ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 10 | October - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

BEYOND ADJUVANT THERAPY: EFFECT OF TOCOTRIENOLS AFTER TREATMENT COMPLETION IN TRIPLE-NEGATIVE BREAST CANCER – A FEASIBILITY STUDY

Oncology

Madhabananda Kar* M.S., Ph D., F.A.C.S. Department of Surgical Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India. *Corresponding Author

Ephraim R DNB Department of Surgical Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Dillip Kumar Muduly M. Ch. Department of Surgical Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Saroj Kumar Das Majumdar M.D, DNB Radiation Oncology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Sudipta Mohakud M.D. Radiology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

ABSTRACT

Triple-negative breast cancer (TNBC) is an aggressive molecular subtype devoid of targeted therapies, unlike hormonal receptor-positive and HER2-overexpressing tumors. The TNBC cells exhibit distinctive mitochondrial dysfunction, higher proportions of reactive oxygen species (ROS), and elevated glycolysis. Triple-negative breast cancer women (n=12) treated with tocotrienols [CA Probret®(Jenome Biophar Pvt. Ltd.)] once-daily post-therapy completion were analyzed. The primary outcomes assessed were compliance and toxicity. Secondary outcomes included disease-free survival (DFS) and overall survival (OS). The median age was 45.6 years (Range 24-68 years). Drug compliance was 91.67%, and no adverse reactions were reported. At a median follow-up of 102.4 months (8.5 years), one (8.33%) patient had died with recurrence after 41 months of initial diagnosis. Tocotrienols have shown encouraging results with an acceptable safety profile in TNBC patients as an adjuvant strategy. However, it needs validation by large-scale randomized clinical trials to augment routine clinical practice.

KEYWORDS

Triple-negative breast neoplasms,Tocotrienols,Breast neoplasms,adjuvant drug therapy.

INTRODUCTTION

Breast cancer is the leading cause of cancer-related mortality in India and second worldwide among females[1]. Its classification has shifted from a primitive anatomical basis to a comprehensive molecular-based staging system, encompassing tumor biomarkers and molecular details. The molecular profile of breast cancer is the crucial determinant of prognosis, reflecting its tumor biology. Triple-negative breast cancer (TNBC) is an aggressive molecular subtype of breast cancer against which endocrine and targeted therapies significantly enhance the prognosis for hormonal receptor-positive and Human epidermal receptor 2 (HER2) overexpressing breast cancers are ineffective as these cancer cells lack any of these receptors. Hence, TNBC patients are practically left with void treatment strategies after completing chemotherapy and radiotherapy.

Oxidative stress is a documented pathway in breast carcinogenesis with differential production of reactive oxygen species in the cancer cells. The TNBC patients have distinctive mitochondrial dysfunction, higher proportions of reactive oxygen species (ROS), and elevated glycolysis than their receptor-positive counterparts[2]. Dysregulation of cellular energetics to meet the demands of the cell cycle by activating glycolysis is one of the hallmarks of carcinogenesis, which also involves mitochondrial activation. Mitochondria have a critical stance in redox balance through the reactive oxygen species released from the electron transport chain in the glucose metabolism, which influences its malignant potential, especially in dysfunctional mitochondrial states, forming the basis for their tumorigenic effect[3].

Tocotrienols have come into the limelight because of their antioxidant and antiproliferative properties in many cancers, demonstrated in in-vitro studies[4]. Antiangiogenic, proapoptotic manifestations and immunological modulation of these agents, in addition, signifies tocotrienols as more than mere antioxidants in holistic cancer management. Delta-tocotrienols were found to reduce lipid droplet biogenesis, whose higher cytoplasmic content is related to more significant breast cancer cell proliferation and malignant potential[5]. These properties provide a positive impact for its usage in cancer prevention. Various forms of vitamin E (alpha and gamma tocotrienols) were quoted to induce docosahexaenoic acid-induced apoptosis in TNBC cells[6].

