PENTOXIFYLLINE, TOCOPHEROL AND SEQUESTRECTOMY ARE EFFECTIVE FOR THE MANAGEMENT OF ADVANCED OSTEORADIONECROSIS OF THE JAWS – A CASE SERIES

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ABSTRACT

Background: The aim of the present study was to evaluate the efficacy of pentoxifylline and tocopherol for the management of osteoradionecrosis of the jaws. **Methods:** Twenty-five patients diagnosed with osteoradionecrosis of the jaws treated with pentoxifylline 400mg + tocopherol 400mg three times daily (*tid*) were evaluated. Clinical records and image tests were reviewed. All patients were previously submitted to head and neck radiation therapy and presented with a clinical and radiographic diagnosis of osteoradionecrosis of the jaws. **Results:** Following therapy with pentoxifylline and tocopherol 76% (19/25) of the patients showed complete mucosal healing, in which 47,3% (9/19) did not undergo sequestrectomy. From this particular group, 77,7% (7/9) were in stage I and 33,3% (3/9) used the protocol for up to three months. Among those who underwent to sequestrectomy, complete mucosal healing was observed in 52,7% (10/19). Among these, 60% (6/10) were in stage I and 100% of the patients were using the protocol for more than three months. In all other patients, partial healing of the mucosa was observed since they presented advanced disease. These represented 24% of the sample (6/25), 66,6% (4/6) were in stage III and 60% (4/6) used the protocol for over six months. **Conclusion:** Pentoxifylline and tocopherol may provide effective management of osteoradionecrosis of the jaws, and the association with sequestrectomy may avoid major surgical procedures.

Keywords: Osteoradionecrosis, Radiotherapy, Pentoxifylline, Tocopherol.

INTRODUCTION

Each year, around 6.4 million new cases of malignant neoplasms are diagnosed worldwide. Approximately 10% of these are located in the oral cavity [1]. In 2018, 14.700 new cases of oral cancer and 7.670 new cases of larynx cancer were estimated to be diagnosed in Brazil. In the Northeast region of Brazil, characterized by low income and limited health care access, 2,810 new cases of oral cancer were estimated for both genders [2]. The treatment of head and neck cancer consists of radiation therapy (RT), surgery, and chemotherapy, used in isolation or in association. Almost 60% of head and neck squamous cell carcinoma have locally advanced disease, that warrants intense treatment [3-5].

Different radiotherapy techniques can be used in the treatment of head and neck malignancy. Conventional or 2D radiotherapy (RT2D), which is performed by delimiting the treatment volume though simple radiographs are still used in developing countries due to budget limitations, particularly in the public health sector. The standard of care in developed countries include three-dimensional conformal radiotherapy or 3D radiotherapy (RT3D) or intensity-modulated radiation therapy (IMRT). Both modalities allow the planning to be carried out based upon computed tomography with the visualization of the tumor and normal tissues in a volumetric way. In addition, RT3D and IMRT are highly accurate and allows the administration of high doses of radiation in the target volume, thus minimizing irradiation of adjacent healthy tissues, lessening potential adverse effects [6, 7].

Although RT is a highly effective local treatment modality for head and neck malignancy several clinically significant adverse events can arise including early-onset oral mucositis, dysgeusia, and dysarthria, shortly followed by variably irreversible salivary gland dysfunction (with resultant dysphagia, dysarthria, increased risk of caries and oral candidiasis and loss of denture retention). Of additional significance later, and irreversible, muscular and cutaneous fibrosis and osteoradionecrosis of the jaws (ORN) may arise [8]. At present, ORN is observed in less than 5% of the patients who have received conventional (2D) head and neck RT. It is clinically characterized as exposed necrotic bone in an irradiated oral site lasting for more than at least three months [7, 9].

