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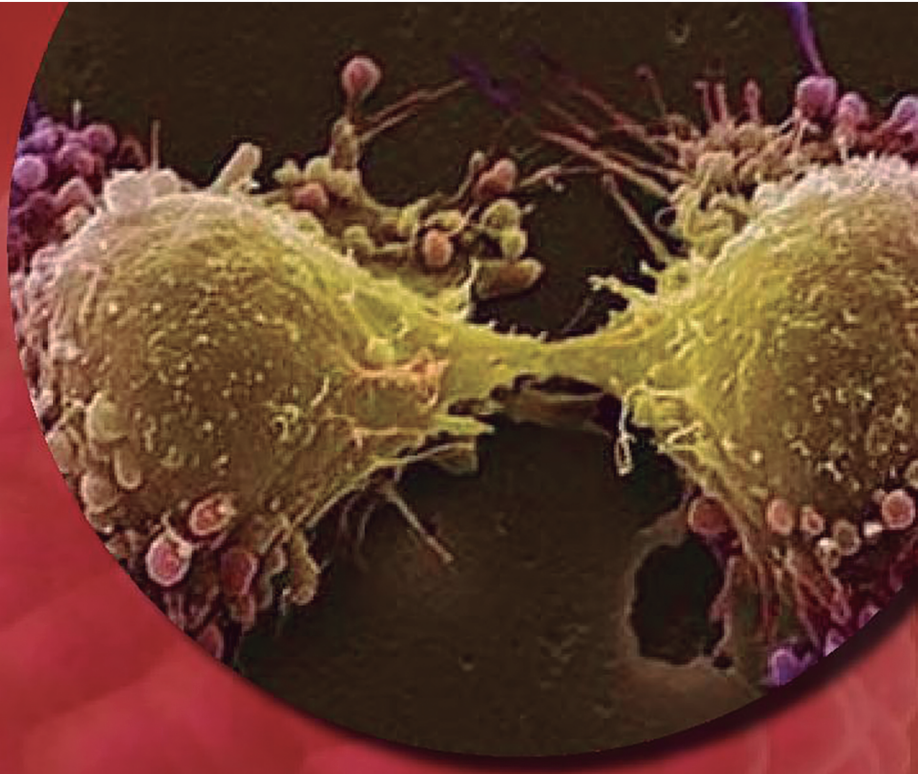

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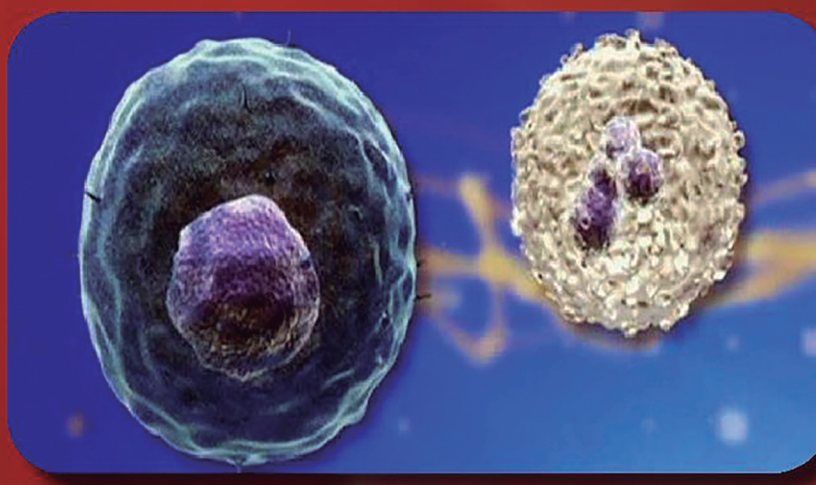

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Oncoxin-Viusid with Radiotherapy and Chemotherapy in Patients with Head and Neck Cancer: Results from a Phase II, Randomised, Double-Blind Study

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Abstract

Objective: Antioxidant supplements seem to reduce toxicity associated with radiotherapy (RT) and chemotherapy (CT) in patients with head and neck (H&N) cancers. Ocoxin-Viusid (OV) has recognized antioxidant, immunostimulant, and anti-tumor effects. Our study was aimed to evaluate the efficacy and safety of OV in patients with H&N tumors during treatment with RT and CT.

Methods: A total of 60 patients with a diagnosis of H&N carcinoma and indication of radiotherapy concurrent with chemotherapy were included in a phase II, randomized, prospective, controlled, double-blind study with two treatment arms: RT+CT+Placebo (n=30) and RT+CT+OV (n=30) during one year at a tertiary referral academic center (National Institute of Oncology from Havana, Cuba) from January 2015 to January 2016, with the objective of evaluating RT-CT toxicity reduction and improving patient quality of life.

Results: There was no significant difference between the two groups in regard to male predominance; median age of 60, histological diagnosis of squamous cell carcinoma of the oropharynx in locally-advanced stages. The experimental OV group obtained better results insofar as a lower number and duration of interruptions in RT and lower severity of RT-CT toxicity levels, with acceptable local tumor control and overall survival in accordance with the clinical stage of the disease. No adverse effects were recorded in relation to the OV supplement.

Conclusion: Our results suggest that administration of ocoxin-viusid during radiotherapy and chemotherapy improves patient quality of life by decreasing the number and level of toxicities from these treatments without interfering with their mechanism of action.

Keywords: Antioxidants; Radiotherapy; Chemotherapy: Free radicals; Oxidative stress; Tumor; Carcinoma; Head and neck cancers

Introduction

Head and neck (H&N) cancer encompasses a variety of neoplasia's with different rates of occurrence, clinical presentations, forms of disease progression, therapeutic approaches and prognoses. They are relatively frequent, being the sixth most common neoplastic location worldwide, representing 4% of all malignant neoplasia's [1]. Around 600,000 new cases are diagnosed annually worldwide [2], with a lifelong risk of 2% for men and 0.6% for women, occurring most frequently after 45 years of age. The primary histological type is a squamous cell carcinoma (SCC). In the US, the overall 5-year survival rate for patients treated in the initial stages is 70% and 30% for advanced stages. In Cuba, 2,600 new cases were reported in 2004 [3] and 1,246 deaths in 2005. At this institution, an annual average of 440 cases are diagnosed [4].

