MAJOR HEALING OF REFRACTORY MANDIBLE OSTEORADIONECROSIS AFTER TREATMENT COMBINING PENTOXIFYLLINE AND TOCOPHEROL: A PHASE II TRIAL

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Accepted 5 July 2004
Published online 7 January 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20121

Abstract: *Background.* Osteoradionecrosis (ORN) is a nonhealing wound of the bone that is difficult to manage. Is a treatment combining pentoxifylline (PTX) and tocopherol (vitamin E) boosted by clodronate effective in reversing this fibronecrotic process?

Methods. Eighteen consecutive patients previously irradiated for head and neck cancer had exteriorized mandible ORN. Length of exposed bone (L) was 13.4 ± 8 mm, and the mean subjective objective medical management and analytic evaluation of injury (SOMA) score was 12.6 ± 4.9. Between June 1995 and January 2002, all 18 were given a daily oral combination of 800 mg of PTX and 1000 IU of vitamin E for 6 to 24 months. In addition, the last eight patients who were the worst cases were given 1600 mg/day clodronate 5 days a week.

Results. The treatment was well tolerated. All patients improved at 6 months, with 84% mean L and 67% mean SOMA score reductions. Sixteen (89%) of 18 patients achieved complete recovery, 14 in 5 ± 2.6 months. The remaining two patients exhibited a 75% response at 6 months.

Conclusion. PTX–vitamin E boosted by clodronate is an effective treatment of mandibular ORN that induces mucosal and bone healing in a median period of 6 months. © 2005 Wiley Periodicals, Inc. *Head Neck* **27:** 114–123, 2005

Keywords: osteoradionecrosis; radiotherapy; pentoxifylline; tocopherol; clodronate

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Presented at European Society of Therapeutic Radiology and Oncology, Istanbul, Turkey, September 2000; Société Française de Radiothérapie Oncologique, Paris, France, November 2002.

Osteoradionecrosis (ORN) is a severe delayed injury caused by failure of bone healing. It usually concerns the mandible and occurs after head and neck cancer treatment, mostly 6 months to 5 years after radiotherapy (RT).[1] Although new strategies designed to improve the therapeutic ratio have reduced the incidence of severe radiation-induced fibrosis (RIF) and necrosis, ORN is still unavoidable in 5% to 15% of cases.[2] Multiple risk factors predispose to its development. Several RT-related factors have been incriminated, including the total dose, the dose per fraction, the irradiated volume, and the use of brachytherapy, especially in cases in which RT is boosted by concomitant chemotherapy or in which patients have undergone extensive surgical intervention.[1,3] However, the increased incidence and severity of ORN are mainly due to poor dental status, local biopsy sites, bone proximity to the initial anatomic tumor

site, and intercurrent illnesses such as microvascular or endocrine diseases, or habits such as excessive tobacco and alcohol consumption. Mandibular ORN symptoms are diverse, ranging from occult disease to major bone destruction associated with soft tissue necrosis, excluding tumor recurrence, and include spontaneous complications like osteomyelitis, fistulation fracture, or sequestra.

Established ORN does not regress spontaneously. It either stabilizes or gradually worsens and is notoriously difficult to manage.[1,3] The conventional conservative medical attitude has consisted of restricting unfavorable associated events (such as dental extraction, infection, tobacco consumption) and prescribing the use of corticoids and antibiotics, which are useful in reducing the acute inflammatory reaction associated with radionecrosis. However, this medical approach is relatively ineffective in reversing the radionecrotic process.[4,5] The next usual steps in ORN management are the use of hyperbaric oxygen (HBO) and devitalized tissue removal (sequestrectomy), which have been found to improve and/or stabilize moderate ORN.[2,6,7] When technically possible, extensive surgical resection and reconstruction may be necessary in cases of refractory progressive ORN.[8] As of yet, no universally accepted medical treatment exists for this chronic pathologic condition.

