The Pharma Innovation Journal 2017; 6(4): 91-94

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating 2017: 5.03
TPI 2017; 6(4): 91-94

www.thepharmajournal.com
Received: 14-02-2017
Accepted: 15-03-2017

Dr. Deepak Kumar
Department of radiation oncology, Jindal hospital. Hisar, Haryana, India

Dr. Arun Kumar Aggarwal
Department of radiation oncology, Jindal hospital. Hisar, Haryana, India

Dr. Deepak Kumar Shukla
Department of medical oncology, Jindal hospital. Hisar, Haryana, India

Gleetus Thimothy
Department of medical physicist, Jindal hospital. Hisar, Haryana, India

Shaili Rani
Department of medical physicist, Jindal hospital. Hisar, Haryana, India

Correspondence
Dr. Deepak Kumar
Department of radiation oncology, Jindal hospital. Hisar, Haryana, India

To study and evaluation of role of gamma and delta tocotrienol in radiation induced fibrosis

Dr. Deepak Kumar, Dr. Arun Kumar Aggarwal, Dr. Deepak Kumar Shukla, Gleetus Thimothy and Shaili Rani

Abstract
Purpose: The main aim of this research was to identify the role of radio prophylactic and/or mitigating agents and their mechanism of action of Gamma and Delta Tocotrienol in Radiation induced fibrosis (RIF) which is rare late radiation toxicity in patients receiving radical radiotherapy in head and neck cancer patients. In this study, we describe the role of Gamma and Delta Tocotrienol in radiation induced fibrosis in head and neck cancer patients. It also up regulates the factors responsible for the apoptosis.
Method: Suitable or eligible patients of head and neck cancer who received radical radiotherapy and having radiation induced fibrosis were included in the study. Gamma and Delta Tocotrienol was given as dosage form for six months. Assessment was done by mouth opening measured by SK Kathaiia *et al* scoring system and associated symptom measures.
Results: All patients had reported reduction in symptom severities within 3 to 7 days of starting of Gamma and Delta Tocotrienol capsules. Four patients were having mouth opening of one finger after taking Gamma and Delta Tocotrienol for 6 month mouth opening was two fingers. Six patients were having mouth opening of two fingers after taking Gamma and Delta Tocotrienol for 6 month mouth opening was three fingers.
Conclusion: Gamma and Delta Tocotrienol given for six months have significant improvement in mouth opening and subjective improvement of symptoms. Further, a larger randomized study is needed to evaluate role of Gamma and Delta Tocotrienol in these patients. Presently at our center we are doing a randomized prospective controlled study on the same.

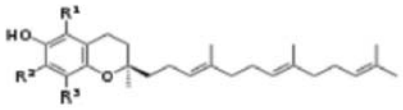
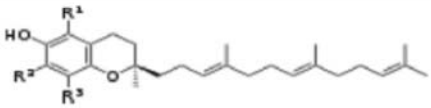
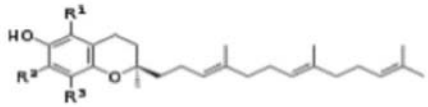
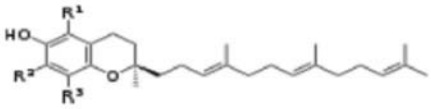
Keywords: Gamma, delta, neck cancer patients, symptoms

1. Introduction
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].
Basically Radiation-induced fibrosis (RIF) is a long-term side effect of external beam radiation therapy for the treatment of cancer. Radiation-induced fibrosis can develop as a late effect of radiation therapy (RT) in skin and subcutaneous tissue, lungs, the gastrointestinal and genitourinary tracts, muscles, or other organs, depending upon the treatment site. Radiation-induced fibrosis may cause both cosmetic and functional impairment, which can lead to death or a significant deterioration in the quality of life.
Although new strategies designed to improve the therapeutic ratio have reduced the incidence of radiation induced fibrosis (RIF), it is still sometimes severe and unavoidable, and slight differences exist in its clinical presentation [3]. Like fibrotic sequelae of any origin, RIF is mainly characterized by nonspecific changes in the connective tissue involving excessive extracellular matrix deposition and hyperactive fibroblasts. [4, 5] Most studies on the effects of vitamin E on radiation injury were conducted with a-tocopherol, the most commonly used vitamin E supplement and the vitamin E isoform that is most abundant in human and animal tissues. [6, 7].
Tocotrienols are members of the vitamin E family. They can be used as a food additive as well as a substitute for Vitamin E. The vitamin E families are essential dietary components as the body cannot synthesise sufficient itself. The body contains four Tocotrienols and four Tocopherols [8, 9]:

