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PREVENTION OF RADIATION INDUCED FIBROSIS AND IMPROVING QOL IN HEAD AND NECK CANCER PATIENTS POST SURGERY AND ADJUVANT RADIATION THERAPY WITH OR WITHOUT CONCURRENT CHEMOTHERAPY TREATED WITH GAMMA AND DELTA TOCOTRIENOL (CA PROBRET) AND PENTOXYPHYLLINE

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ABSTRACT Radiation induced fibrosis is a long term adverse effect compromising quality of life. Patients treated with radiation often present with complications like neck fibrosis, trismus, facial lymphedema and dysphagia. We evaluated 25 patients of head and neck malignancy treated with surgery followed by radiation +/- chemotherapy. All patients were assessed clinically and by mouth opening measured by SK Katharia et al scoring. All patients tolerated treatment well with acceptable hematological toxicity. Out of 25 patients three progressed and were treated with redo surgery and adjuvant palliative chemotherapy. Rest 22 patients completed treatment of six months of gamma and delta tocotrienol and pentoxyphylline.

KEYWORDS : Tocotrienols, Radiation induced fibrosis, QOL, CCRT.

INTRODUCTION:

Radiation induced fibrosis is a long term adverse effect compromising quality of life. Patients with head and neck malignancy often present with post radiation complications like neck fibrosis, trismus, cervical dystonia, facial lymphedema along with difficulty in swallowing and speech. These complications severely affect the quality of life of the patient. Radiation induced fibrosis is mainly characterized by non specific changes in the vascular connective tissues involving excessive extracellular matrix deposition, fibroblast proliferation and presence of inflammatory infiltrate [4, 5]. The development of radiation-induced fibrosis is influenced by multiple factors, including the radiation dose and volume, fractionation schedule, previous or concurrent treatments, genetic susceptibility, and comorbidities such as diabetes mellitus. Although radiation-induced fibrosis originally was assumed to be a slow, irreversible process, contemporary studies suggest that it is not necessarily a fixed process [1, 2]. RIF can develop acutely or as a late effect of therapy causing cosmetic and functional impairment and subsequent deterioration of QOL. Newer techniques like IMRT/IGRT tend to have reduced toxicity, however progression to RIF is albeit the same [3]. Studies have been conducted with a-tocopherol, the commonly used vitamin E supplement [6,7]. Tocotrienols are members of the vitamin E family. The body contains four tocotrienols and four tocopherols [8, 9]. They have antioxidant, antiinflammatory, anticancer, hypocholesterolemic and neuroprotective properties. The tocopherols are saturated forms of vitamin E, whereas the tocotrienols are unsaturated and possess an isoprenoid side chain.

The prevention of radiation-induced fibrosis has focused on improvements in RT technique, which have resulted in higher doses to the tumor target and decreased doses to normal tissue, thus potentially preventing the development of radiation-induced fibrosis. Furthermore, established radiation induced fibrosis may be treatable with combination of pentoxifylline and vitamin E and other combination of vitamin E family member's i.e. Gamma and Delta Tocotrienol. It down regulates the kinases and growth factors responsible for cell survival and proliferation[10,11].

MATERIALS AND METHODS:

This prospective single institution study evaluated 25 patients over a period of two years. All patients were subjected to surgery followed by adjuvant radiation with or without concurrent chemotherapy followed by adjuvant gamma and delta tocotrienol (CA Probret) along with tab pentoxyphylline for a period of six months. Post completion of therapy these patients were assessed clinically and radiologically for neck muscle fibrosis and other quality of life indices. Written informed consent was obtained from all patients before treatment started. Each Soft gel Capsule contained Gamma and delta tocotrienol capsules (CA Probret400mg) administered twice daily.

Assessment was done by mouth opening measured by SK Katharia et al scoring system and associated symptom measures [12] All patients were evaluated for radiation induced fibrosis, restricted mouth opening and symptomatic stiffness in neck.

RESULTS AND OBSERVATION: (TABLES 1 & 2)

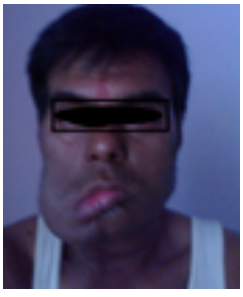
All patients tolerated treatment well with acceptable hematological toxicity. Out of 25 patients three progressed and were treated with redo surgery and adjuvant palliative chemotherapy. Rest 22 patients completed treatment of six months of gamma and delta tocotrienol and pentoxyphylline. These patients were evaluated for neck fibrosis. Clinically all patients had supple neck and there was no fibrosis detected. Neck muscles were soft and there was no trismus seen. USG neck revealed no features of neck fibrosis. Neck movements were normal in all directions. General QOL evaluation revealed that except symptoms of altered taste and dryness of mouth patients were able to present themselves both physically and socially. Patients had lesser symptoms of emotional labiality and they were able to work normally at their workplace. General well being was preserved and symptoms of depression were less.

