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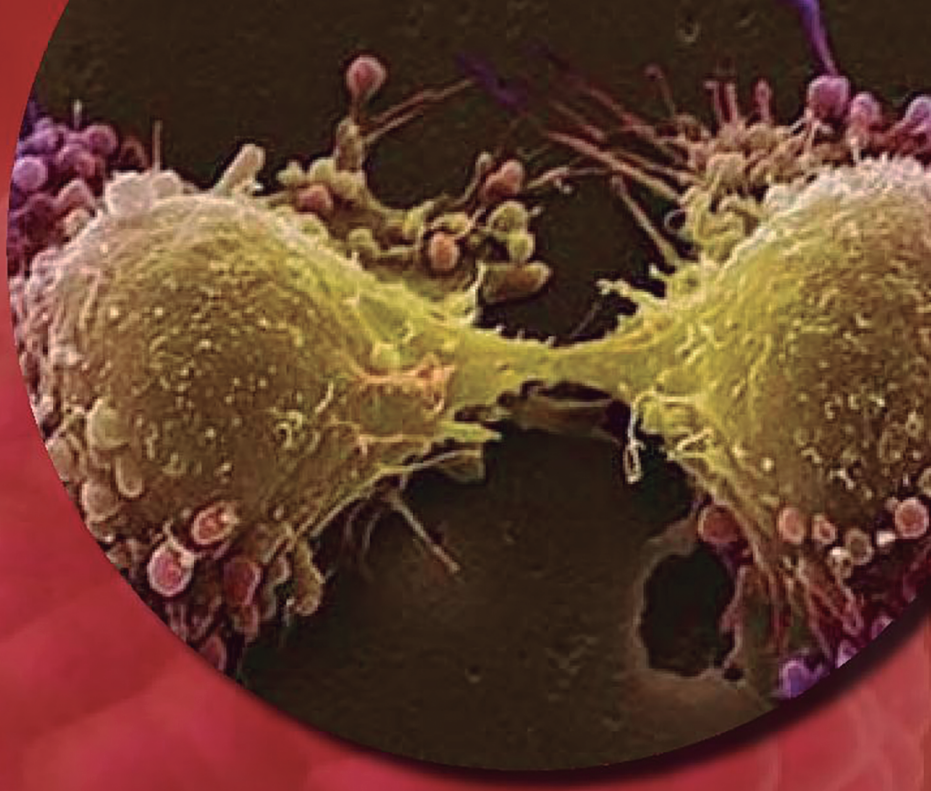

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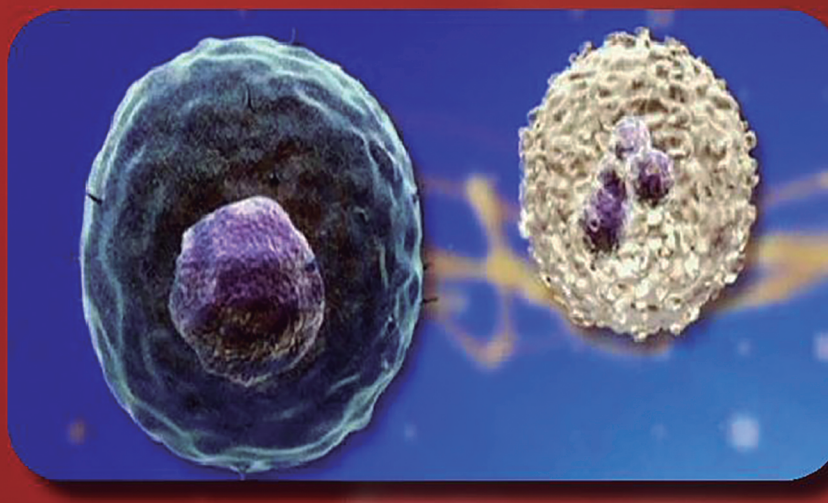