Radiotherapy is administered to cells by way of both photons (i.e. X- and gamma rays) and particles (protons, neutrons and electrons). When these photons or particles interact with biological material, this results in ionization, which either interacts directly with the subcellular structures or with water to create free radicals, which then interact with subcellular structures. The direct effects of radiation are a result of the DNA in energy-absorbing chromosomes that permits ionization. This is the largest mechanism of DNA damage induced by protons and neutrons. The reaction of the photons with other molecules, such as water molecules, results in the production of free radicals, some of which have a long lifespan, long enough to spread to the nucleus of the cell and interact with chromosomal DNA, which is the largest mechanism of X-ray induced DNA damage. Cells subjected to the effects of radiation die when the cellular reproductive system (DNA)

attempts to attack the cellular division process, injuring membranes and microtubules and contributing to cell death. The primary lethal mechanism of radiotherapy is indirect, where radiation ionizes the internal environment of the cell, provoking the formation of hydroxyl radicals; using water molecules, these radicals, strongly attracted to the electrons of the surrounding molecules, injure the DNA by "robbing" electrons, which is helped along by the presence of oxygen in the cellular environment, facilitating the prolongation of hydroxyl radical half-life and their injurious effects [5-7].

The acute secondary effects derived from CT and RT are magnified when administered concurrently due to the insult caused to rapidly proliferating tissues, and present as acute inflammatory symptoms. The chronic effects are the result of their repair, which gives way to dystrophies, atrophies, fibrosis, necrosis and torpid ulcers [7].

Radioprotectors are pharmaceuticals that selectively protect normal cells, but not cancerous cells, from the effects of radiation. In the last few years, they have been studied in laboratories in order to determine their efficacy in preventing damage due to radiation in normal cells. Examples: Keratinocyte growth factor (KGF, palifermin) and antioxidants, such as agent Cu/Zn superoxide dismutase (SOD), have been promising for the reduction of early- and late-stage tissue lesions induced by radiation; Interleukin 11 is a growth factor that has been approved by the FDA to stimulate platelet recovery. Currently, clinical trials are underway to determine if Interleukin 11 can prevent the side effects of CT and RT. S-2-(3-aminopropylamine) ethylphosphorothioic acid (Amifostine) is a selective radioprotector of healthy tissues and cytoprotector against the free radicals generated by RT and CT; it presents severe secondary effects and the only method of administration is intravenous [8-10].

The efficacy of antioxidants in cancer prevention is well-known [11,12] however, their usefulness during RT and CT still requires more exhaustive study. There is a preoccupation regarding whether antioxidants [13] would reduce the oxidation of free radicals created by RT and CT, thereby reducing their efficacy. In addition, there is data that indicates an increase in the effectiveness of oncospecific treatments with a decrease in adverse effects when administered simultaneously with antioxidants [14,15].

Lamson and Brignall studied the mechanism of action of antioxidants and a potential relationship to the oncological treatments of chemotherapy and radiotherapy and reported a "live-acting" synergistic anti-tumor effect, increase in survival rates, and reduction of RT-CT toxicity in patients, and even an increase in overall survival rates [12,16-22].

Pre-clinical and clinical studies have been performed using the Ocoxin-Viusid (OV) nutritional supplement from Laboratories Catalysis in Spain that demonstrate its anti-tumor effects: The supplement limits the angiogenic process, blocks growth factor signal transduction and inhibits cellular proliferation and blocks metastasis; inhibits the urokinase enzyme found in malignant tumors; induces apoptosis in tumor cells; has a synergistic effect with chemotherapy due to an increase in the anti-tumor effects of some cytostatic; it is also a radiosensitizer in malignant cells with cytoprotecting of healthy tissue [15,23-28]. OV is formulated with antioxidants that are effective as anti-carcinogens, treated with a molecular activation process that increases their biological activity, among which the following merit special mention: Polyphenols from green tea, epigallocatechin gallate with antimutagenic and anticarcinogenic activity due to TNF-a receptor blockage, NFkB activation due to nuclear translocation, and inhibition of COX-2 expression. The supplement inhibits the expression of proteins such as VEGF and cellular migration using ephrine A1; it stops release and expression processes for cellular matrix metalloproteinases (MMPs) 2 and 9 related to the invasive process of tumor cells; in addition, it restores apoptosis in tumor cells by stopping the cellular cycle and inducing the expression of the p53, caspase-3 and Bax pro-apoptotic proteins and inhibiting the anti-apoptotic protein Bcl-2 [29-32].

It is estimated that for each week that RT is prolonged due to interruptions, local tumor control decreases by 10-12% due to accelerated cellular re-population, with a relatively low remission index, few disease-free intervals and a low overall survival rate [33,34].

The purpose of the study was to evaluate the effect of the ocoxin-viusid supplement in reducing the toxicity generated by radio-chemotherapy and in-patient quality of life.

Patients and Methods

A phase II controlled, prospective, randomized, double-blind trial with a placebo was performed during the period spanning from February 2015 to October 2017 at the Cuban National Institute of Oncology and Radiobiology (tertiary care center), approved by the Institutional Review Board. The trial was comprised of 60 patients of both sexes over 18-years-old with a histological diagnosis of head and neck carcinoma, independent of the type or grade of histological differentiation and clinical stage, all requiring concomitant treatment with ionizing radiation (RT) and radiodensities chemotherapy (CT), with compensated intercurrent diseases and a Karnofsky index over 59 and acceptable hematological parameters; also, women in the trial were not pregnant nor lactating. All patients authorized their inclusion in the investigation *via* informed consent. Patients with a second primary concomitant tumor and/or contraindications to platinum-based chemotherapy were excluded.

The patients included were randomized using a code system and distributed into 2 groups: One group of 30 patients under the conventional treatment (RT+CT) plus a placebo (RT+CT+Placebo) and another group of 30 patients under the conventional treatment and also associated with the experimental product/nutritional supplement ocoxin-viusid (RT+CT+OV) produced by Laboratories Catalysis in Madrid. The placebo and OV had similar physiochemical properties.

Standardised Treatment Protocol Prior to Patient Inclusion

Radiotherapy+Concurrent radio-sensitising chemotherapy +Ocoxin-Viusid and/or Placebo

External radiotherapy with 2D and/or 3D techniques:

- Equipment=Cobalt-60 and/or Linear Accelerator (energy: photons).
- Daily Tumour Dose (DTD)=180-200 cGy.
- Frequency=1 session/day (5 sessions/week=Monday thru Friday).
- Total Tumour Dose (TTD)=6600-7000 cGy.
- Total expected duration: 7 weeks.

Radio-sensitising chemotherapy-Concomitant with radiotherapy:

- Cisplatin (CDDP)=Cis-diammine-dichlorido-platinum. Bulb: 50 mg/50 ml.
- Dose=100 mg/m^2 (intravenous) upon hospitalisation on day 1, 22, 43.