Despite the few publications published on the management of radiation-induced sequelae, we developed an etiologic treatment on the basis of the understanding of the mechanism of RIF.[3] We concluded that RIF greatly regressed after antioxidant treatment with superoxide dismutase,[9] and subsequently, with the combination of pentoxifylline (PTX)–tocopherol (vitamin E).[10] PTX or vitamin E alone proved unable to reverse the development of human fibrosis. But these drugs were effective by possessing all properties necessary to make them excellent antifibrotic synergic agents. PTX is a methylxanthine derivative that exerts an anti–tumor necrosis factor (TNF)-α effect, increases erythrocyte flexibility, vasodilates, inhibits inflammatory reactions in vivo, inhibits human dermal fibroblast proliferation and ECM production, and increases collagenase activity in vitro. The functions of endogenous tocopherol are to scavenge the reactive oxygen species generated during oxidative stress, whose production is not limited in vivo by antioxidant enzymes, to protect cell membranes against lipid peroxidation, and to partly inhibit TGFβ1 and procollagen gene expression. In a phase II clinical trial, combined PTX–vitamin E treatment induced a 66% regression of the RIF surface area after 12 months of treatment.[10] These results were confirmed in our experimental cutaneomuscular RIF model by a 70% regression of RIF volume after 6 months of treatment[11] and in another randomized clinical trial.[12] In addition, Futran et al[13] showed that 1200 mg/day of PTX alone accelerated the healing of mucosal radiation-induced injury in nine of 12 cases of oral soft tissue necrosis without ORN. On the basis of new pathologic features of RIF, we postulated that the PTX–vitamin E combination could reverse ORN by reducing the microscopic RIF associated with the progressive necrotic process and by stimulating defective osteoblastic healing.[14] Last, in a woman seen with an extensive progressive exteriorized ORN of the sternum, complete cutaneous and bone healing was obtained with a treatment combining PTX–vitamin E and clodronate, a well-known biphosphonate that inhibits osteoclastic bone destruction.[15]

In the present phase II trial, conducted between June 1995 and January 2002 at Saint-Louis Hospital in Paris, 18 consecutive patients were treated for severe mandible ORN (chronic persistent ORN), with combined PTX–vitamin E, boosted in the last eight worst cases (active progressive ORN) by clodronate.

PATIENTS AND METHODS

Included in the trial were 18 ambulatory patients with the clinical and radiographic criteria for ORN of the mandible, which had failed to improve after at least 2 months of conventional conservative treatment (Table 1). Informed consent was obtained from all patients before treatment started. Sixteen (89%) were men with poor oral hygiene and excessive alcohol and tobacco consumption, and two were women with oral leukoplakia. Patient age ranged from 35 to 70 years (mean $\pm$ SD, 55 $\pm$ 9 years). All patients had undergone RT for malignant head and neck tumors, located mainly in the oral cavity or oropharynx, and showed no evidence of recurrent or metastatic disease on entering the trial. The mean latency period between the end of RT and the incidence of ORN was 4.1 $\pm$ 4.3 years (range, 0.5–14 years).

Before this trial, nine patients had received antibiotic therapy, six HBO, and/or six a sequestrectomy. None of these treatments had a beneficial effect on ORN, but in some cases they reduced the acute inflammation. Just before inclusion in the study, patients were given an oral

Table 1. Patient status and results of PTX–vitamin E treatment.

Patient	Head/neck tumor type	Time from RT to ORN (y)	Time from ORN to ToTo (mo)	Initial ORN Epstein stage (SOMA score)*	Time to healing (mo)	ORN Epstein stage at last follow-up	Current status (mo)
1	T3N1 OC	3	2	IIA (9)	2	IA	AWOT (66)
2	T3N1 OP	9	12	IIB (11)	6	IA†	AWOT (56)
3	T2N0 OP	0.5	5	IIIA (17)	4	IA	AWOT (15)
4	T0N3	9	5	IIA (7)	3	IA	AWOT (12)
5	T1N0 OC	2	4	IIA (7)	6	IA	AWOT (24)
6	T2N0 OC	9	2	IIA (8)	9	IA	AWOT (38)
7	T3N0 OP	3	2	IIA (7)	1	IA	AWOT (67)
8	T2N0 OC	14	5	IIA (5)	60	IA	AWOT (62)
9	T3N0 OP	2	3	IIIB (13)	NH	IIA†	D‡ (42)
10	T2N1 OP	0.5	16	IIIA (19)	18	IA	AWOT (29)
11	T3N1 OP	4	5	IIIA (19)	4	IA	AWOT (8)
12	T2N3 RP	5	17	IIIA (22)	6	IA	AWOT (21)
13	T2N0 PL	0.5	3	IIIA (11)	9	IA	AWOT (9)
14	T3N0 OP	0.5	2	IIIA (15)	3	IA	AWT (16)
15	T1N0 OC	1	2	IIIB (10)	6	IA†	AWT (17)
16	T2N0 OP	12	18	IIIB (15)	5	IA†	AWOT (15)
17	T0N2	0.5	2	IIIB (16)	9	IA†	AWOT (11)
18	T4N0 OC	1.5	2	IIIB (15)	NH	IIB†	AWOT (36)