The treatment of ORN is clearly dependent upon its extent but ranges from conservative measures for mild disease through to surgical resection when the disease is extensive and not amenable to simple non-surgical interventions [10]. Conservative measures include systemic antibiotics, local antimicrobial irrigation, hyperbaric oxygen therapy, and medicinal products derived from methylxanthines as well as antioxidants [11-12]. In addition, the combination of systemic pentoxifylline and tocopherol (PENTO) for the treatment of ORN has been proposed as possible therapy [3, 13-17].

The first case series using PENTO for the management of ORN had highly promising results, with complete mucosal healing in six out of seven affected patients after three months of therapy [14]. Five years later the same group published a similar study with a larger sample (n=18) and reported a reduction of the exposed bone area in 15 patients (84%) after six months of PENTO [15]. In a later retrospective analysis of 62 patients with ORN Patel *et al* reported that 14 of 25 patients (56%) treated with PENTO had clinical resolution [16].

It is suggested that the anti-fibrotic effect of PENTO comes from a combination of pentoxifylline inhibiting tumour necrosis factor-alpha (TNF-α), with increased vasodilatation, reduced fibroblast proliferation, and increased local collagenase activity. Tocopherol, a vitamin E related agent, exerts an anti-

oxidant action that helps against lipid peroxidation, as well as a partial inhibition of Transforming Growth Factor-β1, and antagonism of vitamin K [13,18]. Thus, this drug combination offers the prospect of limiting the effects of radiation-induced fibrosis, hence treating its consequences [3, 13].

Given the significant potential morbidity of ORN upon the jaw bones and the potential need for invasive surgery, the present study reports retrospectively the efficacy of PENTO in the management of ORN in a series of affected patients.

MATERIAL AND METHODS

The present study comprises of a case series of 25 patients with ORN or the maxillary or mandibular areas referred to the Oral Oncology unit of Hospital de Câncer de Pernambuco – Brazil, from January 2015 to August 2018. All patients were aged over 18 years and the diagnosis of ORN was based upon relevant clinical and radiological investigations [7]. Treatment with orally administered PENTO (pentoxifylline 400 mg + tocopherol 400 mg (*tid*) was initiated at the time of final diagnosis of ORN and maintained until there was clinical evidence of partial or complete oral mucosal healing or for a minimum of 45 days. Individuals undergoing re-irradiation of the head and neck region and those presenting a metastatic disease of the maxilla and/or mandible were excluded from the study. Sequestrectomy was performed after 45 days of PENTO when no regression was observed.

The study was approved in HCP Ethics and Research Committee under number 86691318.9.0000.5205 (CAAE). The medical records were evaluated, and clinical data were retrieved, including tumor histopathological type, diagnosis, RT planning (adjuvant or neoadjuvant), device, technique, dose and number sessions, history and timing of dental extraction, ORN staging, and ORN management details. Manual double entry of data was performed in an Excel 2010 spreadsheet and analyzed using IBM SPSS 13.0.

RESULTS

The initial clinical aspects of the patients are indicated in Table 1. The mean age was 58.6 years, ranging from 30 to 84 years with the majority of patients being male (80%, 20/25). Squamous cell carcinoma was the most common diagnosis (84%; 21/25 patients), followed by adenoid cystic carcinoma (2/25). The tongue was the most common tumor site (32%, 8/25), followed by the floor of the mouth and oropharynx (6/25 and 5/25, respectively). Radiotherapy was performed in standard patterns; the mean sessions were 32.3 (25 to 39 sessions) and the mean dose was 62.9 Gy (45 to 70,2 Gy). The mean interval between the conclusion of RT and onset of ORN was 1.7 years (ranging from 0 to 5 years).

Adjuvant RT (92%, 23/25) was most commonly used and the cobalt pump the most common device under the conventional technique, both representing 72% (18/25). The mandible was the most common site of ORN (68%, 17/25) while dental extraction was the most frequent precipitant of ORN (72%, 18/25) this usually having been performed after RT (66.7%, 12/18). Among those with ORN not associated with dental extraction, pre-prosthetic surgery was the most common cause (20%, 5/25). Most patients presented with early disease (stage I, 56%, 14/25) although 5 (20%) of patients presented to the clinic with advanced disease (stage III, 20%) (Table 1).

