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Antibiotics and immunotherapy in gastrointestinal tumors: Friend or foe?

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Abstract

The incidence of gastrointestinal (GI) tumors is increasing year by year, and its pathogenesis is closely related to the intestinal flora. At present, the use of antibiotics is very common in the clinic. And cancer patients with low immunity are vulnerable to all sorts of infections, such as respiratory tract infections and urinary tract infections. Moreover, cancer patients easily run into fever and neutropenia induced by myelosuppression. Therefore, antibiotics are used extensively and even overused in many conditions. However, because of the special anatomical location of the gastrointestinal tract, the antibiotic usage will bring changes to the intestinal flora. Besides, with the expanding popularity of immunotherapy, various factors affecting the efficacy of immune checkpoint inhibitors (ICIs) have been extensively explored, including cancer-associated inflammation and the local and systemic factors that lead to immunosuppression. Some biomarkers for ICIs, including the expression of PD-L1, tumor mutation load, and microbiota, also have been investigated, and many studies have confirmed that gut microbiota can affect the efficacy of immunotherapy. But further studies on the influence of antibiotics directly on immunotherapy are rare. In this review, we discuss the relationship between GI tumors and antibiotics, the current status of immunotherapy in GI tumors, and the influence of antibiotics on immunotherapy.

Key words: Antibiotics; Immunotherapy; Gastrointestinal tumor; Microbiota; Immune checkpoint inhibitors

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Core tip: With the widespread use of immunotherapy for almost all types of cancers and the extensive usage of antibiotics in many countries, the association between antibiotics

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and immunotherapy deserves an investigation based on some studies which showed that the gut microbiota plays an important role in immunotherapy. We reviewed the relevant papers and found that antibiotics may attenuate the effect of immunotherapy.

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INTRODUCTION

Gastrointestinal (GI) tumors, including colorectal cancer (CRC), gastric cancer, pancreatic cancer, hepatocellular carcinoma (HCC), and cholangiocarcinoma, account for a large proportion of all cancers^[1,2]. Due to the limited effectiveness of traditional chemotherapy, especially for pancreatic cancer and HCC, great efforts have been made in immunotherapy, which has become a potential treatment option for GI tumors in the last decade. In addition, current management strategies and treatments for GI tumors have also been enriched by immune checkpoint inhibitors (ICIs), such as advanced treatment for microsatellite instable CRC and second-line treatment for HCC. However, only a fraction of patients benefited from ICIs and there are some factors affecting their efficacy, such as tumor genomics, PD1 ligand 1 (PD-L1) levels, and gut microbiota^[3].

The correlations between the gut microbiota community and clinical response to ICIs have been confirmed by an increasing number of investigations. Early studies found that the effects of CTLA-4 blockade were associated with T cell responses specific for distinct *Bacteroides* species and tumors in antibiotic-treated or germ-free mice did not respond to CTLA-4 blockade^[4]. Cancer immunotherapy may be modulated by manipulating the microbiota^[5]. Similarly, the anticancer immunity in mouse models induced by anti-PD-L1 is reported to rely on *Bifidobacterium*, which might improve the effectiveness of anticancer immunity through augmenting dendritic cell functions and subsequently enhancing CD8+ T cell priming and accumulation in the tumor microenvironment. Furthermore, oral administration of *Bifidobacterium* can generate a similar effect to anti-PD-L1 treatment on tumor elimination, indicating the potentially important role of *Bifidobacterium* in strengthening immune functions^[5]. Subsequently, an increasing number of studies have revealed a correlation between the response to anti-PD-1 and the abundance of diversified bacteria, including *Ruminococcaceae* bacteria, *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*^[6-8].

Since extensively and overused antibiotics can lead to an abnormal intestinal microbiota composition, the effect of antibiotics on immunotherapy has also been explored in several studies. For example, some studies have indicated that antibiotics can weaken the effectiveness of immunotherapy, while others argued that antibiotics have no influence on immunotherapy. In this review, we summarize the relationship between antibiotics, microbiota, and GI tumors, the current status of immunotherapy in GI tumors, and the influence of antibiotics on immunotherapy in a comprehensive manner.

ANTIBIOTICS, MICROBIOTA, AND GI TUMORS

The link between antibiotics and cancers has been around for a long time. Several decades ago, the hypothesis that the use of antibiotics may increase the risk of cancer was first proposed^[9]. Studies have shown the association between increased use of antibiotics and increased incidence and mortality of breast cancer^[10,11]. Antibiotics are also known to influence the development and progression of GI tumors, most notably for colorectal cancer. Cao *et al*^[12] reported a study of 1195 newly diagnosed colorectal adenomas in patients who underwent at least one colonoscopy and reported information on antibiotic use. They found that antibiotic use at ages 20-39 and 40-59 was significantly associated with an increased risk of colorectal adenoma after age 60. Two other case-control studies supported this conclusion: one study found a positive association between the use of anti-anaerobic antibiotics and colorectal cancer, but no

association was found for anti-aerobic agents^[13]; another study found that a high (≥ 8) number of prescriptions of antibiotics was associated with an increased risk of colorectal cancer (CRC), and when antibiotics were used for ≥ 70 d compared to no use of antibiotics, the risk of CRC significantly increased, and both anti-aerobic agents and anti-anaerobic antibiotics were associated with an increased risk of CRC^[14]. Indeed, penicillin can lead to an increased risk of esophageal, gastric, and pancreatic cancers^[15], and antibiotic exposure can promote the development of tumors in the liver^[16].

