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EDITORIAL

Evaluation of response to immunotherapy: new challenges and opportunities for PET imaging

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Cancer immunotherapy focuses on the development of agents that can activate the immune system to recognize and kill tumour cells. It encompasses different strategies, the first of which is the activation of innate and adaptive immune effector mechanisms, such as vaccination with tumour antigens, treatment with cytokines (for example, interleukin 2 or interferon α) and enhancement of antigen presentation. Another important strategy involves neutralizing the inhibitory and suppressive mechanisms and includes the use of antibodies to deplete the regulatory T cells and the use of antibodies against immune-checkpoint molecules, for example cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death (PD1) [1].

Monoclonal antibodies (mAbs) that block the immunoregulatory damping mechanisms of the host response to tumour-associated antigens have recently become a practical reality with the first approval by the US Food and Drug Administration of ipilimumab in patients with unresectable or metastatic melanoma. Ipilimumab is a fully human monoclonal immunoglobulin specific for CTLA-4, a molecule that downregulates T-cell activation via a homeostatic feedback loop. Under normal physiological conditions, this mechanism prevents autoimmunity and allows the body to establish tolerance to self-antigens. Anti-CTLA-4 mAbs block CTLA-4 signalling preventing downregulation of the immune response and increasing the proliferation of T cells and the interaction of T cells and cancer cells [2]. Ipilimumab has been extensively tested in patients with melanoma. It was found to be the first compound to improve overall survival in a randomized, phase III trial comparing ipilimumab with or without the gp100 peptide vaccine versus gp100 alone in patients with previously treated, unresectable stage III or IV melanoma. Median overall survival in the combination ipilimumab and vaccine arm was similar to that in the ipilimumab-alone arm, but significantly higher than in the gp100 peptide vaccine-alone arm [3]. Another randomized phase III study demonstrated an increase in overall survival in patients with previously untreated stage IV melanoma receiving dacarbazine in combination with ipilimumab compared to dacarbazine alone [4].

Consistent with the mechanism of action of ipilimumab, that does not rely on the direct killing of tumour cells, the changes in tumour burden observed in clinical trials have often been very different from those observed using chemotherapeutic agents. Four distinct patterns of response have been described: (1) response in baseline target lesions, that is a "chemotherapy-like" response; (2) a slow, steady decline in tumour burden; (3) response after an increase in tumour burden, that is after progressive disease (PD) by standard response criteria; and (4) response in target and new lesions accompanied by the appearance of other new lesions. All these patterns are associated with favourable survival, although the last two may be misinterpreted as PD by standard methods [5].

Antibodies that target CTLA-4 have also been associated with several novel adverse effects that have been described as immune-related adverse events (irAEs). They are found in more than 70 % of patients and are typically responsive to interruption or discontinuation of CTLA-4 blockade in combination with immunosuppressive drugs such as corticosteroids [6]. Symptomatic irAEs have been described mainly in four organ systems: gastrointestinal tract, liver, skin and endocrine system. Clinically silent manifestations, in particular benign lymphadenopathy (sarcoid-like syndrome) and

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inflammatory changes in soft tissues (myositis, fasciitis), have also been reported and may be detected only during follow-up when CT, MRI or PET/CT are performed [6–11]. The different patterns of response and the appearance of irAEs are potentially consistent with the mechanism of action of CTLA-4 blockade, given the time it takes to generate an antitumour immune response and interpatient variability in immune system function. Therefore the assessment of response can be difficult, if not misleading, by standard methods such as the World Health Organization (WHO) criteria or Response Evaluation Criteria in Solid Tumors (RECIST) [12, 13], that were developed primarily to define the effect of cytotoxic drugs. The effectiveness of immunotherapy may also be misinterpreted using the PET Response Criteria in Solid Tumors (PERCIST) [14], owing to the nonspecific mechanism of uptake of the routinely used ^{18}F-FDG.

In order to avoid these misinterpretations we first need specific criteria for evaluation of response to the different types of immunotherapy now available, as have been developed in radiology. Indeed several new response criteria are being proposed and even applied in oncology trials in selected cancer patients receiving molecular targeted agents, such as the response criteria of Choi et al. for metastatic GIST treated with imatinib [15, 16] and the immune-related response criteria (irRC) for metastatic melanoma treated with ipilimumab [17]. Moreover, in patients treated with anti-CTLA-4 mAbs, a close collaboration with the clinician is required to define the optimal timing of the PET/CT scan, given the different times of onset and resolution of irAEs [18]. In this way considering the appearance of new PET-positive lesions as PD, that can lead to the early discontinuation of an effective therapy, can be avoided. We can also suggest the use of FDG PET in the early evaluation of response to treatment with ipilimumab. Indeed, a flare reaction (with an increase in the extent and uptake of known lesions and the appearance of irAE) may be predictive of response to therapy [19, 20]. Prospective studies are needed to resolve this point so that unnecessary treatments can be avoided, the correct timing of re-evaluation scans established and resources optimized.

These considerations will be even more important in the future, as the indications for the use of immunotherapy are expanding. Ipilimumab, for example, has been investigated in a phase II trial in combination with chemotherapy (carboplatin plus paclitaxel, CP) in patients with extensive disease small-cell lung cancer (ED-SCLC) or stage IIIB/IV non-small-cell lung cancer (NSCLC). Two dosing schedules were explored: concurrently with CP or after two cycles of CP (phased). A substantial improvement in immune-related progression-free survival (irPFS) and modified World Health Organization PFS was found in patients with NSCLC who received the phased ipilimumab regimen compared with those who received CP alone. Even patients with ED-SCLC treated with the same regimen had a significant improvement in irPFS [21, 22].

Finally, in the field of melanoma imaging, several specific molecular targets have been evaluated, including the melanocortin receptor, the sigma receptor and melanin [23]. In particular benzamide analogues, that are melanin-targeting agents, have been among the most promising of the newer melanoma radiotracers for both SPECT and PET imaging and therapeutic applications [24]. Different compounds, such as ^{18}F-6-fluoro-*N*-[2-(diethylamino)ethyl] pyridine-3-carboxamide (^{18}F-MEL050), *N*-[2-(diethylamino)-ethyl]-4-^{18}F-fluorobenzamide (^{18}F-FBZA), *N*-[2-(diethylamino)-ethyl]-2-^{18}F-fluoropropanamide (^{18}F-FPDA), ^{18}F-*N*-[2-(diethylamino)ethyl]-6-fluoropyridine-3-carboxamide (^{18}F-ICF01006) and ^{68}Ga-labelled *N*-(2-diethylaminoethyl)benzamide derivative (^{68}Ga-SCN-NOTA-BZA), have been tested in the preclinical setting and have shown high specificity for melanotic tissue and favourable in vivo pharmacokinetics, suggesting great potential for noninvasive clinical evaluation of melanin-positive melanoma [25–29]. These tracers could be useful for the evaluation of response to immunotherapy, given their specificity for melanoma cells that would allow differentiation between disease locations and immune reactions enhanced by treatment. Their investigation in prospective clinical trials is highly desirable, as has already done with scintigraphic tracers such as ^{123}I-*N*-(2-diethylaminoethyl)-2-iodobenzamide (^{123}I-BZA2) that has demonstrated high accuracy in the diagnosis of melanin-positive metastatic melanoma [30]. Benzamide analogues labelled with positron-emitting isotopes will probably be more accurate, due to the higher resolution of PET than SPECT images, and could also be used to noninvasively evaluate patients for selective radionuclide therapy, as is done for neuroendocrine tumours with PET using ^{68}Ga-DOTA conjugates.

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