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PSEUDOPROGRESSION AND HYPERPROGRESSION SECONDARY TO IMMUNOTHERAPY IN LUNG CANCER

**R.F. RIERA-SALA[1], A.M.G. IBARRA-MORALES[2], J. GUZMÁN-CASTA[3],
R. MEDRANO-GUZMÁN[4], A.K. DIP-BORUNDA[5], A.E. MARTIN-AGUILAR[6],
R.C. GRAJALES-ÁLVAREZ[7], R. CORREA-CANO[2], K. ELVIRA-FABIÁN[8],
C.P. SÁNCHEZ-RÍOS[9], A.O. ORZUNA-VÁZQUEZ[2], J.E. ROVELO-LIMA[10],
L.M. MARTÍNEZ-BARRERA[11], J.R. RODRÍGUEZ-CID[12],
J.A. ALATORRE-ALEXANDER[13]**

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[1]Department of Thoracic Malignancies, Clinical Oncologist, Fellow in Thoracic Oncology,
Hospital de Oncología, Centro Médico Nacional Siglo XXI, Mexico City, Mexico.
[2]Clinical Oncology Resident, Hospital de Oncología, Centro Médico Nacional Siglo XXI, Mexico City, Mexico.
[3]Clinical Oncologist, Fellow in Thoracic Oncology, Instituto Nacional de Enfermedades
Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.
[4]Surgical Oncologist, Headmaster of the UMAE Hospital de Oncología,
Centro Médico Nacional Siglo XXI, Mexico City, Mexico.
[5]Clinical Oncologist. Head of Medical Oncology at Hospital de Oncología,
Centro Médico Nacional Siglo XXI, Mexico City, Mexico.
[6]Department of Genitourinary Tumors, Clinical Oncologist, Hospital de Oncología,
Centro Médico Nacional Siglo XXI, Mexico City, Mexico.
[7]Department of Breast Cancer, Clinical Oncologist, Hospital de Oncología,
Centro Médico Nacional Siglo XXI, Mexico City, Mexico.
[8]General Physician, Hospital ABC Santa Fé, Mexico City, Mexico.
[9]Pulmonologist, Fellow in Thoracic Oncology, Instituto Nacional de Enfermedades Respiratorias,
Ismael Cosío Villegas, Mexico City, Mexico.
[10]Surgical Oncologist, Hospital Star Médica, Lomas Verdes, Mexico.
[11]Clinical Oncologist, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas,
Mexico City, Mexico.
[12]Clinical Oncologist and Head of Medical Oncology, Instituto Nacional de Enfermedades
Respiratorias Ismael Cosío Villegas, Mexico City, Mexico.
[13]Head of Thoracic Oncology, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas,
Mexico City, Mexico.

Corresponding Author
Rodrigo Fernando Riera Sala, MD; e-mail: rf_rs@hotmail.com

ABSTRACT – ***Background:*** The treatment of non-small cell lung cancer (NSCLC) has undergone changes that have improved the prognosis of patients. With the advent of immunotherapy, it has been possible to prolong significantly the overall and progression-free survival as well as quality of life. Nevertheless, its use represents clinical challenges which may turn into adverse events, such as progression and pseudo-progression, which are uncontrolled and often deleterious immune responses that simulate tumoral progression, generate worsening of symptoms and performance status of patients and even may lead to non-cancer related death of patients.

Materials and Methods: We assessed 128 records (clinical trials, reports, meta-analyses) in order to provide an updated review of the treatment of NSCLC, current definitions proposed for pseudo and hyperprogression (which are not homogeneous so far), incidence, theories about their physiopathogenesis, importance of making a judicious diagnostic workup, imaging criteria as well as biochemical markers in order to predict their appearance, concluding with a brief discussion about the topic addressed.

Conclusions: Since there is no definition or standardized diagnostic and imaging criteria, these entities are a topic of major interest in the area of oncologic immunotherapy, for which the following review has been generated.

KEYWORDS: Pseudoprogression, Hyperprogression, Immunotherapy, Lung cancer.

INTRODUCTION

Lung cancer has the highest incidence and mortality among all malignancies. In 2018, an analytic study of data from the Cancer World Bank found that there were 209,386 new cases (12.22 per 100,000) and 1,761,007 deaths (19.88 per 100,000) in 185 countries around the world [1]. Due to the absence of symptoms and lack of effective disease prevention programs, the majority of cases are diagnosed at advanced stages. Non-Small Cell Lung Cancer (NSCLC), which includes Adenocarcinoma, Squamous Cell Carcinoma and Large Cell Carcinoma constitute approximately 85% of the cases, while Small Cell Lung Carcinoma (SCLC) represents the remaining 15%[2].

Chemotherapy has been the standard therapy in advanced stages for several decades. Among 90´s and the first years of the 2000´s, first-line treatment consisted in platin-containing duplet regimens. At that time, the Objective Response Rate (ORR) was only 17%-22%, Progression Free Survival (PFS) was 3.1-4.2 months and median Overall Survival (OS) 7.4-8.1 months[3].

In recent years, the development of Immune Checkpoint Inhibitors (ICI) has revolutionized the treatment of a variety of malignancies, becoming for many of them the standard of care in some scenarios. The blockade of the Programmed Cell Death Receptor (PD-1) and/or its ligand PD-L1 (Programmed Cell Death-Ligand 1) as monotherapy or in combination with other agents has shown a clear benefit in terms of overall survival, even in metastatic scenarios and with benefit seen among all histologies NSCLC and SCLC[4-7].

