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Long survival of a patient from Matanzas with lung cancer and brain metastasis. Case report

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ABSTRACT

Lung cancer is the leading cause of death from malignant tumors and non-small cell lung cancer is the most frequent. It is characterized by a tendency to metastasize important organs such as the central nervous system, for which a mean survival of three to six months after treatment with radiation is estimated. We present the case of a 55 year old non-smoker patient, who was seen at the Oncology Department, where studies were performed, showing a nodular image in the lower lobe of the right lung; a sample was taken which reported squamous cell carcinoma, T2aN0M0 Stage Ib. Several treatment schemes were implemented, including surgical intervention. In November 2018, she passed away. This is a patient diagnosed with epidermoid carcinoma of the lung with brain and bone metastasis who achieved an overall survival of six years, exceeding the average established to date.

Keywords: Monoclonal antibodies; Non-small cell lung carcinoma; Neoplasm Metastasis; Survival.

Lung cancer is the third malignant tumor with the highest incidence for both sexes worldwide; however, it is the leading cause of cancer death, accounting for almost 25 %[1].

The incidence of cancer in Cuba shows an increasing tendency, lung cancer is the third most frequent and the first in mortality[2]. In Matanzas, around 200 new cases are diagnosed and more than 300 die from this disease annually[3].

About 84 % of the cases of lung cancer are non-small cell lung cancer and 70 % of these cases are diagnosed in advanced stages, either locally or in metastatic phase, where surgical treatment is no longer possible and therefore an alternative to merely symptomatic treatment is sought, since survival with the best support treatment is four to five months[1,4].

Non-small cell lung cancer (NSCLC) is characterized as a tumor that metastasizes mainly to the central nervous system, adrenal glands and contralateral lung. Metastases can occur at the onset of the disease or after oncospecific treatment. The median survival for patients with multiple brain metastases treated with radiation is three to six months[4,5,6].

The treatment of NSCLC is a real challenge since it is the neoplasm with the lowest survival rate1. Many efforts have been made to achieve increasingly effective and safe therapies; nowadays there are surgical treatments, systemic and combined chemotherapy, radiotherapy, immunotherapy, targeted therapy and hormone therapy.

CASE PRESENTATION

A 55-year-old mixed-race female patient, a printing press worker, with a history of arterial hypertension and bronchial asthma with established treatment, non-smoker, with no history of cancer in the family, who in October 2012 went to the Pneumology office because she reported constant cough for three months, with no other symptomatology.

Physical examination of the respiratory system showed audible vesicular murmur, no rales and respiratory rate of 16 per minute and the rest of the systems without alterations. Imaging studies were performed where a 33 mm nodular image in the lower lobe of the right lung was observed by computed axial tomography (CT) and a sample of the lesion was taken, which reported squamous cell carcinoma. The extension studies were completed and it was staged as T2aN0M0 Stage Ib by the seventh edition classification.

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Conflict of interests
The authors declare no conflict of interest.

Surgical intervention was performed in November 2012 with right lower lobectomy plus mediastinal lymph node dissection; the biopsy of the surgical specimen showed moderately differentiated squamous cell carcinoma, nodule size 42 mm with lymph node formula of 2 nodes removed, both negative. The post-surgical staging was T2aN0M0 and adjuvant treatment was planned with chemotherapy, carboplatin-paclitaxel scheme, the first was calculated at 5 according to the area under the curve and the second was calculated at 175 mg/m^2; the patient had a body surface area (BSA) of 1,55 m^2, both medications every 21 days.

At the end of the third cycle she was admitted urgently due to a throbbing headache difficult to relieve; a cranial CT scan was indicated which showed an image with a nodular hypodense tendency with hyperdense ring, in projection of the right middle temporal gyrus, which did not exert mass effect and did not present perilesional edema (Figure 1). A consultation with neurosurgery was conducted, where a cranial magnetic resonance imaging was indicated and the report showed areas of micrometastasis for which surgery was deferred.

