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LETTER TO THE EDITOR

Efficacy of immunotherapy, gut microbiota and impact of antibiotic use: are there confounding factors?

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The inter-relationship between host microbiota and immunotherapy by checkpoint inhibitors (CPI) is currently actively investigated at experimental, pre-clinical and clinical levels [1]. It has recently been shown that tumor expression of chemokines associated with T-cell infiltration can be stimulated by gut bacteria, and reduced by antibiotic treatment [2]. Antibiotics may impair gut microbiota and their use is logically suspected to have a deleterious impact on the clinical outcome of patients treated with immune checkpoint inhibitors [2]. There is by consequence a current view bridging antibiotic use, impaired gut microbiota and subsequently negative impact on immune checkpoint inhibitors efficacy which stimulates clinical investigations [3]. Specific clinical studies indicate a poor clinical benefit in patients undergoing immunotherapy with a history of previous antibiotic use [4].

However, it must be kept in mind the clinical context where antibiotics are often administrated primarily in patients with aggressive disease require maximal tolerated drug chemotherapy, which potentially triggers hematological toxicities and subsequent sepsis. Advanced disease by itself confers inflammation and infections frequently requiring antibiotic administration. A condition of large tumoral burden may be associated with a reduction in systemic exposure to biologics, in particular the pharmacokinetics of monoclonal antibodies can be modified (i.e., through accelerated clearance) depending on a patient's general status [5]. Lastly, tumor burden itself may play further a critical role impacting drug plasma exposure under immune checkpoint inhibitors, since a large antigenic mass can increase monoclonal antibodies clearance, through a mechanism best known as antigen sink or tumor-mediated drug disposition [6]. Although dose–effect relationships are not clearly established with immunotherapy agents, some links between exposure and effects have been repeatedly demonstrated with anti-CTLA4 ipilimumab, anti-PD1 nivolumab or anti-PD1 avelumab [7].

This context leads us to pay more attention to the general context around clear-cut conclusions that a history of previous antibiotic treatment negatively impacts treatment outcome in patients under immunotherapy by CPI [4]. The possibility may exist that beyond negative impact on gut microbiota, an unrevealed reduced exposure to immune checkpoint inhibitors in advanced patients treated with antibiotics can impact treatment outcome as well. Moreover, a large tumor burden is often accompanied by abnormal LDH levels with a negative impact of LDH-related lactate production on immune tumoral environment [8]. The rising suspicion about antibiotics in the era of immunotherapy as a possible cause for treatment failure due to a possible modification of gut microbiota should be thus considered more cautiously when shifting from bench to bedside. Indeed, as herein mentioned, many other confounding factors associated with the use of antibiotics should be kept in mind and may interfere with CPI treatment outcome independently of the impact on gut microbiota. This effect should be more objectively argumented at the clinical level with specifically dedicated biological explorations. This attitude is particularly recommended in the specific context of clinical trial design where consideration to individual drug pharmacokinetic profile, at least a minima (Css), should also be paid. Pharmacokinetic models have been recently proposed, at a pre-clinical level, which could incorporate host and microbial contributions to drug metabolism. This sophistication of pharmacokinetic coverage associated with clinical trial setup is particularly justified with immunotherapeutic drug development [9]. Last but not the least, there are long established, evidence-based recommendations guiding a broad spectrum of indications of antibiotics in oncology which cannot be underestimated or minimized without detrimental impact in cancer patients [10].

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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