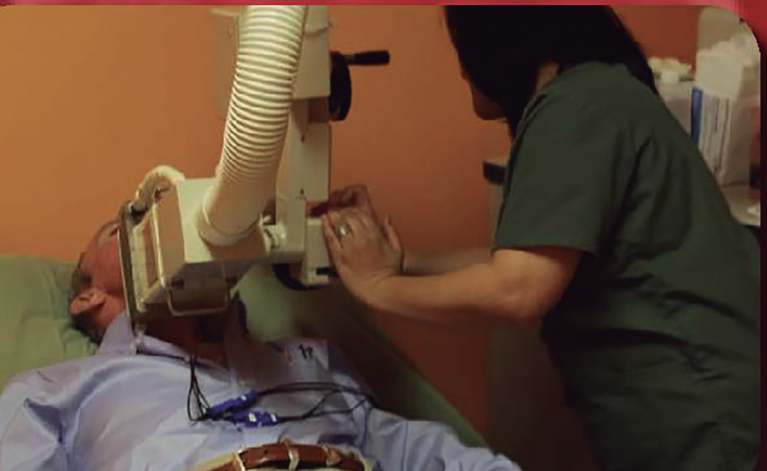

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Efficacy and Safety of Oncoxin-Viusid, a Nutritional Supplement, in Twenty Patients with Stage IIB-III of Cutaneous Melanoma: An open-Label Proof of Concept Study

Olaine R. Gray Lovio[1]*, Alfredo Abreu Daniel[2], Liset A. García Yánez[2], Marta Osorio Rodríguez[3], Carlos Vásquez González[3], Juan J. Lence Anta[4] and Eduardo Sanz[5]

[1]*Department of Dermatology and Infectious Diseases, Manuel Fajardo University Hospital, La Habana, Cuba*
[2]*Department of Dermatology, Manuel Fajardo University Hospital, La Habana, Cuba*
[3]*Department of Oncology, National Institute of Oncology (INOR), La Habana, Cuba*
[4]*Department of Biostatistics, National Institute of Oncology (INOR), La Habana, Cuba*
[5]*Scientific Department, Catalysis Unit, S.L., Madrid, Spain*

Abstract

Objective: Surgery is the treatment of choice of melanoma, but in advanced stages, it is often necessary to combine this with other therapeutic options. Oncoxin-Viusid has demonstrated antitumor and immunomodulating effects in various type of cancers, in addition to boosting the antiproliferative effect of standard chemotherapy agents in experimental studies. Our study was aimed to identify the efficacy and safety of the Oncoxin-Viusid as an adjuvant treatment for patients with stage IIB-III cutaneous melanomas.

Methods: From September 2014 to June 2017, a proof of concept, open label nonrandomized and uncontrolled study was conducted at the Manuel Fajardo University Hospital (Havana, Cuba), including 20 patients with histologically confirmed diagnosis of stage IIB-III of primary cutaneous melanoma. All patients received surgical treatment with or without chemotherapy in combination with Oncoxin-Viusid 25 ml twice a day for 1 year. Progression-free survival rate with its 95% confidence interval was estimated after one year of inclusion and quality of life was measured at inclusion and after a year using QLQ-C-30 EORTC questionnaire.

Results: Most of the patients were women with a median age of 59 years, cutaneous phototypes II-III, occupations without photo exposure, without personal history of skin cancer or family of cutaneous melanoma. 40% of patients presented with superficial spreading melanoma, epithelioid presentation being histologically predominant. Adverse reactions were, for the most part, mild and short-lived. Only 2 patients progressed and one of them died. Two patients were early withdrawal to follow-up. The progression-free survival rate was 90% (95% CI: 0.65-0.97).

Conclusion: Nutritional supplement Oncoxin-Viusid showed safety; meanwhile patients kept a stable quality of life at the end of study and a high progression-free survival rate.

Keywords: Cutaneous melanoma; Nutritional supplement; Oncoxin-Viusid; Proof of concept; Quality of life

Introduction

Incidence rates of cutaneous cancers, including malignant melanomas, has risen worldwide along with the associated mortality rates, although the latter not as quickly as the former. The incidence rate of cutaneous melanoma increased approximately 3% annually over the last 30 years [1-3]. In New Zealand, it has increased by 50 new cases per 100 000 inhabitants each year [4]. In the United States, the estimated standardized incidence rates on 2018 was 21.6 and 13.2 in Europe [5]. Mortality worldwide is reported at close to 75-80% of all patients with melanoma [6,7].

In Latin America, cancer statistics are not exact, since many countries do not have a National Cancer Registry [1]. National Cancer Registry in Cuba reported between 92 and 138 new cases each year since 1990 to 2010, where it began to increase, reaching 176 in 2013 and 205 in 2014.

Now-a-days there is a growing interest in development of anticarcinogenic compounds that are capable of stopping or regressing the progression of melanoma [8] which has a high rate of local metastasis; regionally metastasizing to the lymphatic system and systemically tending towards the lungs, liver, brain, and bones. Surgery is the main treatment, with excellent results in early stages [9].