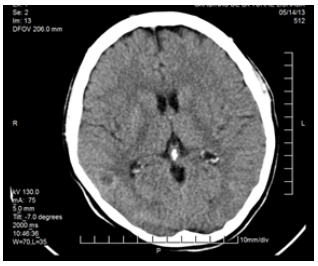

Figure 1. Simple cranial CT scan performed in May 2013 showing an image with a nodular hypodense tendency with a hyperdense ring, in the projection of the right middle temporal gyrus.

On that occasion, it was decided holocranial brain radiotherapy 300Gy as total dose together with a treatment of passive immunotherapy with intravenous (EV) Nimotuzumab, 200 mg weekly for 6 weeks and then every 14 days, and active with Racotumumab 1 mg, divided into 4 intradermal subdoses, in both arms and forearms, the first 5 doses every 15 days, and then every 28 days.

The scheme yielded good results erasing the brain metastases; the patient remained with a favorable clinical and radiological evolution until June 2016 when an evolutionary CT scan showed a recurrence in the right lung with a 10 mm nodule, osteolytic lesion in the right seventh costal arch and a poorly defined hypodense area was observed in the left occipital region that did not exert a mass effect (Figure 2). It was decided to continue with immunotherapy, despite the progression, and to add chemotherapy with docetaxel, which was calculated at 75 mg/m^2, so it corresponded to 116 mg every 21 days for four cycles, and to incorporate zoledronic acid, 4 mg every 28 days, due to bone metastasis.

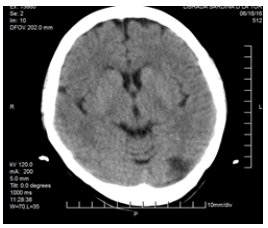

Figure 2. Simple skull CT scan performed in June 2016 showing an ill-defined hypodense area in the left occipital region that did not exert a mass effect.

In April 2017 the patient started with neurological symptomatology (headache and vision loss) and debuted with diabetes mellitus. In the evolutionary CT scan, lesions progression was observed, where two hypodense areas with associated hyperdensities were appreciated inside, one at the level of the right square lobe or precuticle and the other in the left occipital region, which did not present mass effect (Figure 3). Treatment was indicated with NPH insulin (bulb 100 U) at 0,3 IU/kg/day, divided into two subdoses; steroid (dexamethasone: 4 mg tablets, 1 tablet every 12 hours); anticonvulsant (phenytoin: 50 mg tablets, 1 tablet every 8 hours) and diuretic (furosemide: 40 mg tablets, 20 mg every 12 hours). Immunotherapy continued and an oral cyclophosphamide treatment, with 50 mg daily, was added as metronomic chemotherapy.

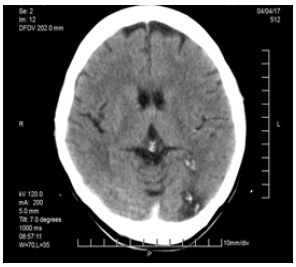

Figure 3. Simple skull CT scan performed in April 2017 showing lesions progression, with two hypodense areas with associated hyperdensities inside, one at the level of the right square lobe or precuticle and the other in the left occipital region.

The patient continued to attend medical appointments with a stable clinical picture despite progressing vision loss. In February 2018, an evolving cranial CT scan was performed, which reported similar characteristics to those reported in the previous study; another area similar to the one described was also found in the left cerebellum, and in the left paraventricular region a small hyperdense nodular image was observed (Figure 4). No signs of the disease were observed in the lung.

However, as expected, the patient developed a series of secondary events to the administration

of cytostatics, such as vomiting, general malaise, decay, hair loss and headache, which were treated symptomatically and satisfactorily. The associated complication she presented was the debut of diabetes mellitus, which was effectively treated.

