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Efficacy of Pentoxifylline–Tocopherol–Clodronate in Mandibular Osteoradionecrosis

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Objectives/Hypothesis: PENTOCLO treatment, associating pentoxifylline, tocopherol, and clodronate, resolves radiation-induced fibrosis. The main aim of the present study was to prospectively assess efficacy in mandibular osteoradionecrosis (ORN).

Study Design: Prospective cohort study.

Methods: Twenty-seven patients with mandibular ORN were included in the Pentoclauvergne Study between January 2014 and February 2016. After an initial 28-day phase of antibiotic, antifungal, and corticosteroid therapy, they received the PENTOCLO association daily until cure or a maximum of 24 months. The main assessment criterion was exposed bone area (EBA); secondary criteria comprised the Subjective, objective, management, and analytic (SOMA) score.

Results: Under PENTOCLO, EBA decreased by 28% at 2 months, 55% at 6 months, and 92% at 24 months; the SOMA score decreased by 23%, 38%, and 50%, respectively. A complete treatment course cured 76.5% of patients at a mean 9.6 months.

Conclusions: PENTOCLO is a simple, well-tolerated, and effective treatment for mandibular ORN.

Key Words: Osteoradionecrosis, mandible, pentoxifylline, tocopherol, clodronate.

Level of Evidence: 4

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INTRODUCTION

Osteoradionecrosis (ORN) consists in exposure of devitalized necrotic bone by mucosal or cutaneous ulceration in territory affected by radiation therapy, persisting without spontaneous resolution for 3 months, without tumor recurrence.[1] It is a serious condition, usually affecting the mandible, in patients who have undergone radiation therapy for upper-airway cancer,[2,3] even if its incidence has tended to stabilize since the 1980s (2%–22%).[4,5]

ORN does not usually show a tendency for spontaneous resolution[2,6]; rather, it tends to stabilize or worsen, with onset of complications (abscess, orostoma, fracture, sepsis, malnutrition, death).[7] Various medical options have been tried (e.g., antibiotics, corticosteroids, hyperbaric oxygen therapy), but provide only partial results, none proving curative.[7–14] Surgery, although mutilating, thus became unavoidable to arrest progression.[4,15–17]

There are three pathophysiological theories: infection, with radio-induced osteomyelitis[18]; circulation disorder, with hypoxia and microvascular fragility[19]; and radio-induced fibroatrophy.[5]

Considering these hypotheses, three molecules were recently assessed: tocopherol (vitamin E) as an antioxidant[7,20]; pentoxifylline, which shows vascular tropism, improving local microcirculation[4,8,21]; and clodronate, a first-generation bisphosphonate that limits bone resorption by reducing osteoclast activity,[22] increases bone apposition by stimulating osteoblasts,[23] and reduces production of inflammatory cytokines (e.g., interleukin [IL]-1β, IL-6, and tumor necrosis factor–α).[24]

A synergic effect of these molecules was demonstrated by Delanian et al.[25,26] Associated pentoxifylline–tocopherol–clodronate (PENTOCLO) was therefore tested in mandibular ORN, with highly encouraging results.[5,25–27] In 2005, in a retrospective clinical trial, Delanian et al. reported 89% early cure.[7] In 2011, in a subsequent trial, Delanian et al. reported 100% cure and 96% reduction in modified SOMA (subjective, objective, management, and analytic evaluation of injury) score at 24 months.[28]

We therefore set up a prospective study with the main aim of assessing the efficacy of PENTOCLO in mandibular

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ORN. The study had local review board approval (South-East of France Ethics Committee VI, N°2014/CE35).

MATERIALS AND METHODS

Population

Twenty-seven patients with mandibular ORN following upper-airway cancer treatment, followed in two centers, were prospectively included in the Pentoclauvergne study between January 2014 and February 2017. Exclusion criteria comprised nonmandibular ORN, active neoplastic pathology at inclusion, and contraindications to any of the study drugs.

Table I presents epidemiological data, and Table II ORN clinical data. There were 24 male and three female patients (sex ratio = 8:1), with mean age 63.6 ± 10.3 years (range, 45–93 years). All patients underwent radiation therapy: exclusive in 14.8% of cases, associated to surgery in 22.2%, to chemotherapy in 22.2%, and to surgery plus chemotherapy in 40.7% (Table I). Total dose was 66 to 70 Gy for 11 patients (40.7%) and 60 to 66 Gy for the other 16 patients (59.3%). Mean time to onset of ORN after the end of radiation therapy was 53.1 ± 42.3 months (range, 5–170 months). Mean time from diagnosis of ORN to initiation of PENTOCLO was 13 ± 22 months.

TABLE I.
Epidemiologic Characteristics.

