VIA MEDICA

REVIEW ARTICLE

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Pseudoprogression during immunotherapy of cancers

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Oncology in Clinical Practice
2017, Vol. 13, No. 2, 57–60
DOI: 10.5603/OCP.2017.0009
Translation:
dr n. med. Dariusz Stencel

ISSN 2450–1654

ABSTRACT

Pseudoprogression denotes apparent, early progression of disease followed by long-lasting regression. This phenomenon is observed during the treatment of different cancers and in approximately 10% of patients receiving immunotherapy. The appearance of pseudoprogression could make difficult the assessment of treatment response based on Response Evaluation Criteria in Solid Tumours (RECIST). In this report, the scope of pseudoprogression was discussed as well as currently proposed alternative methods of treatment response assessment according to Immune-related Response Criteria (irRC).

Key words: pseudoprogression, immunotherapy, cancer, irRC

Oncol Clin Pract 2017; 13, 2: 57–60

Introduction

Pseudoprogression in cancer patients includes a preceding sub-acute reaction to the treatment, with signs of disease progression in imaging examinations, and also with clinical deterioration in a small portion of patients. Pseudoprogression was described for the first time as "bone scan flare phenomenon" in breast cancer and prostate cancer patients receiving hormone therapy or bisphosphonates [1–6]. In this case, it was based on the results of the first follow-up bone scintigraphy, showing increased radiotracer uptake in "hot spots" or even increasing their numbers. A similar phenomenon is not uncommon in magnetic resonance imaging in patients with malignant glioma undergoing radiochemotherapy [7–9].

The mechanism of pseudoprogression is not clear. It is assumed that it is connected with local tissue reaction for developing tumour, extensive inflammatory infiltration, increased vascular permeability, and oedema; as regards bones, engagement of osteoblasts in regenerative processes can play a role and "healing" of micrometastases, not visible in baseline imaging [5, 6, 9]. It could be that increased vascular permeability results from intensified uptake of contrast medium used in imaging examinations.

Pseudoprogression during immunotherapy

For the first time pseudoprogression during immunotherapy was observed in patients with disseminated skin melanoma, receiving ipilimumab, human monoclonal antibody directed against cytotoxic T lymphocyte antigen-4 (CTLA-4) [10]. Of note, despite disease progression during the initial phase of treatment with ipilimumab, some patients subsequently achieved robust clinical benefit [10]. Pseudoprogression in melanoma patients was also reported during treatment with monoclonal antibodies being immune-checkpoint inhibitors (anti-PD), like nivolumab or pembrolizumab [11, 12]. Similar changes were observed when PD inhibitors were used in non-small cell lung cancer (NSCLC) and breast cancer patients [13–18]. It is estimated that early pseudoprogression in imaging examinations occurs in approximately 10% of patients receiving immunotherapy [19]. In these circumstances, it seems that pseudoprogression is connected with infiltrations of active T-cells and other immune cells within metastases [19, 20]. This unusual response could contribute to overall survival (OS) benefits, but without progression-free survival (PFS) benefits in clinical trials with immunotherapy in

Table 1. The clinical trials with immunotherapy in NSCLC and renal-cell cancer patients

Study	Type of cancer	N	Design	PFS HR (95% CI; p)	OS HR (95% CI; p)
POPLAR [13]	NSCLC	287	Atezolizumab *vs.* docetaxel	0.9 (0.7–1.23); NS	0.7 (0.5–0.99); p = 0.04
CHECKMATE-057 [14]	NSCLC	582	Nivolumab *vs.* docetaxel	0.9 (0.8–1.1); p = 0.4	0.7 (0.6–0.9); p = 0.002
CHECKMATE-025 [21]	RCC	821	Nivolumab *vs.* everolimus	0.9 (0.8–1.0); p = 0.1	0.7 (0.6–0.9); p = 0.002

NSCLC — non-small cell lung cancer; RCC — renal-cell cancer; PFS — progression-free survival; OS — overall survival