In the milieu of limited options, researchers had been on the constant search for novel strategies to treat triple-negative (ER-, PR- and HER2-) breast cancer patients. As per the available literature, no clinical trial has been published on tocotrienols in triple-negative breast cancer patients till date. Hence this regimen (Vitamin E supplementation) was administered in the TNBC patients because they have meager available strategies with its hawkish biology.

MATERIALAND METHOD

Data was retrieved from the departmental database and hospital records. Women with non-metastatic, triple-negative breast cancer who had completed treatment with curative intent from June 2009 to January 2019 and had received Gamma and Delta Tocotrienols 400mg soft gel capsule [CA Probret® (Jenome Biophar Pvt. Ltd.)] once-daily dosage, were included in the analysis. The drug was prescribed for a minimum of 12 months after obtaining informed consent. Patients were followed every three months for two years, every six months for the next three years, and annually after that. At each patient's visit, history was taken, and physical examination was conducted. No follow-up imaging was advised apart from annual screening mammography of the contralateral breast for mastectomy patients and both breasts for breast conservation patients unless clinically suspected for disease recurrence.

The primary outcomes assessed were drug compliance and its toxicity profile. Secondary outcomes included disease-free survival (DFS) and overall survival (OS). Overall survival was calculated from the date of diagnosis to death from any cause or last follow-up. Disease-free survival was measured from surgery to the day of recurrence or death from any cause or patient's last contact. Patients were contacted either telephonically or at outpatient visits.

RESULTS

The study population included 12 patients (n = 12). The median age of the population was 45.6 years (Range, 24 - 68years). Seven (58.33%) were right-sided breast cancers. Six (50%) each were pre & postmenopausal women. Half of the patients (50%) were of clinical-stage IIA, and the rest, stage IIB (50%). The majority (66.67%) of patients underwent modified radical mastectomy (MRM), and four (33.33%) underwent breast conservation surgery (BCS). The median duration of tocotrienols (CA Probret®) administered was twelve months (Range 8 – 24 months).

Out of 12, 11 (91.67%) patients have completed the prescribed twelve months of therapy, and 1 (8.33%) patient received eight months. At a median follow-up of 102.4 months (Range, 28.7 – 159.8 months), one (8.33%) patient had distant recurrence (disseminated skeletal and multivisceral metastasis) after 33.9 months following surgery. She received palliative chemotherapy and died after 6.47 months from the date of recurrence [Table 1]. None of the patients reported any adverse events.

DISCUSSION

Cancer biogenesis comprises altered cell cycle pathways, undesired cellular proliferation, and apoptotic imbalance. Dynamics in mitochondria of cancer cells are crucial in fueling the sustained cell division and various molecular stresses similar to the normal cells[3]. The pro-tumorogenic role of mitochondria is based on their impaired fission & fragmentation, leading to the accumulation of mitochondrial DNA mutations and ROS generation [7]. Tocotrienols prevent the oxidation of various cellular components by molecular oxygen and free radicals. They are involved in cellular respiration through the electron transport chain and acts as a coenzyme Q stabilizer.

Palm oil devoid of vitamin E was found to have a tumorigenic effect in rats by Nesaretnam et al.[4], the initial report providing a basis for the anticarcinogenic role of tocotrienols. This was confirmed by further in-vitro studies on breast cancer cell lines showing inhibition of cell proliferation by half at a concentration of only 180 microgram/ml by the tocotrienol-rich fraction[8]. The subsequent study had shown growth inhibitory action of tocotrienols on breast cancer cell lines at just six microgram/ml[9].

Effects of various forms of tocotrienols were studied in highly malignant, neoplastic, and preneoplastic breast epithelial cells. Highly malignant cell lines were identified as more sensitive to apoptotic and antiproliferative effects of delta tocotrienols especially. The presence of the unsaturated phytyl chain enhances cellular uptake of tocotrienols, leading to higher intracellular concentrations amounting to their greater biopotency[10]. Tocotrienols were discovered to have the capacity to augment interleukin-24 (IL-24) mRNA expression, suppressing cancer growth by apoptotic stimulation without disturbing normal cells. Selvaduray et al. found increased levels of IL-24 mRNA expression and lowered IL-8, vascular endothelial growth factor (VEGF) in tocotrienol supplemented models[11].