However, the effect of the microbiota on cancers further complicates the relationship between antibiotics, bacteria, and cancers. The microbiota is reported to be involved in the initiation, progression, and dissemination of cancer both at epithelial barriers and in sterile tissues, and gut microbiota can modulate the response to cancer therapy and susceptibility to toxic side effects^[17]. There are papers showing some microbes associated with GI tumors (Table 1), and common examples of microbes involved in cancer include *Helicobacter pylori*, which is associated with gastric cancer, *Clonorchis sinensis* and *Opisthorchis viverrini*, which are associated with bile duct cancer, and enterotoxigenic *Bacteroides fragilis*, which is associated with colon cancer^[18,19]. In mice receiving broad-spectrum antibiotics, reductions in microbiota, inflammation, and colonic polyposis, which is a precancerous lesion of colon cancer, were observed^[20]. Immune and inflammatory pathways could be regulated by chronic inflammatory conditions, while chronic inflammatory conditions could be affected by microbiota and antibiotics^[20,21]. These observations suggested that a further investigation into the influence of antibiotics on the treatment for GI tumors is necessary.

IMMUNOTHERAPY AND GI TUMORS

Immunotherapy has been a hit in the field of cancer therapy. Unlike melanoma, renal cancer, and non-small cell lung cancer, most GI tumors do not induce effector T-cell responses naturally, which may lead to an unsatisfactory immunotherapy efficacy. Various clinical trials have been conducted to verify the efficacy of ICIs in GI tumors as a single agent or in combination, and tremendous advances have been made (Table 2). For esophageal and gastric cancers, a phase II trial confirmed the safety and activity of nivolumab in 64 patients with treatment-refractory esophageal cancer^[22]. Nivolumab was approved in Japan after the Asian ATTRACTION 02 study^[23], which was a phase III trial performed to compare nivolumab with placebo in patients with unresectable chemorefractory advanced gastric or gastroesophageal junction cancer. Then, the CheckMate-032 phase I/II study evaluated the efficacy and safety of nivolumab and nivolumab plus ipilimumab^[24], and the phase II clinical KEYNOTE-059 trial demonstrated promising activity and manageable safety of pembrolizumab^[25]. All the above studies suggested that immunotherapy may be a potential approach to treating refractory advanced gastric and esophageal cancers. However, the phase III JAVELIN trial^[26] and the KEYNOTE-061 phase III trial^[27] showed negative results.

For HCC, an early phase 1/2 dose escalation and expansion trial to assess the safety and efficacy of nivolumab showed a satisfactory survival end-point and treatment response rate^[28]. Besides, another study evaluated the efficacy and safety of pembrolizumab in patients who had previously experienced sorafenib^[29]. Similarly, small sample clinical trials of camrelizumab (anti-PD-1 antibody)^[30] and tremelimumab (anti-CTLA-4 antibody)^[31] also yielded promising results. For biliary tract cancer, Bang *et al* performed an interim analysis to evaluate the safety and antitumor activity of pembrolizumab in advanced biliary tract cancer and found that pembrolizumab was generally well tolerated and demonstrated promising antitumor activity among 24 enrolled patients. For pancreatic cancer, early studies on BMS-936559 (anti-PD-L1 antibody)^[32] and ipilimumab^[33] showed that they were ineffective when treating advanced pancreatic cancer. Hence, further investigations are suggested to perform.

The immunological benefit in patients with colorectal cancer has been limited to those who had a loss of mismatch repair function and had specific germline mutations in the DNA polymerase gene^[34,35]. A host of current trials are underway in patients with microsatellite stable (MSS) CRC to evaluate the utility of concurrent chemotherapy, VEGF/EGFR inhibitors, radiotherapy, or MEK inhibitors with ICIs; however, more data are still needed to address the efficacy and tolerability of ICIs in MSS CRC patients^[36].

In summary, with respect to advanced gastrointestinal malignancies, ICIs have shown some therapeutic effects. However, for various reasons, such as the stroma

Table 1 Microbes that may cause gastrointestinal tumors

| Tumor | Microbes involved |
|--------------------------|---|
| Esophageal cancer | <i>H. pylori</i> , Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria phyla. |
| Gastric cancer | <i>H. pylori</i> , Porphyromonas, Neisseria, Prevotella pallens, Streptococcus sinensis, Lactobacillus coleohominis, Klebsiella pneumoniae, and Acinetobacter baumannii |
| Colorectal cancer | Faecalibacterium prausnitzii, Eubacterium rectale, Proteobacteria, Bacteroidetes, Fusobacterium |
| Hepatocellular carcinoma | <i>H. pylori</i> , Escherichia coli |
| Biliary tract cancer | Pseudomonadaceae, Oxalobacteraceae, Clonorchis sinensis, and Opisthorchis viverrini |
| Pancreatic cancer | <i>H. pylori</i> |