However, in advanced, high-risk, or metastatic stages, surgery alone is not enough, and although therapies have advanced in recent years, the existing options are limited, not very effective, highly toxic, and very costly. Among the systemic treatments available are interferon alfa-2b according to the Kirkwood schedule, which is a IIB-III melanoma adjuvant medication approved by the FDA in 1995 [3]. In addition, dacarbazine, interleukin 2, temozolamide, ipilimumab, vermurafenib, dabrafenib, trametinib, nivolumab, pembrolizumab and the combinations thereof are included.

This tumor has been shown to be, more than in other neoplasia, resistant to the different systemic therapies and radiotherapy. The reason could be that the cells it originates from are designed to protect

***Corresponding author:** Olaine R. Gray Lovio, Specialist in Dermatology, Master of Infectious Diseases, Department of Dermatology and Infectious Diseases, Manuel Fajardo University Hospital, La Habana, Cuba, Tel: +5378382593; E-mail: ogray@infomed.sld.cu

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the organism from damage to deoxyribonucleic acid (DNA) caused by the sun, locating themselves on the skin, where they are exposed to the damage caused to DNA by ultraviolet rays. These cells seem to have the ability to defend themselves when exposed to cytotoxic drugs, like how they defend themselves in the hostile environment in which they develop [10].

New studies include, with encouraging results, the by-products of medicinal plants, which have lessened side effects, low cytotoxicity, the ability to act against target cells [6]. An example of this was a study where epigallocatechin-3-gallate (EGCG) and dacarbazine reduced metastasis and tumor growth in mice with melanomas [6]. Lozada refers to the study of Coussens [11,12] where demonstrated the presence of growth factors, TNF-α and reactive oxygen species in the tumor microenvironment, which cause damage to the DNA and initiate neoplasia. Thus, the use of antioxidants has become significant according to some trends [6].

Phytochemical compounds, such as the catechins in green tea, can modify the epigenome and transcriptome of tumor cells [11]. Chemoprotective properties have been attributed to polyphenolic compounds. It is currently known that an association between cancer and diet exists. A possible physiopathological relationship has been described between cancer and lipid peroxidation. Therefore, preventing this process with the use of antioxidants such as polyphenols could be fundamental in the prevention of different types of malignant tumors. In addition, antioxidants from polyphenols may induce apoptosis of certain neoplastic cells and cause them to act as contributors to chemotherapeutic agents [13].

Among the main phenolic compounds with antioxidant capacity, the most frequently studied are quercetin and catechin, which are flavonol type phenolic compounds with antioxidant capacity. Quercetin has a wide spectrum of anti-carcinogenic properties, including inhibiting the growth of cancer-derived cells, in addition to suppressing the growth and development of cervical cancer, melanomas, and intestinal tumors. Catechin, which is present in green tea in large quantities, is effective in blocking the growth of human cell lines originating from cancers [13].

Some *in vitro* studies suggest that flavonoids may modulate the regulatory pathways involved in cell division, blood clotting, inflammation and immune response, and as such, their ingestion is important for promoting health in the human body. Flavonoids such as catechin, epicatechin, epigallocatechin gallate (EGCG) and epicatechin gallate, inhibit the production of free radicals due to the inhibition of hepatic xanthine oxidase. In particular, EGCG has demonstrated the ability to inhibit a series of proteins related to inflammation, which includes lipo-oxygenase, nitric oxide synthase, tumor necrosis factor-a and nuclear factor kB (NFkB) [14].

Activation of NFkB controls expression of a large number of pro-inflammatory genes, including cytokines, chemokines, and adhesion molecules. Green tea helps to prevent the occurrence of cancer blocking the formation of chemical carcinogens. Epidemiological studies suggest this role of flavonoids in cancer prevention, based in part on their antioxidant and anti-inflammatory capacities. Recently, it has been demonstrated that EGCG induces apoptosis in cell lines that have been transformed, but not in normal cells, an effect which could be partly mediated by differential induction of a kinase-dependent cyclin and an apoptosis inhibitor [14].

Oncoxin is a compound with a composition very similar to Oncoxin-Viusid, which has proven antitumour and immunomodulating effects, and is also effective in boosting the antiproliferative effect of standard chemotherapy agents in acute myeloid leukemia [15,16]. In addition, it has been used with good results on the progression of colorectal cancer to the liver and in early and late stages of hepatocellular [17-19] and breast [20] carcinomas.