Treatment with ocoxin-viusid and/or Placebo: Oral solution dose=75 ml/day (in three separate doses of 25 ml every 8 hours). 30 days prior to radiation treatment, throughout the entire radiotherapy treatment concomitant with radiosensitising chemotherapy and 30 days following culmination of oncospecific treatment. 18 vials total were calculated for each patient. The chemical components of the ocoxin-viusid nutritional supplement are shown in Table 1.

Chemical	Value
Glycine	2, 000 mg
Glucosamine	2,000 mg
Arginine	640 mg
Cystine	204 mg
Malic acid	1,200 mg
Monoammonium glycyrrhizinate	200 mg
Ascorbic acid	120 mg
Sodium methylparaben	100 mg
Zinc sulphate	80 mg
Green tea extract	25 mg
Calcium pentothenate	12 mg
Pyridoxine	4 mg
Manganese sulphate	4 mg
Cinnamon extract	3 mg
Folic acid	400 mcg
Cyanocobalamin	2 mcg

Table 1: Chemical composition of the product ocoxin-viusid (average values per 100 mL).

Both treatment arms received the same schedule of radiotherapy concomitant with radiosensitising chemotherapy. All of the patients were evaluated weekly throughout radiotherapy (RT) as well as 4-6 weeks following culmination, and finally 12 months from the date of inclusion in the study. During the chemo-radiotherapy follow-up, blood panels were drawn and physical and upper respiratory tract exams completed by otolaryngology specialists every 10 RT sessions. Upon completion of treatment, endoscopic upper respiratory studies and CAT scans with contrast were performed on the head and neck region (at 4-6 weeks after culmination of RT and at the one-year evaluation).

Statistical analysis

Size of the sample: In order to obtain the sample size, the ratio of patients that presented adverse reactions that required interruption to radio-chemotherapy treatment to the number of patients included in the study was taken into account. At this institution, the figure was near 45% (meanwhile, 55% were successful, or without interruption). Given that OV is a dietary supplement, with a large amount of information on product safety, the experimental design was used in a Fleming stage 35 (without early stopping rules). Let us suppose that the oncoxin-viusid product would be definitively declared to be ineffective (maximum inefficacy) if the proportion of patients that presented no adverse reactions, that is, the maximum number of successes, to radio-chemotherapy was equal to or less than 55% ($p0$), below which the product does not show signs of efficacy (this study does not guarantee further research), while taking 80% as the value of $p1$, where $p1$ is the maximum level of efficacy required for the product to be declared effective (or, the results guarantee continuance to a phase III study). Assuming an error α of 5% and an error β of 20% (1 - β=80%), a maximum number of 21 subjects were included.

The trial tests null hypothesis H0: $P \leq p0$ against the alternate hypothesis: H1: $P \geq p1$. a is set at=14, where a is the number of responses that do not undergo treatment interruption at a level equal to or less than the number with which the product would be declared ineffective (H_0 is acceptable). And r=$a+1$ is the cut-off point, that is, the number of responses where the efficiency level generated guarantees moving to a phase III study. In this case, we would hope for ≥ 15 successes.

Given that this is about a randomised, double-blind study with a control placebo group, and assuming 45% loss, 30 patients were included in each group.

Treatment randomisation and assignment: Each patient included in the clinical trial was assigned randomly with a double-blind to one of the study groups (experimental and placebo) to make sure that both arms were homogeneous. A list was drawn up randomly for each stratum and centralised using a table of random numbers generated automatically in a computer using the ASAL system so that there was an equal number of patients in each group.

Blinding technique employed: The product was numbered from the randomised list, which was managed by the study monitor only. Patients were included consecutively whenever their cases fulfilled the inclusion requirements.

Design bias controls: Among the limitations of the study, the impossibility of performing serum studies for antioxidant levels for patients under this treatment must be considered, which would have indisputably proven adequate administration and ingestion of the product by the patients at the established frequency. As an alternative, the patients were asked to return the empty bottle on a weekly basis and a new bottle of antioxidants was provided, which permitted control and monitoring of the study universe.

The data was collected manually by the research physicians in a case report form (CRF) designed for such purpose. The creation of the initial visit, follow-up, and final evaluation were stored in Microsoft Excel and subsequently analysed using the STATA version 11.0 Special Edition statistical package.

Patient sociodemographic and clinical characteristics were recorded using numbers and percentages, and summary and dispersion measures (median and range) in the case of quantitative variables. Absolute and relative frequencies were calculated for adverse reactions whose causality was associated with the product under investigation. Study data were analysed according to the intention-to-treat principle.

In order to measure quality of life (QL), the general questionnaire from the European Organisation for Research and Treatment of

Cancer (EORTC) QLQ-C30 Version 3.0 was used. A high value on the Health/General QL scale indicates a higher quality of life. In order to detect changes before and during the year of the patient's inclusion, the non-parametric test known as the Sign Test for paired data was used [35,36]. In addition, global survival rates were calculated using the Kaplan-Meyer method.

Results

Patient characteristics

All of the 60 patients included were distributed randomly into 2 treatment arms: RT+CT+OV Group (n=30) patients and RT+CT +Placebo Group (n=30) patients without significant differences in respect to age distribution (average 61 and 60 years old, respectively), sex (predominantly male, 87% and 77%, respectively), primary tumour location (most frequently in the oropharynx, 60% and 50%, respectively) and clinical stage (prevalence of advanced stages: stage IV in 53% and 62%, stage III in 30% and 28%, respectively). In the group of patients that received OV, there were 3 cases that had received prior radiotherapy in the current primary tumour region (local relapse). However, none of the cases in the Placebo group required re-irradiation (p=0.076). Patient clinical characteristics are shown in Table 2.

Variables	Overall N=60	OV group N=30	Placebo group N=30	p
Sex				
Male	49 (81%)	26 (87%)	23 (77%)	0.63
Female	11 (19%)	4 (13%)	7 (23%)	
Age, years (Range)	60 (45-78)	61(46-77)	60 (33-75)	0.95
Oral Cavity	6 (10%)	2 (6.7%)	4 (13.3%)	0.38
Oropharynx	34 (56%)	18 (60%)	16 (53%)	0.19
Nasopharynx	1 (1.7%)	0 (0%)	1 (3.3%)	0.31
Larynx	13 (21.7%)	8 (26.7%)	5 (16.7%)	0.60
Paranasal Sinuses	3 (5%)	1 (3.3%)	2 (6.7%)	0.55
Cervical Metastasis	1 (1.7%)	0 (0%)	1 (3.3%)	0.31
Parotid Gland	2 (3.33%)	1 (3.3%)	1 (3.3%)	1.0
Clinical Stage: I	2 (3.4%)	1 (3.3%)	1 (3.3%)	1.0
Clinical Stage: II	7 (11.6%)	4 (13.3%)	3 (10%)	0.38
Clinical Stage: III	17 (28.9%)	9 (30%)	8 (27.6%)	0.73
Clinical Stage: IV	34 (57.6%)	16 (53%)	18 (62%)	0.81
Prior Radiotherapy (No)	57 (95%)	27 (90%)	30 (100%)	0.19
Prior Radiotherapy (Yes)	3 (5%)	3 (10%)	0 (0%)	0.08

Table 2: Patient characteristics.

