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Trabajo Original

Epidemiología y dietética

Antioxidant supplementation during oncology treatment has no effect on cervical cancer recurrence

La suplementación con antioxidantes durante el tratamiento oncológico no tiene efecto sobre la recurrencia de cáncer cervicouterino

Karolina Álvarez-Altamirano[1], Alma Nubia Mendoza-Hernández[2], Carolina Carcoba-Tenorio[3], José Antonio García-García[1] and Vanessa Fuchs-Tarlovsky[1]

[1]Hospital General de México. [2]Facultad de Nutrición. Universidad Popular Autónoma del Estado de Puebla. Puebla. México. [3]Universidad Anahuac del Norte. Huixquilucan. México

Abstract

Introduction and aim: Antioxidant therapy with chemotherapy and radiotherapy in cervical cancer patients is controversial. While some evidence suggests that the use of antioxidants diminishes side effects from anticancer therapy, there is also data to suggest that antioxidants increase the risk of recurrence by affecting oncology treatments.

Methods: We conducted a controlled clinical trial in cervical cancer patients supplemented with an antioxidant mixture or a placebo during four years after their antineoplastic treatment was completed and the effect on recurrence. We also conducted data on used hemoglobin and albumin levels. Differences between groups were analyzed using chi-square test. Survival was calculated by the Multivariate COX regression with omnibus test and the enter method.

Results: 103 treated patients were in clinical stages IIB and IIIB of cervical cancer, 48% (n = 49) of the patients were treated with antioxidant supplementation and 52% (n =54) of the patients were in the placebo group. Of the original 103 patients, were able to follow up on 88 patients for an additional four years. 23.9% (n = 21) of the patients presented cancer recurrence and 76.1% (n = 67) did not, 21.6% (n = 19) patients showed metastasis. 8% (n = 7) patients were in the antioxidant group and 15.9% (n = 14) were in the placebo group ($p > 0.05$).

Regarding implications of cancer survivors, antioxidant supplementation apparently seems not to have interference with recurrence in cervical cancer patients but there is not enough evidence to prove it. A different dosage may have the expected effect; however, further studies with another dosage and criteria are necessary.

Conclusions: Supplementation with antioxidants during treatment of cervical cancer has no effect on cancer recurrence after 4 years of follow-up.

Key words:

Cervical cancer. Recurrence. Antioxidant supplementation.

Resumen

Introducción y objetivos: la terapia con antioxidantes durante la quimioterapia y radioterapia en pacientes con cáncer cervicouterino es controvertida. Mientras existe evidencia que sugiere que el uso de antioxidantes disminuye los efectos secundarios propios del tratamiento contra el cáncer, hay datos que sugieren que los antioxidantes incrementan el riesgo de recurrencia de cáncer por la afectación de la terapia de los tratamientos.

Métodos: se dirigió un estudio clínico controlado en pacientes con cáncer cervicouterino que fueron suplementados con una mezcla de antioxidantes o placebo, con seguimiento por 4 años posteriores al término de su tratamiento antineoplásico para evaluar el efecto de los antioxidantes en la recurrencia. Tomamos datos de niveles de hemoglobina y albúmina. Se analizaron las diferencias entre grupos con la prueba de Chi-cuadrado, la sobrevida se calculó con un análisis multivariado por medio de regresión de COX.

Resultados: se dio seguimiento a 103 pacientes con cáncer cervicouterino en etapa clínica IIB y IIIB de los cuales 48% fueron tratados con suplementación de antioxidantes y el 52% con placebo, originalmente y de estos se dio seguimiento a 88 pacientes durante 4 años. El 23,9% de los pacientes tratados presentaron recurrencia por cáncer mientras que el 76,1% no la presentó. El 21,6% de los pacientes presentaron metástasis, el 8% de los pacientes perteneció al grupo de antioxidantes y el 15,9% al grupo placebo ($p > 0,05$). *Implicaciones para los pacientes supervivientes:* la suplementación con antioxidantes aparentemente no interfiere con la recurrencia por cáncer, sin embargo no hay evidencia suficiente para probarlo. Posiblemente una dosis distinta sea la clave para un mejor efecto, pero serán necesarios futuros estudios que prueben efectos sobre otro tipo de dosis.

Conclusiones: la suplementación con antioxidantes durante el tratamiento de pacientes con cáncer cervicouterino no tiene efectos en la recurrencia por cáncer a 4 años de seguimiento.

Palabras clave:

Cáncer cervicouterino. Recurrencia. Suplementación con antioxidantes.