As for radiotherapy planning, 92% (23/25) of the patients underwent adjuvant radiotherapy and received an average of 62.4 Gy (45 - 70) while 8% (2/25) underwent neoadjuvant radiotherapy and received an average of 68.2 Gy (66 - 70.2). Regarding the radiotherapy technique used, 72% (18/25) of the patients underwent RT2D and received an average of 63.9 Gy (50.4 - 70.2). Among patients who underwent RT2D, the duration of treatment was more than six months for the majority (10/18), followed by more than three months (6/18) and up to three months (2/18). Sequestrectomy was indicated on 10/18 individuals. 28% (7/25) of the patients underwent RT3D and received an average of 60.2 Gy (45 - 70). Among patients who underwent RT3D, the duration of treatment was more than six months for the majority (5/7), being equal between more than three months (1/7) and up to three months (1/7). Sequestrectomy was indicated on 5/7 (Table 2).

Fifteen (60%) of the patients received PENTO for more than 6 months. PENTO was generally well-tolerated, although two patients reported palpitations and another one reported upper gastrointestinal discomfort. Sequestrectomy was performed after treatment failure in (16/25) patients (60%); 10 of them presented complete mucosal healing. In this context, PENTO led to complete mucosal healing in 76% (19/25) of the sample (Table 3). In addition, Figure 1 shows how patients in the sample behaved for complete or partial wound healing as well as whether or not sequestrectomy was performed. Complete mucosal healing was achieved with PENTO in 9/10 patients, and PENTO + sequestrectomy in 10/19 individuals. Also, 60% (6/10) of the complete responders were in stage I, and all were on PENTO for more than three months. Interestingly, all patients who presented partial healing were submitted to sequestrectomy due to advanced disease. Of these, 66,6% (4/6) were in stage III, 33,4% (2/6) were in stage II and none at stage I. Regarding the duration of treatment, 60% (4/6) were on PENTO for more than six months.

DISCUSSION

The present study is a retrospective analysis of the clinical outcomes of 25 patients diagnosed with ORN of the jaws treated with pentoxifylline and tocopherol (PENTO) and represents one of the largest case series describing its efficacy. The present results suggest that the use of PENTO induces oral mucosal healing and may lessen the need for invasive surgical sequestrectomy in both mild and advanced ORN.

The epidemiologic profile of the studied population (mean age 58.6 years) is closely similar to international data, in which the age group most affected by ORN is over 55 years [12], corresponding to the peak of incidence of upper digestive airway cancers [19]. Also, gender predilection is similar to the head and neck cancer situations [20]. The frequencies of sites of the tumors of the present group of patients is also broadly what is expected as regards the frequency of tumor site (tongue (32%), floor of the mouth (24%) and oropharynx (20%)) and distribution of stage at time of presentation is similar to what is expected for head and neck cancers [10, 21].

In the present report, 68% of the cases of ORN were located in the mandible, while 28% in the maxilla and 4% on both sites. The dosage of radiotherapy is known to be an important risk factors for ORN [22] with most cases of disease arising at doses greater than 60 Gy with few patients developing ORN

when the dosage is under 50 Gy [10, 2]. In this study, the mean number of sessions was 32,3 (25 to 39 sessions) and the mean dose was 62,9 Gy (45 to 70,2 Gy).

The occurrence of ORN seems to be greater when RT was exclusively provided rather than when it is adjuvant to surgery, possibly because surgery reduces tumor volume and hence lessens the need for high doses of radiation [19]. In addition, in the present study most patients underwent adjuvant radiotherapy planning (92%) and received an average of 62.4 Gy. Other patients undergoing neoadjuvant radiotherapy planning (8%) had an average radiation dose of 68.2 Gy. Thus, the radiation dose received by patients in adjuvant radiotherapy was lower than in neoadjuvant, findings that corroborate the present literature. In fact, Nabil & Samman [7] stated in their study that the determining factor for the occurrence of ORN is the radiation dose to the bone and is not related to the radiotherapy technique used, indeed ORN can arise with IMRT. In this study, 72% of patients underwent RT2D and no patients had access to IMRT. The use of RT2D in this study reflects the reality of the public health system in Brazil in particular the Northern region, one of the poorest areas in the country, which is linked to the dental oncology sector where this study was conducted, which does not have IMRT.