Abbreviations: RT, radiotherapy; ORN, osteoradionecrosis; ToTo, PTX–vitamin E treatment; OC, oral cavity; OP, oropharynx; RP, rhinopharynx; PL, pharyngolarynx; NH, not healed; AWT, alive with tumor; AWOT, alive without tumor; D, died.
**Epstein classification stage II, chronic persistent ORN; stage III, active progressive ORN; A, without fracture; B, with pathologic fracture; SOMA score, subjective objective medical management and analytic evaluation of injury.*
†With sequestrectomy.
‡With ORN and second cancer.

antibiotic–corticoid treatment for 2 to 4 weeks, according to clinical signs of infection, consisting of 2 g/day amoxicillin-clavulanate, 50 mg/day fluconazole, and 16 mg/day methylprednisolone. A 10% clinical improvement in symptoms was subsequently observed in all cases: pain and purulence reduction.

Radiation Necrosis. Mandible ORN had been observed in patients who had received standard RT with 1.8 to 2.5 Gy per fraction 4 to 5 days a week. The total tumor doses prescribed were 55 to 65 Gy for 13 patients given postoperative RT and 65 to 75 Gy for the other five patients who underwent exclusive RT (external RT in two cases and brachytherapy in three). Before RT, 13 patients had undergone surgery, floor of mouth resection and glossectomy with or without partial mandibulectomy and head and neck node dissection; nine had undergone neoadjuvant or concomitant chemotherapy. Eight patients (44%) had spontaneous ORN develop, and 10 (56%) had ORN caused by trauma (dental extraction, $n = 6$; biopsy, $n = 4$). At the time of the present treatment, ORN had been exteriorized without healing for 6.2 ± 5.7 months (range, 2–18 months; Table 1).

Treatment. As previously described,[10] the modalities of treatment were based on pharmacokinetic data, clinical use in other diseases, and long-term tolerance. All patients were given a daily oral combination of 800 mg of PTX and 1000 IU of vitamin E. This combination was first administered for at least 6 months and, after that, for as long as clinical regression was observed. The PTX dosage in the combination was designed to avoid severe adverse effects in patients without vascular disease, whereas the vitamin E dosage was to supply sufficient antioxidant activity. Patients 1 to 10 constituted group I and were treated with PTX–vitamin E only (Table 1).

Because a treatment combining PTX–vitamin E and clodronate for progressive exteriorized ORN of the sternum recently proved successful,[15] we added clodronate for patients 11 to 18, who made up group II (eight patients with active progressive ORN) and had more severe ORN than those in group I had (seven of 10 patients with chronic persistent ORN) (Table 1). Accordingly, between 2000 and 2002, patients in group II were given the PTX–vitamin E combination, with 1600 mg/day clodronate 5 days a week and 1 g/day ciprofloxacin and 16 mg/day methylprednisolone 2 days a week for at least 6 months until complete

Table 2. Kinetics of the osteoradionecrosis response to treatment in 16 patients who recovered after combined pentoxifylline (PTX)–vitamin E alone (group I) or combined PTX–vitamin E and clodronate (group II).

