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The association between adverse events and outcome under checkpoint inhibitors: Where is the deal?

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ABSTRACT

Recent reports have put into evidence the possibility of a link between immune-related adverse events (IRAEs) and treatment outcome, patients drawing a benefit from treatment being also exposed to the risk to develop toxicity.

A still unanswered question remains the biological origin(s) which can sustain and explain such a relationship.

The purpose of this review paper is to lay out different potential contributions which can help to understand the IRAEs-outcome link and to propose clinical perspectives taking advantage of this association.

In this respect, pharmacokinetics aspects, immunological and immunogenetics implications have been taken into consideration.

Adverse events and treatment outcome

During the last decade, the introduction of immune-checkpoint inhibitors (ICIs) has markedly transformed the therapeutic landscape of a large number of recalcitrant diseases [1]. However, the use of ICI is complicated by the occurrence of serious immune-related adverse events (IRAEs) such as colitis, pneumonitis and hepatitis which are largely unpredictable [2]. Recent reports have examined the possibility of a link between IRAEs and treatment outcome, patients drawing a benefit from treatment being also exposed to the risk to develop toxicity. Although some studies report the absence of such a link [3], more frequent are those who support the existence of a positive association response-toxicity for ICI. As an example, the recent retrospective study by Maher et al. [4] based on seven trials including to a large set of 1,-747 patients with urothelial cancer treated by ICI and reporting an hazard ratio at 0.45 for the link between overall survival and the presence of IRAEs. More recently Maillet et al. reported on IRAEs in single-agent ICI (mostly anti-PD(L)1) in a large retrospective multicentric series with a majority of lung cancer patients [5]. They found a strong association between IRAEs and long-term survival outcomes. There is however a possible bias, frequently advocated, which is the fact that responders are those who benefit from a longer duration of treatment and are thus exposed to a higher risk to develop toxicity throughout time [6]. There are several reports showing that IRAEs actually precede response [5,7,8]. The conclusions of the study by Maillet et al. [5] were established after using an adapted statistical method for limiting time-dependent bias. It follows that an unanswered question remains the biological origin(s) which can sustain and explain such a relationship. This knowledge would help to strengthen and to validate the notion of the link between toxicity and efficacy for ICI, to obtain a better control of adverse events and, more generally, to improve the practice of immunotherapy. The aim here was thus to lay out the different potential contributions which can help to understand the IRAEs-outcome link and to propose clinical perspectives taking advantage of this association.

Could PK-PD relationships with ICIs be of any help?

A close relationship between the occurrence of specific drug-related toxicity and treatment outcome has been repeatedly observed with a large variety of anticancer agents ranging from cytotoxics, hormonotherapy, targeted therapy and even possibly with the latest immune checkpoint inhibitors in agreement with the “no pain, no gain” aphorism [9]. Most of the time, for standard treatments this relationship is related to underlying exposure levels, i.e. patients experiencing severe toxicities having circulating drug levels higher than patients with no toxicity, thus increasing the odds to achieve higher efficacy eventually [10]. However, as recently reported, establishing a clear correlation between drug exposure and pharmacodynamics for ICIs remains challenging [11]. Conflicting data have been reported indeed on possible exposure/effect relationships with currently immune checkpoint inhibitors. For instance, high trough levels of anti-PD1 nivolumab were once associated with better response in NSCLC patients [12], whereas

