Personalized treatment of immune-related adverse events — balance is required

Filipe Martins and Michel Obeid

In their Review article published in *Nature Reviews Clinical Oncology* (Moving towards personalized treatments of immune-related adverse events. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-020-0352-8 (2020))[1], Esfahani and colleagues propose a personalized strategy for the management of immune-related adverse events (irAEs) in patients receiving immune-checkpoint inhibitors (ICIs), on the basis of what they refer to as an "immunohistopathologically guided process"[1] that would guide selection of the appropriate treatment regimen beyond first-line corticosteroid therapy. Unfortunately, we have to question the validity of some of their propositions.

Last year, our group published in *Lancet Oncology*[2] a treatment algorithm for personalized management of irAEs according to the predominant immune infiltrate type present in the relevant tissues. In our article, we proposed that a personalized treatment could be applied to target the predominant immune-cell infiltrate (such as T and/or B lymphocytes, neutrophils and/or monocytic cells) demonstrated on immunohistopathological assessment. Of note, we had based our proposal on practical experience of such strategy that we have applied several times and have already reported in the literature[3,4]. Indeed, in a patient with severe and refractory Sjögren syndrome resulting from treatment with pembrolizumab, we administered a second-line treatment with rituximab based on the histological analysis of a minor salivary gland biopsy sample revealing a rich B cell infiltrate. This treatment led to rapid clinical and biological improvements[3]. We applied the same personalized strategy to treat a patient with severe refractory oesophageal stenosis resulting from treatment with nivolumab based on histological analysis showing the presence of a predominant T cell infiltrate in the oropharynx[4]. For T cell-targeted therapy, we administered a single intravenous dose of the IL-6 receptor-neutralizing antibody tocilizumab, leading to a substantial symptomatic improvement[4]. These examples, therefore, evidence that such a personalized strategy had been proposed and applied by our team well before the Review by Esfahani et al.[1] was published. Of note, this Review seems closely aligned with our original proposal[2], but it does not acknowledge our prior contributions to this field.

In addition, we find some of the propositions of Esfahani et al. questionable. We acknowledge that eosinophils might be mediators of tissue injury when they are the predominant immune-cell infiltrate, but such a scenario should be considered with caution given the dominance of lymphocyte infiltrates in severe cutaneous reactions[5]. Furthermore, targeting eosinophil infiltration with specific treatments, such as anti-IL-5 monoclonal antibodies, should be considered carefully given the substantial risk of not effectively blocking activated T cells, the pathogenic role of which is central in this particular type of process.

We also suggest that the proposal by Esfahani et al. of treating pauci-immune infiltrates with JAK inhibitors should be considered carefully, even in the light of encouraging reported preclinical studies[6], owing to a potential risk of compromising the efficacy of ICIs. Indeed, loss-of-function mutations in *JAK1/2* have been suggested to mediate primary resistance to ICIs in some patients with melanoma or mismatch repair-deficient colon cancer[7]. In addition, the use of inhibitors selective for TYK2, JAK1 or JAK3 is not expected to limit either the damage or the inhibition caused at the level of the IFNγ axis and lymphocyte effector function, proliferation or survival[8].

Finally, we find that the therapeutic algorithm proposed by Esfahani et al. is still questionable in light of the evidence currently available. The proposed sequential treatment is not detailed, and the clinician's stance in case of an unsatisfactory response is not described. Thus, in our opinion, their model does not expand the scope of our previous proposed algorithm.

Despite all the issues we describe, we can only join Esfahani et al. in supporting the value of individualized histology-based strategies for the treatment of irAEs in patients receiving ICIs. We hope that this approach will increasingly benefit patients affected by these challenging adverse events.

There is a reply to this letter by Esfahani, K. & Calabrese, L. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-020-0401-3 (2020).

Filipe Martins[1,2] and Michel Obeid[3,4,5] ✉
[1]School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland.
[2]Service et Laboratoire Central d'Hématologie, Département d'Oncologie, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland.
[3]Centre Hospitalier Universitaire Vaudois (CHUV), Department of Medicine, Division of Immunology and Allergy, Lausanne, Switzerland.
[4]Centre Hospitalier Universitaire Vaudois (CHUV), Vaccinology and Immunotherapy Center, Lausanne, Switzerland.
[5]University of Lausanne, Lausanne, Switzerland.
✉e-mail: michel.obeid@chuv.ch

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1. Esfahani, K. et al. Moving towards personalized treatments of immune-related adverse events. *Nat. Rev. Clin. Oncol.* https://doi.org/10.1038/s41571-020-0352-8 (2020).
2. Martins, F. et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. *Lancet Oncol.* **20**, e54–e64 (2019).
3. Ghosn, J. et al. A severe case of neuro-Sjogren's syndrome induced by pembrolizumab. *J. Immunother. Cancer* **6**, 110 (2018).
4. Horisberger, A. et al. A severe case of refractory esophageal stenosis induced by nivolumab and responding to tocilizumab therapy. *J. Immunother. Cancer* **6**, 156 (2018).
5. Ortonne, N. et al. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: a morphological and phenotypical study. *Br. J. Dermatol.* **173**, 50–58 (2015).
6. Lu, C., Talukder, A., Savage, N. M., Singh, N. & Liu, K. JAK-STAT-mediated chronic inflammation impairs cytotoxic T lymphocyte activation to decrease anti-PD-1 immunotherapy efficacy in pancreatic cancer. *Oncoimmunology* **6**, e1291106 (2017).
7. Shin, D. S. et al. Primary resistance to PD-1 blockade mediated by JAK1/2 mutations. *Cancer Discov.* **7**, 188–201 (2017).
8. Schwartz, D. M. et al. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat. Rev. Drug Discov.* **16**, 843–862 (2017).

Competing interests
The authors declare no competing interests.