	Mean value by no. months			
	Baseline (0 mo.)	2 mo.	4 mo.	6 mo.
Mean superficial necrosis L, mm	13.4 ± 8.0	8.8 ± 7.5	5.3 ± 6.7	2.1 ± 3.5
Mean % regression, total (groupI/groupII)		34 (50/21)	60 (75/57)	84 (86/79)
SOMA	12.4 ± 5.2	8.6 ± 5.8	5.3 ± 5.1	3.4 ± 4.7
Mean % regression		31	57	73

mucosal coverage was obtained. This intermittent clodronate administration was used on the basis of pharmacokinetic data showing that clodronate has a prolonged effect because of its high fixation in the bone combined with secondary release during bone remodeling.[16]

Study Assessments. Patients were individually assessed by two physicians. Routine evaluation included measurement of the length (L) of superficial soft tissue necrosis describing the exposed bone. The main endpoint of the study was the relative L regression [defined as (L at x months − L at inclusion)/L at inclusion] correlated to the extent of recovery. For patients 1 to 16, the mean initial L dimension was less than 2 cm in the oral cavity; these patients had lesions 13.4 ± 8 mm long (Table 2). Patients 17 and 18 had lesions 40 and 60 mm long, respectively.

The secondary endpoint was relative regression, expressed in Epstein stages and subjective objective medical management and analytic evaluation of injury (SOMA) scores (see later). According to the Epstein three-stage classifica-

FIGURE 1. Histogram showing the regression of the mean length of exposed mandible during the first 6 months of treatment with combined pentoxifylline (PTX)–vitamin E alone (group I, $n = 9$) or with combined PTX–vitamin E and clodronate (group II, $n = 7$) in 16 of 18 patients with osteoradionecrosis who recovered.

tion[17] (Table 1), seven patients initially had stage II ORN (chronic persistent), and 11 had stage III ORN (active progressive). The objective signs and subjective symptoms related to the site of ORN were graded from 1 to 4, according to the international SOMA score in which the items assessed were pain, mastication, ulceration dimensions, trismus, medical management of pain, management of exposed bone by antibiotics, debridement, HBO, resection, mandibular radiography for the detection of demineralization, pagetoid mosaic, or sequestra/fracture.[18] Clinical manifestations associated with ORN were osteitis in two patients, fistula in three, and fracture without shifting in six. The mean SOMA score at baseline assessment was 12.6 ± 4.9 (range, 5–22; Table 2).

Clinical data were recorded at 2, 4, 6, 9, and 12 months by measuring the percentage changes in L (length of exposed bone) and the SOMA score. The patients acted as their own controls and compared with themselves at each consultation.

Statistical Analysis. Depending on whether assessments were quantitative or qualitative, paired data were analyzed with Statview software (Statview IV; Abacus Concepts, Berkeley CA) and compared by Student's t test for paired values or the chi-square test for hypothetical correlations. A p value of $\leq .05$ was considered significant. The data for L and SOMA score regression at 6 months were processed by single sample tests and bivariate plots. Median time to recovery was calculated by the Kaplan-Meier method.

RESULTS

Tolerance and Compliance. Immediate and long-term tolerance were very satisfactory, and no patients stopped the treatment because of an adverse event.

Morphologic Changes. A clinical response, defined as the gradual centripetal regression of exposed bone, was observed in all 18 patients (100%), with a median time to complete recovery (CR) of 6 months.

Of the 18 patients included, 16 (89%) recovered with complete mucosal healing: 14 of them experienced rapid CR in 5.2 ± 2.6 months, and