In light of the above, our study was aimed to identify the efficacy and safety of the Oncoxin-Viusid nutritional supplement as an adjuvant treatment for patients with stage IIB-III malignant melanomas. Secondarily, we explored the quality of life of the patients at inclusion and after a year of treatment, and additionally calculated the progression-free survival rate at the end of the study.

Materials and Methods

A proof of concept, open label, non-controlled study in 20 adult patients with histologically-confirmed malignant cutaneous melanoma of stage IIB, IIC and III was performed in the Dermatology Department of the Manuel Fajardo University Hospital in Havana (Cuba) from September 2014 to June 2017, which met the following selection criteria:

Inclusion criteria

1. Patients with a histological diagnosis of malignant cutaneous melanoma of stage IIB, IIC and III.
2. Subjects over 18 years of age and of both genders.
3. General state of health ≥ 70 according to the Karnofsky Performance Scale.
4. Laboratory parameters within normal defined limits, such as:

   Blood count: Haemoglobin ≥ 9 g/L, Total Leukocytes ≥ 3×10^9 cells/L, Neutrophils ≥ 1.5×10^9 cells/L, Platelets ≥ 100×10^9/L.

   Liver count:Hepatic function: Within 2.5 times the upper normal limit and without hepatic disorders as demonstrated by GPT, GOT, alkaline phosphatase, Bilirubin.

   Renal function: Creatinine ≥ 132 μmol/l.
5. Normal electrocardiogram for patients under 60 years old and/or normal electrocardiogram for patients over 60 years old.
6. Women of reproductive age must have a negative pregnancy test and employ effective contraceptive methods, such as intrauterine devices, hormonal, contraceptives, barrier methods or tubal ligation.
7. Patients express their written voluntary desire to enter the study having signed the informed consent document.

Exclusion criteria are taken into consideration

1. Pregnancy or lactation.
2. Patients with a second concomitant tumour.
3. Presentation of an associated no compensates chronic disease (cardiopathies, diabetes and hypertension).
4. History of hypersensitivity to a similar product.
5. Severe acute allergic states.
6. Severe septic processes.
7. Patients where surgery was contraindicated,
8. Patients that are potentially at risk of not finishing the clinical trial

(those whoare going to be travelling during the clinical trial period or whose residence is far away, outside of the city, etc.).

9. Subjects who are participating in another clinical trial.
10. Patients with cognitive disorders or a mental disorder that complicates follow-up.

Interventions

The patients received conventional surgical treatment of the primary cutaneous melanoma, with margins in accordance with Breslow's depth, in conjunction with Oncoxin-Viusid 25 ml oral solution twice a day for one year (Table 1). From five patients staged as III two of them received adjuvant treatment with Interferon according to the Kirkwood schedule, another received Interferon according to the Kirkwood and after Paclitaxel and two received chemotherapy with Temozolomide.

Follow-up

All of the patients, whom finished the study, were evaluated monthly during year of treatment.

Product under study

The nutritional supplement Oncoxin-Viusid made by Laboratorios Catalysis, S.L. in Spain is a compound specially formulated using a molecular activation process without altering the chemical structure, which increases its biological activity. The chemical composition is summarized in Table 1 in attached.

Response variables for efficacy measurement

1. **Quality of life**: It is measured by the EORTC QLQ-C30 questionnaire [21].
2. **Progression-free survival rate:** Calculated according to the Kaplan-Meier estimator (time elapsed between diagnosis and appearance of a relapse or any symptom or sign of metastasis).

Statistical analysis

Patient socio-demographic and clinical characteristics were described 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 with causality associated with the product under investigation. In order to measure quality of life (QL), the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 Version 3.0 questionnaire (neutral Spanish) was used with the item scoring manual suggested by the EORTC [21].

Chemical component	Value
Green tea extract	25 mg
Glycine	2000 mg
Glucosamine	2000 mg
Arginine	640 mg
Cysteine	204 mg
Malic acid	1200 mg
Monoammonium glycyrrhizinate	200 mg
Ascorbic acid	120 mg
Sodium methylparaben	100 mg
Zinc sulphate	80 mg
Calcium pantothenate	12 mg
Pyridoxine	4 mg
Manganese sulphate	4 mg
Cinnamon extract	3 mg
Folic acid	400 µg
Cyanocobalamin	2 µg
Benzoate powder	100 mg
Water	100 ml

Table 1: Oral solution Oncoxin-Viusid chemical composition (per 100 ml).