When comparing the average dose between patients submitted to RT2D and RT3D, the values of 63.9 Gy and 60.2 Gy, respectively, are observed. That is, the average radiation received by the two groups was similar. Regarding the treatment of ORN, the duration of medication use (PENTO) in both groups was more than six months and the need for sequestrectomy also prevailed regardless of the radiotherapy technique employed. Thus, the results suggest that the radiation dose is the main factor linked to the response to ORN treatment.

The onset of ORN is usually within the first three years following RT [23]. Marx and Johnson [24] suggested a bimodal peak of incidence in trauma-induced ORN. The first one arises in the first three months and is related to trauma before or during radiation, while the second peak occurs between two to five years, and maintains itself for a long time. The second peak accounts for the large majority of patients who require dental extractions possibly due to radiation-related (for example salivary gland dysfunction) dental decay a few years after the RT [7]. Indeed, the risk of ORN with dental extractions following RT is almost double that of treatment before RT [25]. In the present ORN was diagnosed after an average of 1.7 years after completion of radiotherapy and often was initiated by dental extractions or other surgical interventions to the mouth, hence confirming that dental extractions after RT are the main cause of ORN. 66,7% of cases of ORN associated with dental extraction originated from the procedure performed after RT, while the remaining patients (33,3%) manifested the disease associated with tooth extractions before RT. Interestingly in the present study, the ORN of five patients arose pre-prosthetic surgery (five cases) while two patients developed the disease after surgery to remove a fragment of the mandible including part of the floor of the mouth and tongue, also known as pelviglossomandibulectomy (PGM). It is evident that surgical interventions that entail perturbation of bone constitute a major risk factor for the later development of ORN.

Notani *et al*. [26] classified the ORN as three stages based upon the extent of the injury. Stage I is defined as ORN confined to the alveolar bone, stage II as limited ORN for the alveolar bone and/or the mandible above the level of the mandibular alveolar canal while in stage III the ORN extends from the mandible below the level of the mandibular alveolar canal and may give rise to cutaneous and/or a

pathological fistula. According to Chronopoulos [27], the Notani *et al*. classification system is the most accurate because it is based upon: (i) the presence or absence of clinical and radiological signs, in contrast to other systems that are non-specific and based on a subjective interpretation of patients; and (ii) in the pre-treatment evaluation, non-response to the proposed or refractory treatment. In the present study, the most common staging was stage I (56%), followed by stage II (24%) and stage III (20%), hence any benefit observed is likely to have application across all extents of ORN.

A recent systematic review and meta-analysis has shown that the dosage of PENTO employed in previous studies has been non-uniform although the treatment protocol described by Delanian et al. [15] is the most cited, comprising 800 mg of pentoxifylline and 1000 IU of tocopherol daily for at least six months until the regression is observed. If there are signs of complications, this treatment regimen must be maintained for six months [17]. In the present paper, pentoxifylline 400mg + tocopherol 400mg every eight hours was used and is hence slightly higher than the overall daily dosage employed in previous studies. PENTO was initiated at the time of diagnosis of ORN, reviewed fortnightly, and after 45 days sequestrectomy undertaken if there were no signs of regression of the ORN. The PENTO was then continued for a variable length of time.