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another study failed to confirm this relationship [13]. Of note, none of these studies have found a link between plasma exposure levels and nivolumab-related toxicities. Conversely, with anti-CTLA4 ipilimumab, trough levels were found to be associated both with progression free survival and toxicities in melanoma patients [14]. The analysis of PK/PD relationships with more recently approved ICIs such as durvalumab, atezolizumab or avelumab is recent, but clinical reports have already identified the through levels required to ensure a maximum target engagement [15–17]. Still, to date, for all these drugs the impact of pharmacokinetic variability as a possible cause for response, non-response or toxicities remain highly speculative considering a routine clinical practice context. Of note, most PK/PD studies have focused thus far on the issue of efficacy, and not safety concerns. In addition, the "the higher the exposure, the better the effect" paradigm usually supporting the link between toxicity and efficacy is less relevant with the recent trend to develop flat dosing with immunotherapy. Flat dosing indeed assumes that all cancer patients weight 80–100 kg, thus leading to plasma levels exceeding by far the minimal concentrations required to inhibit the target [18]. This makes challenging to considerer treatment toxicity as a meaningful surrogate marker for high exposure levels triggering efficacy, because flat dosing already ensures that drug concentrations are always largely above theoretical levels associated with maximal target engagement. In addition and because the PK of ICIs is likely to be influenced by the antigenic mass (a phenomenon known as Target Mediated Drug Disposition (TMDD) resulting in time-varying clearance [19], PK could be actually a confounding factor when trying to decipher next the links between toxicity and efficacy. For instance, tumor shrinkage upon ICI treatment could decrease drug clearance, thus increasing plasma levels and possibly triggering toxicity next. Therefore, toxicity would be rather a consequence of the efficacy through modulation of drug clearance, and not an upfront marker. Along with the fact that plasma concentrations are already above the efficacy level, toxicities are unlikely to be predictive of efficacy with ICIs. This has been recently confirmed in nivolumab patients in a prospective study including mostly NSCLC patients, where no association between immune-related toxicity and efficacy data (i.e., PFS and OS) put into evidence [20]. Much interestingly, this observation in lung cancer patients is fully in line with previous reports failing to establish such a correlation between nivolumab-related toxicities and survival in melanoma patients [21]. Overall, this makes PK/PD relationships rather complicated to help identifying a possible link between efficacy and toxicity, because of too many confounding factors blurring the picture [22].

Are common immunological factors able to explain the association?

At the immunological level, several clues may be followed to understand the link between IRAEs and treatment outcome with ICIs [23]. They can be related, at least, to a common deregulation of the PD1-PDL1 target [24], immune cell infiltration, neoantigen formation and patient characteristics like age and sex.

In particular T cell clonality appears to be an interesting path to herein comment on. A recent study in NSCLC explored the link between autoimmune skin toxicity and a better treatment outcome [25]. The authors reported T cell clonality and more precisely identical antigen-specific T cells, in the patient's peripheral blood mononuclear cells and in both tumor and skin tissues. This finding may support the observed link between toxic effect and response to therapy, and is consistent with previous reports in melanoma patients treated with ICIs showing both the occurrence of vitiligo and a better response to treatment [6]. This supports the hypothesis of an ICI-mediated induction of tumor response against common antigens shared by melanomas and normal melanocytes. These considerations on common antigens call for tumor mutational burden (TMB) since an association between IRAEs and tumor TMB has recently been reported [26]. Because TMB has recently emerged as a potential ICI response predictor [27], it could bridge the gap between efficacy and toxicity.

A possible explanation for this finding was proposed by Bomze et al. [26]. A cross-reaction for T cells between neoantigen and corresponding wild-type proteins was advocated by the authors as well as the phenomenon of tumor cell death released antigens, including neoantigens which could prime T lymphocytes against the wild-type antigens in healthy tissue.

The well-established global inhibitory effect of corticosteroids on T cells [28] may lead to consider that corticosteroid application during ICI treatment triggers a protection to ICI-related toxicity and could be detrimental for treatment efficacy. Several reports, however of retrospective nature, tell us that it is in fact not the case since, in an attempt to protect from toxicity, the use of corticosteroids in patients who received ICIs did not result in a deleterious effect on efficacy outcomes [2,4]. Thus, a link between response and toxicity may be, at the least in part, dissociated from a common origin at the immunological level implicating T cell function.