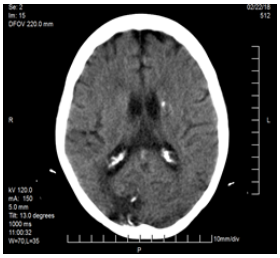

Figure 4. Simple skull CT scan performed in February 2018 showing another area in the cerebellum with similar characteristics to the one described in previous studies and a small hyperdense nodular image in the left paraventricular region.

The patient continued to attend medical appointments and to be administered double immunotherapy until October 2018, plus metronomic chemotherapy until the first week of November 2018, at which time she began with slurred speech, incoherence, loss of muscle strength establishing a coma that led to her death on November 18, 2018.

The patient had an overall survival of 6 years as she was diagnosed in October 2012 and passed away in November 2018. In addition, survival with brain and bone metastasis, with immunotherapy treatment is estimated at 5 years and 6 months.

DISCUSSION

Systemic chemotherapy improves survival of NSCLC when compared to best symptomatic treatment. Chemotherapy options include a platinum-derived drug combined with a taxane (paclitaxel, docetaxel), vinorelbine, or gemcitabine, all of which achieve identical survival improvement with slight differences in side effect profile. Although there is no evidence to suggest that prolonged cycles of double chemotherapy achieve improved survival, it is recommended that systemic chemotherapy is administered for four to six cycles in the absence of disease progression[7]. Reference was previously made to the chemotherapy scheme implemented in this patient (carboplatin plus paclitaxel), which is in perfect agreement with that established in the protocols for action in this entity.

On the other hand, in the presented case there is evidence of brain metastasis. Given this complication, steroids with predominant glucocorticoid activity, such as dexamethasone, are commonly used, especially to treat symptomatic patients. Patients with one to three brain metastases can be treated with just radiosurgery, total brain radiotherapy or both in combination[6]. Specifically in this case, the steroid and anticonvulsant treatment, approved to date, was established since neurosurgery deferred a possible intervention due to the existence of micrometastases.

From 12 to 15 % of NSCLC patients present in the tumor activating mutations in the RFCE gene, especially in the exons 19 and 21. These somatic genomic alterations confer sensitivity to tyrosine kinase inhibitors (TKIs) of RFCE, since RFCE is a 170 kDa membrane glycoprotein composed of three domains: an extracellular ligand-binding domain, a lipophilic transmembrane segment and a cytoplasmic domain with tyrosine kinase activity. There are currently several strategies aimed at inhibiting the function of EGFR, such as: inhibitors of tyrosine kinase activity (TKI), toxin-coupled antibodies, oligonucleotide repressors of EGFR gene transcription, vaccines and monoclonal antibodies (mAbs) specific against the extracellular domain of the receptor or its ligands. Within this wide range of products, anti-EGFR mAbs, such as Cetuximab and Nimotuzumab, and ITKs, such as Gefitinib and Erlotinib, are the most studied[8,9,10,11].

Nimotuzumab (CIMAher) is a humanized monoclonal antibody, an immunoglobulin of IgG1 isotype, obtained by recombinant DNA technology and produced in mammalian cell lines[11]. Immunotherapy with Nimotuzumab has recently gained wide acceptance in the treatment of NSCLC. Initially, it was only indicated for the treatment of advanced head and neck tumors, highly malignant astrocytoma, multiform glioblastoma and malignant esophageal tumors of epithelial origin; however, thanks to its therapeutic potential in malignant tumors of epithelial origin, its use is being evaluated in other oncological conditions such as advanced non-small cell lung tumors, gastric tumors, colorectal tumors, hepatic carcinoma, pancreatic carcinoma, breast cancer, cervical cancer, prostate cancer and malignant meningiomas[9,10].

In vitro assays and in vivo studies have shown that Nimotuzumab inhibits the growth of tumor cells expressing EGFR by inhibiting its phosphorylation, thus reducing tumor proliferation. It also inhibits ERK protein activation and has an adequate safety profile[9,10]. For all these reasons it can be affirmed that the addition of Nimotuzumab to radiotherapy and chemotherapy has a synergistic effect, which justifies its use in the presented case.