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status/QoL scale, and six single items. The global scales scores from 1 to 7, where 1 represents "very poor" and 7 represents "excellent". The rest of the items have four-point scales ("not at all," "a little," "quite a bit," "very much"). The principle for scoring these scales is the same in all cases: Estimate the average of the items that contribute to the scale; this is the raw score and use a linear transformation to standardize the raw score, so that scores range from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale represents a high level of symptomatology and worse quality of live.

In order to detect changes before and after the year of the patient's inclusion, the non-parametric test known as the Sign Test for paired data was used. Significant level ≤ 0.01. In addition, progression free survival (PFS) rates and 95% confidence interval (CI) were calculated using Kaplan-Meier method.

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

Ethical considerations

A signed informed consent was requested from all participating patients for access to the study. The protocol, CRF and consent form were discussed and approved by the centre's research ethics committee. Study data were analysed according to the intention-to-treat principle.

Results

Following the intention-to-treat principle, 20 patients were included in survival-free progression analyses. Two patients were lost to follow-up due unknown reasons. Table 2 illustrates the general characteristics of the patients, who were predominantly women (55%) between 24 and 88 years old, with a median age of 59, cutaneous phototypes II-III were present in 80% (40% each phototype) of patients, occupations without photo exposure in 16 (80%) and only one patient with personal history of basocellular carcinoma and no family medical history of cutaneous melanoma. Only 3 patients mentioned a history of sunburns, and 19 (95%) had previously had a nevus lesion. Nine patients (45%) referred an evolution time close 10 years or more. Most patients had lesions measuring 0-2 cm, ulcerated, clinically presenting as surface spreading (40%), located on the trunk (30%), and lower extremities (30%).

The histological presentation (Table 3) more frequently was epithelioid. Lesions had a mitotic index greater than 1/mm^2 in 75% of patients and a Breslow's index greater than 1 mm in all patients, while there was inflammatory response in 17 patients (85%) and a presence of vascular and lymphatic invasion in just 3 patients (15%). Ulceration was present in 14 patients, regression in only one and satellitosis in 2.

Variables Variables	N=20	(%)
Age (median and rank)	59 years (24 - 88)	
Sex. female	11	(55.0)
Skin phototype		
II	8	(40.0)
III	8	(40.0)
IV	1	(5.0)
V	2	(10.0)
VI	1	(5.0)
Occupations. no photo-exposed photoexposure in 16	16	(80)
Skin cancer personal history		
Basocellular carcinoma	1	(5.0)
Sunburns	3	(15.0)
Prior lesion (mole) nevos	19	(95.0)
Time of evolution		
< 1 año	2	(10.0)
1 – 5 años	6	(30.0)
6-10	3	(15.0)
> 10 años	9	(45.0)
Location of lesion		
Scalp	1	(5.0)
Neck	1	(5.0)
Trunk	6	(30.0)
Upper Extremities	4	(20.0)
Lower Extremities	6	(30.0)
Buttocks	2	(10.0)
Size of lesion		
0-2 cm	17	(85.0)
3-5 cm	3	(15.0)
Ulcerated Lesion	11	(55.0)
Clinical presentations		
Surface Spreading	8	(40.0)
Nodule	5	(25.0)
Lentigo Maligna Melanoma	1	(5.0)
Acral lentiginuos	6	(30.0)

Table 2: General characteristic of included patients.

Nine patients (45%) began the study in IIB clinical stage (Table 3), all of them finished the study in the same stage. From six patients (30%) included with stage IIC (surface-spreading clinical presentation), 2 were withdrawal to following-up for unknown reasons and one progressed; the rest finished the study in the same stage, meaning that there was no progression of the disease.

Five patients were included with stage III (25%); of them, 3 in IIIA and 2 in IIIB stage. At 1 year of follow-up, 2 patients progressed, one of them, with stage IIIA, a man with a nodular clinical presentation, with an ulcerated nodular melanoma on the sole of his foot with an elevated mitotic index, Breslow of 5 mm and microsatellitosis, who was given a regional lymphadenectomy, died close 10 months after inclusion.

In summary, at the end of study, there were 17 confirmed alive patients. One patient died and two were withdrawal to following-up. Figure 1 shows progression-free survival (PFS). One patient in stage IIIA and one staged IIC progressed. PFS rate estimated was 90% (95% CI: 0.65-0.97).

