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Review Article

Understanding the Controversies Surrounding Osteonecrosis of the Jaws

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Abstract

Based on our extensive review and analysis of the literature on osteonecrosis of the jaw, we highlight several areas of controversy that still exist within the realm of this topic. From nomenclature through diagnosis and treatment, there exists a difference of opinion. These highlights demonstrate that there is still much to learn and define with respect to how best to treat these unfortunate patients that develop this complication of various cancer treatments and occasionally osteoporosis therapy. As research and data collection moves forward perhaps there will become a more unified approach to diagnosis and management of this condition. This paper is an attempt to summarize controversies that we feel still exist in the ONJ literature.

Introduction

Osteonecrosis of the Jaw (ONJ) has been a known clinical entity since 2003 [1]. We can still consider this a relatively new disease although in its second decade of awareness. It affects people worldwide, especially those suffering from metastatic cancers and multiple myeloma, secondary to management of these diseases with antiresorptive medications. It is also known to have a much lower incidence in those people on oral and parenteral agents for management of osteoporosis. This makes it a very widespread disorder and, although not exceedingly common, it is well known to medical oncologists, the dental community, and bone and mineral physicians and researchers.

For those of us that see these patients in our clinics, we know that some people are very affected by it in a debilitating and painful way, yet others may be relatively asymptomatic. Some patients will equate 'getting back on their anti restoratives' to 'controlling their metastatic cancer' so it puts both the oncologist and the dentist (dental specialist) in a position to find that balance in managing this disease.

As health care providers, it is beneficial to have established formulas with which to diagnose and treat disorders. However as with any new disease, there can be a significant time required to come to a full understanding of all aspects of that disease. During such time, differences of opinion can arise which lead to controversies. These are all to the benefit of finding the truths about a disease and ONJ is no different in that regard.

The International Journal of Dentistry highlighted ONJ literature related controversies in a special issue in 2014 [2]. Following our recent extensive systematic review on ONJ [3], we understand that controversies still exist. Perhaps more will arise and agreement will be found in some of these areas. This paper is an attempt to summarize controversies that we feel are still present in the ONJ literature.

Nomenclature

Marx first coined the term ONJ in 2003 [1], changed to BRONJ [4] to reflect the relationship with Bisphosphonates (BPs) and more recently to Medication Related Osteonecrosis of the Jaw (MRONJ) [5]. Our international task force prefers to call the entity 'ONJ' [3]. The reason for this is that we recognize that medications such as bisphosphonates and denosumab (Dmab) are primarily responsible for ONJ. The term 'MRONJ' was coined in the AAOMS paper to include medications such as anti-angiogenics as possible sole causative agents of ONJ. It is the opinion of our International Task Force that the role of anti-angiogenic agents is as yet not clear in singularly causing ONJ. In addition to this, there may be reason to consider 'spontaneous' ONJ such as that which occurs in individuals not on any medications and not in an otherwise high risk category. This would therefore be non-medication related ONJ if you will. This may be the case in Oral Ulceration with Bone Sequestration (OUBS) which is a recognized oral diagnosis with virtually identical features to ONJ [6]. These lesions present almost exclusively on the lingual aspect of the posterior mandible usually without a history of trauma and can persist for weeks to months before usually healing spontaneously. Occasionally these lesions will be so symptomatic that surgical reduction of the protruding bone is required. The term 'ONJ' therefore allows for the inclusion of this spectrum under a 'non-medication' related category. Perhaps in time this will become included under the 'ONJ' umbrella or conversely remain a completely separate entity.

Incidence

In looking at incidence, it is important to point out that there are very few high level evidence studies from which to collate data and draw conclusions. There are a few identified etiologic agents responsible for ONJ, including intravenous BPs, oral BPs and Dmab. As mentioned above, anti angiogenic agents may play a primary role but it is our opinion that these have not been proven as causative in and of themselves as yet. When looking at the various patient groups we can separate the osteoporosis group from the oncology group and further subdivide those on oral versus IV BPs and also those on Dmab.

In the osteoporosis population there is a reported incidence of 1.04 – 69 per 100,000 patient-years for those on oral BPs [7-10]. Looking at IV BP treatment for these osteoporotic patients reveals an

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incidence of 0 – 90 per 10,000 patient-years [11-15]. This compares with Dmab via a 0 – 30.2 per 100,000 patient-years [16-19].

