

Survival of Patients with NSCLC Treated with CIMA-vax-EGF® in the Primary Health Care of Ciego de Ávila

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Abstract: In 2015 cancer was the second cause of death in Cuba and the first cause in Ciego de Avila. The bronchus, trachea and lung tumors were the most frequent. The global survival of patient with non-small cell lung cancer (NSCLC) in stage IIIb or IV after treatment with CIMAvax-EGF® vaccine in the Primary Health Care of Ciego de Avila province was evaluated. An observational and descriptive retrospective study was carried out. The medical record of the patients included in a phase IV clinical trial were analyzed. The universe comprised 76 patient evaluated and the sample was 35 who often accomplish the inclusion criteria. The results were presented in tables. The median of survival was determinate. The median of survival to diagnosis was 18 months for patients in IIIb stage who received first line treatment and 6 months for patients who did not receive this therapy. In the patient in IV stage the survival was 14 and 5 months respectively. The survival median to inclusion was 6 and 5 months respectively for patient in IIIb stage who received or did not receive first line treatment and 5 and 3.5 months respectively for patients in IV stage. The survival was high in several months for patients with non-small cell lung cancer advanced who received first line treatment for their disease.

Keywords: Non-small Cell Lung Cancer, NSCLC, Median of Survival, CIMAvax-EGF®, IIIb Stage, IV Stage

1. Introduction

Lung cancer is the malignant disease causing the increased morbidity and mortality among all types of neoplasms. It is estimated that by the year 2020 there will be 9 million new cases in developing countries and 6 million in developed nations. The World Health Organization predicted that 2030 will be presented 17 millions of inhabitants on the planet. [1]

In Cuba, cancer is the second leading cause of death, tumors of the trachea, bronchus and lung cancer the most incised, charging a total of 5454 lives in 2014 and 5474 in 2015. [2]

In Ciego de Ávila province the cancer was the leading cause of death in 2015. [2] Tumors of the trachea, bronchus and lung accounted for 25.6% of deaths from malignant

diseases in the year 2011, 24.1% in 2012 and the 27.4 until October 2013 [3], which is an important health problem in the Territory.

From a 25 to a 30% of patients with lung cancer are diagnosed when the clinical entity is locally advanced (stage III) and 40-70% when presented in a metastatic disease (stage IV) [1]. In these stages symptoms such as cough, dyspnea and chest pain [4].

The goal of cancer treatment is to enable patients to live during the same time and with the same quality of life if you did not have the disease. [5] The Chemotherapies have become an arsenal indispensable for the reduction of tumor burden and the increase of survival, but its impact on lung cancer is only measurable in months, with serious adverse reactions as additional charge. [6]

Usually patients with lung cancer make an initial stage of cancer diagnosis and treatment, which is obtained during the partial or complete remission, followed by a second phase, during which the disease progresses inexorably toward the terminal illness and death. [7] The median survival of patients with non-small cell lung cancer is approximately 11 months after diagnosis even if you receive all the lines of conventional therapy for cancer. For patients treated in Cuba has reported a median survival post platinum-based chemotherapy of 4.93 months for Stage IIIB and 3.17 for stage IV. [8]

The mechanism of action of monoclonal antibodies and therapeutic vaccines, it is much more selective in the elimination of tumor cells and may increase the survival of patients with a better quality of life. The vaccine CIMAvax EGF is a therapeutic vaccine that is based on the active immunotherapy, or manipulates the immune response of an individual to generate its own antibodies against the epidermal growth factor (EGF), the EGF receptor (REGF) can be up-activated in the cells of the lung tumors, to be deprived of the EGF, negative consequences can be seen on cellular proliferation and, therefore, on the tumor. [7]

In Cuba the "Phase IV clinical trial evaluating the safety of CIMAvax®-EGF in patients with tumors of the lung of advanced non-small cell lung cancer (NSCLC) treated in Primary Health Care" was executed. The Ciego de Avila province included patients in this study between February 2011 and January 2013 in three clinical sites: North Polyclinic of Ciego de Avila, Diego del Rosario Polyclinic of Moron and Raul Ortiz Polyclinic of Ciro Redondo.

