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THE IMPACT OF IMMUNOTHERAPY IN CANCER TREATMENT

Fahad Hamoud Albahli, Seham Ali Rajaalluh ALsaedi, Fawaz Abdullqader Albeladi, Abdulrhman Mohammad, Ahmed Alkhaibari, Ahmad Abu Bakr Bajbair, Hakem Awad Alotaibi, Turki Aedh Almutairi, Abdulrhman Mutlaq Halyl Alharby, Majed Bin Zaid Al Muaddi, Faisal Faiz Al-Adiyani, Ahmad Saud Almutairi, Ebrahim Ali Ebrahim Mashhour, Bejad Muteab Saad Alotaibi

Abstract

Immune-checkpoint inhibitors (ICI) are currently the established treatment protocol for several forms of cancer. The lack of a healthy gut microbiome in pre-clinical animals has a detrimental effect on the effectiveness of immune checkpoint inhibitors (ICI). These results helped to uncover the significance of the commensal microbiota in the field of immuno-oncology. Several recent clinical investigations, including a total of over 1800 patients, have shown that the use of broad-spectrum antibiotics (ATB) has a detrimental effect on cancer patients who are taking immune checkpoint inhibitors (ICI). Overall, our findings suggest that dysbiosis caused by ATB may affect the clinical response by altering the gut microbiota. The controversy persists since ATB therapy may just serve as an indicator of people who are not physically fit or have a weakened immune system. This review provides a concise summary of recent papers that examine the influence of the gut microbiota on the effectiveness of immune checkpoint inhibitors (ICI). It also discusses the existing data on the effects of antibiotic (ATB) administration at various time points in relation to the commencement of ICI treatment. Lastly, it explores the therapeutic implications of these results.

Keywords: Immune-checkpoint inhibitors (ICI), microbiome, immunotherapy, cancer treatment, review, antibiotic administration.

1. Introduction

The emergence of innovative cancer therapies, such as immune-checkpoint inhibitors (ICI), has significantly transformed the therapy options available for patients with melanoma and many types of epithelial malignancies. ICI currently serves as the primary therapy for several advanced carcinomas. In addition, new studies have been reported demonstrating the effectiveness of ICI in both neo-adjuvant and adjuvant contexts, thereby increasing its therapeutic applicability [1, 2].

Although there have been significant advancements, long-lasting positive responses to immune checkpoint inhibitors (ICI) are still rare. In conditions such as renal cell cancer (RCC) [3, 4] and non-small-cell lung cancer (NSCLC) [5], the initial resistance rates vary from 35% to

44%, whereas the rates of resistance that develop later on reach 100%. For patients with advanced melanoma, between 40% to 65% have disease progression when treated with anti-PD-1 treatment alone, whereas more than 40% experience progression when treated with a combination of anti-PD-1 and anti-CTLA-4 therapy. Consequently, there is a pressing need in the medical field to create biomarkers that can accurately forecast the response to ICI.

Various factors contribute to the primary or acquired resistance to immune checkpoint inhibitors (ICI). These factors include cancer cell-centric markers such as PD-L1 expression and tumor mutational load [8], the composition of the tumor immune infiltrate [local interferon-gamma gene expression, presence of CD8+, regulatory T cells, and myeloid-derived suppressor cells (MDSC)], as well as environmental factors [9]. A surprising change in the way we understand things happened when researchers found a connection between the types of microorganisms in the gut (known as the microbiota) and how well cancer patients respond to a kind of treatment called immune checkpoint inhibitors (ICI) [10., 11., 12., 13.]. The impact of the gut microbiota on cancer growth and response to immunotherapy, which was previously overlooked in oncology, has been shown via the use of next generation sequencing (NGS) technologies including 16S rRNA and shotgun metagenomics. In addition, the advancement of various culturomics technologies, along with mass spectrometric microbial identification techniques, has expedited the discovery of advantageous and hard-to-culture bacterial strains and species [14].

Dysregulation of the gut microbiota may lead to changes in systemic immune responses, which may increase the risk of developing chronic inflammatory illnesses such as obesity, Crohn's disease, and type II diabetes [15]. Experiments conducted on mice that were germ-free (GF) or treated with broad-spectrum antibiotics (ATB) revealed that the ability of ICI to reduce tumor development depends on the presence of a particular kind of bacteria in the stomach. In this experimental setup, mice with comparable sex, age, and genetic background were used to investigate the immune anticancer effects of anti-CTLA-4, anti-PD-1/PD-L1, or a combination of both antibodies. The lack of immunogenic gut flora resulted in the loss of these immunological activities [10., 11., 12., 13.]. Based on the assumption that the makeup of the gut microbiota influences the ability to resist immune checkpoint inhibitors (ICI), an analysis of the microbiome was conducted in patients with advanced melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). Analysis of the intestinal microbiota in patients who did not experience any benefits from immune checkpoint inhibitors (ICI) showed distinct differences in composition compared to those who reacted positively [11, 12, 16].