Malaysian palm oil board researchers conducted two clinical studies regarding the effect of tocotrienols on breast cancer. The first study, conducted in patients primarily on a palm oil-based diet, showed higher tocotrienol levels in benign breast patients than malignant, supporting their preventive role[12]. A double-blinded, placebo-controlled pilot study (n = 240) was conducted by Nesaretnam et al.[13] on the effect of tocotrienols with tamoxifen combination, given for five years in estrogen receptor-positive early breast cancer women. Complete blood counts and liver function tests were assessed at baseline and periodically, finding no significant differences in the values and well-tolerated by the patients. Similarly, a good compliance rate of 91.67% was observed with no documented side effects in this study.

Nesaretnam et al.[13] also observed reduced recurrence rates and breast cancer-related mortality; however, they were not statistically significant. Breast cancer-related mortality was 60% lower in the intervention arm.

In the current study also, at a median follow-up of 102.4 months, 8.33% of patients had recurrence and died due to the disease, fewer than the previously reported Indian studies[14,15] in triple-negative breast cancer patients.

The current study stands out as the first of its sort to investigate the efficacy & safety of tocotrienols in triple-negative breast cancer patients. Relatively longer follow-up (maximum follow-up of 159.8 months) and strict adjuvant protocol adherence are the additional strengths of this study. Smaller sample size and lack of randomization are the limitations.

CONCLUSION

In short, triple-negative breast cancer is known for its poor prognosis without further adjuvant therapeutic options after completing standard chemo and radiotherapies.

Tocotrienols, especially delta and gamma forms, have shown a promising role in this select group of patients due to their antioxidant, immunomodulator, and growth inhibitory properties without any adverse drug reactions reported. However, it needs validation by large-scale randomized clinical trials to imbibe into standard practice.

LEGENDS:

Table 1: Patient profile with their survival outcomes

Conflicts Of Interest And Funding:
The authors disclose no conflicts of interest. No funding.

Table 1: Patient Profile With Their Survival Outcomes

Case	Age (yrs)	Laterality	Menopausal status	TNM stage	Surgery	Adjuvant	Duration of tocotrienols	Events	Follow-up (months)
1.	68	Left	Post	T3N0M0	MRM	4AC+4P	12 months	None	104.8
2.	47	Right	Pre	T2N0M0	BCS	4FEC+RT	12 months	None	159.8
3.	61	Right	Post	T2N1M0	MRM	4FEC+4P	12 months	None	115.6
4.	32	Right	Pre	T2N1M0	BCS	4FEC+4P+RT	12 months	None	119.5
5.	28	Right	Pre	T2N1M0	MRM	6FEC+RT	24 months	None	145.07
6.	58	Right	Post	T2N1M0	MRM	4FEC+4P	12 months	Died with recurrence	41.03
7.	32	Right	Pre	T2N1M0	MRM	4FEC+4P	24 months	None	86.23
8.	57	Left	Post	T2N0M0	MRM	4FEC+4P	24 months	None	81.1
9.	24	Left	Pre	T2N0M0	BCS	4FEC+4P+RT	12 months	None	107.57
10.	58	Left	Post	T2N0M0	BCS	4FEC+4P+RT	18 months	None	99.93
11.	55	Left	Post	T2N0M0	MRM	4AC+12P	21 months	None	28.7
12.	28	Right	Pre	T2N0M0	MRM	4FEC+12P	8 months	None	30.03

Pre = premenopause, Post = postmenopause, MRM = Modified radical mastectomy, BCS = Breast conserving surgery, OS = overall survival, AC = adriamycin cyclophosphamide, FEC = 5-fluorouracil epirubicin cyclophosphamide, P = platinum compounds, RT = radiotherapy.