When studying the oncology population, although there are more cases of ONJ in these patients, the data is widespread so much so that it is difficult to recommend an incidence with confidence at this point. The reported incidence has a large range and conflicting studies suggest there is no difference between IV BPs and Dmab while others suggest one has a higher incidence than the other and vice versa [3]. Clearly more prospective cohort data is needed before we can report incidence and prevalence with confidence.

In addition, there are many potential confounding variables that may need to be considered when viewing these patients. Homogeneity may be difficult depending on other comorbidities and confounders – diabetes, smoking, alcohol use, steroid use and anti angiogenics to name a few.

We can now appreciate that advising these patients of their likelihood of acquiring ONJ is difficult at best. The range of reports in the literature may be perceived as controversial although in reality good solid data is as yet unavailable in order for us to draw conclusions and be fully confident when having these discussions with our patients.

It is appreciated then that inherent within the subject of ONJ incidence there exists controversy by the mere fact that the range of percentages varies greatly among studies and reports in the literature. We can say with confidence that the incidence is low for those people on BPs or Dmab for osteoporosis while it is significantly higher for those individuals on these agents for control of the skeletal effects of multiple myeloma and metastatic bone cancer.

Staging

There remains debate about defining the various stages of ONJ. Our 2015 update3 discusses stages 1 through 3 whereas the most recent AAOMS position paper includes Stage 0 as well as 1, 2 and 3 [5]. This continues to be a point of discussion and within our own task force this was debated both amongst ourselves and from the information gleaned from the current literature. The consensus suggested that utilizing a Stage 0 may diagnose many individuals with ONJ when in fact they may never develop overt stage 1, 2 or 3 diseases. The feeling is that incorporating a Stage 0 has the potential to lead to an over-diagnosis of ONJ. It also confuses the issue as to whether these 'potential' ONJ lesions represent other dentoalveolar diseases such as endodontic, periodontic or other pathologies. For now this will remain a point of difference and it will add to the confusion about incidence, prevention and possibly treatment.

While the definitions of stages 1 through 3 are fairly agreed upon, there are even proposals for a new staging classification based on lesion dimensions which these authors suggest correlate to different treatment directions [20]. In time perhaps this will get more complicated as researchers and clinicians define their own staging systems.

Biomarkers

Perhaps not as controversial as it was initially, the biomarker C-terminal peptide (CTX) was introduced as a potential marker for susceptibility to ONJ [21]. This marker is indicative of bone turnover and the original suggestion was that perhaps its value could predict ONJ development or susceptibility in some patients. Patients were put into a low, medium or high-risk category depending on the serum CTX value. Generally a higher value suggests more bone turnover and therefore lower risk while the opposite is suggested for those with lower values. This would certainly be valuable information if clinicians could predict the susceptibility of ONJ development if a patient was faced with minor oral surgery. There are a multiple of studies however that have not shown a relationship between the development of ONJ and CTX levels [22-26]. Therefore it is the opinion of our task force that CTX has little role to play in patients with ONJ at the present time.

Oral Ulceration with Bone Sequestration (OUBS)

Another long discussed point by the task force was whether OUBS is a variant of ONJ or its own entity. This was described as far back as 1993 [27] and certainly clinically the presentation is identical to ONJ except that these patients are not on the usual causative medications. Many do not report any history of trauma so another reason is looked for. Most will heal spontaneously and therefore not require any intervention. At this time it is unknown how common this is in the general population. Could it be as common as ONJ in the osteoporosis group taking oral bisphosphonates? Is it simply a spontaneous disorder that can happen to anyone? At this time we don't really know. We know that most of these lesions will heal spontaneously although occasional bony reduction is required to eliminate discomfort for those symptomatic patients. If this were to be considered under the ONJ umbrella it would present a non-drug related category of ONJ, further increasing the controversy of the topic!

Pathophysiology

Is ONJ the result of a primary infective process or is infection secondary to the primary disease? The answer to this question is as yet unclear. It is apparent that suppression of bone turnover has a significant role with bisphosphonates and denosumab leading the way in causality. In addition researchers have studied infection, genetic predisposition and vascularity in attempt to determine the details of why this disease arises in some individuals and not in others [28-44].