One of the most important hallmarks of cancer is evasion of the immune response[8]. Numerous studies have shown the impact of the interaction between tumor cells and the host's immune system in the modulation of tumoral growth. Among the mechanisms of evasion known so far, the interaction between the immune checkpoint receptors of the tumor cells and the immune system is a crucial component in the process. PD-1 is one of the immune checkpoints expressed in T, B, and NK lymphocytes and in some myeloid cells which are targets of ICI[9]. ICI are associated with novel patterns of response not described previously with the use of chemotherapy and targeted therapy. Nevertheless, despite these advantages, there is evidence that in some cases, blocking PD-1/PD-L1 may be associated with progression of disease and worse outcomes than those patients treated with platinum-based chemotherapy[10].

In general, immunotherapy is well tolerated, even when is combined with other therapeutical modalities. For example, in a systematic review by Wang et al[11], the incidence of serious side effects was 12% with combinations of ICI and radiotherapy.

There are two controversial and not well stablished phenomena that aim to explain this occurrence: pseudoprogression and hyperprogression. Pseudoprogression is not a true progression of the disease but an increase in the radiologic appearance of the lesions that is explained by peritumoral infiltration by cytotoxic T lymphocytes, edema and necrosis showing a clinical progression when the RECIST criteria (Response-Evaluation Criteria in Solid Tumors) are used, followed by an objective response[12].

As regards the concept of hyperprogression, it is thought to be an unfavorable effect of immunotherapy consisting in an accelerated tumor growth associated with an early clinical deterioration and worsening of prognosis, suggesting that this therapy could have a deleterious effect promoting cellular pro-

liferation and hastening the progression of the disease. At this point, there's not still a consensus about the definition of these two concepts or any reliable biomarkers to allow its prompt identification [13-15].

These scenarios are currently a matter of debate. For the oncologist, it can be challenging to identify these entities and making accurate therapeutic decisions.

In order to recognize objectively these events, new tools for evaluation of response to treatment have been developed, such as the immune related Response Criteria (irRC), the immune related Response-Evaluation Criteria in Solid Tumors (irRECIST) and rRECIST which defines a new concept: unconfirmed Progressive Disease (uPD), that requires a radiological confirmation in 12 weeks[16]. It is possible that the sustained, albeit deferred response observed in patients treated with immunotherapy is related to the phenomenon of pseudoprogression[17].

ROLE OF IMMUNOTHERAPY IN CANCER TREATMENT

Therapy with ICI has revolutionized the role of medical oncology during the last decade by noticeably prolonging patients' overall survival. A variety of malignancies such as kidney, lung, colon, bladder, melanoma and many others have greatly improved their prognosis with this modality of therapy, placing it as standard of care in the first line setting in selected cases.

The goal of immunotherapy in cancer is potentiating the immune cell response (T lymphocytes in particular) against neoplastic cells without affecting the healthy ones[17]. Hence, the host's immune system plays a key role in the immunological surveillance, recognition, and destruction of neoplastic cells[18,19]. There are current efforts to develop prognostic prediction models to assess reliably whether or not ICI will be useful, such as the hypoxia-related genes and its differential expression, which are related to high or low immune microenvironments and might predict the response to ICI in NSCLC, specifically lung adenocarcinoma (LUAD)[20]

NORMAL IMMUNE RESPONSE TO TUMORAL ACTIVITY

Intrinsic regulation

There are several factors that contribute to an adequate response during immunotherapy and immune suppression plays one of the main roles. Among the major checkpoints known so far, two of the almost ubiquitous ones are Cytotoxic T Lymphocyte Antigen-4 (CTLA-4), the Programmed Cell Death-1 (PD-1) and its ligand (PD-L1), which must be inhibited to potentiate an antitumor immune response[21].

T-lymphocytes recognize peptidic antigens derived from degraded proteins in the intracellular environment and transport them to the cell surface in order to initiate the antigenic presentation by the Major Histocompatibility Complex (MCH). On one hand, CD4+ T lymphocytes act along the MHC II to coordinate the production of cytokines with pro-inflammatory, chemotactic and immunomodulatory properties[22]. On the other hand, CD8 + T lymphocytes detect the antigens in coordination with the MHC I and carry out direct cytotoxic reactions aimed to eliminate neoplastic cells[23].

A protein complex located at the cell surface known as T Cell Receptor (TCR) recognizes the antigens and participates in the selection and development of T lymphocytes[23]. The antigenic activation of TCR is required for the proliferation and activation of T lymphocytes. However, the co-stimulation of a family of proteins found in the cell surface known as CD28 is needed, as they represent the most efficient stimulating receptor to initiate the activation of the T lymphocytes. The CD28, B7 and B7-2 ligands are expressed on the surface of the antigen presenting cells and get activated when T lymphocytes detect microorganisms that stimulate Toll Like Receptors (TLR) and other pathogen sensors[24,25].

Along the activation of immune response, inhibitory molecules such as CTLA-4 and PD1 are induced as checkpoints, exerting a negative feedback to impede the activation of T lymphocytes[26].

Extrinsic regulation

Besides the intrinsic regulation in the activation of T lymphocytes, there is also an extrinsic regulation exerted by the CD-4 regulatory lymphocytes (Treg) and the Myeloid Derived Suppressor Cells (MD-SC). These cells have immunosuppressive properties, are widely expressed in the tumor microenvironment and inhibit antitumoral immunity. The development of drugs inhibiting Treg might represent a key therapeutic target for immunotherapy[27-29].