Multiple publications have contributed to demonstrate a role for gut microbiota in modulating response to ICI [29]. Different gut microbiota profiles characterize responders to treatment and the favorable profiles are linked to enhanced systemic immunity and intratumoral immune composition. Interestingly, several gut bacterial components may be associated with favorable response as well as toxicity. This is notably the case with *Firmicutes* in the development of immunotherapy-induced colitis [30]. Therefore microbiota composition at an individual level could contribute to explain why some patients way exhibit both a favorable response and an increased risk for toxicity.

The part of the host: immunogenetics

There is a cumulative evidence that treatment pharmacodynamics (both tumor response and toxicity) of conventional anticancer therapy may be linked to intrinsic patient genomics characteristics, generally referred to as pharmacogenetics [31].

In fact, genetic polymorphisms affecting either pharmacokinetics or pharmacodynamics could explain, at least partly, the relationship between treatment efficacy and side effects previously reported for conventional anticancer drugs [9]. Interestingly, in this context, the pharmacogenetics related to functional effects affecting drug mechanisms of action and supporting the link between treatment-related toxicities and efficacy have been considered for anti EGFR therapy [32] and more particularly in patients with advanced colorectal cancer receiving anti-EGFR-based treatment [33].

In this respect, we recently hypothesized that the host genetics could be used as predictive biomarkers for ICI response and IRAEs [34]. A retrospective study in 94 patients treated with ICI and based on SNPs analyses was conducted on genes affiliated with immune response and tumor-microenvironment interaction [35]. Several single-nucleotide polymorphisms (SNPs) were identified as able to predict response (7 SNPs) and toxicity (5 SNPs). The fact that the SNPs differed between toxicity and response precluded on these bases to formulate the hypothesis that common SNPs predicting treatment outcome could explain a link between adverse events and outcome. However, among the SNPs identified as predictors of adverse events there was *rs4143815* (*PD-L1*) with an intrinsic weight in the predictive model [34]. Interestingly, this SNP was also recently reported by others investigators [36] as a possible marker for nivolumab efficacy. This SNP was found to be associated with positive eQTL of the downstream *PDCD1LG2* gene, coding for *PD-L2* in several tissues (GTEX portal: https://gtexportal.org/home/). An increase in *PD-L2* expression may contribute to excessive sensitivity to ICI action with toxic reactions in normal tissue and a favorable tumor regression in cancerous lesions. This hypothesis needs to be prospectively validated to support a role for the *rs4143815* as a key element explaining both toxicity and response to ICIs.

