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Role of Adjuvant Therapy in Osteoradionecrosis (Orn) and Bisphosphonate Induced Osteonecrosis of Jaw (Bronj)

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Abstract:
Aim; *A treatment procol with pentoxifylline(PT) and A- tocoferol combination therapy to assess the utility along with standard antimicrobial therapy in a series of cases of ORN (osteoradionecrosis) of jaw and BRONJ.*
Material & Method: *A total of 13 cases of ORN and BRONJ associated with pathological fracture of jaw and wound dehiscence of more than 03 cm was considered in this prospective study. A combination therapy of pentoxifylline (PT) and A- tocoferol was prescribed with standard antimicrobial therapy. PT was prescribed at 400 mg twice daily and A- tocoferol was prescribed at 1000 IU once daily. Chlorhexidine (0.12%), 10-15 ml rinsed more than 30 seconds twice daily. The entire protocol was for two months pre and postoperatively. A treatment response rating scale was defined for categories of excellent, good, fair, and poor.*
Results: *A decrease in overall occurrence of symptoms, and signs was achieved in all the cases. Changes were evident even before surgical intervention. All patients were without pain, erythema, or purulence following initiation of treatment with PT and A tocoferol, in post-operative period. The therapy was beneficial in cases of ORN and BRONJ.*
Conclusion: *this treatment protocol with PT and A-tocoferol therapy is highly beneficial in cases of ORN and BRONJ without any adverse effects.*
Key Words: *Osteoradionecrosis (ORN) And Bisphosphonate Induced Osteonecrosis of Jaw (BRONJ)*

List of abbreviation
1. ORN-osteoradionecrosis.
2. BRONJ- bisphosphonate related osteonecrosis of jaw.
3. PT- pentoxifylline.
4. TNF-tumour necrosis factor.
5. HBO- hyper baric oxygen therapy.
6. IL- interleukin.
7. A tocoferol- alpha tocoferol.
8. CA- Carcinoma

I. Introduction

Osteoradionecrosis (ORN) is a late sequel of irradiation. It either stabilizes or worsens and is very difficult to manage.[1] In 1922 Regaud published the first report of osteoradionecrosis of jaw. The mandible is most commonly involved bone in head and neck cancer patient treated with radiation. It occurs as a serious late complication of adjuvant radiation therapy.[2]

Pathogenesis of ORN has been proposed, with consequent bearing on its treatment. Until recently tissue hypoxia and its consequences was accepted as the primary cause ORN and thereby paved the way for hyperbaric oxygen therapy (HBO) for both treatment and prevention of ORN. Recently, radiation induced fibrosis has been proposed as the new theory that accounts for damage to normal tissues, including bone, after radiotherapy.[3]

Bisphosphonate induced osteonecrosis of jaw (BRONJ) is a well recognized complication following treatment with bisphosphonates. Its pathophysiology is still unknown. The most popular hypothesis is manifestation of necrotic bone resulting from bisphosphonate induced remodeling suppression of bone.[4]
A number of recent studies have shown improved outcome with pentoxifylline (PT) and A- tocoferol therapy, which prompted us to assess the utility of this combination to standard antimicrobial therapy in a series of cases of ORN of jaw and BRONJ.

II. Materials And Method

The sample of this prospective study was composed of a total of 13 cases of ORN and BRONJ associated with pathological fracture of jaw and wound dehiscence of more than 03 cm. ORN constituted 10 cases and the rest 03 cases were of BRONJ. A written informed consent was obtained from all study subjects. All patients were prescribed a protocol of pentoxifylline (PT) and A- tocoferol. PT was prescribed at 400 mg twice daily and A- tocoferol was prescribed at 1000 IU once daily. Chlorhexidine (0.12%), 10-15 ml rinsed more than 30 seconds twice daily. The entire protocol was for two months pre and postoperatively. A treatment response rating scale was defined for categories of excellent, good, fair, and poor. (Table1)

A 1-month and 2-months, dichotomous post treatment assessment of "healed" (healthy mucosal covering of the defect with no wound dehiscence) or "not healed" (exposed bone at resected margin/ dehiscence of reconstruction plate/ persisting orocutaneous lesion) was defined. Follow up assessment included symptoms, signs and progressive wound dehiscence. (Table 2)

Data was collected and analyzed monthly both preoperatively and post operatively. (Table 3 and Table 4) All cases were treated with surgical management. The selected cases were of primary lesion and no cases of recurrence were included in the study.

III. Results

The selected cases of the study were all treated with surgical intervention along with the above mentioned protocol. All the patients included in the study were male. The mean age was 50.8 years. A decrease in overall occurrence of symptoms, and signs was achieved in all the cases. Changes were evident even before surgical intervention of the total 13 cases, 10 cases showed complete symptomatic relief and 02 cases showed persisting bone exposure adjacent to site of resection with exposure of reconstruction plate. All patients were without pain, erythema, or purulence following initiation of treatment with PT and A tocoferol, in post-operative period. All the medications were well tolerated with no complication reported in our study.