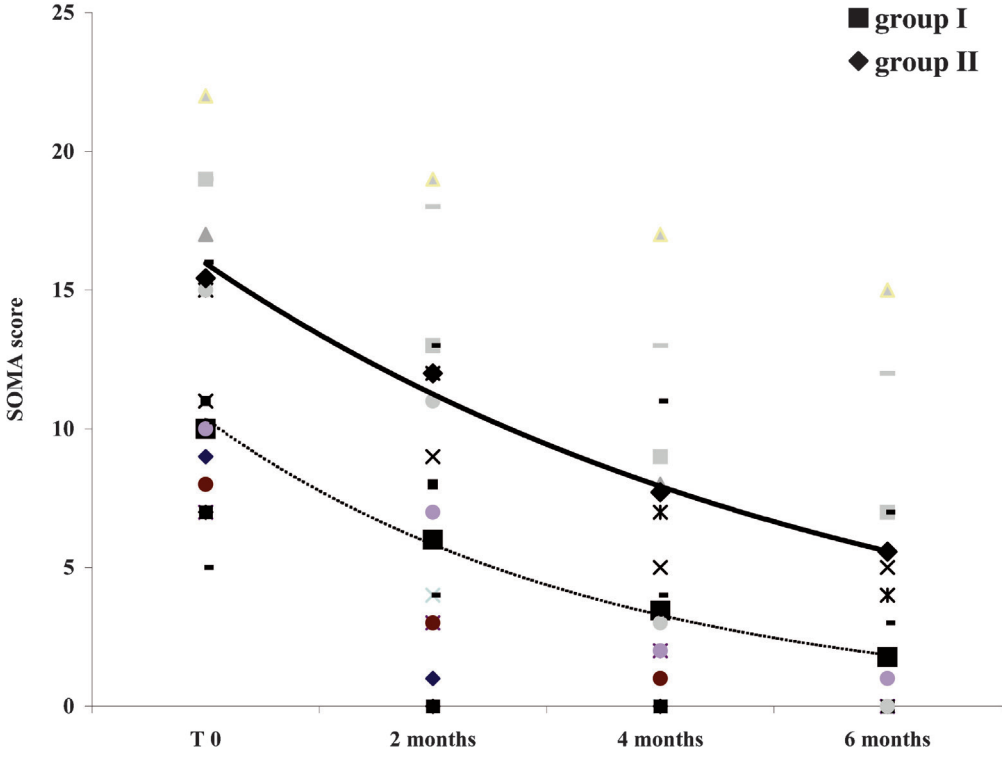

FIGURE 2. SOMA score regression: evolution of the measures with time, computed for each patient of 16 patients with osteoradionecrosis who recovered after combined treatment with combined pentoxifylline (PTX)–vitamin E alone (group I, $n = 9$, full line) and with combined PTX–vitamin E and clodronate (group II, $n = 7$, dotted line). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

two, with severe alcoholism, had delayed CR in 18 and 60 months, respectively. In these complete responders, the 84% of mean L regression at 6 months from 13 to 2 mm was highly significant ($p < .001$; Table 2). Although initially, group II included significantly worse cases, no difference was observed between the two groups regarding the L regression slope (Figure 1), the CR rate (7 + 2/10 vs 7/8), or the mean time to recovery (4.4 $\pm$ 2.7 vs 6 $\pm$ 2.3 months).

The remaining two patients (11%) exhibited objective L regression at 6 months of 75%. Patient 9 (in group I), with severe alcoholism, had not recovered at 3.5 years and died after a second thoracic cancer and a postoperative pulmonary infection. Patient 18 (in group II) had not recovered at 3 years and had ORN develop in the initial tumor bed, without recurrence of the original cancer.

Qualitative Changes. When assessed by the Epstein classification at their last follow-up (Table 1), 16 patients had ORN stage IA (CR), and two had stage II (chronic persistent). Here again, although group II initially included significantly worse cases, no difference was observed between the final Epstein stages of the two groups (Table 1). Of the 10 patients in group I, seven had ORN classified as stage II, and three had ORN classified as stage III in the initial assessment; nine had ORN classified as stage IA, and one had ORN classified as stage IIA in the final assessment. Of the eight patients in group II, all had ORN classified initially as stage III and finally as stage I (7 as IA, 1 as IIB).

When clinical responses were graded qualitatively according to the SOMA score for symptom severity, a mean difference of 67% emerged for the 18 patients at 6 months of treatment compared with the initial score, with a regression from 12.6 $\pm$ 4.9 to 4.2 $\pm$ 5.6 (see Table 1 for the SOMA of complete responders). No difference was observed between groups I and II with respect to the slope of SOMA score regression (Figure 2). We observed delayed radiologic improvement (Figure 3). All necrotic zones improved rapidly, including local pain, and analgesics were stopped within 3 to 6 months of treatment. Clinical manifestations associated with ORN, including closed fistula, osteitis sterilization, and wide trismus reduction, all subsided or resolved during treatment.