Seven patients (35%) presented with immediate-onset, short-lived, mild adverse reactions to the Oncoxin-Viusid syrup, consisting of diarrhea, nauseas and having a metallic taste in their mouths. Two patients (10%) temporarily interrupted use of the supplement due to these reactions. In addition, 9 (45%) of the patients mentioned feeling stronger while taking Oncoxin-Viusid.

Table 4 shows the results of comparison of the beginning and end of the study using the non-parametric test known as the Sign Test, which demonstrates that, in a general sense, the quality of life measurement stabilized at the one-year follow- up in comparison with the initial evaluation, being unable to reject a null hypothesis for the majority of scales. Major (deterioration) but no significant differences were only observed in the emotional functioning scale (p=0.0313). The quality of

Histology	Number	(%)
Histological factors		
Mitotic Index >1/ mm^2	15	(75.0)
Breslow >1 mm	20	(100.0)
Ulceration	14	(70.0)
Vascular Invasion	3	(15.0)
Lymphatic Invasion	3	(15.0)
Regression	1	(5.0)
Inflammatory Response	17	(85.0)
Desmoplasia	0	0
Satellitosis	2	(10.0)
Histological presentations		
Epithelioid	11	(55.0)
Pimented	3	(15.0)
Nodular	2	(10.0)
Fusocellular	1	5.0)
Surface dissemination	1	(5.0)
Lentiginous oligoligoligomelanicmelànico lentiginoso acral	1	(5.0)
Amaelanic	1	(5.0)
Stages at diagnosis		
IIB	9	(45.0)
IIC	6	(30.0)
IIIA	5	(25.0)

Table 3: Histological characteristics of tumor and clinical stage at diagnosis.

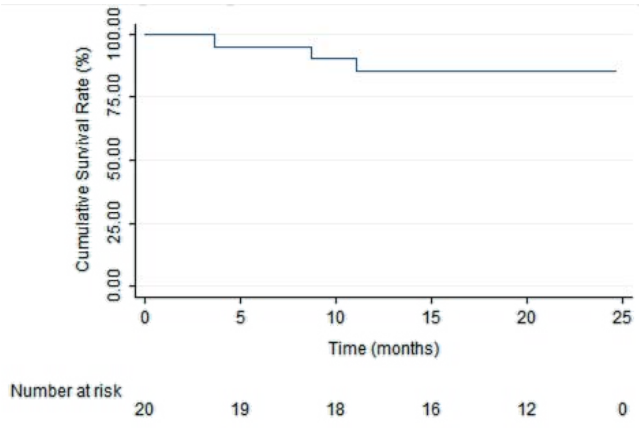

Figure 1: Progression-free survival at the end of study.

life analysis was performed in 17 of 20 patients, given that at the one-year follow up appointment, there were two patients who voluntarily abandoned the study and did not come to the final appointment, and one who died due to progression of the disease.

Discussion

Melanomas are known to affect relatively young individuals, at an average of 52 ±10-15 years old, 25% occurring before 45 years old. The frequency increases in men in particular as they get older, whereas in some countries, such as the United States, the majority of cases in females present before 40 years old. Other studies widen the average age at presentation to 60 years old, leaving us with a range of 52-60 years old, predominantly in persons with white skin [2].

Analysis of these epidemiological variables pertains to this study, given that the average age was 59 years old, predominantly with phototypes II and III, which in Cuba corresponds to persons with lighter skin, women being most affected, even 24-year olds. Older men have a greater mortality rate, while the mortality rate for women and young people has stayed stable, or even decreased [2]. This coincides with the results of this investigation, where the patient that died was man.

Risk factors include ultraviolet radiation, which is a complete carcinogen that is significantly related to the appearance of this cancer. However, in this study we can only speculate that workplace exposure was not a predominant factor, since there was a majority of patients in occupations without photoexposure. Therefore, we cannot affirm that photoexposure was not important, since recreational exposure was unknown. In addition, 3 patients had a history of sunburns, knowing that this increases the possibility of suffering from this disease [2].