REFERENCES:

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018 Nov;68(6):394-424.
[2] Sarmiento-Salinas FL, Delgado-Magallón A, Montes-Alvarado JB, Ramírez-Ramírez D, Flores-Alonso JC, Cortés-Hernández P, Reyes-Leyva J, Herrera-Camacho I, Anaya-Ruiz M, Pelayo R, Millán-Pérez-Peña L. Breast cancer subtypes present a differential production of reactive oxygen species (ROS) and susceptibility to antioxidant treatment. Frontiers in oncology. 2019 Jun 7;9:480.
[3] Maycotte P, Marín-Hernández A, Goyri-Aguirre M, Anaya-Ruiz M, Reyes-Leyva J, Cortés-Hernández P. Mitochondrial dynamics and cancer. Tumor Biology. 2017;39(5):101042831769839.
[4] Nesaretnam K, Meganathan P, Veerasenan SD, Selvaduray KR. Tocotrienols and breast cancer: the evidence to date. Genes & nutrition. 2012 Jan;7(1):3-9.
[5] Pizato N, Kiffer LF, Luzete BC, Assumpção JA, Correa LH, Melo HA, Sant'Ana LP, Ito MK, Magalhães KG. Omega 3-DHA and delta-tocotrienol modulate lipid droplet biogenesis and lipophagy in breast cancer cells: The impact in cancer aggressiveness. Nutrients. 2019 Jun;11(6):1199.
[6] Xiong A, Yu W, Tiwary R, Sanders BG, Kline K. Distinct roles of different forms of vitamin E in DHA-induced apoptosis in triple-negative breast cancer cells. Molecular nutrition & food research. 2012 Jun;56(6):923-34.
[7] Parone PA, Da Cruz S, Tondera D, Mattenberger Y, James DI, Maechler P, Barja F, Martinou JC. Preventing mitochondrial fission impairs mitochondrial function and leads to loss of mitochondrial DNA. PloS one. 2008 Sep 22;3(9):e3257.
[8] Nesaretnam K, Guthrie N, Chambers AF, Carroll KK. Effect of tocotrienols on the growth of a human breast cancer cell line in culture. Lipids. 1995 Dec;30(12):1139-43.
[9] Nesaretnam, Selvarajan Dorasamy, Philippa D. Darbre K. Tocotrienols inhibit growth of ZR-75–1 breast cancer cells. International Journal of Food Sciences and Nutrition. 2000 Jan 1;51(1):95-103.
[10] McIntyre BS, Briski KP, Tirmenstein MA, Fariss MW, Gapor A, Sylvester PW. Antiproliferative and apoptotic effects of tocopherols and tocotrienols on normal mouse mammary epithelial cells. Lipids. 2000 Feb;35(2):171-80.
[11] Selvaduray KR, Radhakrishnan AK, Kutty MK, Nesaretnam K. Palm tocotrienols

inhibit proliferation of murine mammary cancer cells and induce expression of interleukin-24 mRNA. Journal of Interferon & Cytokine Research. 2010 Dec 1;30(12):909-16.
[12] Nesaretnam K, Gomez PA, Selvaduray KR, Razak GA. Tocotrienol levels in adipose tissue of benign and malignant breast lumps in patients in Malaysia. Asia Pacific Journal of clinical nutrition. 2007 Sep 1;16(3).
[13] Nesaretnam K, Selvaduray KR, Razak GA, Veerasenan SD, Gomez PA. Effectiveness of tocotrienol-rich fraction combined with tamoxifen in the management of women with early breast cancer: a pilot clinical trial. Breast Cancer Research. 2010 Oct;12(5):1-8.
[14] Chandra D, Chandra Doval D, Suresh P, Sinha R, Azam S, Batra U, Talwar V, Kumar K, Mehta A. Eight year survival analysis of patients with triple negative breast cancer in India. Asian Pacific Journal of Cancer Prevention. 2016 Jul 1;17(6):2995-9.
[15] Rajendran T, Prasad K. Clinical profile of triple negative breast cancer in Indian women: Long term follow-up study. Journal of Clinical Oncology. 2018;36(15_suppl).