Treatment administration and efficacy

All of the 60 patients in the study received chemotherapy (CT) concomitant to radiotherapy (RT) with the intention of radiosensitisation according to the standard treatment protocol established at the corresponding institution.

A) In the RT+CT+OV group, a greater number of patients, 20/30 (67%), received treatment on Co60 equipment, according to a two-dimensional (2D) treatment planning system (TPS). For the RT+CT +Placebo group, the distribution was more homogeneous: 53% (16/30) of the patients received radiotherapy with a linear accelerator using three-dimensional (3D) contouring techniques (Table 3).

B) Interruptions and total duration of radiotherapy (Therapeutic Interval): Half of the patients in the RT+CT+OV group completed treatment in 7 weeks (without interruptions to the total planned dose), while the other half (15/30) presented with interruptions to RT. A significantly greater number of patients (p=0.01) in the RT+CT +Placebo group presented with interruptions: 27/30 (90%). Additionally, the difference in average duration of interruption was statistically significant between the two groups, with an average duration of 2 weeks (1-3 week range) for the group that received OV and 6 weeks (1-11 weeks) for the Placebo group.

Treatment	RT+CT+OV N=30	RT+CT+PLACEBO N=30	TOTAL N=60	p
Technique/RT Equipment				
2D/Co60	20 (67%)	14 (47%)	34 (57%)	0.23
3D/LINAC	10 (33%)	16 (53%)	26 (43%)	
Average RT Duration (Range in Weeks)	8 (7-15)	12 (7-28)		0.01
Patients with RT Interruptions	15 (50%)	27 (90%)	42 (70%)	0.01
Average Duration of RT Interruptions (Range in Weeks)	2 (1-3)	6 (1-11)	--	0.01
Patients with CT Interruptions	10 (33.3%)	14 (46.7%)	24 (40%)	0.29
OV/Placebo: Average vials consumed/18 (range)	10/18 (8-18)	12/18 (5-16)	--	--
Average Total Dose-RT	68 Gy (62-70 Gy)	65 Gy (60-68 Gy)	--	0.93
Abbreviations: OV, Ocoxin-Viusid; RT, Radiotherapy; 2D, Two-Dimensional Radiotherapy; 3D, Three-Dimensional Radiotherapy; Co60, Cobalt Equipment; LINAC, Linear Accelerator Equipment; CT, Chemotherapy.				

Table 3: Treatment with radiotherapy and chemotherapy concurrent with ocoxin-viusid or Placebo in 2 comparative groups.

Adverse events	RT+CT+OV N=30	RT+CT+Placebo N=30	p
Nausea	2 (6.6%)	7 (24%)	0.071
Vomiting	1 (3%)	3 (10%)	0.301
Myelosuppression	2 (6.6%)	5 (17%)	0.228
Dermatitis	16 (53%)	20 (67%)	0.196
Mucositis	16 (53%)	15 (50%)	0.228
Anorexia	0	4 (87%)	0.038
Xerostomia	12 (40%)	14 (47%)	0.866
Weight Loss	6 (20%)	3 (10%)	0.372
Dysphagia	8 (26%)	5 (17%)	0.347
Dysphonia	6 (20%)	2 (6.6%)	0.226
Dysgeusia	9 (30%)	10 (33%)	0.124
Dysnea	1 (3%)	3 (10%)	0.302
Nephrotoxicity	1 (3%)	5 (17%)	0.085
Hepatotoxicity	2 (6.6%)	3 (10%)	0.640
Anaphylaxis	0	0	ns
Symptoms Related to OV/Placebo	0	0	ns
Total Number of Toxicities	82	99	ns
Abbreviations: OV, Ocoxin-Viusid; RT, Radiotherapy; CT, Chemotherapy.			

Table 4: Radio-chemotherapy toxicities and OV/Placebo in both treatment groups.

The total duration of radiation treatment in the OV experimental group was an average of 8 weeks with a 7-15 week range. The duration of RT in the Placebo group was prolonged significantly (p=0.01), with an average of 12 weeks (7-28 week range) shown in Table 3.

Interruptions to the CT schedule had very similar behaviour (p=0.292) on both treatment arms, with 33% (10/30 patients) from the OV nutritional supplement arm and 47% (14/30 patients) from the arm receiving the placebo.

C) Total dose of planned radiotherapy: There was no significant difference (p=0.935) in the administration of total therapeutic doses of RT (around 66 Gy) in both comparative groups in Table 3.

D) Radio-chemotherapy toxicity: The rate of toxicity from the treatments is reflected in Table 4, with a discrete predominance of the total number in the Placebo group (99 toxicities) *versus* 82 in the group that received the OV supplement. The most frequent type of toxicity during the series was radiodermatitis, which was diagnosed at a very similar rate in both groups (53% in OV and 67% in Placebo) followed by mucositis in half of the patients in both groups. No toxicities were recorded in relation to the product under investigation, OV.

Toxicity Grades	RT+CT+OV	RT+CT+Placebo	p
	N=30	N=30	
Grade I	47 (57%)	23 (23%)	<0.001
Grade II	35 (43%)	64 (65%)	0.01
Grade III	0%	12 (12%)	0.01
Grade IV-V	0	0	--
Total Toxicities	82 (100%)	99 (100%)	--

Abbreviations: RT, Radiotherapy; CT, Chemotherapy; OV, Ocoxin-Viusid; CTCAE, Common Terminology Criteria for Adverse Events

Table 5: Toxicity grades (Adverse Effects) of RT-CT oncospecific treatments: CTCAE (version 4).

However, as shown in Table 5, no severe toxicities were recorded in the RT+CT+OV, differing significantly (p=0.01) with the RT+CT +Placebo group which had 12% (12/99) of grade-III toxicities, which required placement of feed tubes in 3 patients due to dysphagia and tracheotomies in 2 patients due to severe dyspnea.

E) Ocoxin-Viusid: Administration and safety: No adverse reactions to the OV nutritional supplement nor to the placebo were reported during the study (Table 4). The administration of the nutritional supplement by patients (Table 3) was very irregular and in insufficient doses, with an average consumption of 10 vials (range: 8-18) of the 18 prescribed to each patient according to the calculated dose schedule.