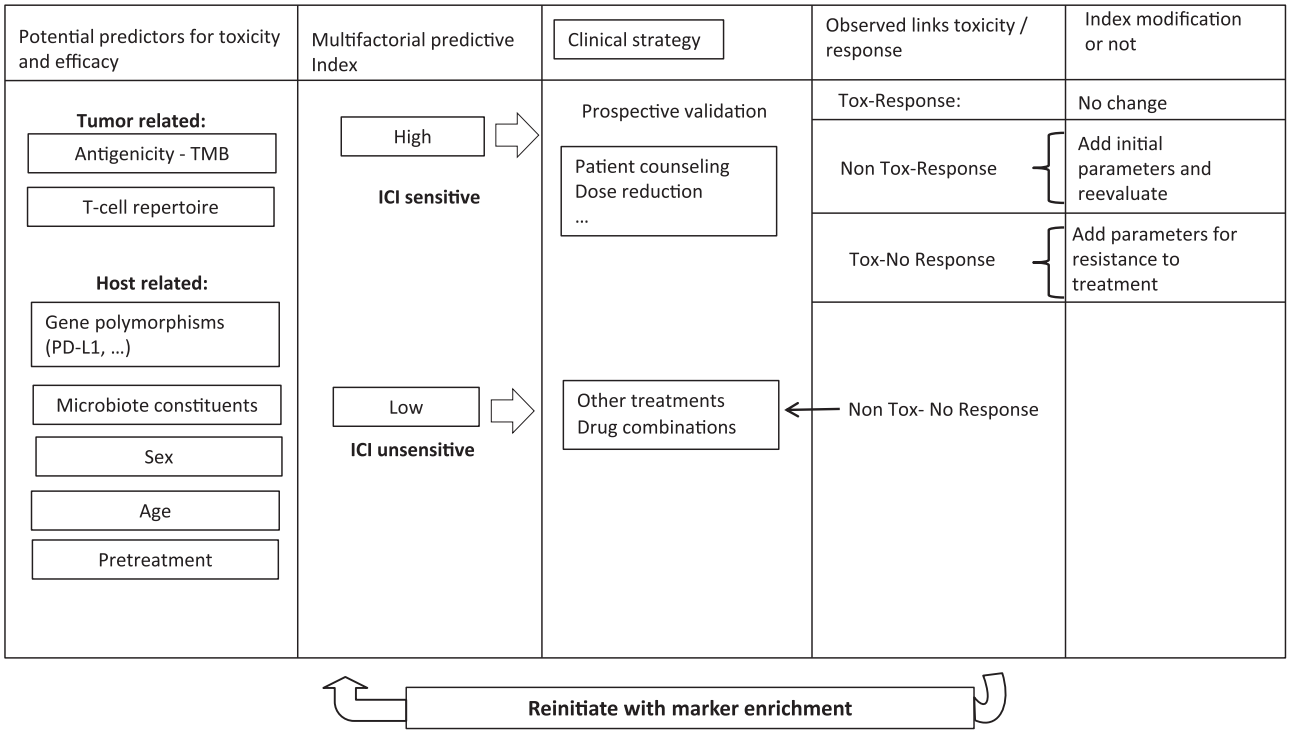

Fig. 1. A global vision on the possible link between texicity and response with ICIs considering potential explaining factors, the establishment of a predictive index, a clinical strategy for a prospective validation and fine-tuning of the index taking into account observed link revealed by clinical study.

Clinical perspectives taking advantage of the association

The question is now clearly addressed about over-treating patients with ICIs taking into account their elevated costs [37,38]. To be able to identify patients who will be responders both at the tumoral and normal tissue level is a true opportunity to personalize treatment by avoiding treating potentially refractory patients. The above-considered aspects tell us that among other potential factors including conventional parameters like age and sex are tumor-linked TMB and patient-related factors like germinal gene polymorphisms with rs4143815 (PD-L1) as good examples to characterize a multifactorial profile characterizing responders to ICIs [39]. Fig. 1 illustrates a global strategy aiming to establish, on rigorous clinical bases of prospective trials, concrete applications highlighting the association between adverse events and outcome under ICIs. The strategy is based on the possibility to compute a multifactorial index which can help to characterize patients as ICI sensitive or ICI unsensitive. The index may be prospectively fine-tuned following a clinically-based prospective evaluation. This proposed global strategy concurs well with Johnson and coworkers [40] considerations who recently reported on prospective trials with ICIs which are now feasible to provide the opportunity to shape patient care beyond the simple us of high-dose steroids. The present position paper may provide, among others possible, concrete perspectives in this view.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Gerard Milano: Conceptualization, Writing - original draft. **Federico Innocenti:** Writing - review & editing. **Joseph Ciccolini:** Writing - review & editing.

