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Letter to the Editor

Adverse events 2.0—Let us get SERIOs
New reporting for adverse event outcomes needed in the era of immunooncology

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Dear Editor,

Given the rapid expansion of the number of patients receiving immune checkpoint inhibitors (ICIs), including special patient groups (with autoimmune disease or transplant patients), as well as increasing use of combination treatments involving ICIs (either together or with other cancer treatments), the knowledge base on incidence, management and outcome of side-effects needs to be addressed to first document and then reduce therapy-associated morbidity and mortality. Because all organ systems can be affected, some with permanent sequelae and occasionally even after cessation of therapy, it reemphasises the need for standardised reporting of side-effects in trials and beyond. Furthermore, ICIs are being used in earlier tumour stages, including the adjuvant and neoadjuvant setting. Because in these settings the risk–benefit ratio is less clear, it is particularly important to optimally document immune-related toxicity, especially when permanent sequelae or fatalities occur. There is evidence that toxicity reporting could be improved in immunotherapy trials [1], and as a community, we need to best leverage our resources to acquire knowledge on the unique side-effects induced by ICIs, the risk factors for their occurrence and the best management. A working group of oncologists developed the Side Effect Reporting in Immuno-Oncology (SERIO) recommendations to increase knowledge on immune-related adverse events (irAEs) with the following issues:

1 Document life-changing AEs
Reporting of toxicity within clinical trials needs to include the frequency of therapy-induced permanent sequelae. These numbers are crucial for patients when choosing between a generally well-tolerated checkpoint inhibitor therapy with rare permanent impairment and a less well-tolerated therapy, which has nearly no risk of permanent sequelae (for example, combined BRAF/MEK inhibitor treatment in melanoma). This is particularly important for patients with a low risk of recurrence and, thus, death due to tumour progression as even very rare permanent treatment-induced disabilities, such as type-1 diabetes mellitus or neurologic toxicities with permanent disabilities, become much more relevant.

2 Analyse rare and fatal AEs
Rare and fatal treatment-related AEs need to be prominently represented and analysed in clinical trial reports. So far, these events may not be represented in publications if they do not reach a frequency above a threshold of 5%, e.g., cardiac toxicity. Subsequently, there was inconsistent mention of the increased rate of cardiovascular side at international conferences, despite the very high fatality rate [1–3]. Importantly, frequency does not necessarily correspond to the severity of a given side-effect [4]. A non-standardised format for reporting AEs is insufficient, an issue already raised in the 'trial reporting in immune-oncology' initiative [5]. Furthermore, rare AEs might only become apparent with treatment of larger cohorts; thus, a registry is necessary.

3 Acquire prospective data on toxicity
Data on side-effects need to be gathered prospectively because side-effect management critically determines morbidity and mortality in patients receiving ICIs. However, there are only scarce assessments with regard to risk factors, incidence, pathogenic characterisation and management of side-effects included in the clinical studies. Investigating side-effects is crucial, especially in severe, rare and steroid-, infliximab- or mycophenolate-refractory cases. Funding for studies on side-effects remains a challenge. Thus, we rely on retrospective data with all the known limitations of such approaches. Japan has shown the way forward with a prospective postmarketing survey including examinations of more than 10,000 patients treated with ICIs [6], resulting in important clues on immune-related neurological side-effects.

4 Attend patients at special risk
Data on patient groups at special risk who were excluded from clinical trials, such as patients with autoimmune disease, HIV or hepatitis B/C infection or patients with solid organ transplants, need to be gathered. Many initiatives try to gain insights because these cases represent a conundrum for the treating physician [7–10]. Being able to anticipate the exacerbation of autoimmunity or transplant rejection would greatly alleviate these situations. Here, a register could help.

5 Report long-term outcomes
Finally, the long-term follow-up of side-effects and quality of life in patients enrolling for clinical trials is needed. Immunotherapy has opened a new era of 'survivorship', particularly in malignancies such as advanced melanoma for which this is new. However, side-effects may occur long after completion of checkpoint inhibitor therapy, especially as the immunotherapies are applied in earlier settings.

Limiting therapy-associated morbidity and mortality is necessary to optimise the benefit of immunotherapies. This requires high-quality data to analyse pathogenesis and response to side-effect management to increase patient safety. The SERIO recommendations are intended to improve reporting of side-effects of immunotherapy within clinical trials, postmarketing surveillance and beyond, and to gain insights into risk factors, management and sequelae, especially of rare and severe side-effects.

Conflict of interest statement

Some of the authors have conflicts of interest attached as separate items.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.01.015.

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