Drugs approved for NSCLC treatment

Currently, the Food and Drug Administration (FDA) has approved several drugs that block the function of these checkpoints. Among those available, there are the anti PD-1 (Nivolumab, Pembrolizumab), anti PD-L1 (Durvalumab, Atezolizumab, Avelumab) and anti CTLA-4 (Ipilimumab, Tremelimumab)[17].

In the setting of NSCLC first line of treatment, Durvalumab has shown to be of benefit only in stage III as consolidation therapy following treatment with chemoradiotherapy[30]; Pembrolizumab has been used in monotherapy as first line agent in recurrent or metastatic disease in tumors expressing PD-1 >50% [31] or in combination with chemotherapy when PD-1 is >1% [32]. In this scenario, Nivolumab has not increased overall survival as monotherapy[33]. However, in combination with Ipilimumab has shown to increase the PFS and OS as well, with or without added chemotherapy[37,38], particularly in patients with negative PD-L1.

As regards the second line of treatment, immunotherapy options include Nivolumab, Pembrolizumab or Atezolizumab in patients that haven't received immunotherapy in the first line setting, Eastern Cooperative Oncology Group (ECOG) 0-1 and those whom have not shown progression of the disease as best response to first line therapy based on RECIST criteria[36].

Currently, there is a limited number of therapeutic targets (PD-1, PD-L1, CTLA-4, ESO-1 and CD19) that have shown clinical benefit. Although many more therapeutic targets have been identified, some of them can't be used due to their toxicity profile and the risk of a cross reaction with the host's own antigens in vital tissues[21].

Concept of primary resistance to immunotherapy

In spite of all these remarkable advances, still approximately 30% to 50% of patients do not respond to ICI therapy from the beginning, a situation known as primary resistance[37]. Primary resistance to immunotherapy is multifactorial and comprises intrinsic and extrinsic mechanisms. Among the intrinsic ones, there are the alteration in the antigenic processing, decrease in the expression of tumoral antigens, alterations in the signaling pathways MAPK, PI3K, WNT, JAK1/2, resistance to cell death directed by Interferon gamma, etcetera. As regards the extrinsic mechanisms, other factors affecting the tumoral stroma have been proposed, such as migration of immunosuppressive cells to the tumor microenvironment with an M2-like effect; the presence of Cancer Associated Fibroblasts (CAFs) which cause a remodeling of the extracellular matrix creating a physical barrier impeding the infiltration of T lymphocytes, affecting the antigen presentation and impairing the function of dendritic cells, the loss of function of the chromatin remodeling genes (PBRM1, ARID2, BRD7), among many others [37,38].

MATERIALS AND METHODS

We assessed 128 records (clinical trials, reports, meta-analyses) in order to provide an updated review of the treatment of NSCLC, current definitions proposed for pseudo and hyperprogression (which are not homogeneous so far), incidence, theories about their physiopathogenesis, importance of making a judicious diagnostic workup, imaging criteria as well as biochemical markers in order to predict their appearance (Figure 1).

PSEUDOPROGRESSION

Concept

Pseudoprogression has been defined in a temporary fashion (since there is still no consensus about the entity) as the growth of the target lesion or the presence of new-onset tumor lesions before regression while maintaining the same treatment. The concept was described for the first time in a patient with high degree gliomas treated with temozolomide, where an initial increase in the size of the target lesions or the appearance of new lesions were observed without clinical worsening and even with improvement of signs and symptoms before witnessing a decrease in the size of the same lesions (clinical-radiological discordance)[17].
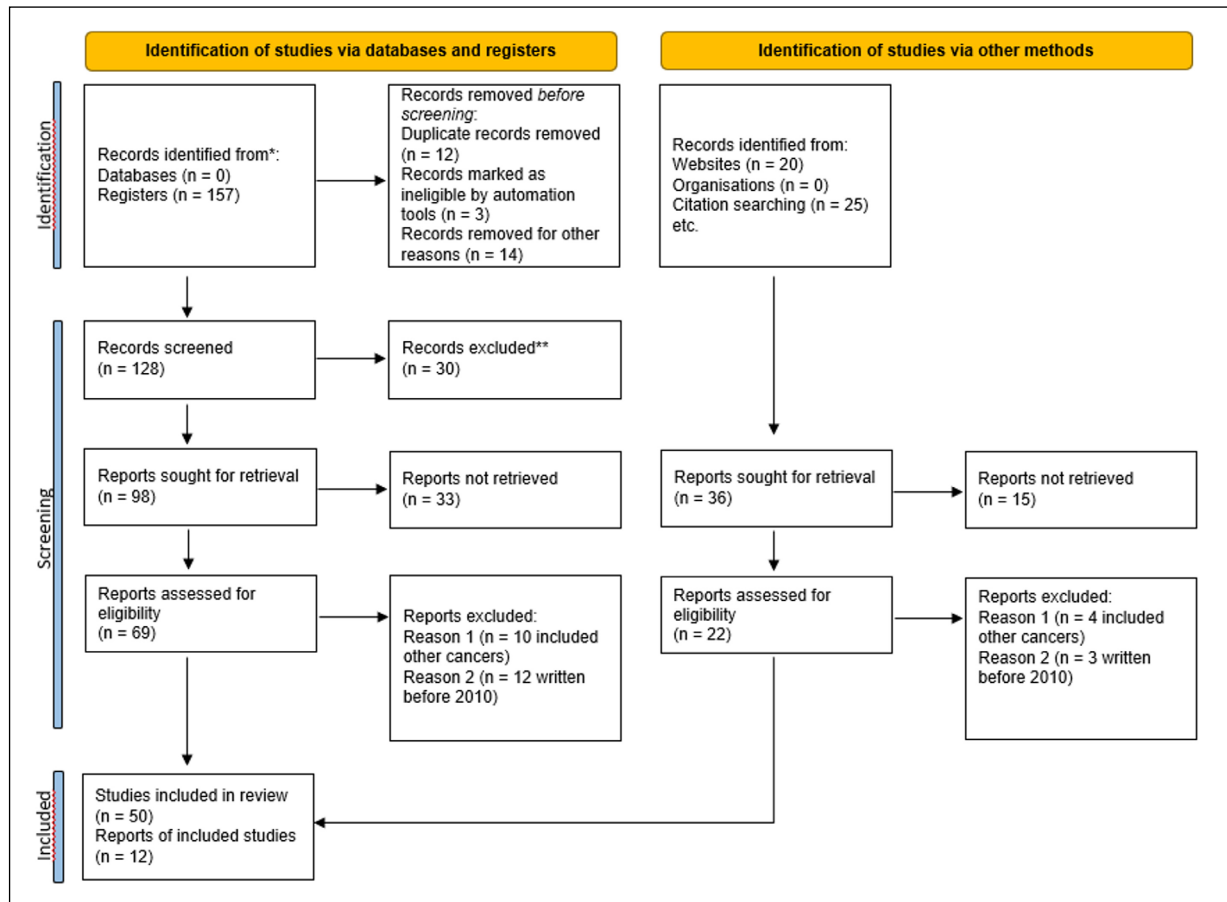
Figure 1. PRISMA flow diagram.