F) Tumor control: In Table 6, no significant difference (p=0.284) was recorded between the two treatment arms in relation to the anti-tumor response that was evaluated between 4 and 6 weeks after culmination of RT+CT. According to RECIST, 33% (10/30) of the OV arm and 41% (11/30) of the placebo arm achieved a complete response. In the group that received RT+CT+Placebo, 6 patients were not able to be evaluated due to lack of confirmation of diagnostic images from contrast CAT scans 4-6 weeks after the conclusion of concomitant radio-chemotherapy.

G) Quality of life: In the initial research protocol evaluation consultation, prior to administration of the OV/Placebo and RT+CT treatments, the QLQ-C30 quality of life questionnaire was applied to all of the 60 patients included, as shown in Table 7, the symptoms and different scales of functioning exhibiting very similar behaviour between both study groups.

In the RT+CT+OV group, the scales of physical functioning (p=0.0017) and symptoms (asthenia p=0.0009, nausea/vomiting p=0.0107 and pain p=0.0112) show significant difference when comparing the data at the time of culmination of RT+CT with the data at the time of inclusion of this patient group in the study. (Sign Test. Table 8).

Recist	Total	RT+CT+OV	RT+CT+Placebo	p value
Complete response	21 (36.8%)	10 (33.3%)	11 (40.7%)	ns
Partial Response	12 (21%)	7 (23.3%)	5 (18.5%)	ns
Stable Disease	1 (1.75%)	1 (3.3%)	0 (0%)	ns
Progressive Disease	20 (35.1%)	12 (40%)	8 (29.6%)	ns
Cannot be Evaluated	3 (5.26%)	0 (0%)	3 (11.1)	ns
Total	57 (100%)	30 (100%)	27 (100%)	ns

Pearson chi2 (4)=5.0370; pr=0.284; Fisher's exact=0.320

Abbreviations: OV, Ocoxin-Viusid; RT, Radiotherapy; CT, Chemotherapy

Table 6: Evaluation of response by neoplastic disease 4-6 weeks post-RT+CT, according to RECIST.

Result of the analysis of the comparison of quality of life questionnaire scales QLQ-C30 (after-before) in the experimental group.

Scales	No. of observations		Prob > |z|
	Experimental	Placebo	
Global Health/QL	30	27	0.19
Functioning Scales			
Physical functioning	30	28	0.64
Personal Functioning	30	28	0.08
Emotional Functioning	30	28	0.57
Cognitive Functioning	30	28	0.74
Social Functioning	30	28	0.83
Symptoms			
Fatigue	30	28	0.28
Nausea-vomiting	30	28	0.28
Pain	30	28	0.57
Dyspnea	30	28	0.77
Insomnia	30	28	0.55
Loss of appetite	30	28	0.75
Constipation	30	28	0.75
Diarrhea	30	28	0.33
Economic Difficulties	30	28	0.27
Note: There is no evidence of significant differences between groups with respect to the different scales of the QLQ C-30 at the time of inclusion in the study.			

Table 7: Result of the analysis of the comparison of quality of life questionnaire scales QLQ-C30 between groups at the beginning (Wilcoxon rank sum test).

Scales	No. of negative signs/total (n)	p (Median of the difference) *
Global Health/QL	10/21	0.22
Functioning Scales		
Physical functioning	12/22	<0.01
Personal Functioning	7/22	0.27
Emotional Functioning	9/21	0.30
Cognitive Functioning	5/21	0.36
Social Functioning	6/21	0.50
Symptoms	**No. of negative signs/total (n)**	**p (Median of the differences0) ***
Fatigue	12/22	<0.01
Nausea-vomiting	9/22	<0.01
Pain	11/22	0.01
Dyspnea	0/22	1.0
Insomnia	2/22	0.81

Loss of appetite	6/22	0.14
Constipation	3/22	0.50
Diarrhea	1/22	0.94
Economic Difficulties	4/20	0.74
* The scale of physical functioning and the symptomatic scales (fatigue, nausea-vomiting and pain), show significant differences when comparing the moment after the moment of inclusion in the study. The rest of the scales do not show significant differences.		

Table 8: Analysis of the quality of life questionnaire, at the beginning and at the end of the concurrent treatment of radiotherapy+chemotherapy +ocoxin-viusid.

RECIST	RT+CT+OV Group	RT+CT+Placebo Group	Total
Complete Response	11 (78.6%)	6 (60%)	17 (71%)
Partial Response	0	1 (10%)	1 (4.2%)
Stable Disease	1 (7.14)	1 (10%)	2 (8.3%)
Progressive Disease	2 (14.3%)	2 (20%)	4 (16.7%)
Total Patients Evaluated	14 (100%)	10 (100%)	24 (100%)
Pearson chi2 (3)=1.8555, P=0.603, Fisher's exact=0.703 Abbreviations: OV, Ocoxin-Viusid; RT, Radiotherapy; CT, Chemotherapy			

Table 9: Patient evaluation one year after beginning of study.

Patient Status	Experimental Group	Placebo Group	Total	p
Alive, n (%)	20 (66.67)	19 (63.33)	39 (65.00)	0.879
Dead, n (%)	10 (33.33)	10 (33.33)	20 (33.33)	1.000
Lost to Follow-Up	0 (0.00)	1 (3.33)	1 (1.67)	0.313
Total, n (%)	30 (100.00)	30 (100.00)	60 (100.00)	ns
Pearson chi2 (2)=1.0256, P=0.599, Fisher's exact=1.000				

Table 10: Patient status upon termination of study.

Post-treatment follow-up

A) After a year of patient inclusion: In Table 9, an evaluation of tumor diameter was performed using confirmation from contrast CAT imaging studies of the whole head and neck region that did not show differences (p=0.603) between the RT+CT+OV group (14 patients evaluated from a total of 30, of which 79% had a complete response) and the RT+CT+Placebo group (10 patients evaluated from a total of 30 with 60% 6/10 that achieved complete response). Patient status is summarized in Table 10 and was very similar between groups (p=0.599) upon conclusion of research, with 67% of patients living at the end of the year in the OV arm and 63% in the placebo arm.

B) Global survival rate: In Supplementary Figure 1, a similar average rate of survival between both groups is shown, keeping in mind the follow-up period of one year following the patients' date of inclusion; 67% were alive in the experimental group that received the OV nutritional supplement and 63% of the group that received placebo (Supplementary Table 1).

Discussion

Head and neck (H&N) cancer patients are generally diagnosed in locally advanced stages (III-IV) at over 50 years old and with associated chronic co-morbidities, a prior history of toxic habits such as smoking and ingestion of alcoholic beverages and varying levels of malnutrition by default, as well as psycho-socio-economic difficulties [7]. These patients require concomitant chemotherapy and radiotherapy treatment that produces toxicities that usually interfere with the administration of these anti-neoplastic treatments at radical doses within the established treatment interval, which affects their quality of life, which coincides with the majority of the results of this study. Therefore, the study of maintenance therapies in order to improve tolerance to anti-neoplastic treatments shall continue.