Characteristics	Value
No. of patients	27
Gender M/F	24/3
Age, yr, mean ± SD (range)	63.6 ± 10.3 (45–93)
Upper airway cancer, no. (%)	
Tongue	9 (33.3%)
Oral floor	6 (22.2%)
Other oral cavity	4 (14.8%)
Oropharynx	6 (22.2%)
Other (parotid, primary adenopathy)	2 (7.4%)
Second location upper airway cancer, no. (%)	4 (14.8%)
Tumor stage, main location, no. (%)	
T1	2 (7.7%)
T2	7 (26.9%)
T3	12 (46.2%)
T4	5 (19.2%)
Total radiation dose, no. (%)	
66–70 Gy	11 (40.7%)
60–66 Gy	16 (59.3%)
Treatment of main location, no. (%)	
Exclusive RT	4 (14.8%)
Surgery + RT	6 (22.2%)
Surgery + RT + CT	11 (40.7%)
Radiochemotherapy	6 (22.2%)
Reirradiation, no. (%)	4 (14.8%)
Active intoxication, no. (%)	
Smoking	5 (18.5%)
Alcohol	5 (18.5%)

CT = chemotherapy; F = female; M = male; SD = standard deviation; RT = radiation therapy.

TABLE II.
Clinical Characteristics at Inclusion.

Clinical characteristics	Value
ORN trigger factor	
Dental extraction	9 (33.3%)
None, spontaneous	18 (66.7%)
Intervals, mo	
RT-to-diagnosis of ORN	53.1 ± 42.3 (5–170)
Diagnosis of ORN-to-PENTOCLO	13.5 ± 21.8 (3–110)
Main ORN location	
Horizontal branch	17 (63.0%)
Angle	7 (25.9%)
Symphysis	3 (11.1%)
Multiple	7 (25.9%)
Revelation	
Follow-up	13 (48.1%)
Healing defect	7 (25.9%)
Pain	5 (18.5%)
Abscess	1 (3.7%)
Fracture	1 (3.7%)
Albuminemia at inclusion, g/L	40.5 ± 5.1 (30–50.9)
BMI at inclusion, kg/m^2	23.9 ± 4.4 (17.6–34)
ORN characteristics at inclusion	
Marx-Myers classification	
1	0
2	18 (66.6%)
3	9 (33.3%)
Orostoma	1 (3.7%)
Fistula	6 (22.2%)
Fracture	1 (3.7%)
Epstein classification	
1 (A/B)	0
2 (A/B)	A: 2 (7.4%) B: 0
3 (A/B)	A: 24 (88.9%) B: 1 (3.7%)
Exposed bone area, mm^2	145.7 ± 196.2 (4–800)
SOMA score	12.9 ± 3.5 (7–21)

Results are reported as mean ± standard deviation (range) or number (percentage).

BMI = body mass index; ORN = osteoradionecrosis; RT = radiation therapy; SOMA = subjective, objective, management, analytic evaluation of injury.

PENTOCLO Treatment

The treatment protocol comprised two distinct phases. The first, the disinfiltration phase, lasted 28 days. It associated ciprofloxacin 500 mg oral suspension, morning and evening; clindamycin 300 mg, two capsules, morning, midday, and evening; fluconazole 50 mg oral suspension, once daily; prednisone 20 mg, once daily; and omeprazole 20 mg, once daily. The second, therapeutic phase—the actual PENTOCLO phase—began at the end of phase 1. Drug choice and dosages were founded in the studies by Delanian et al.,[7,20,25,26,28–30] and comprised: pentoxifylline 400 mg, 1 tablet, morning and evening; tocopherol 500 mg, 1 capsule, morning and evening; clodronate 800 mg, 1 tablet, morning and evening, Monday to Friday (5 days per week); prednisone 20 mg, once daily, Saturday and Sunday (2 days per week); and omeprazole 20 mg, once daily, Saturday and Sunday (2 days per week). The end of treatment was determined by a complete clinical cure (mucosal healing, no exposed

bone), with all treatment definitively terminated at that date or at the end of a maximum 2 years without complete cure, in which case PENTOCLO treatment was deemed to have failed.

Assessment

Follow-up was set at a minimum 2 years. Clinical assessment was based on 10 scheduled consultations: inclusion, 0, 1, 2, 4, 6, 9, 12, 18, and 24 months (I, M0, M1, M2, M4, M6, M9, M12, M18, M24, respectively). Treatment phase 1 (disinfiltration) began at inclusion (I); phase 2 (PENTOCLO) began at M0. At each consultation, weight, body mass index, alcohol abuse and smoking status, adherence to treatment, and any adverse effects or ablation of bone sequester (sequestrectomy) were assessed. The main assessment criterion was clinical measurement of the exposed bone area (EBA) through the mucosal ulceration, in