Two hypotheses have been proposed in order to explain this phenomenon. The first one suggests that tumors could continue their process of growing until the activation of an effective antitumor immune response has been stablished. The second one theorizes that this pattern is the result of the influx of immune cells in the tumor environment caused by the reactivation of the immune system which, in turn, would cause an inflammatory process and a transient increase of the tumor burden. The second hypothesis was confirmed later through biopsies of patients with melanoma who experienced a transitory progression while receiving CTLA-4 inhibitors[17]. However, currently the most widely accepted theory is that there is an initial release of neoantigens during treatment and these promote a pro inflammatory environment through multiple pathways, among them, differentiation of macrophages to an M1-like phenotype, increase in the recruitment of neutrophils and T lymphocytes and remodeling of the extracellular matrix.

Pseudoprogression during treatment with ICI was initially described in patients with melanoma receiving Ipilimumab and later in studies of patients receiving Pembrolizumab and Nivolumab. The rate of pseudoprogression varies between studies and types of cancer but very seldom is higher than 10%[39] *(Table 1)*. Later on, with the authorization of these therapies for the treatment of other malignancies, it was also described in lung cancer, which is the topic of this review.

Currently, the identification of this phenomenon represents an important challenge for clinicians. It's of major importance to be able to differentiate pseudoprogression from a true progression or even from hyperprogression, all of which require a multidisciplinary evaluation.

These considerations led to modifications for some radiologic criteria to evaluate the therapeutic response, developing new protocols of radiologic evaluation emphasizing specific interval times before reevaluation[42] *(Table 2)*.

For example, in patients with NSCLC (Non-Small Cell Lung Cancer), Concetta el al[44] reported that 2 of the 41 patients treated with ICI were classified as having disease progression by RECIST criteria but not by irRC (immune related Response Criteria). Eventually, these patients continued treatment and experienced a late tumor regression. This data suggests that RECIST might underestimate the benefit of

Table 1. Reported Incidence of Pseudoprogression in Different Studies: NSCLC.

	Study Type	Type of Cancer	Agent	Definition	Number of Patients	%
Nishino et al[40]	Retro-spective	Non-Squamous Cell NSCLC	Pembro-lizumab	PR following PD according to RECIST	107	2.8
Borghaei et al[41]	Prospective Study Phase III	Squamous Cell NSCLC	Nivolumab	Appearance of a new lesion followed by a decrease of ≥ 10% from the start in the sum of target lesions or an initial increase from the nadir of ≥ 20% in the sum of target lesions followed by a reduction of ≥ 30% from the start, or the appearance of new lesions followed by at least two tumor evaluations not showing additional progression defined as a ≥ 10% increase in the sum of target lesions and new lesions	292	5.4
Tazdait et al[42]	Retrospective Monocentric	NSCLC	Anti PD-1 / PD-L1	PR following PD according to RECIST	160	5
Katz et al[43]	Retrospective Monocentric	NSCLC	Anti PD-1	PR following PD according to RECIST	166	1.8

therapy with ICI in some patients. In patients receiving treatment with ICI, the radiological evaluation requires a new control at 4-8 weeks to differentiate between a true progression from a pseudoprogression[45]. ***Figure 2*** shows an example of this evaluation by CT.

HYPERPROGRESSION

Definition and incidence

Considering that immunotherapy has changed the outlook in the treatment of different malignancies, there are some sub-groups that not only do not draw any benefit from it but also present a rapid progression of the disease, known as "Hyperprogression" or "Hyper progressive Disease (HPD)". This term is not yet universally accepted and lacks a consensus definition to this date. The incidence of this entity has been described to be between 4% and 29% in retrospective studies[46].

