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Original Research

Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy

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† We like to commemorate Martin Leverkus who was a wonderful colleague, a talented researcher and a good friend.

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Abstract ***Background:*** Anti-programmed cell death 1 (PD-1) antibodies represent an effective treatment option for metastatic melanoma and other cancer entities. They act via blockade of the PD-1 receptor, an inhibitor of the T-cell effector mechanisms that limit immune responses against tumours. As reported for ipilimumab, the anti-PD-1 antibodies pembrolizumab and nivolumab can induce immune-related adverse events (irAEs). These side-effects can involve skin, gastrointestinal tract, liver, the endocrine system and other organ systems. Since life-threatening and fatal irAEs have been reported, adequate diagnosis and management are essential.

Methods and findings: In total, 496 patients with metastatic melanoma from 15 skin cancer centres were treated with pembrolizumab or nivolumab. Two hundred forty two side-effects in 138 patients have been analysed. In 77 of the 138 patients side-effects affected the nervous system, respiratory tract, musculoskeletal system, heart, blood and eyes. Not yet reported side-effects such as meningo-(radiculitis), polyradiculitis, cardiac arrhythmia, asystolia, and paresis have been observed. Rare and difficult to manage side-effects such as myasthenia gravis are described in detail.

Conclusion: Anti-PD-1 antibodies can induce a plethora of irAEs. The knowledge of them will allow prompt diagnosis and improve the management resulting in decreased morbidity.

1. Introduction

Nivolumab and pembrolizumab have been shown to enhance pre-existing immune responses, including anti-tumour response, by directly blocking programmed cell death 1 (PD-1) receptor which is a checkpoint of the effector stage of the immune system [1,2]. Currently, both nivolumab and pembrolizumab are approved for treatment of metastatic melanoma, nivolumab also for squamous non-small-cell lung cancer after prior chemotherapy and will soon be used against other cancer entities. Therefore, physicians should be aware of potential side-effects.

Grade 3 and 4 adverse events (AEs) are observed in 22–24% of ipilimumab-treated patients [3], in 5–10% of nivolumab- or pembrolizumab-treated patients, respectively [4,5], and in 55% of ipilimumab plus nivolumab-treated patients [6]. In principle, all checkpoint inhibitors can potentially induce immune-related AEs (irAEs) in any organ. Since anti-PD-1 treatment is continuously applied, irAEs can occur late after initiation of therapy but possibly also after cessation of therapy. To date cases of rare life-threatening or even fatal side-effects have been reported under anti-PD-1 antibody therapy like acute heart failure [7], rhabdomyolysis [8], and dyspnoea due to myositis [9]. Prompt diagnosis and adequate management are indispensable to reduce morbidity of these patients.

Here, we have summarized neurological, respiratory, musculoskeletal, cardiac and ocular side-effects induced by anti-PD1 antibodies from 15 skin cancer centres in Germany and Switzerland. Rare and therapeutically challenging side-effects are described in detail.

2. Methods

2.1. Ethics statement

This retrospective study was approved by the local institutional review board of the Friedrich-Alexander-University Erlangen-Nuremberg (approval number 17_16Bc). In addition, all clinical protocols were reviewed and approved by the local institutional review boards of each participating centre and were performed according to Good Clinical Practice and the Helsinki Declaration.

2.2. Study centres and treatment settings

Fifteen participating study centres in Germany and Switzerland screened patient records for pembrolizumab- and nivolumab-associated AEs and reported them. AEs were graded according to the National Cancer Institute Common Toxicity Criteria (CTC version 4.0). If not otherwise stated, pembrolizumab was administered intravenously over 30 min at a dose of 2 mg/kg body weight every 3 weeks and nivolumab over 60 min at a dose of 3 mg/kg body weight every 2 weeks. Based upon the authors' discretion, additional information was requested for the 11 most compelling and instructive cases of neurological, respiratory, musculoskeletal, cardiac and haematopoietic side-effects.

3. Results

A total of 496 melanoma patients were treated with nivolumab or pembrolizumab at 15 skin cancer centres. A total of 242 irAEs in 138 patients were reported. In 77