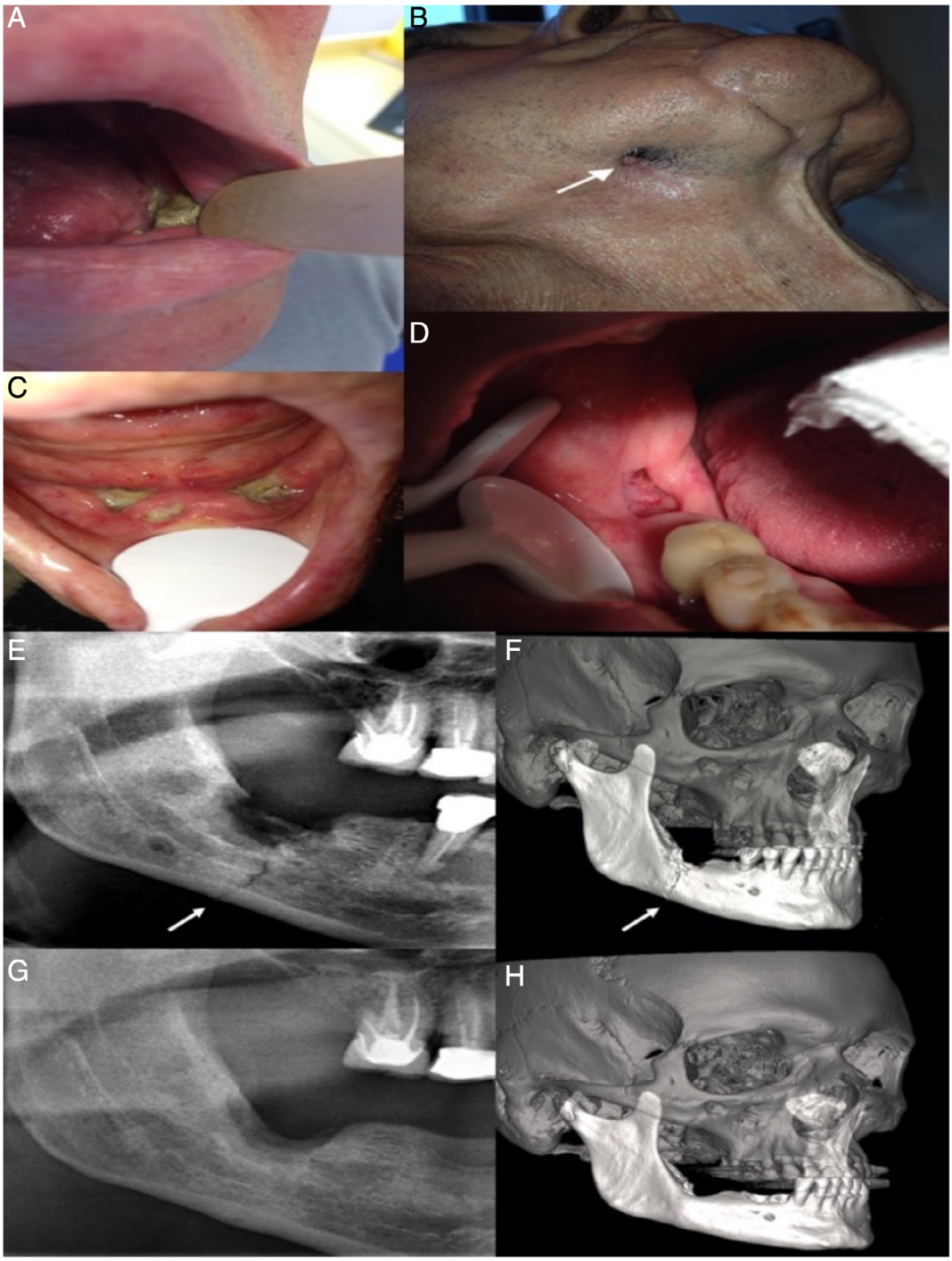

Fig. 1. Photographs of osteoradionecrosis. (A) Single left horizontal branch location. (B) Cutaneous fistula. (C) Multiple symphysis locations. (D) Cure of single right mandibular angle location (healthy mucosa defect cover). Images of a case with right horizontal branch fracture. (E) Dental. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.] [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

square millimeters: length (mm) × width (mm) (Fig. 1). In case of multiple sites, EBAs were summed. At first consultation, a local sample was taken for bacteriological analysis, specifically screening for *Actinomyces*, and for mycologic analysis.

Secondary assessment criteria comprised modified SOMA score, as described by Pavy et al.[31] and adapted by Delanian[28] (see Supporting Information, Appendix 1, in the online version of this article), and Marx-Myers and Epstein scores.[2,19] A panoramic dental x-ray was taken at each consultation, with facial computed tomography and biologic assessment (albumin) at inclusion and 1 and 2 years.

