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Neoadjuvant Treatment Option with Atezolizumab Plus Platinum Based Chemotherapy in Resectable Early Stage Non-Small Cell Lung Cancer

*Sánchez-Ríos Carla Paola[1], Guzmán-Casta Jordi[1], Riera-Sala Rodrigo[1], Aguirre-Vásquez Natalia[2], Peña Mirabal Erika Sagrario[2], Martínez-Herrera José Fabián[3], Guzmán-Huesca Jorge[4], Carrasco-Cara Chards Sonia[5], Martínez-Barrera Luis Manuel[1], Alatorre-Alexander Jorge Arturo[1] and Rodríguez-Cid Jerónimo Rafael[1]**

[1]Department of Thoracic Oncology, National Institute of Respiratory Diseases, Mexico

[2]Department of Pathology, National Institute of Respiratory Diseases, Mexico

[3]ABC Medical Center Observatory Cancer Center, Mexico

[4]Department of Internal Medicine, Bonita Community Health Center, USA

[5]Department of Medicine, National Autonomous University of Mexico, Mexico

Introduction

In recent years Immune Checkpoint Inhibitors (ICI) have played a prominent role in the treatment of lung cancer. Anti-PD-1, anti-PD-L1 and anti CTLA-4 are some of the ICI agents that have been used, they act inhibiting the modulation of the response mediated by T cell lymphocytes, resulting in a better prognosis for patients with lung cancer in terms of progression free survival and overall survival in advanced disease. On the heels of the success obtained in the treatment of advanced disease, there is an attempt now to translate those benefits to the early and locally advanced stages either as adjuvant or neoadjuvant therapy [1].

One more of the current challenges are the preoperative evaluation, requiring an experienced multidisciplinary team in a tertiary care environment to select ideal candidates for neoadjuvant therapy. At this time we don't have solid data in terms of ideal timing for surgery after neoadjuvant therapy, rates of recurrence, need for adjuvant therapy and if so, if this therapy should be with ICI or not. Moreover, it's necessary to design markers and other tools that allow selecting the ideal candidates for this treatment strategy [2].

There are currently significant challenges for the recommendation of neoadjuvant immunotherapy. Among them are the selection of the agent, dose, treatment schedule, length of therapy and the decision, posterior to the surgical treatment, to continue it or not as adjuvant treatment. Surgery continues to be initially the standard of treatment whenever possible. Results obtained from clinical essays where a single drug immunotherapy was used in the context of neoadjuvant treatment have failed to show a clear benefit with such strategy; however, in the last few years several studies have been developed with combination therapy with promising results [2]. The NADIM Phase II trial included 46 patients with stage IIIA lung cancer achieved a Major Pathological Response (MPR), which is defined as <10% residual viable tumor after neoadjuvant chemotherapy, in 85% of the patients and a Pathological Complete Response (pCR) in 71.4% of patients, using a treatment schedule conformed by Nivolumab+Carboplatin+Nab-Paclitaxel [3].

A trial by Shu et al. [4] of only 18 patients with stage IB-IIIA used Atezolizumab+Nab-Paclitaxel+Carboplatin as neoadjuvant therapy achieving a RPM of 50% and a pCR of 21% [4], and the NEOSTAR trial which included 44 patients in clinical stage I-IIIA reported RPM of 33.3% and pCR of 29% with the combination of Nivolumab+Ipilimumab [5].

Finally, in some of the abovementioned trials, one of the most utilized endpoints to assess the efficacy of the treatment has been the Major Pathological Response (MPR). Having a surrogate for survival, such as pathologic response to neoadjuvant chemotherapy, has the potential to improve the efficiency of trials and expedite advances [6].

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Patient is a 63 years old female with a diagnosis of Adenosquamous carcinoma of the right

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Correspondence:
Rodríguez-Cid Jerónimo Rafael, Department of Thoracic Oncology, National Institute of Respiratory Diseases, Mexico, E-mail: cidjeronimo@yahoo.com.mx

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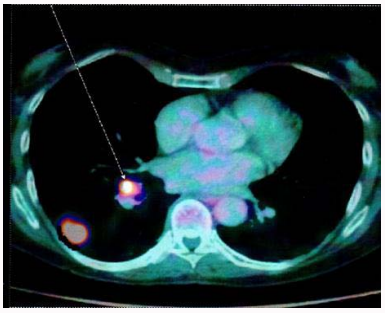

Figure 1: Prior to lobectomy.

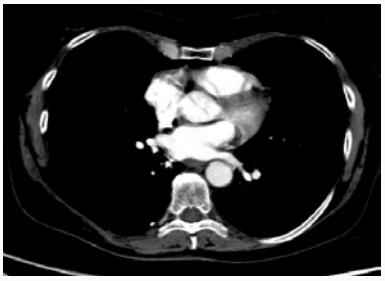

Figure 2: 9 months after lobectomy.

