Editorial Commentary

Is the onset of adverse effects of immunotherapy always bad news for the patients…?—certainly not!

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Despite the identification of promising and validated biomarkers the response to immunotherapy can be unexpected or variable, including rapid regression (complete or partial) of the tumor mass, stability, progression, pseudo progression or hyper tumor progression (1-5). Immunotherapy, in general, is less toxic than chemotherapy for patients with cancer. However, the side effects [adverse events (AE)] linked to these new treatments [treatment-related adverse events (trAEs)] are often described and have variable severity (6). Stimulation of an immune response by checkpoint inhibitors can lead, in particular, to side effects of immunological origin [immune-related adverse events (irAEs)], which are variable depending on the series, the therapeutic molecule, the pathology, the tumor and the patient (6). These irAEs cause the formation of lesions in one or different organs according to the patient with very variable consequences (6-10). While immunotherapy and most of the AEs are relatively well tolerated the irAEs are sometimes very severe running a risk of death of the patient, leading rapid and adapted therapeutic care (9,11-13).

Lisberg *et al.*, showed that the emergence of trAEs in a cohort of patients receiving first-line treatment with pembrolizumab for advanced stage or metastatic non-small cell lung carcinoma (NSCLC) correlated with, a better tumor response, a better survival free progression and longer overall survival, compared to patients who did not experience trAEs (14). This mono centric (University of California) and retrospective study concerned analyses from 97 patients included in the KEYNOTE-001 (clinicaltrials.govNCT01295827), which contained a total of 495 patients from several centers (14,15). In the study performed by Lisberg *et al.*, the most frequent AEs were fatigue (50%), pain (36%) and dyspnea (29%) (14). This study included all the trAEs) and not only those defined as irAEs. Among 94/97 (97%) patients one or several AEs were reported for a total of 826 AEs (14). In fact, only 85/826 (10%) of these AEs occurring in 39/97 (40%) patients were considered by the investigators as being trAEs (14). The results obtained with the cohort of patients hospitalized in a single center were different from of the total cohort of patients included in the KEYNOTE 001 since more than 71% of trAE were reported in the latter (14,15). This difference can be explained by the increased experience of investigators of the University of California with the use of immunotherapy and the better identification of side effects associated to treatment (14). Other explanations were put forward to explain this difference, including the epidemiological factors of patients, the fact that the cohort of the University of California contained, for example, more non-smoking patients (14).

Several recent studies have shown that irAEs of patients with metastatic NSCLC with second-line immunotherapy

showed better survival free progression and longer overall survival than those of patients without irAEs survival (16-18). The study of Ricciuti *et al.* reported that stage IV NSCLC patients treated with second-line nivolumab who experienced one or two irAEs had a survival of 11.9 or 26.8 months, respectively compared to survival for 4.6 months for patients who did not experience irAEs (17). In this series some irAEs (skin and hepatic-gallbladder reactions) were not associated with longer overall survival in opposition to other irAEs (lung, endocrine and gastro-intestinal reactions) (17). In contrast, Suresh *et al.* recently reported results showing that the development of checkpoint inhibitor pneumonitis (CIP) when on immunotherapy was associated with shorter overall survival (19). It is noteworthy that the frequency of CIP was evaluated at 3–5% of patients receiving immunotherapy, but this frequency is probable underestimated (20).

It is interesting to note that the number and severity of the irAEs arising in a population of elderly patients (more than 70 years old) with NSCLC treated with immunotherapy appeared to be identical to that of a population of patients less than 60 years old, even if the elderly patients benefited less from this treatment (21). The biological mechanisms behind this difference still remain uncertain and need to be investigated. A number of studies are ongoing and are being developed to better understand the molecular and biological origins of the occurrence of irAEs in response to therapy (22). Prediction of the onset (and the potential severity) of irAEs depending on the administered therapeutic molecule may participate in the development of new predictive biomarkers of therapeutic efficacy. It is within this context that factors predictive of the emergence of irAEs have been studied based on the clinical and biological data, taken individually or in association (6,23,24). These factors include the sex of the patient, auto-immune diseases or allergies, the level of circulating eosinophils, corticoid treatment, gene expression of CD177, the plasma level of interleukin 17, a score combining several plasma cytokines, analysis of the microbiome, …. (6,23,24). The analysis of the repertoire of TCR of T lymphocytes of tissues and/or blood is of particular interest in predicting the emergence and severity of irAEs and/or the therapeutic response and is strongly investigated currently (25,26).

Finally, the study by Lisberg *et al.* shows how difficult it is to define and diagnose AEs of patients treated with immunotherapy and to distinguish among the AEs those that are irAEs (14). The frequency and severity of the AEs of patients can be very variable depending on the treatment, the cancer type but also the expertise and evaluation of the physicians (14). The study by Lisberg *et al.* confirms that the presence but also the number of trAEs the patient experiences, strongly correlate with increased efficacy of immunotherapy of patients with advanced stage or metastatic NSCLC.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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