The location most frequently encountered in the peer-reviewed literature is on the trunk (back) in men, and lower extremities in women, followed by the trunk [2] which coincides with the results of this investigation. Spreading melanomas, specifically, are the most frequent; they also carry the greatest association with nevus lesions according to descriptions in the literature [2]. The majority of patients in this investigation developed their tumors from a nevus and the prevalent clinical presentation was surface spreading, as reported in the literature, but at a lower percentage (40%), it is the most frequent clinical subtype and is represented in the literature at about 70%. The nodular clinical presentation, as referenced in the scientific literature, is the second most frequent (15-30%), generally beginning at 52 years old and more often located on the trunk [2]. It generally appears de novo, but no radial phase of growth is recognized, only vertical growth from the beginning; as such, it is very aggressive [2]. This presented in 25% of the patients in this study.

Scales	No. (%) negative signs (n=17)	P (Median of differences<0)*
Global health status/QoL	4 (23.5)	0.3437
Functional scales		
Physical functioning	3 (17.6)	0.3125
Role functioning	1 (5.9)	0.7500
Emotional functioning	5 (29.4)	0.0313
Cognitive functioning	4 (23.5)	0.0625
Social functioning	2 (11.8)	0.2500
Symptom scales	**No. (%) positive signs (n=17)**	**P (Median of differences>0) ***
Fatigue	6 (35.3)	0.0625
Nausea and vomiting	2 (11.8)	0.2500
Pain	2 (11.8)	0.5000
Dyspnea	1 (5.9)	0.7500
Insomnia	4 (23.5)	0.0625
Appetite loss	1 (5.9)	0.5000
Constipation	1 (5.9)	0.5000
Diarrhea	0 (0.0)	1.0000
Financial difficulties	0 (0.0)	1.0000
*Significant level<0.01		

Table 4: Results of sign test to comparing after-before quality of live scales from QLQ-C30 questionnaire.

Melanomas are rapidly evolving cancers, the time of evolution at diagnosis generally being short, but in our results, the time of evolution was prolonged for more than 10 years. It is believed that this is due to a high association with nevus lesions, as the majority of our patients could not specify the time of development of their lesion or mole.

Treatment of melanomas in advanced stages has always been a challenge, since once they become metastatic, there are no curative therapeutic protocols. The pathogenesis of melanomas is multifactorial and is not fully understood; a malignant transformation of the melanocytes is necessary for its development, which occurs both in genetically normal individuals as well as genetically predisposed. This involves interactions between environmental and microenvironmental factors, accumulation of genetic sequence alteration, genetic interactions, activation of oncogenes, inactivation of tumor suppressing genes and DNA damage, which translate to an alteration of the skin's homoeostasis [1].

Among most important prognostic factors isolated for patient survival are Breslow's depth, the mitotic index, and ulceration. Survival decreases with inverse proportion to Breslow's depth or the mitotic index and whether or not ulceration is present, as these factors increase the stage of the patient [2]. In addition, vascular involvement indicates invasion of the microvasculature of the dermis by tumor cells and increases the risk of metastasis and relapse, along with invasion of the lymphatic system [2].

In a survival study adhering to TNM classification, it was observed that in regard to the Fitzpatrick scale, patients with stage IIB had an overall survival rate ranging from 94.8 to 95.2% at one year whereas it was of 100% in our study [2]. Likewise, one-year survival rates are estimated in 89.9% for patients with stage IIC and 76.8% with stage IIIA respectively. Our results show that one-year survival rates were 83.3% and 80% among patients with stage IIC and IIIA. Compared with the current literature, our data suggest slight increase on overall survival rates among patients treated with Oncoxin-Viusid and IIB-IIC stages, although our results may be warrant further large-scale RCT studies. With treatment, Stage II melanoma is considered intermediate to high risk for local recurrence or distant metastasis, and then high mortality, thereby, the use of new therapeutic and even adjuvant options in the management of patient at intermediate or high risk of progression are highly needed.

Conclusion

Although new options exist on the market, they very often have numerous adverse reactions and limitations on circumstances of use depending on the existence or nonexistence of genetic conditions that affect their efficacy. Therefore, it is necessary to continue active research in this area. Our results warrant further randomized controlled trial to

explore the efficacy and safety of Oncoxin-Viusid in monotherapy or along the standard of care among patients with melanoma at different stages. In conclusion, the nutritional supplement Oncoxin-Viusid showed a good safety profile, meanwhile patients kept a stable quality of life at the end of study and a high progression-free survival rate.

Conflict of Interest

Authors declare no conflicts of interest relevant for this paper.

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Author Contributions

The authors were collectively responsible for the study design, data collection, statistical analysis and interpretation of data, the writing of the manuscript and the decision to submit the manuscript for publication.

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