These preliminary findings prompted other investigations aimed at determining if prescribing antibiotics to cancer patients at the start of immune checkpoint inhibitor (ICI) treatment will have a similar impact on their clinical response as shown in preclinical models. Although ATBs have the potential to save lives by treating both common and serious bacterial diseases, Alexander Fleming, the developer of penicillin, issued a warning to the scientific community about the danger of ATB resistance during his Nobel prize acceptance address in 1943. Nevertheless, the

influence of ATB use on the process of recolonization and subsequent alterations in the composition of microbiota, resulting in a reduction in the variety of commensal organisms, has only been recognized in recent times [17]. The dysbiosis caused by ATB has particularly harmful impacts on children's health, leading to permanent changes in their growing microbiota that may have long-term health consequences extending into adulthood [18, 19]. Antibiotics can cause intestinal dysbiosis by reducing the population of important species or completely eliminating beneficial bacteria, which disrupts the normal balance in the gut and has significant effects on local and overall metabolism, as well as significant impacts on the immune system [10].

Most papers and abstracts that discuss the impact of antibiotics (ATB) on the clinical outcome of immunotherapy for cancer treatment show similar results to studies conducted on mice. These studies indicate that the effectiveness of antibodies targeting CTLA-4 and PD-1/PD-L1 is diminished in patients who have taken antibiotics shortly before or after starting immunotherapy. Nevertheless, the significance of these crucial findings and their influence on the everyday clinical practices of oncologists are still a subject of debate. It is difficult to determine if the use of ATB is an indication of poor physical health, namely a weakened immune system, which may lead to negative outcomes. This may not be related to the impact of ATB on the gut flora [20-25]. This review will analyze the existing evidence on the influence of antibiotic (ATB) use on immune checkpoint inhibitor (ICI) response in cancer patients and address the practical implications in therapeutic settings.

2. Impact of concurrent medicines on the effectiveness of immune checkpoint inhibitors (ICI)

ATBs are not the only immunomodulatory drugs that might possibly impact the clinical effectiveness of ICI. For instance, in a group of 640 patients with non-small cell lung cancer (NSCLC) who were treated with immune checkpoint inhibitors (ICI), the consistent use of corticosteroids at a dosage above 10 mg per day was shown to be linked to a reduction in both progression-free survival (PFS) and overall survival (OS). This association was supported by both univariate and multivariate analysis [26]. In addition to its potent anti-inflammatory and immunosuppressive properties, corticotherapy can significantly alter the composition of the gut microbiota. For example, the administration of dexamethasone in mice has been shown to increase the abundance of Clostridiales and Lactobacillaceae [27].

Additionally, glucocorticoids are often used in conjunction with proton pump inhibitors, which may potentially have an effect on the gut flora [28]. Nevertheless, more research is needed to explore the possible impact of the microbiome on the lasting consequences of glucocorticoids. It is worth mentioning that non-steroidal anti-inflammatory medicines have been shown to enhance the entry of tumors by CD4+ and CD8+ T cells and to strengthen the effects of immune checkpoint inhibitors in laboratory models [29]. Comprehensive clinical studies should investigate the effects of co-medications on the gut microbiota and the immune responses triggered by anticancer immunotherapy (ICI).

Therapeutic manipulation of the microbiota involves the use of innovative methods to introduce bacterial communities, such as patient-to-patient fecal microbiota transplantation (FMT), or individual bacterial species in the form of freeze-dried encapsulated bacteria. These approaches aim to enhance the effectiveness of anticancer immunotherapies (Figure 1). In this growing field of clinical research, researchers performed a phase I trial where they administered FMT from third-party donors to an allo-HSCT population. The purpose of the study was to demonstrate an increase in gut microbial diversity [30-33]. Taur et al. [34] published the findings of a randomized clinical study showing that giving patients an auto-FMT (fecal microbiota transplantation) from their own feces collected before antibiotherapy and chemotherapy increased the variety of microorganisms in allo-HSCT patients [34]. Probiotics are also believed to potentially treat dysbiosis caused by antibiotics. Nevertheless, in both mice and humans, the use of commercially available probiotics resulted in a slower and less thorough restoration of the gut microbiota after antibiotic treatment, as compared to fecal microbiota transplantation (FMT) [17].