Hyperprogression was first described in case reports and retrospective studies of patients treated with ICI, where it was found that some of the patients exhibited an accelerated tumor growth seemingly related to treatment[16].

In order to provide a definition to help clinicians to make a differential diagnosis between these entities and true progression, several studies have tried to stablish an accurate one. In the meta-analysis of Park et al[47], the definitions of HPD varied and were categorized according to the calculation of tumor growth acceleration, using different measurements for each one. Categories are mentioned as follows:
- Category 1: tumor growth rate (TGR) ratio in order to compare the speed of increase in tumor volume before and after treatment.
- Category 2: tumor growth kinetics (TGK) ratio in order to compare the speed of increase in tumor size before and after treatment.
- Category 3: early tumor burden increases between baseline imaging and the first time point after treatment.
- Category 4: combinations of these categories.

Table 2. Radiologic Criteria in Immuno-Oncology.

	RECIST 1.1 Unidimensional	irRC Bidimensional	irRECIST Unidimensional	iRECIST Unidimensional	imRECIST Unidimensional
Initial size of the lesion	≥ 10 mm	5 × 5 mm	≥ 10 mm	≥ 10 mm	≥ 10 mm
Number of initial lesions	5 total, 2 per organ	10 total, 5 per organ	5 total, 2 per organ	5 total, 2 per organ	5 total, 2 per organ
CR	Disappearance of all lesions.	Disappearance of al llesions.	Disappearance of all lesions.	Disappearance of all lesions.	Disappearance of all lesions.
PR	Decrease of ≥ 30% in the maximum diameter of target lesions.	Decrease of ≥ 50% in the maximum diameter of target lesions.	Decrease of ≥ 30% in the maximum diameter of target lesions.	Decrease of ≥ 30% in the maximum diameter of target lesions.	Decrease of ≥ 30% in the maximum diameter of target lesions.
SS			Does not meet criteria for PR or PD		
PD	Increase of ≥ 20% from the nadir (≥ 5 mm).	Increase of ≥ 25% from the nadir.	Increase of ≥ 20% from the nadir (≥ 5 mm).	Increase of ≥ 20% from the nadir (≥ 5 mm).	Increase of ≥ 20% from the nadir (≥ 5 mm).
Confirmed PD	Does not apply	At least 4 weeks after	At least 4 weeks after	and up to 12 week	At least 4 weeks after
Appearance of New Lesions	Always PD	Add to the sum of all lesions	Add to the sum of all lesions PD, not included	Not confirmed of all lesions in the sum of all lesions	Add to the sum

ABBREVIATIONS - RECIST: Response Evaluation Criteria in Solid Tumors. CR: complete response, PD: progression of disease, PR: partial response, irRC: immune related response criteria, iRECIST: immune RECIST, imRECIST: immune modificated RECIST, irRECIST: immune related RECIST.

A summary of definitions is shown in Table 3.
To this date, the most widely utilized parameters incorporate at least a doubling of TGR (tumor growth rate), that is a two-fold increase in the volume of the tumor for a month after the start of therapy[45].
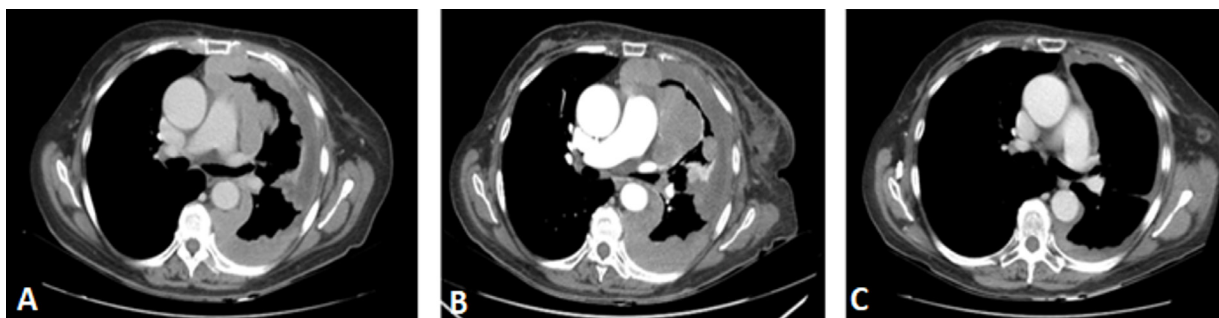

Figure 2. Evolution of pseudoprogression. A 67-year-old man diagnosed with metastatic NSCLC (A, start point) received treatment with pembrolizumab in the second line setting, showing an increase of the tumoral size (B) at week 4 of beginning of treatment, with a notable shrinking of tumoral size at week 12 from the beginning of immunotherapy (C).

Table 3. Definitions of HPD according to some studies.