- ✓ Alpha tocotrienols
- ✓ Beta tocotrienols
- ✓ Gamma tocotrienols
- ✓ Delta tocotrienols
- ✓ Alpha tocopherols,
- ✓ Beta tocopherols,
- ✓ Gamma tocopherols
- ✓ Delta tocopherols

However these have different antioxidant activities when measured in human plasma and also several studies have reported the antioxidant, anti-inflammatory, anticancer, hypocholesterolemic and neuroprotective properties of tocotrienols in different cell lines, animal models, and in humans. The tocopherols are saturated forms of vitamin E, whereas the tocotrienols are unsaturated and possess an isoprenoid side chain (Table 1). The name "tocotrienol" was first suggested by Dr. Banyan, for the isomers of vitamin E, with isoprenoid side chain present in nature, when isolated from the latex of the rubber plant, Havea brasiliensis. Tocotrienols attracted no real attention until the 1980's and 1990's when their cholesterol-lowering potential and anticancer effects were described [10, 11, 12].

Table 1 Structures of various homologs of tocotrienols

Type	R1	R2	R3	Structure
alpha(α)-Tocotrienol	Me	Me	Me	
beta(β)-Tocotrienol	Me	H	Me	
gamma(γ)-Tocotrienol	H	Me	Me	
delta(δ)-Tocotrienol	H	H	Me	

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 novel therapeutic approaches, particularly the combination of pentoxifylline and vitamin E and other combination of vitamin E family member's i.e. Gamma and Delta Tocotrienol. Gamma and Delta Tocotrienol belongs to the class of Biological Response Modifier. It down regulates the kinases and growth factors responsible for cell survival and proliferation. [13, 14]

This study addressed the extent to which HMG-CoA reductase inhibition is involved in the mechanisms of radioprotection by GT3 and DT3 in vivo. The protective effects of GT3 were examined in three organ systems that play critical roles after exposure to ionizing irradiation, the hematopoietic system, the intestine, and the vascular system. We demonstrate here that, in addition to protecting against hematopoietic radiation toxicity, GT3 also ameliorates intestinal radiation injury, enhances recovery of the intestine after TBI, and reduces vascular oxidative stress in an HMG-CoA reductase- dependent manner.

These findings may have significant implications for the future development of tocols as radioprophylactic agents and pertain particularly to tissue injury in organs where vascular damage is presumed to play a mechanistic role. Our data also suggest that combination therapies with tocols and statins should be explored in order to take advantage of possible synergistic or additive effects. Tocols exert their biological effects not only by virtue of their antioxidant properties but also by inhibiting the enzyme hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, i.e., an effect similar to that of the drug class GT3 exerts substantially stronger inhibitory effects on HMG-CoA reductase compared to other tocols and also accumulates in endothelial cells at much higher levels [15, 16].

Patients and Methods

The targeted population was defined as Men and women who had radiotherapy for Head and Neck cancer and exhibited clinically measurable RIF that had occurred more than 6 months after radiotherapy completion, without evidence of recurrent or evolutionary cancer or skin pathology. Written informed consent was obtained from all patients before treatment started. The study was approved by the Jindal Hospital in Hisar.

Chemicals

GT3 and DT3 was obtained from CA Probret, Brand of JENOME Biophar Pvt. Ltd. Shortly before administration,

Each Soft gel Capsule contains:
- ✓ CA-Probret – 400 mg
- ✓ Dose: Standard dosage is 800 mg/day.
- ✓ Administration: Twice a day orally for six months.
- ✓ Packing : 30 Soft gel Capsules in a container

Generally there are no differences in dosage among children and adults, though children under the age of 10 are advised not to use tocotrienols at all unless under the recommendation by a physician

Randomization

Before starting the study firstly randomized the database with proper code. The capsules for drugs and placebo were identical in appearance, taste, and labeling. The drug code was revealed after the database had been completed and locked. In an individual, Assessment was done by mouth opening measured by SK Kathaiia *et al* scoring system and associated symptom measures.