The adverse effects of radiotherapy are associated with cellular oxidation processes, which increase reactive oxygen species and reduce antioxidant levels in the tissue and the resulting damage to the surrounding healthy cells.

There is proof of a decrease in the plasma levels of some antioxidant vitamins and minerals in patients during radiotherapy [37-39].

Over the last several years, multiple studies have been conducted, including clinical trials aimed at evaluating the feasibility of administrating antioxidant vitamins to counteract RT and CT toxicities by protecting healthy tissues from the damaging effects of the free radicals generated during their cytotoxic anti-tumor mechanism of action without protecting the tumor cells, but there is insufficient evidence to demonstrate possible interference of antioxidants with the radio-chemotherapy action mechanism [40].

Among the substances with the greatest potential to modulate cellular antioxidant defenses and promote radio sensitivity are antioxidating vitamins C, E, beta-carotene, tetrahydrobiopterin (BH4) and g-tocotrienol. However, the convenience of administering this antioxidant during anti-neoplastic treatment continues to be controversial and not well-defined for two fundamental reasons [40].

1. Antioxidants may increase the efficacy of radiotherapy through a direct inhibiting effect on the growth of tumor cells, allowing administration of larger doses to the tumor, thanks to the radioprotective effect to normal tissues. In addition, they may have a radiosensitising effect on malignant cells.

2. Antioxidants may diminish the efficacy of radiotherapy, due to elimination of free radicals or reactive oxygen species induced by radiotherapy, both in normal tissues and tumor cells.

The protection given by these anti-oxidant vitamins is dependent on their concentration and only occurs in micromolar and sub micromolar concentrations, which suggests that lower concentrations may have a radioprotective effect on tumor cells, while at the same time, higher concentrations of vitamins would only increase the efficacy of radiotherapy as they increase radio-induced apoptosis on tumor cells [41].

Evidence from some researchers suggesting that administration of pharmaceutical doses of antioxidants may protect the tumor, thus diminishing the anti-tumor effects of oncological therapies, is still very limited [18,42,43]. Nonetheless, the majority of current research is focused on the study of antioxidant dosage and time of administration, that is, prior/during/after anti-neoplastic treatment, as well as antioxidant type, anti-tumor therapy agent and tumor type [19], indicating that antioxidants increase the anti-tumor effect of radiotherapy, as they improve tumor's response to treatment by decreasing radio-induced toxicities [44].

Bairati [45] reported the results of a randomized double-blind trial of 540 patients for the purpose of evaluating the effects of a supplement with alpha-tocopherol and beta-carotene during and after head and neck radiotherapy, which concluded that there was a reduction in radiotoxicities but an increase in local recurrence due to a potential decrease in the effects of radiotherapy. On the other hand, to this end Simone [46,47] published very encouraging results, with a randomized clinical trial that concluded that antioxidant vitamins reduce radiotoxicities without interfering with the anti-tumor mechanisms of action in radiotherapy and chemotherapy, and even boost the mechanism of apoptosis and increase the cytotoxic effects of certain cytostatic.

OV does not include antioxidants β-carotene and α-tocopherol in its components (Table 1), which have been thoroughly studied in meta-analyses with apparently unsatisfactory results regarding malignant tumor control during RT and CT oncological treatments [45]. Omenn GS [48] performed a randomized trial of 18,314 patients with high risk factors for development of lung cancer to evaluate the efficacy of administering carotene and retinol, an A vitamin that acts as an antioxidant in microenvironments with low oxygen concentrations. The research was stopped early on due to finding that the group receiving the supplement experienced an increase in incidence and mortality from lung cancer as compared to the group that received the placebo; it was interpreted that this was partially due to the pro-oxidant nature of β-carotene in high doses or oxygen-rich environments (the lungs) [49]. There is an interesting randomized trial performed by Ferreira [50] in 54 patients with cancer of the oral cavity and oropharynx evaluating the effect of tocopherol (daily mouthwash solution) during head and neck radiotherapy, the results of which showed a significant increase in mucositis without addressing the local recurrence rate and a decrease in the overall survival rate of the experimental arm, although this group had a greater number of patients with advanced disease.

Several meta-analysis studies pinpoint the oropharynx as the primary site with the greatest incidence of cancer in the H&N region and the highest frequency of diagnosis in locally advanced stages [5,7], which coincides with the data obtained from the small group of patients in this study.

Re-irradiation of head and neck tumors requires great complexity in planning high-tech techniques, such as three-dimensional (3D) conformal and intensity-modulated radiotherapy (IMRT) and administration of treatment using the latest linear accelerator equipment with the possibility of image-guided radiotherapy. This is in order to achieve high radical doses to the tumor region with maximum protection of the surrounding healthy tissues previously irradiated with the maximum tolerable dose. These treatments, therefore, specify very strict dose limits (constrains) to at-risk organs [7,51,52] in order to achieve the desired therapeutic doses without interruption to radiotherapy due to minor toxicities. In this series, there were 3 patients with re-irradiation who all belonged to the RT+CT+OV arm and who reached the maximum dose planned without interruptions (except one case who was suspended for 7 days due to grade II radiomucositis) within an acceptable therapeutic interval using 3D RT on linear accelerator equipment without planning for IMRT nor image-guided radiation therapy (IGRT).

No significant difference was shown in this study between the treatment arms in relation to the anti-tumor response during the post radiotherapy evaluation: at 4-6 weeks, a complete response was present in 10/30 patients (33%) of the OV arm and 11/30 (41%) in the placebo arm. At the one-year evaluation, complete response had been obtained by 11 of 14 patients (79%) evaluated in the OV group) and by 6 of 10 patients (60%) evaluated in the placebo arm, which could be due to the low patient sample number, but also suggests non-interference by OV in the RT and CT mechanisms of action [26,53,54]. It should be pointed out that self-administration of the nutritional supplement by the patients (who had toxic habits: alcoholics and irresponsible attitudes) was very irregular, at insufficient doses, and without an established system, which could have decreased OV effectiveness; some even continued with their alcohol-smoking toxic habits during radiotherapy.