Statistical Analyses

All tests were two-tailed, using Stata software (version 13; StataCorp, College Station, TX). The significance threshold was set at $P < .05$ (α risk = 5%). Categorical variables were reported as numbers and percentages and quantitative variables as mean ± standard deviation or median with interquartile range, depending on normal distribution on Shapiro-Wilk test. Time to cure was taken as a censored variable for Kaplan-Meier estimation and compared between groups on a log-rank test (univariate analysis) or Cox proportional risk models. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). No multivariate analysis was applied. Longitudinal analysis of SOMA and EBA used nonlinear mixed regression to model and predict individual SOMA score and EBA at a given assessment time point, considering the patient's progression and inter- and intrasubject variability (subject effect being considered random). Intergroup comparisons used the Student *t* test or analysis of variance, or Kruskal-Wallis test if conditions for parametric tests were not met, and quantitative variables were compared on Pearson or Spearman correlation coefficients, depending on the distribution.

RESULTS

Fifteen of the 27 patients (55.6%) followed treatment until cure or the 24-month treatment deadline. Twelve patients were withdrawn from the study: five (18.5%) for neoplastic reasons (local or remote recurrence or new cancer), two (7.4%) voluntarily, two (7.4%) due to ORN progression requiring surgery, one (3.7%) due to death, and two (7.4%) lost to follow-up.

The mean treatment duration was 9.3 ± 7.6 months (range, 1–24 months), and the mean follow-up was

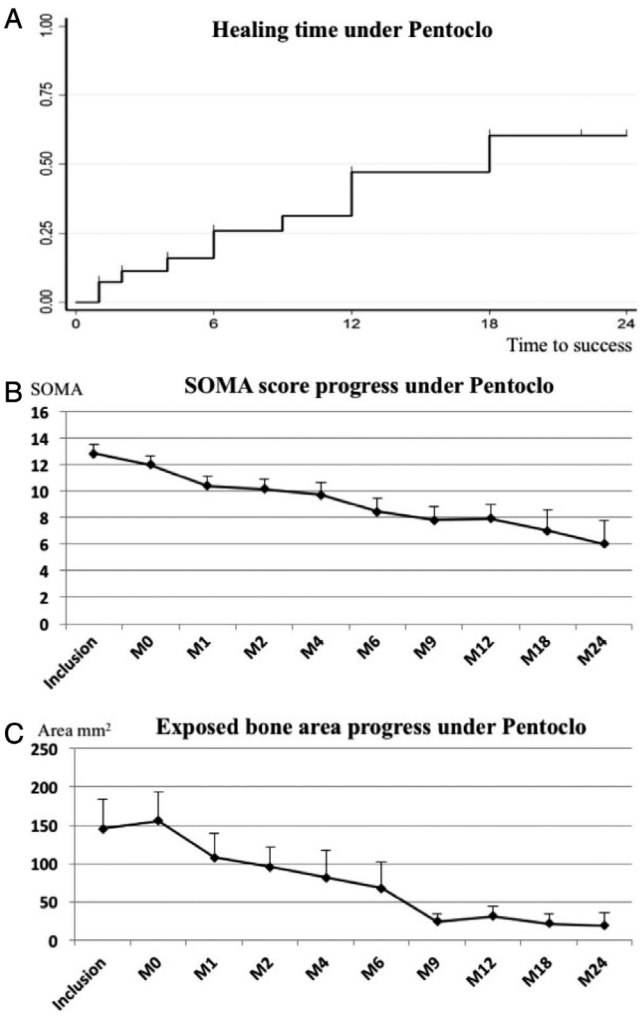

Fig. 2. Results of PENTOCLO treatment on success, SOMA score, and exposed bone area. (A) Kaplan-Meier curve with success of PENTOCLO treatment as event. Censored data are shown as a bar. (B) Change in SOMA score under PENTOCLO. (C) Change in exposed bone area under PENTOCLO. Results reported as mean and standard deviation. M = month; PENTOCLO = pentoxifylline-tocopherol-clodronate; SOMA = subjective, objective, management, analytic evaluation of injury.

TABLE III.
Success Rate, Exposed Bone Area, and SOMA Score Under PENTOCLO (N = 27).

Treatment Duration	No. of Patients Under Treatment	No. of Patients Cured (%)	Exposed Bone Area, mm^2, median (IQR)	SOMA Score, mean ± SD
Inclusion	27	0	75 (30–145)	12.9 ± 3.6
0 months	27	0	96 (25–240)	12.0 ± 3.5
1 month	27	2 (7.4%)	50 (6–102)	10.4 ± 3.6
2 months	23	3 (11.1%)	50 (4–120)	10.2 ± 3.6
4 months	19	4 (14.8%)	19.5 (2.5–80)	9.7 ± 4.5
6 months	17	6 (22.2%)	4 (1.5–85)	8.5 ± 4.6
9 months	13	7 (25.9%)	4 (0–25)	8.4 ± 4.9
12 months	12	10 (37.0%)	4 (0–30)	8.6 ± 5.0
18 months	6	12 (44.4%)	2 (0–25)	8.7 ± 6.1
24 months	3	13 (48.1%)	0 (0–00	8.0 ± 6.7

IQR = interquartile range; SOMA = subjective, objective, management, analytic evaluation of injury; PENTOCLO = pentoxifylline, tocopherol, clodronate; SD = standard deviation.