References

[1] A Ribas, JD. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (6382) (2018) 1350–1355.
[2] JM Michot, A Lappara, J Le Pavec, et al., The 2016–2019 ImmunoTOX assessment board report of collaborative management of immune-related adverse events, an observational clinical study, Eur. J. Cancer 130 (2020) 39–50, doi:10.1016/j.ejca.2020.02.010.
[3] TZ Horvat, NG Adel, TO Dang, et al., Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center, J. Clin. Oncol. 33 (28) (2015) 3193–3198.
[4] VE Maher, LL Fernandes, C Weinstock, et al., Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody, J. Clin. Oncol. 37 (30) (2019) 2730–2737.
[5] D Maillet, P Corbaux, JJ Stelmes, et al., Association between immune-related adverse events and long-term survival outcomes in patients treated with immune checkpoint inhibitors, Eur. J. Cancer 132 (2020) 61–70.
[6] Y Toi, S Sugawara, Y Kawashima, et al., Association of immune-related adverse events with clinical benefit in patients with advanced non-small-cell lung cancer treated with nivolumab, Oncologist 23 (11) (2018) 1358–1365.
[7] C Hua, L Boussemart, C Mateus, et al., Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab, JAMA Dermatol. 152 (1) (2016) 45–51.
[8] F Martins, L Sofiya, GP Sykiotis, et al., Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance, Nat. Rev. Clin. Oncol. 16 (9) (2019) 563–580.
[9] G Milano, F Innocenti, B Lacarelle, J Ciccolini, et al., "No pain, No gain" still true with immunotherapy: when the finger shows the moon, look at the moon, Crit. Rev. Oncol. Hematol. 127 (2018) 1–5.
[10] M Donnette, C Solas, M Giocanti, et al., Simultaneous determination of cytosine arabinoside and its metabolite uracil arabinoside in human plasma by LC-MS/MS: Application to pharmacokinetics-pharmacogenetics pilot study in AML patients, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 1126-1127 (2019) 121770.
[11] A Desnoyer, S Broutin, J Delahousse, et al., Pharmacokinetic/pharmacodynamic relationship of therapeutic monoclonal antibodies used in oncology: part 2, immune checkpoint inhibitor antibodies, Eur. J. Cancer (2020) S0959-8049(20)30005-8, doi:10.1016/j.ejca.2020.01.003.
[12] EA Basak, SLW Koolen, DP Hurkmans, et al., Correlation between nivolumab exposure and treatment outcomes in non-small-cell lung cancer, Eur. J. Cancer 109 (2019) 12–20.
[13] A Bellesoeur, E Ollier, M Allard, et al., Is there an exposure-response relationship for nivolumab in real-world NSCLC patients? Cancers 11 (11) (2019) pii: E1784.
[14] Y Feng, A Roy, E Masson, TT Chen, R Humphrey, JS Weber, Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma, Clin. Cancer Res. 19 (14) (2013) 3977–3986.