However, statistical differences were demonstrated in favour of the RT+CT+OV group, where despite the fact that 67% of the patients received RT on Co60 equipment with 2D techniques (lower cytoprotection of healthy tissue), they presented with a lower severity of RT+CT treatment toxicities, as well as a lower number and duration

of interruptions in radiotherapy, a shorter therapeutic interval (half of the patients that received OV completed RT without interruptions within the 7 weeks established by the protocol, which coincides with the standards recommended in the specialized literature [7]. This could suggest that OV has a radioprotective effect for healthy cells against the oxidative damage caused by anti-neoplastic therapy, the same as the reports by Lamson [18] when studying antioxidants during oncological therapy. In addition, the RT+CT+Placebo group registered a greater number and severity of complications from radiotherapy, of which 17% (5/30) required hospitalization for placement of enteral tubes (nasogastric probe or gastrostomy) and tracheotomies due to severe complications, with prolonged therapeutic radiotherapy intervals greater than 10 weeks due to the extensive duration of frequent interruptions to CT+RT.

The OV experimental product showed safety in administration as no adverse reactions were recorded for the nutritional supplement, which is reported in pre-clinical and clinical studies [15,23-32].

Quality of life showed a significant improvement in the OV group when comparing the start and end of RT in relation to important symptoms such as asthenia, nausea, vomiting and pain (Table 8), which allowed for greater tolerance to radiotherapy in this experimental treatment arm. These results coincide with studies that found a reduction of radio-induced toxicities using concomitant administration of antioxidants during radiotherapy [55-58].

Although overall survival rate was not the objective of this study due to diverse patients in different clinical stages and locations of primary H&N cancer, it was very similar in both groups after an average follow-up period of 12 months, with 60% of individuals alive at one year, which corresponds to the literature in regards to low survival rates of patients in advanced stages of head and neck cancer 7, since in our study, 85% (51/60) of all patients were diagnosed in locally advanced stages III-IV.

Conclusion

Administration of the ocoxin-viusid nutritional supplement during radiotherapy or concomitant with chemotherapy, improves the quality of life of patients as it decreases the number and level of toxicities from these treatments without interfering with their mechanism of action. Continuing research related to the synergistic effect of antioxidants during RT and CT in cancer patients, emphasizing the mechanisms of action on healthy and tumor cells and oxidative stress, as well as evaluating different types of antioxidants and their recommended doses based on the type of tissue affected by the tumor, along with meta-analysis studies, hopefully can clear up a still very controversial subject.

Author's contributions

Ivonne Chon Rivas, José Alert Silva, Gagmar Alfonso, Helga Candanedo, Yelena Cuervo, Braulio Mestre, Johannes R. Mestre Cabello, Juan Lence, Martha Lugoyo and Eduardo Sanz were involved in the study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and statistical analysis. They approved the final draft submitted.

References

1. Globocan (2000) Cancer incidence, mortality and prevalence worldwide, Version 1.0. IARC Cancer base No. 5. Lyon, 2001 IARC Press.
2. Stewart BW, Kleihues PE (2003) World cancer report. Lyon, France, International agency for research on cancer press.
3. Data from the National Cancer Registry of Cuba.
4. Data from the National Registry of Cancer and Hospital Registry INOR.
5. De Vita V, Hellman S, Rosemberg S (2008) Cancer: Principles and practice of oncology. 8th (Eds.) New York: Lippincott Williams & Wilkins.
6. Marin Caro MM, Laviano A, Pichard C (2007) Nutritional intervention and quality of life in adult oncology patients. Clin Nutr 26: 289-301.
7. Edward H, Carlos P, Luther B (2008) Principles and practice of radiation oncology. 5th (Eds.) New York: Lippincott Williams & Wilkins.
8. Koukourakis MI (2003) Amifostine: Is there evidence of tumor protection? Semin Oncol 30: 18-30.
9. Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, et al. (2000) Phase III randomized trial of Amifostine as a radioprotector in head and neck cancer. J Clin Oncol 18: 3339-3345.
10. Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N, et al. (2002) Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 52: 739-747.
11. Bardia A, Tleyjeh IM, Cerhan JR, Sood AK, Limburg PJ, et al. (2008) Efficacy of antioxidant supplementation in reducing primary cancer incidence and mortality: Systematic review and meta-analysis. Mayo Clin Proc 83: 23-34.
12. Lamson DW, Brignall MS (2001) Natural agents in the prevention of cancer, part two: Preclinical data and chemoprevention for common cancers. Altern Med Rev 6: 167-187.
13. Gonzalez MJ, RiordanNH, Matos MI, Argüelles M (1997) Antioxidants and cancer: A brief discussion on controversies, contradictions and paradoxes. J Orthomol Med 12: 145-148.
14. Prasad KN, Cole WC (2006) Antioxidants in chemotherapy. J ClinOncol 24: 8-9.
15. Màrquez J, Mena J, Hernandez-Unzueta I, Benedicto A, Sanz E, et al. (2016) Ocoxin oral solution slows down tumor growth in an experimental model of colorectal cancer metastasis to the liver in Balb/c mice. Oncol Rep 35: 1265-1272.
16. Rodriguez MJ, Bouyon A, Alexandre J (2009) Role of antioxidant complements and supplements in oncology in addition to an equilibrate regimen: A systematic review. Bull Cancer 96: 677-684.
17. Gómez-Candela C, Rodríguez L, Luengo L, Zamora P, Celaya S, et al. (2003) Nutritional intervention in the adult cancer patient. Barcelona. Editorial Glosa.
18. Lamson DW, Brignall MS (1999) Antioxidants in cancer therapy; their actions and interactions with oncologic therapies. Altern Med Rev 4: 304-329.
19. Lamson DW, Brignall MS (2000) Antioxidants and cancer therapy II: Quick reference guide. AlternMed Rev 5: 152-163.
20. Mahdavi R, Faramarzi E, Sevedrezazadeh E, Mohammad-Zadeh M, Pourmoghaddam M (2009) Evaluation of oxidative stress, antioxidant status and serum vitamin C levels in cancer patients. Biol Trace Elem Res 130: 1-6.
21. Hernàndez I, Benedicto A, Olaso E, Sanz E, Viera C, et al. (2017) Ocoxin oral solution as a complement to irinotecan chemotherapy in the metastatic progression of colorectal cancer to the liver. Oncol Lett 13: 4002-4012.
22. Díaz-Rodríguez E, Hernández-García S, Sanz E, Pandiella A (2016) Antitumoral effect of Ocoxin on acute myeloid leukemia. Oncotraget 7: 6231-6242.
23. Al-Mahtab M, Akbar SM, Khan MS, Rahman S (2015) Increased survival of patients with end-stage hepatocellular carcinoma due to intake of Ocoxin, a dietary supplement. Indian J Cancer 52: 443-446.

