the therapy (4-6 weeks). If the beginning of therapy was not postponable, it should consider alternative treatment such as surgical extraction.

As for non-cancer patients, periodontal surgery procedures should be made minimizing bone surgery. Moreover, from a speculative point of view, the anti-angiogenic effect of NBP could have a negative effect, or at least not predictable, on bone regeneration procedures or guided tissue regeneration, although this still requires experimental evidence. If the treatment plan requires the involvement of bone and/or periosteum in different sextants, some authors have recommended to treat first a sextant or a single tooth (trial sextant approach). If after treatment, during the 2-month follow-up, there is no evidence the onset of signs or symptoms of BRONJ, treatment can be performed reasonably well in the other sextants. If there is a complete success in the first sextant (no inflamed, irritated or erythematous areas) a surgical approach with involvement of more contemporary sextants should be considered. The "sextant approach" for prevention of BRONJ a still has a low level of evidence ¹²².

Is the opinion of this Commission that therapeutic procedures (periodontal/endodontic surgery, which has as its purpose the elimination of significant infectious-inflammatory processes in place in the jaw bones) are always indicated in patients with osteometabolic disease; elective procedures (see periodontal surgery with aesthetic purposes), although burdened with a pretty low risk, are indicated up to 3 years of treatment, and remain possible even after 3 years of therapy and in the presence of additional risk factors. The Commission also stressed the importance of a case by case assessment and adequate information to patients about the risk, although low, to develop BRONJ.

Prosthetic therapy

Regardless of the category of oncologic or osteometabolic patients, attention should be paid to the potential trauma on the oral mucosa caused by compression of the denture base, in the case of removable rehabilitation. The role of the dentist and dental hygienist are essential to prevent and inter-

cept mucosal lesions determining bone exposure, which are often asymptomatic or mildly symptomatic.¹²³ Very often these events are interpreted and managed by the patient as commonplace decubitus, alternating the use of the prosthesis with the temporary removal to alleviate the pain thus inducing a worsening of the process, that became chronic.

The fixed prosthesis must be placed with supragingival margins easily controlled and cleanable: the prosthetic crowns should be arranged to exert as little damage as possible on marginal periodontal tissues. The removable prosthesis must not exert pressure sores, especially in areas at risk (the lingual margin of the jaw, the middle portion of the palate, vestibular side of edentulous maxillary ridges). The mechanical compression exerted by incongruous removable dentures or the presence of anatomical structures easily traumatising (exostoses, mandibular or maxillary tori) is referred to as responsible for the onset of osteonecrosis.

It should be considered, especially for patients who have developed BRONJ or having undergone surgery, the opportunity to perform soft rebasing to minimize the trauma on the alveolar ridges.¹²⁴ When possible the endodontic recovery of remaining teeth, the design of an overdenture (possibly with the aid of telescopes conometric crowns) reduces mucosal support and spread the masticatory load on the radicular abutment and, giving greater stability to the device, reduces confrication movements and therefore, the risk of decubitus.^{119, 125}

Partially or totally edentulous patients should be informed about the risk posed by inflammatory processes to a mucous membrane placed under the denture, which can compromise the integrity and promote any dehiscence with bone exposure, be instructed in hygiene and the proper maintenance of the prosthetic. It is generally advisable the removal of dentures during the night; finally, there is no evidence that alterations of masticatory forces or malocclusion may lead to an increased risk of ONJ.¹²⁶

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