

TYPES OF RESPONSE AND PSEUDOPROGRESSION TO IMMUNOTHERAPY IN LUNG CANCER

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The new frontier in the treatment of lung tumors is represented by immunotherapy. Pseudoprogression denotes apparent, early progression of disease followed by long-lasting regression. This phenomenon is observed in approximately 10% of patients receiving immunotherapy. The appearance of pseudoprogression could make difficult the assessment of treatment response based on RECIST criteria. In this paper, the scope of pseudoprogression was discussed as well as currently proposed alternative methods of treatment response assessment according to Immune-related Response Criteria (irRC).

Keywords: lung cancer, pseudoprogression, immunotherapy.

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer (11,6% of the total cases) and the leading cause of cancer death (18,4% of the cancer deaths) conform GLOBOCAN 2018.¹

Tumour micro medium is a very complex and dynamic ecosystem in which different cell populations coexist. Major factors include tumour cells, immune and support (fibroblasts, stromal and endothelial cells). Immune cells circulating in the blood enters tumours by trans endothelial migration and are attracted to chemokines produced by tumour cells, fibroblasts or inflammatory cells. Within the tumour mass, immune cells proliferate locally, differentiate, exert their functions and die, and some can migrate back into circulation. In this population, cells associated with acute inflammation (neutrophils, basophils and eosinophils), innate immune response cells (macrophages, NK and DC cells) and adaptive immune response cells (CD8 + T cells, Th1 / and B cells).²

IMMUNOTHERAPY

Currently available therapies for the treatment of lung tumours, especially in advanced disease, offer little benefit except in the subgroup of patients with “oncogene-driven” neoplasia, which

represents 15–20% of the entire population, so Molecular-target agents are already available in clinical practice²⁻³. The new frontier in the treatment of lung tumours is represented by immunotherapy. This happened thanks to the significant progress made in understanding the immune system that led to the development of new molecules able to enhance the immune response of patients. Therefore, all cancer patients, regardless of genetic or metabolic abnormalities, can potentially benefit from treatment because the target is precisely the patient's immune response and not the cancer cell. Immuno-checkpoints refer to a series of inhibitory pathways in the immune system that are crucial for the maintenance of self-tolerance and prevention of excessive, prolonged, and potential deleterious activity of T cells in peripheral tissues⁴.

It is increasingly evident that lung cancer can use these immuno-checkpoints to evade the anti-tumor immune response, for example through loss of expression of tumour-associated antigens (TAA) and/or system antigens. Greater histocompatibility (major histocompatibility complex, MHC), or through the production of cytokines and the expression of new membrane molecules with inhibitory activity. This phenomenon of continuous molecular remodelling is defined as “cancer immune editing” which consists of three main and sequential phases: elimination (complete destruction of tumor cells by the host's immune system), balance (cancer cells, through a selection operated by T cells, become resistant to the

immune system), and evasion (cancer cells originate clinically detectable lesions)³. At present, the immuno-checkpoints known to be involved in the evolution of lung cancer are the cytotoxic receptor T-lymphocyte antigen-4 (CTLA-4) and the programmed cell axis death-1 (PD1) / programmed cell death- ligand 1 (PD-L1). CTLA-4, also known as CD152, is a receptor belonging to the immunoglobulin superfamily (Ig) expressed on cytotoxic T lymphocytes. Following binding with one of its ligands, B7-1 or B7-2 expressed on the antigen-presenting cell (APC), it transmits an inhibitory signal inside the lymphocyte, thus contributing to the homeostatic regulation of the immune response⁴.

The ipilimumab and tremelimumab, anti-CTLA-4 monoclonal antibodies, are currently in clinical development in lung carcinoma. PD-1 is also a surface receptor belonging to the Ig superfamily and is expressed on T and pro-B cells and recognizes PD-L1 and PD-L2 as ligands. PD-L1 is a transmembrane protein whose binding to its receptors, PD-1 and B7.1, on the surface of T cells determines their deactivation⁵. Nivolumab and pembrolizumab are anti-PD-1 monoclonal antibodies, whereas atezolizumab and durvalumab are anti-PDL1 monoclonal antibodies. These drugs are at an advanced stage of clinical development in pulmonary neoplasms. Immunotherapy has led to a change in how objective responses should be

measured, both in clinical trials and in clinical practice. From the studies conducted in the immunotherapy treatment of melanoma, it has been seen that the antitumor response becomes evident not earlier than weeks or months with respect to the beginning of treatment, with a survival gain that manifests itself after several months. This is because the immunotherapeutic drugs activate the immune system which in turn determines a cell-mediated response.^{6,9}

PROGRESSION OR PSEUDO PROGRESSION?

Evaluation of the treatment response is based on the use of the RECIST or WHO criteria. In the course of immunotherapy these conventional criteria are not adequate for the presence of peritumoural inflammatory infiltrate which can mimic a pseudo-progression and which is a typical phenomenon during this type of treatment. To overcome this problem, the criteria for the evaluation of the immune correlated response (irCR) have been created, according to which an initial radiological progression, understood as the appearance of new lesions and / or increase in the size of pre-existing lesions, in the absence of clinical progression, must be confirmed at a later assessment¹⁰.