TABLE IV.
Prognostic Factors for Success Under PENTOCLO.

	Descriptive Analysis, n = 27	HR (95%CI)	*P*
Age, mean ± SD	63.6 ± 10.3	0.95 (0.87–1.03)	.19
BMI, mean ± SD	23.9 ± 4.4	0.98 (0.86–1.11)	.71
Alcohol abuse	5 (18.5%)	0.75 (0.16–3.45)	.72
Active smoker	5 (18.5%)	1.06 (0.29–3.92)	.93
T stage (T3 + T4)	17 (65.4%)	0.28 (0.08–0.97)	.045
Surgery	17 (63.0%)	0.49 (0.16–1.54)	.22
Chemotherapy	17 (63.0%)	1.06 (0.33–3.43)	.92
Radiation therapy, 70–80 Gy	11 (40.7%)	2.58 (0.81–8.23)	.11
No trigger factor	18 (66.7)	0.48 (0.15–1.50)	.21
Symphyseal involvement	3 (11.1)	0.97 (0.12–7.54)	.97
Bilateral involvement	6 (22.2)	0.52 (0.11–2.40)	.40
Sequestrectomy	10 (37.0)	0.90 (0.28–2.85)	.86
Fistula	6 (22.2)	0.14 (0.02–1.11)	.06
Marx-Myers classification (class 3)	9 (33.3)	2.65 (0.71–9.92)	.15
SOMA score, inclusion, mean ± SD	12.9 ± 3.6	0.72 (0.55–0.93)	.01
Exposed area, inclusion, median (IQR)	75 (30–145)	0.38 (0.21–0.70)	.002
Exposed area < 35 mm^2, inclusion	7 (25.9%)	6.11 (1.91–19.59)	.002
Albumin, g/L, mean ± SD	40.5 ± 5.1	1.09 (0.97–1.22)	.13
Albumin ≥45 g/L	5 (23.8%)	2.31 (0.73–7.34)	.16

Results reported as mean ± SD, median (IQR), or number (percentage). Significance threshold: $P < .05$ (N = 27).
BMI = body-mass index; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; PENTOCLO = pentoxifylline, tocopherol, clodronate; SD = standard deviation; SOMA = subjective, objective, management, analytic evaluation of injury.

12.9 ± 9.1 months (range, 1–24 months). Fifteen patients (55.6%) required one or more sequestrectomies. For nine patients (33.3%), clinical status required antibiotic therapy during the second phase of treatment, due to highly symptomatic and infected ORN; in some cases, this treatment was continued for several months. One patient had mandibular fracture at inclusion, with clinical and complete radiological resolution (Fig. 1).

Main Criterion

Thirteen of the 27 patients (48.1%) were cured, at a mean 9.6 ± 7.2 months. The rate with respect to those following treatment to cure or the 24-month deadline was 76.5% (considering the two patients excluded due to ORN surgery as failures). Table III and Figure 2 show these results.

Under PENTOCLO, percentage change in EBA from baseline was +13% ± 47% at M0 (end of disinfiltration phase), –9% ± 83% at M1, –28% ± 66% at M2, –56% ± 44% at M4, –55% ± 93% at M6, –74% ± 47% at M9, –72% ± 40% at M12, –82% ± 24% at M18, and – 9% ± 21% at M24. Change in mean SOMA score was –6% ± 12% at M0, –19% ± 16% at M1, –23% ± 16% at M2, –27% ± 24% at M4, –36% ± 24% at M6, –38% ± 29% at M9, –38% ± 30% at M12, –42% ± 36% at M18, and – 50% ± 39% at M24.

Secondary Criteria

Prognostic factors for cure under PENTOCLO treatment and ORN severity factors. Low SOMA score (HR = 0.73, 95% CI: 0.58–0.93; $P = .01$), small EBA (HR = 0.98, 95% CI: 0.97–0.99; $P = .04$), and low T stage (HR = 0.28, 95% CI: 0.08–0.97; $P = .045$) were significant predictors of success (Table IV). Initial EBA <35 mm^2 was strongly predictive of cure (HR = 6.11, 95% CI: 1.91–19.59). No predictive factors emerged for change in SOMA score or EBA. No severity factors at inclusion proved significant.

