European Journal of Cancer 88 (2018) 38–47

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria

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Received 30 September 2017; accepted 22 October 2017

KEYWORDS
Carcinoma;
Non–small cell lung cancer;
Immunotherapy;
Imaging evaluation

Abstract ***Background:*** Immune checkpoint inhibitors are an important tool in the therapeutic strategy against metastatic non–small cell lung cancer (NSCLC); however, radiological evaluation is challenging due to the emergence of atypical patterns of responses. Several evaluation criteria have been proposed, such as the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, immune -related RECIST (irRECIST) and iRECIST, but have not been systematically compared in a homogeneous population.

Patients and methods: We conducted a monocentric retrospective analysis of consecutive advanced NSCLC patients treated with an anti–programmed cell death-1 or anti–program death-ligand 1. Response patterns and the discordance between RECIST 1.1, irRECIST and iRECIST guidelines were described, and associations of response patterns and clinical outcome were explored.

Results: Overall, 160 patients treated between February 2013 and October 2016 were included. Atypical responses were observed in 20 patients (13%), including eight pseudoprogressions (PsPDs) (5%) and 12 dissociated responses (8%). Thirteen of the 20 patients demonstrated clinical benefit. Per the RECIST 1.1, 37 patients (23%) showed an objective response or stable disease, and 123 patients (77%) exhibited progression. Eighty progressive patients were assessable for irRECIST and iRECIST: 15 patients were assessed differently; however, only three (3.8%) mismatches with a theoretical impact on the therapeutic decision were identified.

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https://doi.org/10.1016/j.ejca.2017.10.017

Patients with PsPD or dissociated response had higher overall survival than patients with true progression.

Conclusion: Atypical responses (PsPD/dissociated response) occurred in 13% of NSCLC patients under immune checkpoint inhibitors. Based on survival analyses, the RECIST 1.1 evaluation underestimated the benefit of immune checkpoint inhibitors in 11% of the progressive patients. Immune-related RECIST and iRECIST identified these unconventional responses, with a 3.8% discrepancy rate.

1. Introduction

As the most common cancer type across the globe [1], lung cancer is now the leading cause of cancer death worldwide. Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) or program death-ligand 1 (PD-L1) have become an important treatment avenue for metastatic lung cancer [2–6], resulting in increased overall survival (OS) compared with standard chemotherapy [7–12]. Since 2015, nivolumab, pembrolizumab and recently atezolizumab, have been approved by the US Food and Drug Administration for the treatment of non–small cell lung cancer (NSCLC), irrespective of the histologic subtype after first-line therapy, whereas pembrolizumab is also authorised as first-line therapy in patients with PD-L1 overexpression (>50%) [13].

Nevertheless, response patterns of tumours treated with immunotherapies may differ compared with conventional chemotherapeutic agents or targeted therapies, and accurate assessment of the response can be radiologically challenging [14]. Initially described in metastatic melanomas treated with ipilimumab [15], immune-related response patterns such as an initial increase in tumour burden or the appearance of new lesions termed 'pseudoprogression' may lead to misinterpretation of the patient's status and by consequence generate suboptimal clinical decisions [16]. As there are no reliable clinical or biological markers of activity for immune checkpoint inhibitors, radiological evaluation plays a leading role in decision-making care [17].

Conventional radiological response criteria, the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, [18] are insufficient for capturing pseudoprogression (PsPD) and can result in underestimation of the therapeutic benefit of immune checkpoint blockade. Several radiological criteria have been developed specifically for immunotherapy to better define the tumour response. Two-dimensional immune-related response criteria (irRC) were proposed in 2009 [15]. A simplification of these criteria was proposed in 2013, irRECIST (immune-related) [19–22]. More recently, the RECIST working group published a proposition of new criteria called iRECIST, to standardise response assessment among immunotherapy clinical trials [23].

The objectives of the present study are to describe the response patterns and the differences between RECIST 1.1, irRECIST and iRECIST criteria assessments in a homogeneous population of advanced NSCLC patients treated with anti-PD-1 or anti-PD-L1 therapy.

2. Materials and methods

2.1. Study design

A retrospective analysis of all consecutive patients receiving anti-PD-1 or anti-PD-L1 agents for advanced NSCLC after failure of first-line chemotherapy, was conducted at the Gustave Roussy, France between February 2013 and October 2016. Informed consent was obtained from all patients, and the local ethics committee approved the protocol. Patients with a concomitant second cancer, who had received concomitant radiation therapy or intrathecal therapy, or without adequate computed tomography (CT) evaluation (absence of confirmatory CT after initial progression or no target lesions on baseline CT imaging) were excluded. Follow-up scans were performed periodically according to study protocols or clinical routine (mostly every 6 weeks); anticipated CTs for clinical deterioration were analysed.

2.2. Patterns of responses

Stable disease (SD), partial responses (PRs) and complete responses (CRs) were identical for all guidelines. For progressing patients evaluated per the RECIST 1.1, PsPD was defined as a decrease or stabilisation of the tumoral elements that had constituted an initial assessment of progression, and dissociated responses were defined as concomitant decrease in certain tumoral elements and increase in other elements. Clinical benefit was defined as patients receiving at least 6 months treatment.

2.3. Tumour response assessment per RECIST 1.1, irRECIST and iRECIST (Table 1)

Two radiologists, specialised in immunotherapy evaluation (1 senior, 1 junior), centrally reviewed all consecutive CT scans to reach a consensus. At baseline, the