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Correspondence:

Vanessa Fuchs. Servicio de Oncología. Hospital General de México. Pabellón 111. Doctor Balmis No. 148, Col. Doctores. Del. Cuauhtémoc. ZIP 06726 México, D.F.
e-mail: vanessafuchs@hotmail.com

INTRODUCTION

Cervical cancer is characterized by cellular alterations originating in the cervical epithelium. Initial manifestations are lesions of slow and progressive evolution, which may be present in mild, moderate and severe stages. These may evolve into cancer *in situ* (*i.e.,* confined to the epithelial surface) or invasive cancer, which surpasses the basal membrane (1). Cervical cancer is the second most common cancer in women worldwide (2). Among Mexican women, it is the second type of cancer just after breast cancer and it is also the second cause of death with a rate of 7.9% among women with cancer (2,3). The type of oncology treatment for cervical cancer depends on its clinical stage and the extension of the lesion; it can be a combination of chemotherapy, radiotherapy and surgery (1,4). These days, there is still controversy on the use of antioxidants during the oncology treatment (5,6). Antioxidants provide protection to tissues and cells against oxidative stress caused by free radicals that, in turn, are augmented during antineoplastic treatment (7). These free radicals have mechanisms that damage proteins, lipids and cellular DNA. Antioxidant capacity may be jeopardized due to an increased oxidative stress and injury can occur to healthy cells (8). Oncology treatments cause toxicity and oxidative stress and the use of antioxidants can be related to having a protective effect on healthy cells (9-12). On the other hand, it has been argued that antioxidants can reduce the effect of free radicals intended to damage cancerous cells, which could interfere with the efficacy of cancer therapy (12,13).

Several preclinical studies, clinical trials and meta-analysis have concluded that the antioxidant supplementation does not interfere with cancer therapy, and may offer a positive alternative in terms of toxicity and protection of healthy cells and on the other hand also there are papers that avoid antioxidant supplementation (9-12). Clinical studies have shown that vitamin C and E reduced the incidence and severity of cell damage caused by radiation therapy as well as having a positive effect on tissue regeneration and functional improvement on the treatment of chronic radiation proctitis (14-15). The consumption of beta-carotene has been shown to reduce cancer recurrence and thus provides protection for the survival of patients (16-18). Patients with early diagnosis of cervical cancer can receive opportune treatment with a survival rate of around 93% in five years, but this percentage decrease in advanced stages down to 30% or less (19). The survival of patients with cervical cancer is strongly influenced by the socioeconomic factor, which is reflected in the accessibility that patients may have to different programs for prevention and detection. Thus, cancer treatment and its repercussions or injury have a major impact on public health (20-21). Given that the evidence of positive or negative antioxidant supplementation effect is not consistent, the aim of this study is to ascertain the late effect of an antioxidant supplement on the recurrence of cervical cancer four years after completion of cancer therapy.

MATERIALS AND METHODS

A single blinded randomized clinical trial was performed between September 2007 and 2008 and all enrolled patients signed an informed consent before to the participation in the study. Patients with a histologically proven diagnosis of cervical cancer and patients with surgical treatment after diagnosis were not included in the study. All patients were randomly assigned to receive supplementation with an antioxidant supplement or a placebo during antineoplastic treatment with chemotherapy and radiotherapy and were following up for 4 years after treatment or up to presented cancer recurrence.

Both groups of patients received 25 radiotherapy sessions in a dosage of 50 Gy and concomitant chemotherapy with cisplatin in a dosage of 40 mg/m^2. At the same time patients were supplemented with a daily capsule of a mixture of antioxidants and placebo during oncology treatment; compositions are described in table I. To assure single blind, the supplement and placebo capsules were given to patients in a purple capsule for both groups and the only difference was in composition.

Four years after completion of anticancer therapy all patients were followed by medical appointment or phone call and with the revision of their clinical record. The incidence of recurrence and metastasis was documented after antineoplastic treatment. Recurrence was assessed from the end of treatment to the detection of tumor in the original or to another place in the body. Metastasis was determined in the revision of the clinical record of patient.

The study complied with the guidelines stated in the Declaration of Helsinki and the General Health Law. All data collected from the patients clinical records were handled confidentially. Names or other personal data of patients were not reported.

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Table I. Antioxidant and placebo composition of the supplement administered to both groups

Supplement composition	
β-carotene 30%	Equivalent to 4.80 mg of β-carotene
Ascorbic acid (vitamin C)	200 mg
L α-tocoferol acetate (vitamin E)	200 U.I.
Selenium yeast	Equivalent to 50 mcg of selenium
Zinc oxide	Equivalent to 15 mg of zinc
Ginkgo biloba extract (standarized to 24% of glucosides)	40 mg
Panax ginseng extract (standarized to 5.3% of ginsenosides)	40 mg
Placebo composition	
Granulated sugar	10 mg

the clinical field to develop this study. Authors established disclosure statements on this study, without existence of either financial or professional conflicts of interest.

STATISTICAL ANALYSIS

Sample size was calculated in the initial trial with 80% of power with different proportions in the formula. To describe all data, we used percentages in case of qualitative variables and quantitative continued variables were presented with mean, deviation standard and confidence intervals with 95% of power (IC 95%). To analyze inferential statistics we used statistical package SPSS (Statistical Product and Service Solution) version.21.0, (IBM Innovation Centers®, IL, USA). To compare proportions of recurrence in patients between the supplemented group and the placebo group we used the Chi-square test. A survival analysis was conducted using the Multivariate Cox regression curves using Enter method with the Omnibus test.