One year after recovery from ORN, progressive cancer was observed in patients 14 and 15. At 16 months of follow-up, patient 14 had a recurrence in the form of a cervical node (2.5 years after the initial cancer treatment). At 15 months

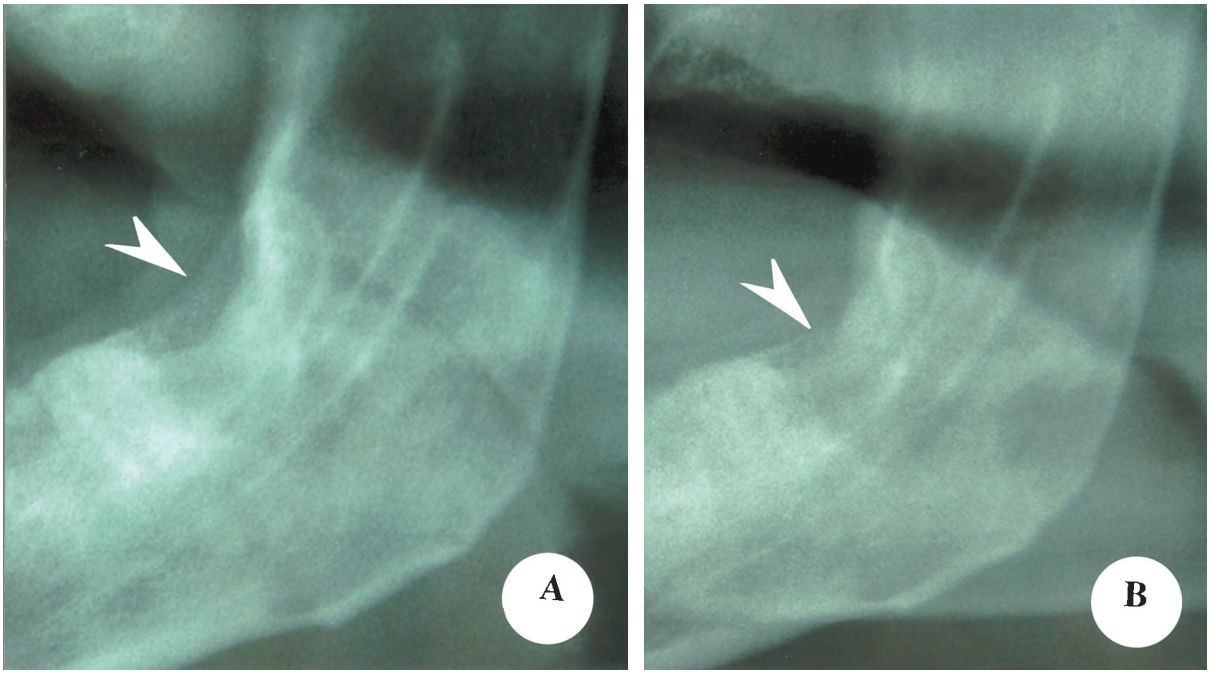

FIGURE 3. Mandible x-ray. **(A)** Left horizontal mandible osteoradionecrosis at baseline (arrow). **(B)** After 6 months of treatment with combined pentoxifylline-vitamin E–clodronate (group II): partial mandible restoration with new filling tissue and strong reduction of bone loss (arrow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of follow-up, patient 15 experienced a second head and neck cancer (2.5 years after the first cancer treatment).

DISCUSSION

ORN is a severe form of delayed injury by healing bone failure after head and neck cancer treatment; furthermore, it is important to prevent trauma, such as dental extraction after radiation, to reduce its incidence.[1] The clinical course of ORN is highly variable and ranges from minimal to extensive bone exposure with major rarefaction of the mandibular bone.[19] The recent clinical classification by Epstein[17] has facilitated the development of protocols for ORN treatment, and conservative measures were commonly instituted, including optimization of oral hygiene, irrigation, and oral antibiotics.[4,5] In the last decades, the results of most published series suggested that such measures facilitated complete ORN resolution in 8% to 33% of patients at 1 year (Table 3). However, most patients failed to heal with such medical measures. In contrast, surgery was more successful in stemming active progressive ORN, by operations ranging from sequestrectomy to hemimandibulectomy and closure of orocutaneous fistulae, sometimes by use of myocutaneous flaps.[8,20] These large resections helped to obtain good local control of necrosis yet involved significant human factors and financial resources. As early as 1973, HBO was reported to be effective as an adjunctive treatment for ORN.[21] However, the results reported for HBO in the literature vary considerably (Table 3) and range from 15% to 43% recovery after HBO alone versus 18% to 90% after HBO combined with limited surgery.[2,22–31] This limited retrospective published experience soon established that without aggressive surgical management, HBO would not resolve the disease process in most cases.[24] In addition, a recent French randomized trial involving 68 patients failed to demonstrate that HBO had any beneficial effect in patients with

Table 3. Main trials of osteoradionecrosis treatments reported in the literature.

