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Original Research

Detection of immune-related adverse events by medical imaging in patients treated with anti-programmed cell death 1

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Abstract ***Background:*** Programmed death receptor-1 blocking antibodies (anti-PD1) are a new standard of care in many cancer types. Patients benefit from improved survival but have the risk of immune-related adverse events (irAE). We evaluated if medical imaging procedures, used for anti-tumour response assessment, can detect irAEs.
Materials and methods: All consecutive patients treated with anti-PD1 and with a medical imaging acquisition performed within 2 weeks with irAEs ≥2 were retrospectively included. Data were gathered from June 2014 to February 2017, and a central review was performed. The

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primary and secondary end-points were i) to evaluate the overall detection rate of irAEs by medical imaging and ii) to provide a comprehensive radiological description of irAEs.
Results: Fifty-three patients (31 women, 22 men; average age: 61 years) were included. The primary tumour was melanoma (n = 32), lung cancer (n = 18) and other (n = 3). Patients were treated with nivolumab (n = 27) or pembrolizumab (n = 26). Of 74 medical imaging procedures analysed (ratio = 1.4 medical imaging per patient), 55 irAE were detected. The detection rate was overall: 74% (95 confidence interval: 63–84%), positron emission tomography with 18F-fludeoxyglucose integrated with computed tomography (18F-FDG PET/CT): 83% (n = 10/12), magnetic resonance imaging: 83% (n = 5/6), computed tomography scan: 79% (n = 19/24), ultrasonography: 70% (n = 19/27), standard X-rays: 40% (n = 2/5), lung/mediastinum: 100% (n = 7/7), enterocolitis: 100% (n = 8/8), hypophysitis: 100% (n = 3/3), thyroiditis: 75% (n = 15/20), hepatitis: 67% (n = 2/3), arthralgia or arthritis: 40% (n = 2/5) and pancreas: 28% (n = 2/7).
Conclusion: Medical imaging detected 74% of irAE in patients treated with anti-PD1. Beyond response assessment, medical imaging can detect irAE and guide towards specific management. We described the most frequent sites and patterns of imaging findings.

1. Introduction

Many cancers are known to escape immune surveillance through the expression of PD1, and therefore, anti-programmed cell death 1 (PD1) therapy has become a focus of anti-cancer therapy. Programmed cell death 1 inhibits T-cell action against tumour cells and also normal cells. The importance of programmed death receptor-1 blocking antibodies (anti-PD1) therapies is attested to by their registration as a 'breakthrough therapy' in many cancer types, such as melanoma, lung cancer, Hodgkin and primary mediastinal B-cell lymphoma, and this list will expand in the near future [1] (Table 1). Their use is no longer limited to the hospitals involved in clinical trials, and they are prescribed in a much wider range of clinical oncology settings across the world. Anti-PD1 therapies improve the overall survival of many patients living with cancer, and durable response, over 5 years or probably beyond, have been observed in patients with metastatic melanoma [2]. Consequently, the number of patients exposed to these new therapies will dramatically increase in the near future.

The monitoring of anti-PD1 treatment efficacy is different from chemotherapy and could be sometimes complex because anti-PD1 generates atypical patterns of response and progression [3–7]. Of note, new features as pseudoprogressive [8] and hyperprogressive disease [6] have been observed. In addition, a key role of medical imaging in oncology is to provide the prognostic and predictive biomarkers that allow for precision medicine approaches [6,7,9–11].

As one of the primary functions of PD-1 in healthy individuals is the suppression of auto immune response, the inhibition of this system has the potential to trigger T-cell inflammatory response against not only the cancer being targeted but also any susceptible healthy tissues. Adverse events with anti-PD1 are immune related, also called immune-related adverse events (irAEs). These irAE are mainly colitis, thyroiditis, rash, pneumonitis and arthritis, and some irAE have the potential to be life threatening if they are not rapidly detected and treated (Table 2). Most irAEs are of low intensity, but around 10% of patients treated with immune checkpoint blockers (ICBs) anti-PD1/PD-L1 will develop severe irAEs [12]. In addition, a misunderstanding of these irAEs may distort the assessment of actual treatment effectiveness. irAEs need to be both identified and well differentiated from metastatic progression of disease to alert the treating physician and to guide the next appropriate course of action (see Table 3).

The knowledge of irAE sites, frequency, timing and grading is essential for the physician to be able to improve its detection and management. The current expert opinion [13] recommends having a complete baseline physical profile (physical examination, laboratory values and relevant imaging) to serve as a benchmark before anti-PD1 initiation. Identification of gradual trend away from baseline may allow for early identification of an irAE and give the clinician a chance to preempt any serious complications. irAEs are generally detected by clinicians, and the role of radiologists to recognise the early signs of irAEs is unknown.

The role of medical imaging in the monitoring of anti-PD1 tumour response has recently been updated by the modified Response Evaluation Criteria in Solid Tumours in cancer immunotherapy trials (iRECIST) working group [8]. However, there are no guidelines and consensus on the detection of immune-related complications by medical imaging. The objective of the study was to describe the irAE imaging characteristics on medical imaging and to assess the detection rate of irAEs.