In addition to pentoxifylline treating the side effects of radiotherapy (ORN, radiodermatitis, and fibrosis), the medication generates radiosensitization of malignant cells. The drug inhibits the G2 phase checkpoint during mitosis, therefore cells have less time to repair DNA damage induced by radiotherapy which causes apoptosis of malignant cells [28]. For this reason, pentoxifylline has anti-cancer activity and anti-metastatic properties, as it reduces tumor angiogenesis [29]. However, these topics were not addressed in the present study. On the other hand, pentoxifylline may cause cardiac arrhythmia, dizziness, headache, restlessness, and sleep disorders [18]. But, the most common side effect is gastrointestinal upset that can often be easily managed with anti-emetics [17]. Pentoxifylline can also decrease plasma levels of fibrinogen and increase the risk of bleeding in patients with platelet dysfunctions [30]. In this study, only three patients had side effects, two having palpitations and one upper gastrointestinal upset. In addition, none of these patients needed to stop the medication following a reduction in the frequency of PENTO to twice daily.

Clinical observable regeneration of the oral mucosa is the main method of determining ORN regression [17] and in the present study partial or complete healing was noted in 25 patients, 19 (76%) had complete healing of the ORN site while the others showed partial healing. In other words, all patients had some degree of positive response to PENTO. This data confirms Patel *et al*. [16] who performed a retrospective analysis of 62 patients with ORN and reported resolution of ORN in 14 of 25 patients treated with a combination of pentoxifylline and tocopherol. Nonetheless, the data described in the previous and current studies do not segment the patients who were submitted to sequestrectomy concomitant with the use of the drug protocol. It is important to note that cases of spontaneous sequestrectomy are reported in the literature and this may accelerate the healing process of ORN. Indeed, Delanian et al., reported that 67% their patients (36/54) had spontaneous sequestrectomy following the use of PENTO [17]. In this study, ten of 19 patients who had complete healing received sequestrectomy as well as PENTO: Of these 10 individuals (60%) had stage I ORN and all had used the drug protocol for more than three months. In contrast, in the other nine patients (47,3%) who had complete healing and did not require sequestrectomy, 77,7% had stage I ORN, and 33,3% used the drug protocol for less than three months. The six patients who

had partial healing (24%) all had sequestrectomy, none had stage I ORN while 66,6% had stage III. 60% of this group with partial healing had used PENTO for more than six months. Although this is a retrospective analysis, the observed trend is that early ORN (stage I) can be completely resolved with sequestrectomy plus PENTO for less than 3 months, while later stages of the disease may be lessened, but not resolved with sequestrectomy. In addition, more than 3 months therapy with PENTO should be prescribed. This is also supported by the observations of Delanian *et al.* [14] who reported a case series where six of the seven patients with stage I ORN who were treated with PENTO were completely healed after three months. Delanian *et al.* [15] also published a similar study in which 18 patients with late stage ORN had clinical improvement after six months of drug protocol, having a reduction of approximately 84% the exposed bone area. The present evidence thus points towards the need for ORN to be diagnosed at an early stage to hence allow immediate use of PENTO and lessening the need for extensive surgical removal of non-vital bone.

The limitations of the present study are related to its retrospective nature, the absence of any appropriate control group, and the fact that the patients had received 2D radiotherapy. Nevertheless, as ORN can also arise with IMRT and to date there is no internationally agreed treatment protocol the results of the present study do point towards a safe and potentially effective means of at least managing ORN in the short term. Until proper randomized and controlled trials of ORN are not published the combination of pentoxifylline and tocopherol should be used in the management of ORN, particularly when early diagnosis is possible and/or the disease is limited.

CONFLICTS OF INTEREST

There was no funding for this research. The costs were covered by the main researcher. There is full control of all primary data and we allow the journal to review the data if requested.

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Table 1. Baseline clinical featuares of the patients diagnosed with ORN and treated with pentoxifylline and tochopherol.