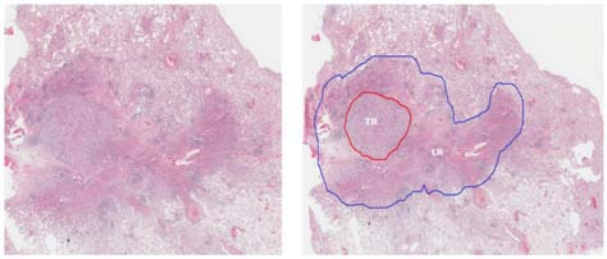

Figure 3: Image of the tumor regression area with a viable tumor in the center of the lesion. Image of the tumor regression area (Blue Line) with viable tumor in the center of the lesion (Red Line).

lung T4N1M0, clinical stage IIIB, potentially resectable, what was started on neo-adjuvant chemotherapy with 2 cycles of Atezolizumab 1200 mgs. IV D1+Chemotherapy with Carboplatin 400 mg. IV D1, Paclitaxel 270 mg. IV D1 every 21 days, subsequently underwent right lower lobectomy without evidence of lymphatic or vascular invasion, the residual viable tumor was estimated at 20%, mediastinal lymphadenectomy of stations 4R [7], 10 and 11R were negative, the previously reported N1 became negative in the pathology sample. Postsurgical result was pT4N0M0 Stage IIIA.

The histopathological study identified a residual tumor with a solid pattern, surrounded by a tumor regression area that corresponds to 20% of the viable residual tumor that is classified as partial pathological response. In the tumor regression area, typical morphological findings were found in response to immunotherapy related to tissue repair (proliferative fibrosis and neovascularization), cell death (cholesterol crystals and foamy macrophages) and activation of the immune system (tertiary lymphoid structures and peri and intratumoral lymphoplasmacytic infiltration).

After surgery, the patient only received 1 cycle of adjuvant chemotherapy with Carboplatin, Paclitaxel and Atezolizumab due to the risk of the COVID-19 pandemic. Currently the patient is under

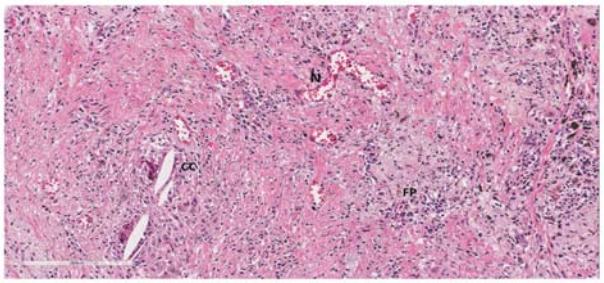

Figure 4: Photomicrograph 20x, tumor regression bed showing signs of death and tissue repair (CC: Cholesterol Crystals; FP: Proliferative Fibrosis; N: Neovascularization).

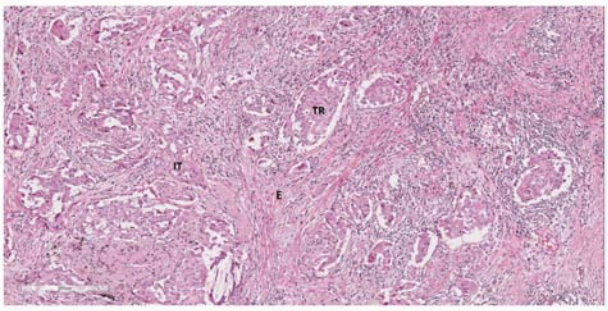

Figure 5: Photomicrograph 20x, Reducing Tumor area (TR) with the presence of an inflammatory infiltrate in the Intratumoral stroma (E) (IT).

surveillance, with good performance, last tomography did not show tumor activity with a recurrence-free interval of 9 months (Figures 1-5).

Discussion

Considering a previous outlook, there are 2 Phase II clinical trials in which neoadjuvant immunotherapy was used in resectable clinical stages with promising results. The main current challenge in the neoadjuvant treatment is the progression of the disease due to a delay in the surgical treatment. Nonetheless, there are some early studies with Nivolumab as immune, single agent, PD-L1 neoadjuvant therapy that showed that 45% of the patients had a Major Pathological Response (MPR) and that 15% of them had a Complete Pathological Response (pCR). Neoadjuvant therapy with Atezolizumab showed that 19% of patients had a MPR and 5% achieved a pCR7.

In particular, previous studies of neoadjuvant chemotherapy showed that the partial pathological response is more likely to occur in patients with squamous cell lung cancers (26%) than those with adenocarcinomas (12%), possibly due to an increased response to necrosis in squamous cell carcinomas [8].

We still lack more robust Phase III studies to really assess the impact of partial response versus complete response in the primary tumor, likewise we need to know if negativization of the lymph nodes has an effect on disease free survival and if the neoadjuvant treatment with immune agents has a sustained impact in the elimination of distant micro metastasis and relevance on the Overall Survival (OS) and on Recurrence Free Survival (RFS) [9].

In our case, the patient had a MPR of 80% with a residual viable tumor of 20% without any lymphatic or vascular infiltration and without lymph node involvement according to the pathology report and although adenosquamous lung cancers are infrequent the

immune activity of the therapy was significant with an 80% fibro-inflammatory stroma reported by pathology.

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