THE UNIVERSITY OF KANSAS CANCER CENTER

A Punch to the Gut: Antibiotics May Diminish the Therapeutic Effect of Immune Checkpoint Inhibitors

NCI Designated Comprehensive Cancer Center

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BACKGROUND

- Immune checkpoint inhibitor (ICI) therapy is a mainstay of treatment for many cancers.
- Patients with cancer often present with generally poor health and weakened immunity, and as a result, the incidence of infection and the probability of using antibiotics is relatively high [insert cite].
- Exposure to antibiotics before, during, and after ICI therapy may reduce treatment efficacy. However, due to discordant findings discordant, additional studies are underway to assess the effects of antibiotic use on the efficacy of ICI therapy.

OBJECTIVE

- To summarize the literature evaluating the response and survival rates of patients with cancer who were treated with an ICI with or without antibiotics.

METHODS

- Electronic databases, including Google Scholar, PubMed, Science Direct, and major oncology conference proceedings, were searched by using specific keywords and medical subject headings.
  - Primarily, the search term “nivolumab antibiotics,” “pembrolizumab antibiotics,” and “immune checkpoint inhibitor antibiotics” were used, followed by several other extensions, including the words “penicillin,” “fluoroquinolone,” "response," “survival,” “tumor,” “node,” “metastasis,” and “TNM.”
- ICIs included in this search included those listed in Table 1.

Table 1. List of ICIs Included in the Data Search

Name	Brand Name
Programmed cell death protein 1 (PD-1) inhibitors	
Cemiplimab	Libtayo
Dostarlimab	Jemperli
Nivolumab	Opdivo
Pembrolizumab	Keytruda
Programmed cell death 1 ligand 1 (PD-L1) inhibitors	
Atezolizumab	Tecentriq
Avelumab	Bavencio
Durvalumab	Imfinzi
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors	
Ipilimumab	Yervoy
Tremelimumab	Imjudo
PD-1 inhibitor and lymphocyte activation gene-3 (LAG-3) inhibitor combination	
Nivolumab and relatlimab	Opdualag

- The scope of the search encompassed research articles published in English before January 1, 2023.
- Results were reviewed and summarized by the author.

RESULTS

Antibiotics Diminish the Therapeutic Effect of ICIs

- A meta-analysis of 6 studies evaluating nivolumab for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC) found progression-free survival (PFS) and overall survival (OS) were decreased by 1.6 months and 8.8 months, respectively, among patients exposed to antibiotics before, during, or after nivolumab therapy.[1]
- A retrospective analysis of 635 patients treated with ICI found antibiotic use was associated with significantly decreased overall survival (8 vs. 23 months), progression-free survival (4 vs. 7 months), and tumor response (57% vs. 71%).[2]
- An analysis of 149 patients with bladder cancer treated with neoadjuvant pembrolizumab in a clinical trial found a significantly lower pathologic complete response (15% vs. 50%, respectively) and a significantly higher recurrence rate (HR 2.64) among patients treated with concomitant antibiotics compared with those who did not receive antibiotics.[3]
- Several analyses of patients treated with pembrolizumab[4,5,6,7,8], nivolumab[5,7,8,9,10,11,12], atezolizumab[12,13], cemiplimab[8], or dostarlimab[8] for a variety of cancers similarly found decreased PFS, OS, or both among patients who received antibiotics before or during therapy with ICIs compared with patients who did not receive concomitant antibiotics.
- Other analyses of patients treated with anti-PD-L1 agents with PD-L1 expression of at least 50% have found significant decreases in PFS and OS with concomitant antibiotic therapy.[14,15]
- A case report also describes a patient with NSCLC treated with nivolumab who developed pulmonary tuberculosis (TB) and experienced a paradoxical response (eg, worsening of clinical findings after initiating anti-TB therapy without evidence of disease relapse) after initiating anti-TB antibiotics.[16]

Antibiotics Do Not Diminish the Therapeutic Effect of ICIs

- A study of 302 patients with stage 4 NSCLC treated with first-line chemo-immunotherapy combinations found patients with prior exposure to antibiotics had similar OS, PFS, and objective response rate (ORR) compared with patients who had not received prior antibiotics.[17]
- A retrospective study of 74 patients with NSCLC treated with nivolumab found no significant effect of antibiotic use within the 3 months prior to or during nivolumab therapy on PFS or nivolumab response rate.[18]

DISCUSSION

- Although existing data and reports are inconsistent, several observational studies have demonstrated decreased PFS, OS, and tumor response in patients treated with ICIs who received antibiotics near or during ICI therapy.
- The mechanism for this interaction has not been thoroughly investigated, but antibiotic-induced changes of the microbiota have been proposed as a mechanism of resistance to ICIs.[8,9,10,11]
- Unanswered questions
  - Are certain antibiotics at higher risk of long-term changes to the gut microbiome?
  - Are certain patients with cancer more likely to receive antibiotics during ICI treatment?
  - Are certain patients with cancer more likely to develop antibiotic-induced changes in the microbiota?
  - What about combination therapies with traditional and targeted therapies?
  - Are there specific antibiotics that should be avoided? Or are there antibiotics that should be preferred when used near or during ICI therapy?
- Limitations
  - Most evidence in NSCLC.
  - Most evidence in patients with advanced cancer. None of the trials evaluated ICI therapy in adjuvant or neoadjuvant settings.
  - None of the studies included PD-1-LAG3 inhibitor combination (ie, nivolumab-relatlimab) or CTLA-4 inhibitors (ie, ipilimumab, tremelimumab).
  - None of the studies focused on pediatric patients.

CONCLUSION

- Antibiotics may diminish the therapeutic effects of ICIs; therefore, antibiotics should be used judiciously.
- More evidence is required to evaluate specific antibiotic and ICI therapies with the highest risk of poor outcomes.

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