Variables	Mean±DP	Median	n	%
Age				
	58,6±14,0	61 (47,5;69,5)	-	-
Gender				
Male	-	-	20	80,0
Female	-	-	5	20,0
Diagnosis	-	-		
Orals squamous cell carcinoma	-	-	15	60,0
Head&Neck squamous cell carcinoma (non-oral)	-	-	6	20,0
Adenoid cystic carcinoma	-	-	2	8,0
Central giant cell lesion	-	-	1	4,0
Dermatofibrosarcoma	-	-	1	4,0
Disease location				
Tongue	-	-	8	32
Floor of the mouth	-	-	6	24
Oropharynx	-	-	5	20
Palate	-	-	2	8
Other sites	-	-	4	16
Radiotherapy planning				
Neoadjuvant	-	-	2	8,0
Adjuvant	-	-	23	92,0
Radiotherapy device				
Cobalt pump	-	-	18	72,0
Linear accelerator	-	-	7	28,0
Radiotherapy technique				
Conventional	-	-	18	72,0
3D	-	-	7	28,0
ORN site				
Mandible	-	-	17	68,0
Maxilla	-	-	7	28,0
Both	-	-	1	4,0
Dental extraction				
Previous to radiotherapy	-	-	6	33,3
After radiotherapy	-	-	12	66,7
ORN non-associated with dental extraction				
Pre-prosthetic surgery	-	-	5	71,4
After pelviglosomandibulectomy	-	-	2	28,6
ORN staging				
Stage I	-	-	14	56,0
Stage II	-	-	6	24,0
Stage III	-	-	5	20,0

[a] Mean ± standard deviation (maximum, minimum)

Table 2. Characteristics of the radiotherapy treatment used in the sample.

Radiotherapy planning	Dose (Gy)	Radiotherapy device	Radiotherapy technique	Tretament duration (PENTO)	Sequestrectomy
Adjuvant	70	Cobalt pump	Conventional	More than 6 months	No
Adjuvant	56	Cobalt pump	Conventional	More than 6 months	No
Neoadjuvant	66	Linear accelerator	3D	More than 6 months	Yes
Adjuvant	45	Linear accelerator	3D	More than 6 months	Yes
Adjuvant	54	Cobalt pump	Conventional	More than 3 months	Yes
Adjuvant	67.3	Cobalt pump	Conventional	More than 6 months	Yes
Adjuvant	60	Cobalt pump	Conventional	Until 3 months	No
Adjuvant	50.4	Cobalt pump	Conventional	Until 3 months	No
Adjuvant	60	Cobalt pump	Conventional	More than 3 months	No
Adjuvant	50	Linear accelerator	3D	More than 3 months	No
Adjuvant	70	Linear accelerator	3D	Until 3 months	No
Adjuvant	70	Cobalt pump	Conventional	More than 3 months	Yes
Adjuvant	66	Cobalt pump	Conventional	More than 6 months	Yes
Adjuvant	63	Cobalt pump	Conventional	More than 3 months	Yes
Adjuvant	63	Cobalt pump	Conventional	More than 6 months	Yes
Neoadjuvant	70.2	Cobalt pump	Conventional	More than 3 months	No
Adjuvant	70	Cobalt pump	Conventional	More than 6 months	No
Adjuvant	70	Cobalt pump	Conventional	More than 6 months	No
Adjuvant	70	Linear accelerator	3D	More than 6 months	Yes
Adjuvant	50.4	Linear accelerator	3D	More than 6 months	Yes
Adjuvant	59.4	Cobalt pump	Conventional	More than 6 months	Yes
Adjuvant	70	Cobalt pump	Conventional	More than 6 months	Yes
Adjuvant	70	Cobalt pump	Conventional	More than 3 months	Yes
Adjuvant	61.2	Cobalt pump	Conventional	More than 6 months	Yes
Adjuvant	70	Linear accelerator	3D	More than 6 months	Yes

Table 3. Overview ORN treatment.

Variables	n	%
Tretament duration (pentoxifylline and tochopherol)		
<3 months	3	12,0
3 to 6 months	7	28,0
>6 months	15	60,0
Side effects		
Yes	3	12,0
Gatrict discomfort	1	
Tachycardia	2	
No	22	88,0
Sequestrectomy		
Yes	15	60,0
No	10	40,0
Site response to treatment		
Complete mucosal healing	19	76,0
Partial healing	6	24,0

Figure 1 – Flowchart contemplating sample characteristics regarding ORN healing and need for sequestrectomy.