Radiation dose in the mandible. Mean radiation dose was significantly higher in the ORN zone than in the rest of the mandible (66.8 ± 14.3 vs. 53.7 ± 11.8 Gy; $P < .001$; n = 13). Segmenting the mandible anatomically as right and left horizontal branches, right and left vertical branches, angle and symphysis revealed that segments including ORN received ≥60 Gy significantly more often than the rest of the mandible (70.3 ± 29.4 vs. 48.9 ± 16.5; $P = .005$). Radiation dose in the ORN segment showed no correlation with success, SOMA score, or EBA.

Treatment-related adverse events. In treatment phase 1, there were four cases (14.8%) of maculopapular exanthema immune-allergic toxidermy, without severity or need to interrupt the implicated treatment. In phase 2 (PENTOCLO phase), no severe adverse events occurred. Twenty-four patients (88.9%) showed complete adherence to treatment and protocol duration. The main adverse events comprised: diarrhea (22.2%), epigastralgia (11.1%), asthenia (11.1%), nausea (7.4%), and insomnia (3.7%). Most received symptomatic treatment or were managed by dose reduction (as foreseen in the protocol).

Microbiology data. Bacteriological and mycological samples were taken from 96% of patients. Table V shows the results.

TABLE V.
Microbiologic Characteristics of Osteoradionecrosis (n = 26).

	Genus, species	No. (%)
Family or class of bacteria		
Polymicrobial		10 (38.5%)
Enterobacteriaceae	*Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Serratia marcescens, Proteus mirabilis, Citobacter amalonaticus*	10 (38.5%)
Streptococci and assimilated	*Streptococcus constellatus, Streptococcus parasanguinis, Streptococcus anginosus, Streptococcus mitis, Streptococcus oralis, Gemella morbillorum*	6 (23.1%)
Actinobacteria	*Actinomyces israelii*	2 (7.7%)
Enterococci	*Enterococcus faecalis*	2 (7.7%)
Staphylococci	*Staphylococcus aureus*	2 (7.7%)
Other gram negative	*Stenotrophomonas maltophila*	1 (3.8%)
Family or class of fungus		
Saccharomycetes	*Candida albicans, Candida parapsilosis, Candida dubliniensis, Candida tropicalis, Candida glabrata, Candida kefyr, Saccharomyces cerevisiae*	9 (34.6%)

DISCUSSION

PENTOCLO has been successfully used in mandibular ORN.[27,28,32,33] Nevertheless, to the best of our knowledge, the present study is the first prospective assessment. The success rate was satisfactory, at 76.5% of patients following complete treatment up to cure or for 24 months. Two of the cases of failure were uncured after 24 months' treatment, and two progressed without control, requiring surgery.

These findings agree with the literature. Robard et al. reported a 56% success rate,[32] and, more recently, Delanian et al., in a series of 54 patients, reported a rate of 100% after a median 9 months' treatment.[7,28] Results seem more divergent when clodronate is not associated to the other two drugs: Patel et al.[33] and Hayashi et al.[27] reported 45% and 86% success, respectively.[27,33] Several studies also reported success with PENTOCLO or associated pentoxifylline-tocopherol in treating ORN in other locations, such as temporal bone or sternum,[29,31] and in cases of drug-related osteonecrosis.[34,35]

EBA and initial SOMA score were predictive of success; the two are complementary and well-suited to follow-up of mandibular ORN. Although not identified in the present study, history of tumor resection (associated with mandibular bone resection or not) has been reported as predictive of failure; surgery weakens the operated zone, especially in vascular terms by interrupting the inferior alveolar artery or the facial artery.

Surprisingly, total radiation dose did not emerge as a prognostic factor. However, the osteonecrotic mandibular segment was shown to receive significantly higher doses than the rest of the mandible, suggesting a dose effect on onset but not on progression of ORN.

PENTOCLO treatment is safe; there were no severe adverse events in the present series, but only some minor side effects reported by patients. This good tolerance enabled total adherence to treatment in 88.9% of cases. Some authors[28] reported several deaths from severe sepsis under PENTOCLO, which was not the case in the present series; the disinfiltration phase probably stemmed bacterial dissemination.

Delanian et al. raised the issue of a rebound effect when treatment duration is less than 12 months.[8] In the present study, two patients experienced recurrence after treatment cessation, with onset later than the scheduled end of follow-up. The patients had had, respectively, 9 and 18 months' treatment. In one case, recurrence was at the primary site, and in the other at a new contralateral location. The long-term effects of PENTOCLO and especially the duration of benefit are not known, and could be assessed in a longitudinal study.

Microbiology analyses in the present series confirmed almost systematic superinfection of mandibular ORN sites, lending support to the hypothesis that irradiated bone is highly susceptible to infection. In agreement with the literature, the most frequent isolates were enterococci and streptococci or assimilated bacteria.[36] Although a specific protocol was set up in collaboration with our center's microbiology department, the rate of actinomycosis (7.7%) was much lower than reported in the literature (64.5%).[36,37] In our study, 36.4% of patients showed fungal infection, indicating use of antifungal medication in the disinfiltration phase.