24. Hernández-García S, González V, Sanz E, Pandiella A (2015) Effect of Ocoxin oral solution in HER2-Overexpressing breast cancer. Nutr Cancer 67: 1159-1169.
25. Uddin DMA, Mahmood I, Ghosha AK, Khatuns RA, Kundu S (2009) Findings of the 3-Month supportive treatment with ocoxin solution beside the standard modalities of patients with different neoplastic diseases. TAJ 22: 172-175.
26. Garg AK, Buchholz TA, Aggarwal BB (2007) Chemosensitization and Radiosensitization of tumors by plant polyphenols. Antioxid Redox Signal 7: 1630-1647.
27. Peng G, Dixon DA, Muga SJ, Smith TJ, Wargovich MJ (2006) Green tea polyphenol Epigallocatechin-3-gallate inhibits cyclooxygenasa-2 expression in colon carcinogenesis. Mol Carcinog 45: 309-319.
28. Roomi MW, Ivanov V, Kalinovsky T, Niedzwiecki A, Rath M (2005) In vivo antitumor effect of ascorbic acid, lysine,proline and green tea extract on human colon cancer cell HCT 116 xenografts in nude mice: Evaluation of tumor growth and immunohistochemistry. Oncol Rep 13: 421-425.
29. Annabi B, Currie JC, Moghrabi A, Béliveau R (2007) Inhibition of HuR and MMP-9 expression in macrophage-differentiated HL-60 myeloid leukemia cells by green tea polyphenol EGCg. Leuk Res 31: 1277-1284.
30. Zhao X, Tian H, Ma X, Li L (2006) Epigallocatechin gallate, the main ingredient of green tea induces apoptosis in breast cancer cells. Front Biosci 11: 2428-2433.
31. Vermorken JB (2005) Medical treatment in head and neck cancer. Ann Oncol 16: 258-264.
32. Bentzen SM, Dorr W, Anscher MS, Denham JW, Hauer-Jensen M, et al. (2003) Normal tissue effects: Reporting and analysis. Semin Radiat Oncol 13: 189-202.
33. De Rycke Y, Kramar A (1999) Program for calculating the number of subjects needed (nPII: Plan in a Fleming stage). Version 0.15. Medical Section of the Institut Curie, Paris.
34. Lehmann EL (1998) Nonparametric: Statistical methods based on ranks. 1era (eds.) Universidad de California, Berkeley. Ed. Prentice Hall, New Jersey.
35. Guren MG, Tobiassen LB, Trygg KU, Drevon CA, Dueland S (2006) Dietary intake and nutritional indicators are transiently compromised during radiotherapy for rectal cancer. Eur J Clin Nutr 60: 113-119.
36. Matos A, Nogueira C, Franca C, Carvalho A, Lannes Vieira S, et al. (2014) The relationship between serum vitamin A and breast cancer staging before and after radiotherapy. Nutr Hosp 29: 136-139.
37. Franca CA, Nogueira CR, Ramalho A, Carvalho AC, Vieira SL, et al. (2011) Serum levels of selenium in patients with breast cancer before and after treatment of external beam radiotherapy. Ann Oncol 22: 1109-1112.
38. Mumtaz A, Shabeer A, Reyhan A, Mahmood A, Mahmood S (2017) Antioxidant supplementation: A linchpin in radiation-induced enteritis. Technol Cancer Res Treat 16: 676-691.
39. Miller AL (1999) Should antioxidants be used in cancer therapy?. Altern Med Rev 4: 303.
40. Labriola D, Livingston R (1999) Possible interactions between dietary antioxidants and chemotherapy. Oncology (Williston Park) 13: 1003-1008.
41. Moding EJ, Kastan MB, Kirsch DG (2013) Strategies for optimizing the response of cancer and normal tissues to radiation. Nat Rev Drug Discov 12: 526-542.
42. Lobo V, Patil A, Phatak A, Chandra N (2010) Free radicals, antioxidants and functional foods: impact on human health. Pharmacogn Rev 4: 118-126.
43. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, et al. (2005) Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. J Clin Oncol 23: 5805-5813.
44. Simone CB, Simone NL, Simone V, Simone CB (2007) Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 1. Altern Ther Health Med 13: 22-28.
45. Simone CB, Simone NL, Simone V, Simone CB (2007) Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 2. Altern Ther Health Med 13: 40-46.
46. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, et al. (1996) Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. J Natl Cancer Inst 88: 1550-1559.
47. Palozza P, Serini S, Di Nicuolo F, Piccioni E, Calviello G (2003) Prooxidant effects of betacarotene in cultured cells. Mol Aspects Med 24: 353-362.
48. Ferreira PR, Fleck JF, Diehl A, Barletta D, Braga-Filho A, et al. (2004) Protective effect of alphatocopherol in head and neck cancer radiation-induced mucositis: A double blind randomized trial. Head Neck 26: 313-321.
49. Parsons J (1994) The effect of radiation on normal tissues of the head and neck. In: Million R, Cassisi N. Management of head and neck cancer: A multidisciplinary approach, JB Lippincott, Philadelphia pp: 245-289.
50. Trotti A (2000) Toxicity in head and neck cancer: A review of trends and issues. Int J Radiat Oncol Biol Phys 47: 1-12.
51. Guerrero l, Maldonado M, Calderón J (2016) The paradox of the use of antioxidants during cancer treatment: Protect the body from the toxic effects of antineoplastics would decrease the pharmacological efficacy to prevent the development of cancer?. J Biochem Educ (REB) 35: 71-88.
52. Álvarez K, Mendoza A, Carcoba C, García-García J, Fuchs-Tarlovsky V (2016) Antioxidant supplementation during oncology treatment has no effect on cervical cancer recurrence. Nutr Hosp 33: 411-414.
53. Luna J, Amaya E, Torres M, Pena M, Prieto I (2015) Nutrients and radiotherapy: Review of the literature. Nutr Hosp 32: 2446-2459.
54. Hall S, Rudrawar S, Zunk M, Bernaitis N, Arora D, et al. (2016) Protection against radiotherapy-Induced toxicity. Antioxidants 5: 22.
55. Fuchs-Tarlovsky V (2013) Role of antioxidants in cancer therapy. Nutrition 29: 15-21.
56. Amber KT, Shiman MI, Badiavas EV (2014) The use of antioxidants in radiotherapy-Induced skin toxicity. Integr Cancer Ther 13: 38-45.
57. Faria A, Coriat J, Rueda M, Cardona C, Rosselli D (2017) Nutritional supplements as modifiers of morbidity and mortality in patients with cancer. Latin American Nutrition Files p: 67.
58. Singh K, Bhori M, Arfat Y, Bhat G, Marar T (2018) Antioxidants as precision weapons in war against cancer chemotherapy induced toxicity-Exploring the armoury of obscurity. Saudi Pharm J 26: 177-190.

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