First author, year	ORN cases evaluated	Medical conservative	Medical + sequestrectomy	Resection	HBO	HBO + Sequestrectomy	HBO + resection
Marx 1983[6]	*N* = 112	*n* = 112 8% R 1 year					
Morrish 1981[5]	*N* = 22	*n* = 16 4 (25%) R 3–24 mo		*n′* = 6 3 (50%) R			
Wong 1960–95[4]	*N* = 32	*n* = 12 3 (25%) R 26 mo	*n′* = 20 11 (55%) R 25 mo				
Epstein 1987[17]	*N* = 32	*n* = 26 8 (31%) R			*n′* = 6 2 (33%) R		
Mainous 1975[21]	*N* = 14				*n* = 4 4 (100%) R	*n′* = 10 10 (100%) R	
Marx 1988[22]	*N* = 268				*n* = 38 15% R (st.I) delay?	*n′* = 48 18% R (st.II) delay?	*n″* = 182 if severe (st.III)
Mounsey 1980–85[26]	*N* = 41				*n* = 41 6 R (15%)		
McKenzie 1975–88[27]	*N* = 26				*n* = 7 3 (43%) R 24 mo	*n′* = 12 8 (67%) R 24 mo	*n″* = 7 7/7 controlled
Maier 2000[28]	*N* = 41		*n* = 11 10 (91%) R 59 mo	*n′* = 10 4 (40%) R 13 mo		*n″* = 19 12 (63%) R 18 mo	*n‴* = 1 controlled
David 1985–97[30]	*N* = 51				*n* = 19 7 (37%) R	*n′* = 20 18 (90%) R	*n″* = 12 11(91%) R
Annane 1997–01 randomized[32]	*N* = 68	*n* = 37 placebo 12 (33%) R 12 mo			*n′* = 31 6 (19%) R 12 mo		

Abbreviations: ORN, osteoradionecrosis; HBO, hyperbaric oxygen; N, total number of cases evaluated; n, n′, n″, n‴, number of cases in each treatment group; R, recovery (rate).

ORN of the jaw, because only 19% recovered in the HBO group versus 33% in the placebo group.[32] In this trial, a conservative medical treatment based on the combination of PTX–vitamin E and clodronate proved able, for the first time, to heal patients with severe ORN of the jaw. The results showed that 16 (89%) of 18 patients with ORN recovered after a median 6 months of treatment and exhibited mean decreases of 84% in the length of their exposed bone and 67% in their SOMA score. This therapeutic efficacy was also recently illustrated in a patient with severe exteriorized ORN of 7 cm of the sternum, who exhibited complete clinical healing and radiologic restoration on MRI 3 years after treatment.[15]