Diagnosis of ORN and assessment of progression are basically clinical. EBA is a relevant parameter for objective disease monitoring. Intraoral measurements were, however, difficult for certain patients, due to problems of access (e.g., trismus). Moreover, intraorally, healing consisted not in bone defect filling but in simple coverage of the bottom of the defect by healthy mucosa (Fig. 1D); physicians treating this pathology should be aware of this particularity so as better to assess cure.

The modified SOMA score, combining clinical and radiologic criteria, is helpful and complementary to EBA,

with which it correlates closely. However, certain modified SOMA items concern status prior to onset of ORN, and notably oral opening, pain, and mastication, which may be affected by previous head and neck surgery and especially by previous radiation therapy.

The Marx-Myers and Epstein classifications seemed useful for initial assessment, although scores did not prove predictive of success of PENTOCLO treatment. For purposes of follow-up, on the other hand, they are noncontributive.

Primary and secondary prevention of mandibular ORN is the essential complement to curative treatment, and it is vital that physicians managing these patients be aware of this. It has been shown that competent management of dental care before, during, and after radiation therapy, associated to improved irradiation techniques, can significantly reduce the incidence of ORN.[38,39]

Three-dimensional conformal and intensity-modulated radiation therapy have minimized irradiated volumes and reduced maximal doses and hence xerostomia. Risk of orodental deterioration and onset of ORN has thus considerably decreased.[38,40]

Some authors have recommended using PENTOCLO treatment in dental care for at-risk patients. It was recently reported that prophylactic pentoxifylline–tocopherol treatment for 11 weeks before and 13 weeks after dental extraction reduced the incidence of mandibular ORN to 1.2%, from the usual 7%.[41] Prophylactic PENTOCLO treatment in dentistry is thus worth considering in the future.

CONCLUSION

The association of pentoxifylline–tocopherol–clodronate is a new, simple, and safe medical option in the treatment of mandibular ORN. In some cases, PENTOCLO should be an interesting alternative to difficult and mutilating surgery in irradiated areas. This therapeutic success should not overshadow prevention of risk factors by optimizing dental care in irradiated patients and by developing new conformal radiation techniques. Longitudinal studies are also needed to study long-term effects, as the risk of late recurrence has been little studied.