Sk Kathaiia *et al* (1992) have given different scores assigned to the patients on the basis of mouth opening between upper and lower central incisors as follows: [17]

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

10 patient included were randomly assigned, for 6 months, to a combination of 800 mg/d of GT3 and DT3 in two 400-mg Capsules.

Outcome Measures

Participants or patients were reviewed by the clinical investigators before randomization. Experiencing radiation induced fibrosis; restricted mouth opening and symptomatic stiffness in neck were included in the study. Routine evaluation included opening of mouth and measurement of the length of mouth opening during the head and neck cancer. Objective signs and subjective symptoms relating to the site of fibrotic involvement were graded from 1 to10, according to the SK Kathaiia *et al* scoring system. Assessment was done by improvement in mouth opening measured and associated symptom measures.

Results

All patients had reported reduction in symptom severity within 3 to 7 days of starting of GT3 and DT3 combination. Four patients who were having mouth opening of one finger, after taking GT3 and DT3 combination for six month, mouth opening was increased to two fingers. Six patients were having mouth opening of two fingers after taking GT3 and DT3 combination for six month mouth opening was increased to three fingers. Better results were observed in postoperative patients. We evaluate subjective patient and got there response with the questioner which is given below in the tabular form. (table2)

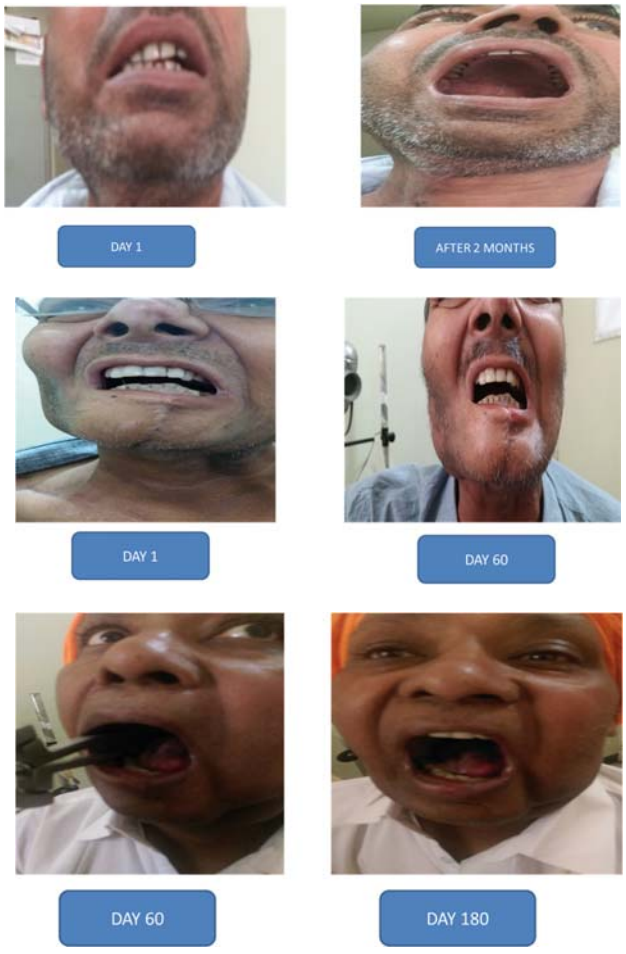
Table 2:-To Evaluate Subjective Patient Response in QOL We Asked A Questionier: After 15 Days

Questions	Answers
Was It Beneficial	YES - 10 NO - 0
How much improvement in mouth opening according to patient?	Significant
Was relief in neck stiffness and ease in neck movement?	YES – 10 NO - 0
Whether he is now able to eat solid food?	YES – 10 NO - 0

GT3 and DT3 combination Features
- ✓ Clinically proven.
- ✓ No apparent observable side effects reported.
- ✓ Can be used in any stage of cancer as a palliative care treatment.
- ✓ GT3 and DT3 combination targets the Multiple cell signaling pathways, thus elevating the immuno-compromised state of the cancer patients.

After the administration of GT3 and DT3 combination to the patients following primary and secondary analysis were observed and provide scoring to the patients for mouth opening.