Table 2. The comparison of WHO, RECIST, and irRC criteria of treatment response assessment

Finding	WHO	RECIST	irRC
New, measurable lesions (i.e. ≥ 5 × 5 mm)	Always represent PD	Always represent PD	Incorporated into tumour burden
New, non-measurable lesions (i.e. < 5 × 5 mm)	Always represent PD	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining best overall response (BOR) of CR, PR, SD, and PD	Changes contribute to defining best overall response (BOR) of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
Complete response (CR)	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
Partial response (PR)	≥ 50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 weeks apart, in absence of new lesions or unequivocal progression of non-index lesions	At least a 30% decrease in the SLD of target lesions, taking as reference the baseline sum diameters	≥ 50% decrease in tumour burden compared with baseline in two observations at least 4 weeks apart
Stable disease (SD)	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD	50% decrease in tumour burden compared with baseline cannot be established nor 25% increase compared with nadir
Progressive disease (PD)	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm (two lesions increasing from 2 to 3 mm, for example, does not qualify)	At least 25% increase in tumour burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

WHO — World Health Organisation; RECIST — Response Evaluation Criteria in Solid Tumours; irRC — Immune-related Response Criteria

NSCLC and renal-cell cancer (RCC) patients (Table 1) [13, 14, 21]. Considering pseudoprogression, Wolchok et al. [19] proposed four types of response to treatment in melanoma patients receiving ipilimumab. The first two: regression of baseline lesions during first 12 weeks of therapy and disease stabilisation with possible subsequent slow shrinkage, were included into traditional criteria of response evaluation. On the other hand, the remaining two: disease regression after initial enlargement or regression during or after transitional occurrence of new lesions, are considered the phenomenon of pseudoprogression.

Assessment of treatment response in cancer patients receiving immunotherapy

Appropriate assessment of treatment response plays a crucial role in clinical decision-making processes. In 1981 the World Health Organisation (WHO) tried for the first time to standardise response criteria [22]. For majority of cancers, computed tomography (CT) is currently considered as the best method, both as regards to response evaluation and reproducibility. At present Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) are used while interpreting CT images. These criteria were developed based on database including more than 6500 patients participating in prospective clinical trials, mainly with chemotherapy [23]. As regards immunotherapy, characterised by kinetics other than chemotherapy, RECIST or WHO criteria do not always reflect the actual treatment effect. Consequently, in patients with pseudoprogression it could lead to abandonment of potentially effective treatment. So, in 2009 some modifications of standard criteria of response assessment were proposed for patients receiving immunotherapy in prospective clinical studies, e.g. immune-related response criteria (irRC), encompassing occurrence of pseudoprogression during the initial phase [19]. According to these criteria, in the case of suspected disease progression it is required to confirm this during the next examination, and occurrence of the new lesion or lesions does not automatically mean a progression but is included into the total tumour burden (TTB), which is a sum of the products of the two largest perpendicular diameters (SPD) and a SPD of new, measurable lesions. SPD assessment includes maximally up to five lesions in one organ, up to 10 visceral and five skin lesions, and minimal magnitude of new measurable lesion must be 5 mm. During subsequent measurements, TTB changes should be taken into account. Table 2 presents a comparison of WHO, RECIST, and irRC criteria of treatment response assessment. In the meantime, these new response criteria are proposed for use in patients with solid tumours receiving immunotherapy; however, they need to be validated in prospective clinical studies.

Summary

Response to immunotherapy in patients with solid tumours frequently occurs later than after chemotherapy and not uncommonly is preceded with pseudoprogression in imaging examinations. Considering this phenomenon as actual, progression and premature treatment discontinuation could blight the possible chance for clinical benefit. This misinterpretation could be avoided by using new irRC response criteria, which take into account the possibility of images only resembling disease progression. However, these criteria need to be validated in prospective clinical trials.

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