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BIBLIOGRAPHY

1. Harris M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. *Br J Oral Maxillofac Surg* 1992;30:313–318.
2. Epstein JB, Wong FL, Stevenson-Moore P. Osteoradionecrosis: clinical experience and a proposal for classification. *J Oral Maxillofac Surg* 1987;45: 104–110.
3. Thorn JJ, Hansen HS, Specht L, Bastholt L. Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. *J Oral Maxillofac Surg* 2000;58:1088–1093; discussion 1093–1095.
4. Dhanda J, Pasquier D, Newman L, Shaw R. Current concepts in osteoradionecrosis after head and neck radiotherapy. *Clin Oncol* 2016;28: 459–466.
5. Delanian S, Lefaix JL. Mature bone radionecrosis: from recent physiopathological knowledge to an innovative therapeutic action. *Cancer Radiother J* 2002;6:1–9.
6. Marx RE, Johnson RP. Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 1987;64: 379–390.
7. Delanian S, Depondt J, Lefaix J-L. Major healing of refractory mandible osteoradionecrosis after treatment combining pentoxifylline and tocopherol: a phase II trial. *Head Neck* 2005;27:114–123.
8. Delanian S, Porcher R, Rudant J, Lefaix J-L. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *J Clin Oncol* 2005;23:8570–8579.
9. D'Souza J, Lowe D, Rogers SN. Changing trends and the role of medical management on the outcome of patients treated for osteoradionecrosis of the mandible: experience from a regional head and neck unit. *Br J Oral Maxillofac Surg* 2014;52:356–362.
10. Costa DA, Costa TP, Netto EC, et al. New perspectives on the conservative management of osteoradionecrosis of the mandible: a literature review. *Head Neck* 2016;38:1708–1716.
11. Nadella KR, Kodali RM, Guttikonda LK, Jonnalagadda A. Osteoradionecrosis of the jaws: clinico-therapeutic management: a literature review and update. *J Maxillofac Oral Surg* 2015;14:891–901.
12. Myers RA, Marx RE. Use of hyperbaric oxygen in postradiation head and neck surgery. *NCI Monogr* 1990;(9):151–157.
13. Annane D, Depondt J, Aubert P, et al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;22:4893–4900.
14. Wong JK, Wood RE, McLean M. Conservative management of osteoradionecrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:16–21.
15. Sanger JR, Matloub HS, Yousif NJ, Larson DL. Management of osteoradionecrosis of the mandible. *Clin Plast Surg* 1993;20:517–530.
16. Jeyaraj P, Bandyopadhyay TK. Diagnostic features and management strategy of a refractory case of osteoradionecrosis of the mandible: case report and review of literature. *J Maxillofac Oral Surg* 2016;15:256–267.
17. Jacobson AS, Zevallos J, Smith M, et al. Quality of life after management of advanced osteoradionecrosis of the mandible. *Int J Oral Maxillofac Surg* 2013;42:1121–1128.
18. Meyer I. Infectious diseases of the jaws. *J Oral Surg* 1970;28:17–26.
19. Marx RE. A new concept in the treatment of osteoradionecrosis. *J Oral Maxillofac Surg* 1983;41:351–357.
20. Delanian S, Lefaix J-L. Current management for late normal tissue injury: radiation-induced fibrosis and necrosis. *Semin Radiat Oncol* 2007;17: 99–107.
21. Samlaska CP, Winfield EA. Pentoxifylline. *J Am Acad Dermatol* 1994;30: 603–621.
22. Rodan GA, Fleisch HA. Bisphosphonates: mechanisms of action. *J Clin Invest* 1996;97:2692–2696.
23. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;62:527–534.
24. McCaul JA. Pharmacologic modalities in the treatment of osteoradionecrosis of the jaw. *Oral Maxillofac Surg Clin North Am* 2014; 26:247–252.
25. Delanian S. Striking regression of radiation-induced fibrosis by a combination of pentoxifylline and tocopherol. *Br J Radiol* 1998;71:892–894.
26. Delanian S, Balla-Mekias S, Lefaix JL. Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. *J Clin Oncol* 1999;17:3283–3290.
27. Hayashi M, Pellecer M, Chung E, Sung E. The efficacy of pentoxifylline/tocopherol combination in the treatment of osteoradionecrosis. *Spec Care Dentist* 2015;35:268–271.
28. Delanian S, Chatel C, Porcher R, Depondt J, Lefaix J-L. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;80:832–839.
29. Delanian S, Lefaix J-L. Complete healing of severe osteoradionecrosis with treatment combining pentoxifylline, tocopherol and clodronate. *Br J Radiol* 2002;75:467–469.
30. Delanian S, Lefaix J-L. The radiation-induced fibroatrophic process: therapeutic perspective via the antioxidant pathway. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 2004;73:119–131.
31. Pavy JJ, Denekamp J, Letschert J, et al.; EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 1995;35:11–15.
32. Robard L, Louis M-Y, Blanchard D, Babin E, Delanian S. Medical treatment of osteoradionecrosis of the mandible by PENTOCLO: preliminary results. *Eur Ann Otorhinolaryngol Head Neck Dis* 2014;131:333–338.
33. Patel V, Gadiwalla Y, Sassoon I, Sproat C, Kwok J, McGurk M. Use of pentoxifylline and tocopherol in the management of osteoradionecrosis. *Br J Oral Maxillofac Surg* 2016;54:342–345.
34. Epstein MS, Wicknick FW, Epstein JB, Berenson JR, Gorsky M. Management of bisphosphonate-associated osteonecrosis: pentoxifylline and tocopherol in addition to antimicrobial therapy. An initial case series. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:593–596.
35. Owosho AA, Estilo CL, Huryn JM, Yom SK. Pentoxifylline and tocopherol in the management of cancer patients with medication-related osteonecrosis of the jaw: an observational retrospective study of initial case series. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2016;122:455–459.
36. Hansen T, Kunkel M, Kirkpatrick CJ, Weber A. Actinomyces in infected osteoradionecrosis—underestimated? *Hum Pathol* 2006;37:61–67.

37. Hansen T, Kunkel M, Springer E, et al. Actinomycosis of the jaws—histopathological study of 45 patients shows significant involvement in bisphosphonate-associated osteonecrosis and infected osteoradionecrosis. *Virchows Arch Int J Pathol* 2007;451:1009–1017.
38. Ben-David MA, Diamante M, Radawski JD, et al. Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* 2007;68: 396–402.
39. Beech NM, Porceddu S, Batstone MD. Radiotherapy-associated dental extractions and osteoradionecrosis. *Head Neck* 2017;39:128–132.
40. Duarte VM, Liu YF, Rafizadeh S, Tajima T, Nabili V, Wang MB. Comparison of dental health of patients with head and neck cancer receiving IMRT vs conventional radiation. *Otolaryngol Head Neck Surg* 2014;150:81–86.
41. Patel V, Gadiwalla Y, Sassoon I, Sproat C, Kwok J, McGurk M. Prophylactic use of pentoxifylline and tocopherol in patients who require dental extractions after radiotherapy for cancer of the head and neck. *Br J Oral Maxillofac Surg* 2016;54:547–550.