The usual clinical features of late RT damage to normal tissues are mainly a lack of spontaneous reversibility and an inevitable tendency toward aggravation with time.[33] During the last decades, various concepts concerning the pathogenesis of radiation-induced lesions have been proposed. The descriptions of the axis of the lesions clarified the nature of the mechanisms that cause late RT injury and suggested that the process involved was either hypovascular-hypoxic or bone fibroatrophy. Hypoxia was suggested by the presence of histologic areas of necrosis in severely damaged tissues, and this was partly supported by measurements of oxygen tension (pO_2) in irradiated tissues. Marx[24] analyzed the effect of irradiated cervical tissue perfusion by measuring pO_2 in 112 patients and found a linear relationship indicating loss of microvascular perfusion with time as a probable risk index for ORN. In contrast, Rudolph et al[34] found similar transcutaneous pO_2 in the irradiated and nonirradiated skin of 100 patients breathing air. Furthermore, in experiments on rabbits, subcutaneous tissue pO_2 decreased during the acute phase of irradiation injury but remained unchanged in tissues affected by late fibrosis and blood vessel changes.[35] Recently, Bras et al[36] attempted to explain the reasons for the strong predisposition of the mandible to ischemic radionecrosis.[36] This predisposition was mostly due to the obliteration of the inferior alveolar artery and to concomitant impairment of revascularization by branches of the facial artery because of radiation-induced vascular fibrosis, which weakened the most vulnerable part of the mandible (ie, the buccal cortex of the premolar-molar and retromolar region). The fibroatrophic hypothesis focused on the defective irradiated bone and on the imbalance between tissue synthesis and degradation.[3] The traditional histopathologic picture of ORN was a mosaic of persistent areas of osteogenesis within extended areas of osteolysis. This mosaic corresponded to the description of the pagetoid mottled radiologic appearance of these areas.[33] Recently, Dambrain[37] showed the following four types of bone destruction in postsurgical ORN patients by use of microradiographic analysis[37]: (1) osteoclastic resorption (macrophagic activity), progressive osteoporosis not followed by relevant osteogenesis; (2) periosteocytic lysis, a pathognomonic sign of ORN damage linked to the deterioration of osteocyte activity; (3) massive demineralization, in the form of chemical resorption because of saliva and purulence (infection); and, more rarely, (4) accelerated bone aging. Fajardo[33] described this bone defect as true tissue atrophy because of bone destruction and the enhanced death of osteoblasts that have reached the end of their lifespan and disappeared without replacement.[33] In this atrophic process, the bone gradually becomes hypocellular, and the number of osteoblasts diminishes, which reduces bone matrix formation. Such bone atrophy is associated with, or maybe compensated by, the formation of fibrous connective tissue composed of usual fibrotic elements such as an excess of proliferative fibroblasts and collagenic extracellular matrix.

The significant regression observed in all the patients with ORN in this clinical trial of the PTX–vitamin E combination, associated with clodronate in the worst cases, does not support the concept that an established sequela such as ORN is irreversible. The physiopathologic approach to ORN developed here prompted us to devise a therapeutic strategy designed to improve tissue healing by limiting bone destruction and enhancing bone formation with three aims in view: (1) resolution of the mucosal and bone infection in the irradiated fibrotic tissue by a vigorous initial antiseptic treatment of 2 to 4 weeks with amoxicillin-clavulanate/ciprofloxacin, fluconazole, and methylprednisolone; (2) marked reduction of the often microscopic radiation-induced fibrosis, sometimes combined with phenotypic reversion of the irradiated osteoblasts that enhance osteogenesis by the synergistic combination of PTX–vitamin E[10]; and (3) the arrest of osteolysis by biphosphonate (Bp) inhibition of bone destruction with clodronate. Biphosphonates effectively control in vivo bone destruction by reducing the osteoclastic resorption caused by the inhibition of osteoclast recruitment and activity and the

shortening of the osteoclast lifespan by increased apoptosis.[16] Bps have also been shown to possess excellent therapeutic properties in chronic inflammatory disease by inhibiting the delayed hypersensitivity granuloma response.[38] Last, Bps were observed to reduce in vitro fibroblastic proliferation[39,40] and thus potentiate the antifibrotic effect of PTX–vitamin E. At the opposite of the new generation of Bps (pamidronate, zoledronate), clodronate has a significant direct action on the osteoblastic cells, increasing bone formation,[41] without antiangiogenic properties.[42,43] Long-term administration of clodronate is well tolerated[44] and reduced vertebral fracture risk in women with postmenopausal osteoporosis in a recent randomized 3-year study.[45]

CONCLUSION

Continuous treatment of patients with combined PTX–vitamin E and clodronate was proven effective in reducing chronic progressive septic ORN of the mandible. Because there is, at present, no standard medical treatment, we believe this treatment constitutes a useful alternative to existing therapies in treating ORN. All three drugs are available, well tolerated, inexpensive, and beneficial to the patient. Last, the results of this phase II trial raise many questions, primarily about the precise mechanisms of action of the drugs used. Some of the answers will be provided by a future randomized clinical trial.

Acknowledgments. We are grateful to surgeons from several institutions in Paris for entrusting their ORN patients to our care.

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