Objective

To evaluate the global survival of patients with non-small cell lung cancer in stages IIIB and IV treated with CIMAvax-EGF® in the Primary Health Care of the Ciego de Avila province.

2. Material and Method

An observational and descriptive retrospective study using the medical record of the patients included in the clinical trial phase IV "Assessment of the safety of CIMAvax®-EGF in patients with tumors of the lung of advanced non-small cell lung cancer treated in Primary Health Care" was conducted, in which the universe of study was composed of 76 patients evaluated in Ciego de Ávila province and the sample was made up of the 35 that met the inclusion criteria and were in the stages IIIB and IV of the disease.

Inclusion criteria

1. Diagnosis of non-small cell lung cancer (NSCLC), stage IIIB/IV in secondary care.
2. Patient of any sex, greater than or equal to 18 years.
3. Patient not eligible for chemotherapy or radiation therapy, or who have received the treatment available for lung cancer and do not have other therapeutic option.
4. Which had signed the informed consent for the research.
5. The ECOG clinical criteria of 0 to 3.

Exclusion Criteria

1. Patients who have previously received treatment with the therapeutic vaccine CIMAvax-EGF and/or Nimotuzumab.

2. Patients with acute infectious diseases, chronic illness, or inflammatory decompensated
3. Patients with decompensated diabetes.
4. Patients of childbearing age who do not accept the use of appropriate contraceptive methods (intrauterine devices, barrier methods or tubal ligation, hormonal methods).
5. Patients who are pregnant or breastfeeding.
6. Patients with acute allergic or history of severe allergic reactions.
7. Patients who could not go to receive the proposed treatment or who had difficulties in gaining access to the center.

Treatment Schema

The first 4 immunizations were performed every 14 days (induction phase), subsequently to be vaccinated every 28 days, using the same dose until you changed the clinical conditions of the patient at the discretion of the principal investigator and/or toxicity of the patient.

In each immunization patients received 2.4 mg total vaccine prepared in 4 sites of inoculation. In each of the 4 sites of inoculation (the two Deltoid muscles and both buttocks) the amount of EGF was equivalent to 0.6 mg.

The medical records of the patients included in the clinical trial in Ciego de Ávila province were analyzed. The results were grouped in tables, the mean and median survival were used as summary measures of the data obtained.

Survival to diagnostics: time elapsed from diagnosis until the date of death of the patient, regardless of the cause of death.

Survival to the inclusion: time elapsed from the inclusion up to the date of death of the patient, regardless of the cause of death.

Median of survival: time after diagnosis or treatment during which half of the patients continues with life.

3. Results and Discussion

Lung cancer is the malignant tumor that causes more deaths in the world above other cancers with the highest incidence in the general population as well as the colon or breast cancer, since early detection is difficult and in 90% of cases are diagnosed in advanced stages where the treatment is not as effective. [9]

Table 1. Distribution of patients included in the study according to sex and age.

Ranges of Age	Sex		Total
	Male	Female	
50-60 years	7	2	9
61-70 years	12	2	14
71-80 years	8	1	9
81 and more	2	1	3
Total	29	6	35

As can be seen in Table 1, the highest number of patients included was of the male sex (29/35) and at the ages between 50 and 80 years, with the largest number of patients between the ages of 61 and 70 years and an mean of 67.68 years,

which corresponds to what has been reported in Spain, where it is stated that the average age of onset of lung cancer is between 55 and 75 years of age, and is more common in men than in women [10]. It also coincides with a study conducted in the province of Guantanamo in Cuba raises the average age of the patients with non-small cell lung cancer is 68 years old and is dominated by the male. [11] In another study conducted in the Hospital Antonio Luaces of Ciego de Avila, more than half of the patients are between 55 and 74 years, and also a predominance of male patients. [4]