Publication	Description	Units and Measurement	Definition of HPD
Champiat et al[14]	It was considered that 12 patients (9%) had HPD. HPD was not initially associated with an increase of the tumoral burden or with a specific type of tumor. During the progression, patients with HPD had a lower rate of new lesions than patients with progression of the disease but without HPD ($p<0.05$). HPD was associated with advanced age ($p<0.05$) and worse overall survival.	TGR = Δ Tumoral volumen / Δ Time (months)	PD and TGR defined by RECIST >2 TGR
Saâda-Bouzid et al[15]	Hyperprogression was observed in 29% of patients with R/M HNSCC treated with PD-1/PD-L1 inhibitors and was correlated with a shorter Progression Free Survival (PFS).	TGK = Δ Sum of tumor diameters /Δ Time (months)	TGK/TGKpre>2
Ferrara et al[48]	56 patients (13.8%) were classified as exhibiting HPD. HPD was significantly associated with more than 2 metastatic sites before therapy with PD-1/PD-L1 inhibitors was started in contrast with those patients whom did not develop HPD (62.5%) 35 out of 56 vs. 42.6% (149 out of 350); $p=0.006$.	TGR = Δ Tumoral volumen / Δ Time (months)	PD and TGR defined by RECIST ≥ TGR + 50%
Kato et al[49]	After monotherapy with anti-PD-1 / PD-L1, four of these patients showed notable increases in tumor size (55% -258%), new-onset great masses and an accelerated rate of growing	TGR = Δ Tumoral volumen / Δ Time (months)	Time to Treatment Failure <2 months and > 50% increase of the tumor burden and TGR ≥2 TGR

ABBREVIATIONS - HPD, Hyperprogressive Disease; PD, Progressive Disease; RECIST, Response Evaluation Criteria in Solid Tumors; TGK, Tumor Growth Kinetics; TGR, Tumor Growth Rate.

A study by Champiat et al[14] defines HPD as an increase in the tumor growth rate (TGR) of at least two-fold when the first radiologic evaluation is performed after the start of immunotherapy and compared to the size of the tumor before therapy. In a cohort of 282 patients HPD was described in 9% of them. These patients had a higher mortality compared to those who exhibited a partial response (PR), complete response (CR) or stable disease (SD) (HR=25.94, CI 95% 5.57-120.74 $p=$ 0.000033).

Saâda-Bouzid et al[15] used the tumor growth kinetics (TGK), understood as the change in the sum of diameters (according to RECIST) per unit of time and defined hyperprogression as a relation between control TGK and basal TGK >2.

Other criteria have incorporated Time to Treatment Failure (TTF) and an absolute increase of TGR[49].

Studies reporting cases of HPD eliminate those patients lost during follow-up or those who fail to show up for control radiologic studies, generally due to worsening disease. Hence, it's possible that the number of cases where HPD is present can be underestimated. However, since there is not yet a universally accepted definition for HPD, the risk of describing as HPD assorted biological behaviors and not just one entity is a major concern.

Kas et al[50] conducted a retrospective cohort study of 406 patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors in 8 institutions in France. Measurable lesions were defined utilizing RECIST Criteria 1.1 in at least 2 tomographic evaluations before treatment with ICI and 1 tomographic evaluation during the treatment and. It was found that among the 406 patients with NSCLC included in the analysis,

Table 4. Incidence and Predictive Markers for HPD.

Study	Therapy	Type of Cancer	Number of Patients	Predictive Factors Incidence
Champiat et al[114]	PD-1 / PD-L1 Inhibitors (Phase I assay)	Any	131	9.0% Age > 65 yrs
Kato et al[49]	ICI or Costimulatory Molecules	Any	155	4% Alterations in EGFR, MDM2 / 4 y DNMT3A
Matos et al[51]	ICI (Phase I assay)	Any	214	15%
Ferrara et al[48]	PD-1 / PD-L1 Inhibitors	NSCLC	152	13.8% > 2 Metastatic Sites
Russo et al[52]	ICI	NSCLC	152	25.7% Myeloperoxidase (MPO) Density of Myeloid Cells Inside the Tumor. Low PD-L1 Expression in Tumor Cells
Tunali et al[53]	PD-1 / PD-L1 Inhibitors ± CTLA4 Inhibitors	NSCLC	228	Combination of Radiomic Functions and RMH Score.
Kim et al[54]	PD-1 / PD-L1 Inhibitors	NSCLC	263	18.9% LDH> Upper Normal Limit, Liver Metastasis, Metastasis in > 2 locations. RMH Score, GRImScore, LIPI Score.
Saâda-Bouzid et al[15]	PD-1 / PD-L1 Inhibitors	HNSCC	34	29.0% Regional Recurrence Irradiated Field

ABBREVIATIONS - CTLA-4 Cytotoxic T-lymphocyte-Associated 4, HNSCC Head and Neck Squamous Cell Carcinoma, ICI Immune Checkpoint Inhibitors, LDH Lactate Dehydrogenase, LIPI Lung Immune Prognostic Index, NSCLC Non Small Cell Lung Cancer, PD-1 Programmed Cell Death Protein 1, PD-L1 Programmed Cell Death Protein Ligand 1, RMH Royal Marsden Hospital Score, TGK Tumor Growth Kinetics, TGR Tumor Growth Rate, TTF Time to Treatment Failure.

the different definitions of HPD resulted in an incidence of 5.4% (n=22) of the phenomenon for a definition based in a rate of progression > 2 and a time to treatment failure of < 2 months, and of 18.5% (n=75) for a definition based on TGR.

The concordance between these different definitions (using Jaccard Similarity Index) ranged from 33.3% to 69.3%. For each definition, HPD was associated with a shorter survival, the difference between TGR before and after therapy (ΔTGR) had the best correlation with a poor overall survival, with an initial plateau for a larger number of patients and then a slower increase and also had a higher capacity to distinguish patients with HPD from those with progression of the disease not classified as hyperprogression, suggesting that the 5 previous HPD definitions were not associated with the same tumor behavior and concluding that additional studies with larger number of patients are needed to confirm and validate the precision of the proposed definition.