On the other hand, Racotumomab is highly specific against mAbs P3 and inhibits the binding of P3 to the ganglioside Neu-GcGM. Its antimetastatic activity is accompanied by an increase in tumor apoptosis and a decrease in the number of blood vessels and its adverse reactions are mostly mild and transient. So far, treatment with Racotumomab has shown an adequate safety profile, which is why it was also included in the treatment of the presented case [11,12].

The first studies with first and second generation ITKs showed that the administration of these drugs in

first line, compared with conventional chemotherapy treatment, extended progression-free survival (PFS) up to 10 to 13 months, in addition to presenting a favorable toxicity profile, especially in the case of the first generation drugs (erlotinib and gefitinib)[8]. In this case, it was impossible to determine whether the patient was a carrier of the aforementioned EGFR mutations, since during the period in which her disease developed, molecular biology studies were not yet available in Cuba to establish them, and therefore ITKs could not be included in the oncospecific treatment.

The key points of this case management were the early diagnosis of the primary tumor at T2aN0M0 Stage Ib, which means that there was no lymph node infiltration or metastasis; the excellent cooperation and adherence to treatment of the patient from diagnosis to death and the availability of the necessary drugs for all the treatment schemes that were imposed. However, the authors recognize as weaknesses the rapidity with which the tumor metastasized in a period of six months; the aggressive nature of the disease and the association of diabetes, which overshadowed the prognosis.

In the case of this patient with a diagnosis of squamous cell carcinoma of the lung with brain and bone metastasis, an overall survival of 6 years was observed, exceeding the average established to date in the international medical literature. It also surpassed the survival expectation in patients with brain metastasis and immunotherapy treatment of 5 years and 6 months; accompanied by a good quality of life. Undoubtedly, this case is a clear example that oncology is making great strides in the treatment of lung cancer.

CONCLUSIONS

The international scientific community has made significant improvements in all modalities of lung cancer treatment, including minimally invasive surgery, improved direction and delivery of radiation therapy, a diverse range of systemic agents, and methods of palliation of many associated symptoms. Undoubtedly, treatment with Nimotuzumab and other vaccines has revolutionized the field of oncospecific treatment of non-small cell lung tumors. This presentation shows that the combination of several oncospecific therapies can be very effective in achieving an objective response, with prolonged survival and good life quality.

AUTHORSHIP

Yuslian Sánchez-Lazo: conceptualization, investigation, visualization and writing-original draft.
Kirenia Camacho-Sosa: conceptualization, formal analysis, investigation, methodology, supervision, writing-review and editing.
Cristina Martí-Coruña: investigation and validation-article verification.

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Larga supervivencia de paciente matancera con cáncer de pulmón y metástasis cerebral. Informe de un caso

RESUMEN

El cáncer de pulmón constituye la primera causa de muerte por tumores malignos y el de células no pequeñas es el más frecuente. Este se caracteriza por una tendencia a metastizar órganos importantes como el sistema nervioso central, para lo cual se estima una supervivencia media de tres a seis meses después de tratado con radiación. Se presenta el caso de una paciente de 55 años, no fumadora, que fue atendida en el servicio de Oncología, donde se le realizaron estudios, observándose imagen nodular en el lóbulo inferior del pulmón derecho; se tomó muestra que informó carcinoma epidermoide, en estadio T2aN0M0 etapa Ib. Se implementaron varios esquemas de tratamiento, incluida intervención quirúrgica. En noviembre de 2018 fallece. Se trata de una paciente con diagnóstico de carcinoma epidermoide de pulmón con metástasis cerebral y ósea que logró una supervivencia global de seis años, superando la media establecida hasta la actualidad.

Palabras clave: Anticuerpos monoclonales; Carcinoma de pulmón de células no pequeñas; Metástasis de la Neoplasia; Supervivencias.