In Spain it is reported that patients diagnosed with non-small cell lung cancer that they made their debut with

advanced-stage disease have a worse prognosis, as reflected in their lower survival rates or even worse in metastatic stage with survivals medium 9-10 months. [10]

The clinical trial was first developed in the Primary Health Care in the province, with the aim of bringing the treatment with the vaccine CIMAvax EGF to the places of residence of the patients, thereby facilitating access to these novel therapeutics. In the Ciego de Avila province were included in the clinical study 35 patients, 18 of them in stage IIIB and 17 patients in stage IV, 8 patients with IIIB stage and 11 did not receive it. 9 patients in Phase IV stage had received first-line treatment for cancer, and 7 did not receive it.

Table 2. Survival of the patients according to stage of disease and treatment prior to inclusion in the clinical trial.

		IIIB Stage		IV Stage	
		Yes FLTC	No FLTC	Yes FLTC	No FLTC
Survival to diagnostics (Months)	mean	18.5	6.2	18.4	5
	median	18	6	14	5
Survival to the inclusion (Months)	mean	9.7	5.1	12.28	3.6
	median	6	5	5	3.5

FLTC: First Line Treatment for Cancer

As shown in Table 2, the median survival in the diagnosis of patients who received first line treatment for cancer and after the vaccine CIMAvaxEGF®, was 18 months for those who were in stage IIIB and 14 months for stage IV. Taking into consideration that the previous reports pose a median survival of approximately 11 months after diagnosis even if you receive all the lines of conventional therapy for cancer [8], survival to diagnosis increased in 7 months for patients with stage IIIB and 3 months for those that were diagnosed in stage IV.

In the case of the patients who have not previously received a first line therapy for cancer the median survival at diagnosis was lower than that reported for both stages of the disease, 1 patient of the Stage IIIB and 4 patients with Stage IV did not receive any doses of the vaccine.

The median survival to the inclusion was also higher for patients who received a first-line treatment in the case of the Stage IIIB was 6 months, about 2 months longer than the platinum-based masses survival reported for this stage of the disease. In the case of stage IV was 5 months, approximately 1 month more than reported in the literature. [8] For patients who received no first line treatment for cancer had a value similar to that reported for stage IIIB and slightly lower than the revised for stage IV.

In a study carried out in Santiago de Cuba was found a median survival of 13 months for all patients with non-small cell lung cancer treated at the Oncology service, regardless of the stage of diagnosis. [12]

In a clinical trial developed in Japan found a median survival of 30.5 months for the group treated with Gefitinib and 23.6 months for those who received chemotherapy, but this series of patients had mutations in the EGF receptor, which was a target for the small molecule, with slowing of the malignant cell proliferation, tumor angiogenesis and the postponement of the development of metastasis. Other

research developed in Southeast Asia had a median survival of 18.8 months in patients treated with gefitinib. [12]

It should be noted that 5 of the 20 patients with 6 or more months of survival to the diagnosis had previously received chemotherapy and radiation therapy, these results could be due to the fact that these patients have had an objective response to this treatment, but this fact is unknown, because in the summary of oncology clinical history was not provided.

The CIMAvax-EGF vaccine has positioned itself as a therapeutic option in the struggle to provide patients with lung cancer, greater survival and quality of life. It is stated that the therapies to inhibit tumor growth by blocking the EGF receptor, represent a new opportunity for success in patients with tumors of the lung. [12]

The possibility of receiving the treatment in the primary health care represents a great opportunity, especially for those patients with lung cancer who cannot go to hospitals to be vaccinated with the expected frequency, either because of their clinical condition or by the remoteness of their homes.

4. Conclusions

The survival of patients with advanced non-small cell lung cancer treated with first-line treatment for cancer and were subsequently treated with the vaccine CIMAvax-EGF® in the Primary Health Care in the province of Ciego de Ávila, was higher in some months with regard to what has been reported in Cuba, which does not occur in the case of the patients who not had received prior treatment for their disease. These results suggest that further studies should be carried out taking into account the response to first-line treatment, with the aim of particularize the treatment of each patient with lung cancer.

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