There are still challenges when it comes to deciding which definition to use, given that all of them have strengths and weaknesses. On one hand, HPD could be overestimated or underestimated if the assessment was limited to tumor growth rate or tumor growth kinetics ratio, target lesions, or response evaluation criteria in solid tumors (RECIST)–defined progressors, or if the assessment time frame conformed to RECIST. On the other hand, there are still concerns about when it is suitable to make new measurements of the lesions, if current definitions of HPD can appropriately reflect the change in overall tumor burden, if HPD is truly associated with the clinical outcome by discriminating between patients with HDP *vs.* natural progression of disease (PD). About the latter one, the reported outcomes were heterogeneous across studies, raising, once again, the question regarding the clinical significance of HPD definitions[49].

Evaluation of Response

Immunotherapy has changed the natural course of some neoplasms and has shown clinical scenarios never seen previously, therefore the need to generate new tools to evaluate the response to these treatments has arisen.

RECIST and iRECIST[9]

RECIST Criteria (Response Evaluation Criteria in Solid Tumors) has undergone multiple modifications through time, among them we can cite irRC (immune related response criteria) that incorporate changes in the selection of target lesions (at least 5 x 5 mm, with a maximum of 10 lesions in total and up to 5 per organ). In 2013 this modification was published using unidimensional lesions.

iRECIST criteria added the scenarios of confirmed and non-confirmed progression. In the latter scenario the most appropriate plan is to continue with the proposed treatment and to repeat imaging studies at 4 weeks as long as the condition of the patient allows for that. If progression is not confirmed, then reevaluation has to be carried out as originally planned. Although different reported definitions for HPD consider 2D and 3D imaging measurements and mathematical formulas to calculate the rate of tumor growth through time, clinical evaluation cannot be dismissed and must be pointed out that currently there isn't an ideal gold standard to evaluate the response of patients to treatment with immunotherapy.

Predictive Markers for HPD

Different features of patients and tumors have been assessed in order to find correlations between them and the probability of developing HPD, with heterogeneous findings among the studies made. These include genomic variations such as MDM2 amplification, previous radiotherapy and advanced age. In patients with NSCLC or Melanoma treated with ICI, high levels of LDH (lactic dehydrogenase) and a neutrophil/lymphocyte ratio of >3 were significantly associated with a worse survival. In a study by Ferrara et al[48] there was no association between the age of the patients, the serum levels of LDH or the neutrophil/lymphocyte ratio and HPD. However, the authors did identify a correlation between HPD and an increase of the tumor burden defined as more than 2 metastatic sites before the start of therapy with anti PD-1/PDL-1 agents (p= 0.006). While Champiat et al[14] registered an observed age of 65 and older as a risk factor for hyperprogression, this has not been confirmed in other studies[15, 49, 51-54] **(Table 4).**

Saâda-Bouzid et al[15] observed that 50% (n=9 out of 18) of patients with local recurrence had hyperprogression during therapy with anti PD-1/PD-L1 drugs, whereas only 6% of those not having local recurrence experienced hyperprogression (p= 0.008). Previous radiotherapy could play a role because all cases of hyperprogression happened in those who had at least one locoregional recurrence[46].

Kim et al[54] recently published a meta-analysis study where they analyzed predictive factors for hyperprogression among 1519 patients treated with PD-1 or PD-L1 inhibitors. In this study 4 parameters correlated with hyperprogression: LDH above normal limits (OR 1.89), more than 2 metastatic sites (OR 1.86), liver metastasis (OR 2.33), and RMH score ≥ 2 (OR 2.33). Furthermore, the authors discovered an inverse correlation between the expression of PD-L1 by the tumor cells and hyperprogression (OR 0.6). Due to the fact that there is still a very low level of certainty to prove this, it's not yet recommended to limit the prescription of ICI in function of any of these factors. Nonetheless, patients with elevated LDH levels, liver metastasis or multiple metastatic locations should be closely monitored to quickly identify hiperprogression. Summarizing, there aren't currently statistically strong predictive factors for hyperprogression.

Theories about Hyperprogression

Different hypotheses have been proposed to explain the hyperprogression phenomenon. One of them suggests punctual mutations that confer a worse prognosis, and among them one of the most researched mutations is MDM2 (Murine Double Minute-2), this one is described in the study by Kato et al[49]. A TTF of less than 2 months was found in 6 patients with MDM mutation (n=5 MDM2, n=1 MDM4.) and in these patients 67% exhibited HPD.

Another theory proposed to explain HPD is Immunosenescence. In the study by Champiat et al[14] higher rates of HPD were observed with advanced age. 19% (7/36) of patients older than 65 years developed HPD compared with only 5% (5/95) in the rest of the patients (p= 0.018). One hypothesis trying to explain this difference is that the production of virgin T lymphocytes decreases in older adults whereas memory T lymphocytes increase with age[55].

Alterations in p53 gene have been proposed as one of the possible triggering factors in HPD. This gene is inactivated either by mutation or by loss of its function in approximately 50% of tumors, situation more prevalent in advanced stages of the disease. The other 50% of tumors present mutations in MDM2 which acts as a regulator gene of the activity and stability of p53 and compromises the ubiquitination through this pathway. It has been observed that MDM2 is amplified in certain tumor types, such as central nervous system, gastric, lung, skin, breast, soft tissue sarcomas, among others[56].