Treatment

Conservative therapy continues to be the mainstay management of ONJ lesions. This is universally accepted and not so controversial. Recent case reports of successful treatment of ONJ with teriparatide are encouraging [45,46] and this may become a conservative treatment choice for those with osteoporosis and without cancer or prior radiation therapy to bone. Because teriparatide has been reported to facilitate osseous wound healing in the oral cavity it may be a viable approach for patients on antiresorptive therapy for the treatment of osteoporosis [45].

Surgical therapy does have a role in management of this disease [47]. There is still no established protocol of who needs surgery and who can be safely and successfully operated. There are certainly many reports of successful surgery and our experience has been that

problematic, symptomatic cases have been successfully managed with sequestrectomy, ostectomy down to healthy, bleeding bone and tension free primary closure of mucosa [3]. This approach is recommended in the literature [47]. Localized surgical debridement may be indicated; some authors have reported success with larger resections compared to limited debridement and/or conservative therapy [48,49].

There are a multitude of investigational therapies being studied. These for the most part require further validation. They include topical ozone [50], bone marrow stem cell intraregional transplantation [51], and addition of pentoxifylline and tocopherol to standard antibiotic regimens [52]. Laser therapy has also been proposed to be of benefit [53,54]. Enhanced healing has been observed in a retrospective survey of patients undergoing antibiotic therapy in addition to surgery followed by low-level laser therapy [55]. Surgery together with platelet-derived growth factor applied to the local site has achieved good results in stage 2 ONJ cases [56]. Hyperbaric oxygen in combination with surgery has been investigated with encouraging results [57,58]. Further research is required with these new strategies, thus making each of them at this time controversial.

There often exists an intramural conflict with respect to management of patients on antiresorptives who develop ONJ. The treating oncologist usually stops the medication immediately and is often reluctant to restart until the lesion is healed or surgically treated and healed, if they are comfortable to resume it at all. This presents a conflict for each patient. How important is it for them to resume this medication to control their skeletal disease? If the answer is "very important", then perhaps surgery should be considered so that these individuals can resume their usual care. So this dilemma in itself presents a potential controversial turning point in management. Patients in this category that have been surgically managed in our unit (AM) have met with successful resumption of their antiresorptives and continued with their pre ONJ routines. However the number of patients in our unit in this category is limited.

So while there is still no consensus on overall management of these patients, we are constantly assessing various management strategies including surgery and other newer adjunctive or de novo primary therapies in attempt to formulate a recipe that will provide evidence based guided care of these patients.

Drug Holiday

Initially most clinicians involved in ONJ care felt a 'drug holiday' may be prudent once an ONJ lesion was diagnosed and perhaps even more so if minor oral surgery such as dental extraction was being considered. If extraction is being considered because a lesion has arisen adjacent to a tooth or because of an abscessed tooth, it may not be practically possible to delay the extraction, thus making the idea of a drug holiday moot. Clearly an individual could potentially get into more trouble from an odontogenic infection that gets out of control than the extraction may cause. Furthermore there is no evidence to definitively suggest that a drug holiday for any period of time will make a difference. Our most recent recommendation is to remove the need for drug holiday if minor oral surgery is planned such as an extraction, dental implant or periodontal surgery. We feel that in understanding the healing process in the jawbone and antiresorptive drugs' pharmacodynamics, there will be an increased concentration of the drug at the local surgery site when the next dose is given after the extraction due to the localized inflammatory response. Therefore this could interfere with healing thereby leading to a suggestion that the subsequent dose of antiresorptive be withheld until the surgery site has healed to the point where there is a reasonably mature mucosal barrier over the wound to offer mechanical protection of the underlying bone. This would typically translate into a period of 6 – 8 weeks that usually means missing one dose of IV BP or s/c Dmab. This is our recommendation and may conflict with other clinicians' suggestions. At present you cannot find prospective, randomized, well controlled studies along these lines with definitive findings.

There is no recommended drug interruption before or after for those agents and doses used for osteoporosis patient management.

Conclusion

As can be appreciated there are still unanswered questions surrounding ONJ. As data is collected and knowledge of the disease and its management grows, we look forward to clarification of the many controversial areas that still exist. At the same time we recognize that there may be options available for treatment as there are with many diseases and more than one rigid way in which to name, classify, diagnose and treat ONJ.

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