These data suggest that FMT might be a successful method for restoring the makeup of microbiota. However, it is still uncertain if FMT may lead to enhanced clinical responses to ICI. Randomized controlled trials are now being conducted to assess the effects of Fecal Microbiota Transplantation (FMT) on patients with melanoma (NCT03353402; NCT03341143), as well as studies examining the influence of probiotics on Renal Cell Carcinoma (RCC) patients undergoing Immune Checkpoint Inhibitor (ICI) treatment (NCT03829111).

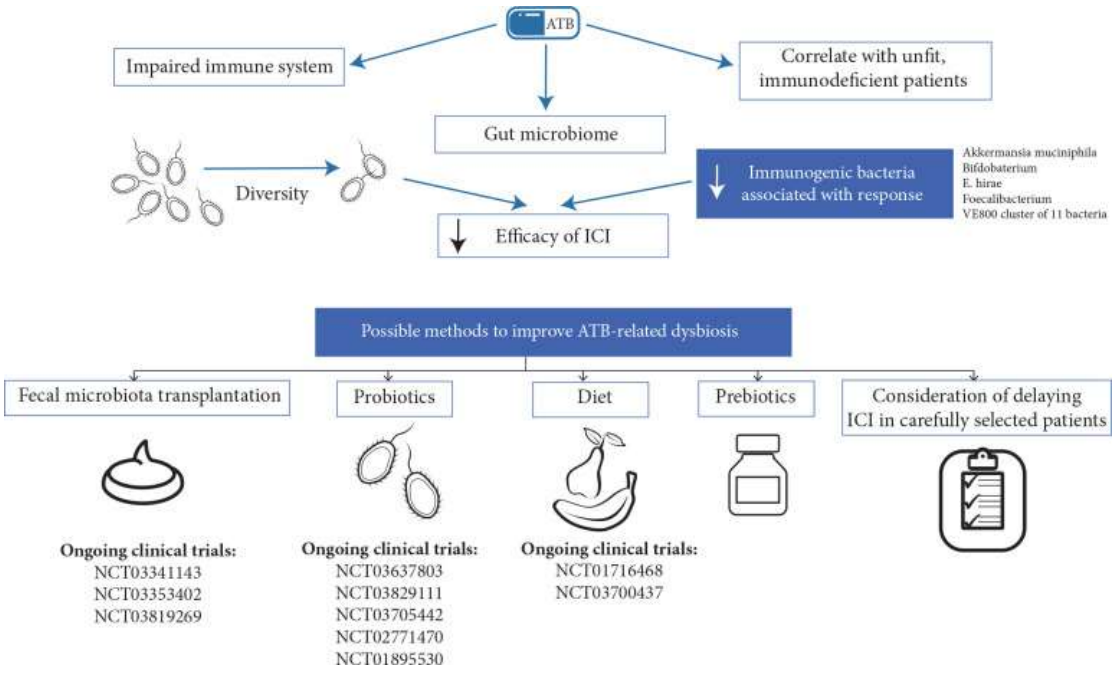

Figure 1. An overview of potential methods for transforming an unfavorable gut microbiota into a favorable one, with the aim of enhancing therapeutic results. ICI refers to immune-check point inhibition, whereas ATB stands for antibiotics.

3. Conclusion

Receiving broad-spectrum antibiotics (ATBs) in the month before to starting immunotherapy is very harmful, more so than if ATBs were given earlier. Alternatively, are there any particular antimicrobial agents that might potentially cause beneficial changes in the human immune system? Currently, the existing clinical data are insufficient to provide definitive answers to all of these inquiries.

In addition to the strong suggestion to use antibiotics (ATB) cautiously, there is a need for more comprehensive and future-oriented data to develop recommendations for the most effective care of patients who need ATBs immediately before or during immune checkpoint inhibitor (ICI) treatment. Additional research is necessary to ascertain if delaying the start of ICI-based immunotherapy might lead to a natural restoration of ATB-mediated dysbiosis, hence enhancing the effectiveness of the treatment. Nevertheless, this strategy may not be feasible for individuals with a high tumor load, since immediate beginning of immune checkpoint inhibitor (ICI) treatment is necessary. Currently, clinical studies are being conducted in this field to assess the effectiveness of specific therapies aimed at quickly reversing dysbiosis caused by antibiotic treatment. These strategies include fecal microbiota transplantation (FMT), prebiotics, and probiotics.

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