Other suggested mechanisms are the activation of alternative signaling pathways after the blockage of PD-1/PD-L1; the changes produced in the tumoral microenvironment by ICI in reference to the effect of CAFs (Cancer associated fibroblasts) that cause a remodeling of the tumoral stroma, creating a physical barrier that affects the free transit of T lymphocytes and the presentation of antigens by the dendritic cells. One more mechanism proposed is the activation of ILC3 (Type 3 Innate Lymphoid Cells) stimulating the production of interleukins 17 and 22 and favoring the recruitment of neutrophils[37].

DISCUSSION

Some of the unfavorable effects of Immunotherapy had been described initially in patients with melanoma treated with adjuvant alpha interferon in which the progression free survival (PFS) and overall survival (OS) were lower than in the control group[54]. The extent of its use in the treatment of other malignancies, such as NSCLC has led to the spotlight these entities as an emergent matter of interest.

Although immunotherapy can induce deep and long-lasting responses in certain cases, there are subgroups of patients whom experience a "flash in the pan" effect or an uncontrolled activation of the disease. One of the first studies reporting the hyperprogression phenomenon was the one by Champiat et al[14] in which it is described that 9% of the patients experienced hyperprogression, defined in that study as at least the duplication of the tumor size during the first radiologic evaluation after the start of therapy associated with clinical deterioration and 8% of the patients could not be evaluated because they presented progression of the disease before the first radiologic evaluation, suggesting that the phenomenon is not infrequent.

The CheckMate 017 study compared Nivolumab *vs.* Docetaxel in patients with Non-Squamous NSCLC. The curves of PFS and OS in patients with PD-L1 negative tumors seem to favor Docetaxel during the first months of treatment, suggesting that possibly there was a subgroup of patients treated with Nivolumab who progressed or died immediately after the start of treatment[41].

Clinicians must take into account as plenty of differential diagnosis as they can in order to make a judicious distinction from hyperprogression and other entities. As an example, the resistance to the PD-1 / PD-L1 blockage, which is knows as primary when there is no response to treatment from the beginning or as acquired resistance when, after an initial response of variable duration, there is progression of the disease. Patients with hyperprogression or those whom their best response was progression of the disease are considered to have primary resistance and it is thought to be multifactorial. Some of the mechanisms described for primary resistance are inadequate infiltration of T lymphocytes due to the absence or insufficiency of immunogenic antigens, the exclusion of T lymphocytes where they can't penetrate the tumor microenvironment. One of the described mutations that contribute to the exclusion of T lymphocytes is the activation of the Wnt/β-catenin pathway, demonstrating in animal models a correlation between the activation of this pathway and the decrease infiltration capacity of the T-CD8 lymphocytes[58].

Other mechanisms include the tumor resistance to interferon, where mutations in JAK1 and JAK2 binding the receptor for gamma interferon (IFN-γr) don't allow the phosphorylation and activation of STAT1 and STAT3 for its nuclear translocation and in that way activate the interferon regulatory factor (IRF-1) which is associated with the anti-proliferative effect of interferon; and lastly there also are immunosuppressive factors of the tumor microenvironment like Tregs and MD-SC[58].

In a different context, specific clinical characteristics that allow predicting pseudoprogression have not been identified. Fujimoto et al[59] described 14 patients with pseudoprogression where he found no differences in age, ECOG, gender, number of previous chemotherapy treatments or smoking history.

A small series of 3 cases with KRAS mutation lung adenocarcinoma described 2 patients who presented pseudoprogression and showed a dramatic decline in the Circulating tumor DNA (ctDNA), while the patient with true progression showed an increase of this measurement. Although still preliminary, ctDNA could be a promising marker during the first weeks of treatment with ICI to distinguish pseudoprogression from true progression. Matsuo et al[60] found that a decrease in CXCL2 and an increase of metalloproteinase MMP2 were associated with a longer PFS in patients with NSCLC treated with Pembrolizumab or Nivolumab.

The precise relationship between these phenomena is still unknown. However, CXCL2 has been identified as a chemokine with capacity to recruit MD-SC in bladder cancer. Interleukin-8 (IL-8) has also been identified as a marker for resistance to immunotherapy. Sanmamed et al[58] determined periodically the serum values of IL-8 in 14 patients with melanoma and in 12 with NSCLC treated with anti PD-1 immunotherapy and found lower levels of IL-8 during the time of higher tumoral response and a rapid increase during progression. Taking pre and post immunotherapy treatment biopsies should be part of the routine evaluation as an effort to identify molecular markers or immunological patterns that allow to predict the possibility that a patient is having pseudo or hyperprogression, and in this fashion, to be able in the future to select the best treatment option[61,62].

CONCLUSIONS

Pseudoprogression and hyperprogression continue to be a topic of ongoing debate. The accurate identification of these phenomena is still a challenge for the clinician. The finding of an ideal biomarker for atypical responses like these might allow to identify those patients with a higher risk for hyperprogression during treatment with ICI and consequently, select an alternative treatment and, moreover, to correctly identify those with a higher risk for pseudoprogression in order to avoid a premature discontinuation of therapy[46]. At this point, there aren't still adequate, standardized and homogeneous tools for the evaluation of response to therapy with ICI. Obtaining a CT scan as an early evaluation at the beginning of the treatment with immunotherapy and confirming the progression by imaging in selected patients at 4 weeks seems to be a reasonable strategy. A better understanding of these events will allow the improving of selection of patients for treatment with immunotherapy and adequately direct the treatment to achieve the highest possible benefit with these agents.

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