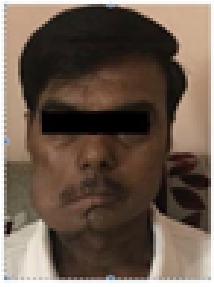
TABLE 1: BASELINE CHARACTERISTICS

Age	50-60	15
	60-70	10
Gender	Male	20
	Female	05
Comorbidity	HTN	06
	DM	02
	CAD	--
Smoker/ tobacco chewer	Yes	22
	No	03
Presentation	Trismus	15
	Pain	23
	Neck stiffness	04
	Ulceroproliferative	25
	Neck nodes	15
	T1	NIL
	T2	10
	T3	10
	T4	05
Surgery		25
HPE	WDSCC	16
	MDSCC	06
	PDSCC	03
Margin	Positive	05
	Negative	20
Adverse factors (pT3/pT4/PNI/LVSI)	Yes	5
	No	20
Radiation Dose		60 Gy/30 Fractions
Chemotherapy, Inj Cisplatin	40 mg	15
	50 mg	10

TABLE 2: Response assessment (clinically and as per SK Katharia et al scoring system)

	03 months	06 months
Neck stiffness	15	03
Score 0: Mouth opening is 41 mm or more.	4	11
Score 1: Mouth opening is 37 to 40 mm	-	4
Score 2: Mouth opening is 33 to 36 mm	4	2
Score 3: Mouth opening is 29 to 32 mm	5	3
Score 4: Mouth opening is 25 to 28 mm	-	-
Score 5: Mouth opening is 21 to 24 mm	4	-
Score 6: Mouth opening is 17 to 20 mm.	3	-
Score 7: Mouth opening is 13 to 16 mm	2	3
Score 8: Mouth opening is 09 to 12 mm	3	2
Score 9: Mouth opening is 05 to 08 mm	-	-
Score 10: Mouth opening is 0 to 04 mm	-	-





CONCLUSION:

Treatment of carcinoma head and neck by radiation therapy is limited by the need to avoid excessive late damage to normal tissues. Although new strategies designed to improve the therapeutic ratio have reduced the incidence of radiation induced fibrosis, it is still sometimes severe and unavoidable. Like fibrotic squeal of any origin, RIF is mainly characterized by nonspecific changes in the connective tissue involving excessive extracellular matrix deposition and hyperactive fibroblasts. Constituted RIF does not regress spontaneously, but no effective treatment for it has yet been established. RIF either stabilizes or gradually worsens, with acute inflammatory periods. Several categories of drug seem potentially useful for managing all types of fibrotic squeal, but are only effective when administered early in the fibrotic process. These include corticosteroids, pentoxyphylin, NSAIDS, zinc, antioxidants, and interferon. The antioxidant efficiency of tocotrienols was evaluated as the ability of the compounds to inhibit lipid peroxidation, reactive oxygen species (ROS) production, and heat shock protein expression. Delta-tocotrienol was found to have the greatest antioxidant properties among the tocotrienol isomers, which is due to the decreased methylation of the chromanol ring that allows the molecule to be more easily incorporated into cell membranes. In addition to its superior antioxidant, hypocholesterolemic, and anti-thrombotic activities, tocotrienol has shown consistent anti-tumor benefits. Tocotrienols have repeatedly been shown to inhibit proliferation and induce cancer cell death, and cells with the greatest degree of malignancy are most sensitive to the apoptotic action of tocotrienol. Armed Forces Radiobiology Research Institute (AFRRI, Bethesda, MD) has performed extensive research on tocotrienol as a radiation countermeasure agent. Of the tocotrienol isomers, delta and gamma tocotrienol are among the most effective radioactive countermeasure agents. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the primary source of radiation-induced damage, and tocotrienols as potent antioxidants are effective radio protectors, supporting the hypothesis that “strong antioxidants make strong radio protectors”.

Tocotrienol combination given for six months have significant improvement in mouth opening and subjective improvement of symptoms because of radiation induced fibrosis. Although radiation induced fibrosis originally was assumed to be slow, irreversible process, contemporary studies suggest that it is not necessary a fixed process. Further, a larger randomized study is needed to evaluate role of tocotrienols in these patients. Tocotrienol affects numerous pathways linked with tumorigenesis and thus has potential in both the prevention and the treatment of cancer.

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