RESULTS

In the previous study a total of 103 patients with cervical cancer were evaluated and divided in 2 groups: 48% (n = 49) with antioxidant supplementation and 52% (n = 54) with placebo. Only 88 patients were available for 4 year follow-up: 47.7% (n = 42) patients received antioxidants and 52.3% (n = 46) received placebo. However, 14 patients did not return to medical monitoring or were not located because most of them live in rural areas where access to phone or other way of communication to complete the study was not possible.

The average age in the antioxidant group was 48.76 years (± 10.56 years), the average age in the placebo group was 48.04 years (± 12.74 years). No significant differences between ages of both groups were found (p = 0.775). Clinical stages of patients were reported between IIB and IIIB, none of the patients was in an advanced stage in the initial intervention with antioxidants.

After the 4 year follow up, only 23.9% (n = 21) of patients presented local recurrence and 76.1% (n = 67) did not; out of these 8% (n = 7) were supplemented and 15.9% (n = 14) received placebo. Chi-square test was measured to determine the association between patients with recurrence and type of supplementation but these results showed no statistical differences between groups (p = 0.176). Metastasis was present in 21.6% (n = 19) of patients, out of which 11.4% (n = 10) were part of the antioxidant supplementation group and 10.2% (n = 9) were part of the placebo group. There was no differences between groups (p = 0.629). However patients with both conditions recurrence and metastasis showed in table II indicate that are positively related.

The survival of patients was calculated with the number of months of duration since the end of the antineoplastic treatment and up to the presence of recurrence in patients. The Multivariate COX regression curves for cancer recurrence after receiving antioxidant supplementation in figure 1 showed that recurrence between groups has no statistical differences ($\chi^2 = 2.388$; p = 0.303).

DISCUSSION

Treatment success for cancer depends on the well-executed application of chemotherapy, radiotherapy and surgical procedures. In addition, it is important to consider that recurrence is influenced or determined by other causes and major risk factors such as obesity and smoking, which have been described in literature. Hence, it is important to provide clinical alternatives that offer a protective effect in the short and long term (4-18).

The results of our past study in patients showed no differences in cancer recurrence or metastases after antioxidants supplements or placebo during oncology therapy (22). This supports other publications showing that antioxidants during cancer treatment therapy do not interfere with the efficacy of chemotherapy and radiotherapy, so no influence in recurrence was shown (10,18,23-24). Our study found increased survival in the group who was supplemented with antioxidants during oncology treatment four years before.

The results between groups seem to suggest that antioxidant supplementation did not shown a negative long term effect in

Table II. Incidence of recurrence and metastasis in patients with cervical cancer

		Metastasis		Total
		Yes	No	
Recurrence	Yes	70.5% (62)	5.7% (5)	76.1% (67)
	No	8.0% (7)	15.9% (14)	23.9% (21)
	Total	78.4% (69)	21.6% (19)	100.0% (88)

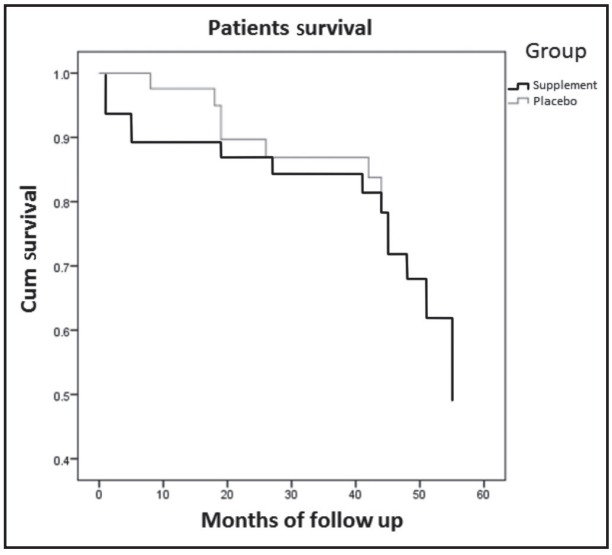

Figure 1.

Cox-Regression curves of cancer survival after receiving antioxidants supplementation during oncology treatment.

cancer recurrence, compared to the placebo group, but short term effect was the decrease of oxidative stress in supplemented patients when their radiotherapy and chemotherapy treatment concluded (18-25).

As cervical cancer is one of the most important health problems in Mexico, we suggest that patients should be continually monitored to provide greater protection against cancer recurrence and maintenance of the health status of patients (3,4,14).

CONCLUSION

In patient with cervical cancer during treatment antioxidant supplementation did not show any benefit. Additionally survival and mortality rates were not affected.

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