[15] PG Baverel, VFS Dubois, CY Jin, et al., Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status, Clin. Pharmacol. Ther. 103 (4) (2018) 631–642.
[16] I Netterberg, CC Li, L Molinero, et al., A PK/PD analysis of circulating biomarkers and their relationship to tumor response in atezolizumab-treated non-small cell lung cancer patients, Clin. Pharmacol. Ther. 105 (2) (2019) 486–495.
[17] CR Heery, G O'Sullivan-Coyne, RA Madan, et al., Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial, Lancet Oncol. 18 (5) (2017) 587–598.
[18] MS Chatterjee, J Elassaiss-Schaap, A Lindauer, et al., Population pharmacokinetic/pharmacodynamic modeling of tumor size dynamics in pembrolizumab-treated advanced melanoma, CPT Pharmacometr. Syst. Pharmacol. 6 (1) (2017) 29–39.
[19] H Li, J Yu, C Liu, et al., Time dependent pharmacokinetics of pembrolizumab in patients with solid tumor and its correlation with best overall response, J. Pharmacokinet. Pharmacodyn. 44 (5) (2017) 403–414, doi:10.1007/s10928-017-9528-y.
[20] L Hirsch, A Bellesoeur, P Boudou-Rouquette, et al., The impact of body composition parameters on severe toxicity of nivolumab, Eur. J. Cancer 124 (2019) 170–177.
[21] M Freeman-Keller, Y Kim, H Cronin, et al., Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes, Clin. Cancer Res. 22 (4) (2016) 886–894.
[22] T Freshwater, A Kondic, M Ahamadi, et al., Evaluation of dosing strategy for pembrolizumab for oncology indications, J. Immunother. Cancer 5 (2017) 43.
[23] JV Cohen, KT. Flaherty, Response to immune checkpoint antibodies: not all responses are created equal, Clin. Cancer Res. 25 (3) (2019) 910–911.
[24] J Chen, CC Jiang, L Jin, XD Zhang, Regulation of PD-L1: a novel role of pro-survival signalling in cancer, Ann. Oncol. 27 (3) (2016) 409–416.
[25] F Berner, D Bomze, S Diem, et al., Association of checkpoint inhibitor-induced toxic effects with shared cancer and tissue antigens in non-small cell lung cancer, JAMA Oncol. 5 (7) (2019) 1043–1047.
[26] D Bomze, O Hasan Ali, A Bate, L Flatz, Association between immune-related adverse events during anti-PD-1 therapy and tumor mutational burden, JAMA Oncol. (2019), doi:10.1001/jamaoncol.2019.3221.
[27] A Addeo, GL Banna, GJ Weiss, Tumor mutation burden-from hopes to doubts, JAMA Oncol. 5 (7) (2019) 934–935.
[28] L Cari, F De Rosa, G Nocentini, et al., Context-dependent effect of glucocorticoids on the proliferation, differentiation, and apoptosis of regulatory T cells: a review of the empirical evidence and clinical applications, Int. J. Mol. Sci. 20 (5) (2019).
[29] BA Helmink, MAW Khan, A Hermann, V Gopalakrishnan, JA Wargo, The microbiome, cancer, and cancer therapy, Nat. Med. (3) (2019) 377–388.
[30] N Chaput, P Lepage, C Coutzac, et al., Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab, Ann. Oncol. 28 (6) (2017) 1368–1379.
[31] DL Hertz, HL. McLeod, Use of pharmacogenetics for predicting cancer prognosis and treatment exposure, response and toxicity, J. Hum. Genet. 58 (6) (2013) 346–352.
[32] ML Amador, D Oppenheimer, S Perea, et al., An epidermal growth factor receptor intron 1 polymorphism mediates response to epidermal growth factor receptor inhibitors, Cancer Res. 64 (24) (2004) 9139–9143.
[33] F Graziano, A Ruzzo, F Loupakis, et al., Pharmacogenetic profiling for cetuximab plus irinotecan therapy in patients with refractory advanced colorectal cancer, J. Clin. Oncol. 26 (9) (2008) 1427–1434.
[34] S Refae, J Gal, P Brest, et al., Germinal immunogenetics as a predictive factor for immunotherapy, Crit. Rev. Oncol. Hematol. 141 (2019) 146–152.
[35] S Refae, J Gal, N Ebran, et al., Germinal immunogenetics predict treatment outcome for PD-1/PD-L1 checkpoint inhibitors, Invest. New Drugs 38 (1) (2020) 160–171, doi:10.1007/s10637-019-00845-w.
[36] T Nomizo, H Ozasa, T Tsuji, et al., Clinical impact of single nucleotide polymorphism in PD-L1 on response to nivolumab for advanced non-small-cell lung cancer patients, Sci. Rep. 7 (2017) 45124.
[37] V Verma, T Sprave, W Haque, et al., A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors, J. Immunother. Cancer 6 (1) (2018) 128.
[38] S Danson, J Hook, H Marshall, et al., Are we over-treating with checkpoint inhibitors? Br. J. Cancer 121 (8) (2019) 629–630.
[39] TG Soldatos, S Kaduthanam, DB Jackson, Precision oncology – the quest for evidence, J. Pers. Med. 9 (3) (2019).
[40] DB Johnson, KL Reynolds, RJ Sullivan, et al., Immune checkpoint inhibitor toxicities: systems-based approaches to improve patient care and research, Lancet Oncol. 21 (2020) e398–e402.