IV. Discussion

The management of ORN continues to be debated. ORN symptoms can resolve with conservative treatment. The present study was performed to identify the effects of adjuvant therapy on ORN and BRONJ. Most of the work on the PT and A tocoferol therapy in ORN is documented by Delanin et al. PT Improve peripheral blood flow, reduces viscosity of blood, increases flexibility of red blood cell membranes, improves microcirculation, and enhances tissue oxygenation.**[4]** In addition, PT has anti tumor necrosis factor alpha (anti-TNF A) effects, inhibits dermal fibroblasts, and increases collagenase activity.**[5]** Decreased levels of TNF a and reduced production of interleukin (IL)-12 is observed in patients treated with PT.**[6]**

A number of mechanisms of actions of A tocoferol may decrease inflammation and stimulating healing. A tocoferol impairs tissue fibrosis and acts as potent oxygen radical scavenger that may reduce damage caused by free radicals impacting necrosis.[3] A tocoferol scavenges free oxygen species generated during oxidative stress, thereby protecting cell membranes. Although the pathogenesis of ORN may often involvevascular hypoxia **[7]**, ORN was recently suggested to be triggered by a predominantly fibro- atropic mechanism **[8,9,10]**

Bisphosphonates are widely used in the management of metastatic disease to the bone and in the treatment of osteoporosis. Bisphosphonates are non-metabolized analogues of pyrophosphate that are capable of localizing to bone and inhibiting osteoclastic function. Bisphosphonates bind readily to exposed bone mineral around resorbing osteoclasts, causing very high levels of bisphosphonates in resorption lacunas. Since, they are not metabolized by the body, these high concentration arte maintained in the bone for long time. Bisphosphonates are then ingested by the osteoclasts- causing disruption of osteoclast- mediated bone resorption.**[11]**

All the 03 cases of BRONJ were treated with zolendronic acid (04 mg monthly infusion) for various etiologies as documented in table-1. The combination therapy with PT and A tocoferol has several positive outcomes. First, PT alone has shown to reduce the duration of healing of late soft tissue necrosis.**[12]** Second, the combined PT and A tocoferol treatment have shown to reduce radiation induced fibrosis in clinical trials. With our present protocol, the healing process was observed in pre surgical period only and with improved result post surgically. The patients experienced less discomfort and faster recovery.

V. Conclusion

All the patients in this study improved with the introduction of PT and A-tocoferol therapy without any noticeable adverse effects. Future studies of potential therapeutic and prophylactic efficacy of this therapy for high- risk patients with larger sample size and longer duration should be considered.

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Table 1

Excellent: Surgical site healed with good healthy mucosal coverage.

Good: Surgical site has some mucosal coverage; no exposed bone or orocutaneous lesion.

Fair: Healing activity is apparent, but bone exposure evident and orocutaneous lesion.

Poor: Extensive dehiscence, with exposed bone/ reconstruction plate/ persisting orocutaneous lesion or pathological fracture of mandible

Table 2 : Response to drug therapy

S.No	AGE	SEX	DIAGNOSIS	ETIOLOGY	SYMPTOMS PRE OPERATIVE 01 MONTH	SIGNS PRE OPERATIVE 02 MONTH	SIGNS POST OPERATIVE 01 MONTH	SIGNS POST OPERATIVE 02 MONTH	COMPLICATION
1	51	M	BRONJ	OSTEOPOROSIS	FAIR	FAIR	EXCELLENT	EXCELLENT	Nil
2	62	M	ORN	CA TONGUE	POOR	POOR	POOR	POOR	PROGRESSIVE WOUND DEHISCENCE
3	54	M	ORN	CA TONGUE	FAIR	FAIR	GOOD	EXCELLENT	Nil
4	61	M	ORN	CA TONGUE	FAIR	FAIR	EXCELLENT	EXCELLENT	Nil
5	47	M	BRONJ	MULTIPLE MYELOMA	FAIR	FAIR	GOOD	GOOD	Nil
6	49	M	ORN	CA TONGUE	FAIR	FAIR	EXCELLENT	EXCELLENT	Nil
7	47	M	ORN	CA LARYNX	FAIR	FAIR	GOOD	EXCELLENT	Nil
8	46	M	ORN	CA THYROID	FAIR	FAIR	GOOD	GOOD	Nil
9	53	M	ORN	CA TONGUE	POOR	POOR	GOOD	EXCELLENT	Nil
10	50	M	ORN	CA LARYNX	POOR	POOR	EXCELLENT	EXCELLENT	Nil
11	47	M	ORN	CA TONGUE	POOR	POOR	POOR	POOR	PROGRESSIVE WOUND DEHISCENCE
12	36	M	BRONJ	MULTIPLE MYELOMA	FAIR	FAIR	EXCELLENT	EXCELLENT	Nil
13	58	M	ORN	CA TONGUE	POOR	POOR	GOOD	EXCELLENT	Nil

Table 3: Statistics for evaluating significance of drug protocol effectiveness (After 1 month)

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
Post op 01month- pre op	Negative Ranks	0[a]	.00	.00
	Positive ranks.	11[b]	6.00	66.00
	Ties	2[c]		
	Total	13		

a. POSTOP 1 MONTH< PREOP
b. POSTOP 1 MONTH> PREOP
c. POSTOP 1 MONTH = PREOP

Test Statistics[b]

	POSTOP 1 MONTH - PREOP
Z	-3.002[a]
Asymp. Sig. (2-tailed)	.003

a. Based on negative ranks.
b. Wilcoxon Signed Ranks Test

Table 4: Statistics for evaluating significance of drug protocol effectiveness (After 2 months)

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
Post op 02month- pre op	Negative Ranks	0[a]	.00	.00
	Positive ranks.	11[b]	6.00	66.00
	Ties	2[c]		
	Total	13		

d. POSTOP 2 MONTH< PREOP
e. POSTOP 2MONTH> PREOP
f. POSTOP 2 MONTH = PREOP

Test Statistics[b]

	POSTOP 1 MONTH - PREOP
Z	-3.002[a]
Asymp. Sig. (2-tailed)	.003

c. Based on negative ranks.
d. Wilcoxon Signed Ranks Test