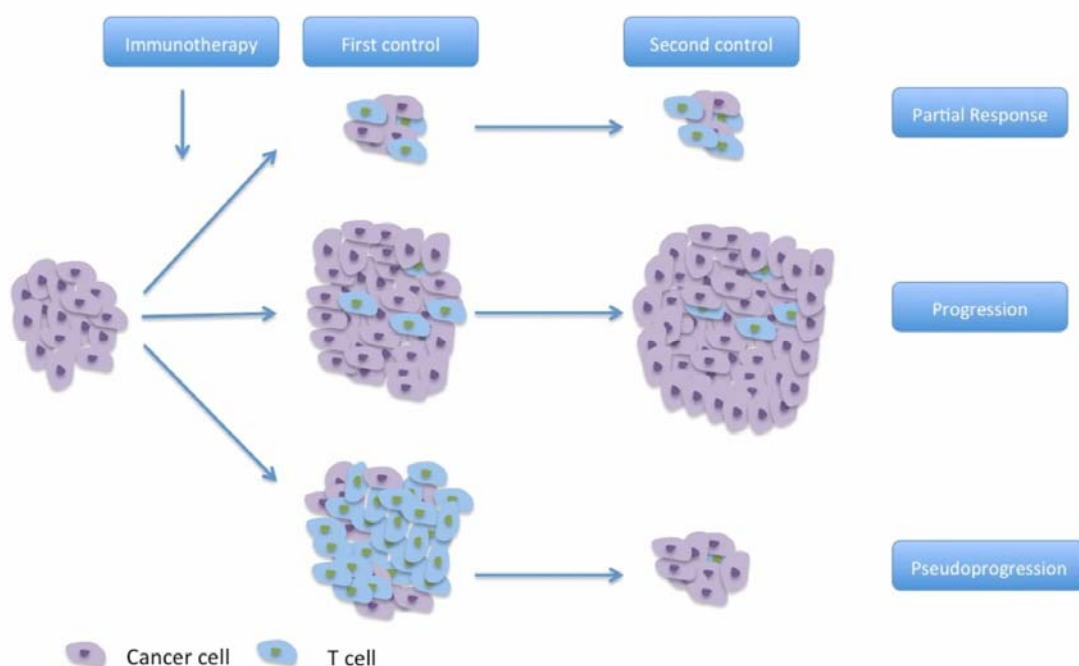


Figure 1. Patterns response during treatment with immunotherapy.
Adaptated after Antoni Ribas *et al.* Clin Cancer Res 2009;15:7116-7118.

Table 1

iRECIST criteria: patterns of response iCR = complete response, iPR = partial response, iSR = stable response,
iUPD = unconfirmed progressive disease, iCPD = confirmed progressive disease

Adapted after Wolchok *et al.* Clin Cancer Res 2009 Hodi *et al.* JCO 2016

Measurement	
	Sum of length diameter of maximal target lesion diameter (measurable lesion are > 10 mm and nodal lesion >15 mm) Max 2 target lesion per organ Max 5 target lesion in total New tumour lesion (maximum 2 per organ, 5 in total) are recorder and followed-up separately.
iCR	Disappearance of all target lesion. Any pathological lymph nodes must have reduction in short axis to <10 mm
iPR	• 30% decrease in SLD taking as reference the sum of diameters and no new lesion
iSD	SLD <30% decrease and <20% increase, non-target lesion
iUPD	SLD < 30, increase (min 5 mm). Confirmation scan after 4–8 weeks
iCPD	Further increase of tumour mass a additional new lesion appear an increase in size of a new lesion

The proper use of irCR may allow the identification of a group of long-surviving patients among those who could be considered progressively with the conventional criteria and who therefore could not continue to benefit from the specific treatment. Another aspect that immunotherapy has highlighted is the need to understand whether this treatment is for everyone or it is important to select the patients who most benefit from immunological therapy, optimizing the results and costs for sustainability by the national system.^{11,12} Unfortunately, to date we have little data available, the target identified is the expression of PD-L1 but it is not clear which cutoff and methodology to use to define the group of patients to be treated.^{13,14} Another consideration that further complicates this aspect is that the immune system tends to change over time therefore the expression of PD-L1 may also be different depending on when the tumor tissue was taken, at diagnosis, or progression.¹⁵ This must be considered in reading the results of the studies available to date. Clinical studies with extensive casuistry currently underway in the treatment of pulmonary neoplasms are further evaluating this aspect.

CONCLUSIONS

Responses to immunotherapy may become apparently after a period of pseudo-progression, in which immune cell infiltration is manifest as new lesions or growth of old lesions that are mistaken for tumour progression.

We can Differentiating a real progression from a Pseudo-progression by biopsy tumour formations that will show tumour infiltration with T lymphocytes.

Treatment past RECIST progressions should only be considered when the patient is stable symptomatically and where there is a short period before reassessment.

In the future it will be possible to quantify the differences in outcome estimation between RECIST and irRECIST.

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