Primary Analyses **Secondary Analyses**



Conclusion

GT3 and DT3 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 GT3 and DT3 combination in these patients. Presently at our center we are doing a randomized prospective controlled study on the same. According to Clinical Evidence a Randomized, Placebo-Controlled Trial of Combined Pentoxifylline and a combination of Tocotrienol with Tocopherol complex significantly reduce superficial RIF. Gamma and delta isoforms, exhibits superior anticancer effects in comparison with TP, which include anti-inflammation, anti-invasion, anti-angiogenesis, chemo sensitization and Radiosensitization.Delta-tocotrienol performing equal to or better than gamma-tocotrienol, also restoring the fresh blood supply damaged by radiation insults. Tocotrienol affects numerous pathways linked with tumorigenesis and thus has potential in both the prevention and the treatment of cancer.

References

1. Delanian S, Porcher R, Rudant J, Lefaix JL. Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. J Clin Oncol. 2005; 23:8570.
2. Haase O, Rodemann HP. Fibrosis and cytokine mechanisms: relevant in hadron therapy? Radiother Oncol. 2004; 73(Suppl2):S144.
3. Delanian S, Lefaix JL. Reversibility of radiation-induced fibroatrophy (in French). Rev Med Interne. 2002; 23:164-174,
4. Lefaix JL, Daburon F. Diagnosis of acute localized irradiation lesions: A review of the French experimental experience. Health Phys. 1998; 75:375-384.
5. Delanian S, Martin M, Bravard A *et al.* Cu/Zn superoxide dismutase modulates phenotypic changes in cultured fibroblasts from human skin with chronic radiotherapy damage. Radiother Oncol. 2001; 58:325-331.
6. Prasad KN, Ramanujam S, Gaudreau D. Vitamin E induces morphological differentiation and increases the effect of ionizing radiation on neuroblastoma cells in culture," Proceedings of the Society for Experimental Biology and Medicine, 1979; 161(4):570–573.
7. Sarria A, Prasad KN. dl-α-tocopheryl succinate enhances the effect of γ-irradiation on neuroblastoma cells in culture," Proceedings of the Society for Experimental Biology and Medicine, 1984; 175(1):88-92.
8. Whittle KJ, Dunphy PJ, Pennock JF. The isolation and properties of δ-tocotrienol from Hevea latex. The Biochemical Journal. 1966; 100(1):138-45.
9. Brigelius-Flohé R, Traber MG. Vitamin E: function and metabolism. The FASEB Journal. 1999; 13(10):1145-55.
10. Guthrie N, Gapor A, Chambers AF, Carroll KK. Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination. J Nutr. 1997; 127(3):544S-548S.
11. Kato A, Gapor A, Tanabe K, Yamaoka M, Mamuro H. Esterified & alpha-tocopherol and tocotrienols in palm oils. J Jpn Oil Chem Soc. 1981; 30(9):590-591.
12. Qureshi AA, Mo H, Packer L, Peterson DM. Isolation and identification of novel tocotrienols from rice bran with hypocholesterolemic, antioxidant, and antitumor properties. J Agric Food Chem. 2000; 48(8):3130-3140.
13. Bockorny B, Dasanu CA. HMG-CoA reductase inhibitors as adjuvant treatment for hematologic malignancies: What is the current evidence? Ann. Hematol. 2015; 94:1-12.
14. Berbee M, Fu Q, Garg S, Kulkarni S, Kumar KS, Hauer-Jensen M. Pentoxifylline enhances the radioprotective properties of γ-tocotrienol: Differential effects on the hematopoietic, gastrointestinal and vascular systems. Radiat. Res. 2011; 175:297-306.
15. Noguchi N, Hanyu R, Nonaka A, Okimoto Y, Kodama T. Inhibition of THP-1 cell adhesion to endothelial cells by alpha-tocopherol and alpha-tocotrienol is dependent on intracellular concentration of the antioxidants. Free Radic Biol Med. 2003; 34:1614-1620.
16. Naito Y, Shimozawa M, Kuroda M, Nakabe N, Manabe H, Katada K *et al*. Tocotrienols reduce 25-hydroxycholesterol-induced monocyte-endothelial cell interaction by inhibiting the surface expression of adhesion molecules. Atherosclerosis. 2005; 180:19-25.
17. Katharia SK, singh SP, kulshresthra VK. The effects of placenta extract in management of osmf. Indian journal of pharmacology. 1992; 24:181-183.