H. pylori: *Helicobacter pylori*.

providing a formidable barrier to effector T-cell infiltration in pancreatic cancer, the therapeutic effect of ICIs needs to be further improved. Therefore, various clinical trials are planned using combinations of ICIs with chemotherapy, molecular targeted therapy, radiation therapy, or other novel immunomodulatory agents in patients with advanced GI tumors. And the factors affecting the immunotherapeutic efficacy for GI tumors are also worthy of further studying, especially the unclarified but important role of antibiotic usage in patients receiving ICIs treatment.

ANTIBIOTICS AND IMMUNOTHERAPY

PD-L1 expression in the tumor tissue has been considered to be a biomarker for pembrolizumab in NSCLC^[37]; however, some PD-L1-positive patients do not benefit from pembrolizumab, while some PD-L1-negative patients could benefit from nivolumab or other ICIs. How to select the appropriate population for ICIs is still a question. A recent study found that tumor mutation burden or tumor infiltrating lymphocytes might be relevant biomarkers for patients treated with ICIs^[38,39], and accumulating evidence supports the hypothesis that the gut microbiota has a great influence on immunotherapy, including ICIs^[40]. Therefore, tumor mutation burden, tumor infiltrating lymphocytes, and the gut microbiota are considered potential immunotherapy biomarkers. The gut microbiota plays a crucial role in balancing inflammation, infection, and commensal antigens, which can modulate the host immune system both locally and systemically^[40]. As interest in the influence of microbiota on immunotherapy has escalated, microbiota and cancer, specific gut microbes, and administration of antibiotics have also attracted extensive attention.

Early studies focusing on the relationship between immunotherapy and antibiotics were all conducted in murine models. For example, cyclophosphamide (CTX) is a well-known chemotherapy that can stimulate antitumor immune responses, including inducing the death of immunogenic cancer cells, destroying immunosuppressive T cells, and promoting Th1 and Th17 cells to control tumor growth. However, mice treated with antibiotics to kill gram-positive bacteria have been found to have a reduction in the number of pathogenic Th17 cells and a worse treatment response^[41]. When pathogenic Th17 cells were transferred to antibiotic-treated mice, the antitumor efficacy of cyclophosphamide was partially restored, which suggests that antibiotics may influence the efficacy of immunotherapy by regulating the gut microbiota. Another study also found that antibiotic-treated mice showed a low response to CpG-oligonucleotides. They found that TNF expression and frequencies of TNF-positive leukocytes induced by CpG-oligonucleotides were significantly impaired^[42]. It is mainly because those antibiotics could affect the microbiota and further affected local and systemic inflammation and the tumor immune microenvironment. Further studies showed that immunotherapy CTLA-4 and/or PD-1/PD-L1 efficacy could be improved by transferring patient fecal samples into germ-free (GF) or antibiotic-treated SPF mice^[7].

In addition to the above animal experimental findings, several independent retrospective analyses in human cohorts of advanced NSCLC, RCC, and urothelial carcinoma have found contradictory results (Table 3). An early study found that antibiotics do not affect the efficacy of nivolumab in NSCLC patients^[43]. A total of 74 locally advanced or metastatic NSCLC patients were treated with nivolumab as a second- or third-line therapy, 15 patients were exposed to antibiotics, and the

Table 2 Completed clinical trials of immune checkpoint inhibitors on gastrointestinal tumors

| Trial | Phase | Treatment | ORR% (95%CI) | DCR% (95%CI) | Median PFS months (95%CI) | Median OS months (95%CI) | Adverse events |
|--------------------------------|-------|---|---------------|---------------|---------------------------|--------------------------|--------------------------|
| Esophageal and gastric cancers | | | | | | | |
| | II | Nivolumab (<i>n</i> = 64) | 11 (10-28) | 27 (31-54) | 1.5 (1.4-2.8) | 11 (7.3-13) | G3/4 25%; All-grade 73% |
| ATTRACTION 02 | II | Nivolumab (<i>n</i> = 330) | 11 (8-16) | 40 (34-46) | 1.6 (1.5-2.3) | 5.3 (4.6-6.4) | G3/4 27%; All-grade 43% |
| | | Placebo (<i>n</i> = 163) | 0(0-3.0) | 25 (18-34) | 1.5 (1.5-1.5) | 4.1 (3.4-4.9) | G3/4 4%; All-grade 27% |
| CHECKMATE32 | I/II | Nivolumab 3 (mg/kg) | 12 (5-23) | NR | 1.4 (1.2-1.5) | 6.2 (3.4-12) | G3/4 17% |
| | | Nivolumab 1 + Iplilimumab 3 | 24 (13-39) | NR | 1.4 (1.2-3.8) | 6.9 (3.7-12) | G3/4 47% |
| | | Nivolumab 3 + Iplilimumab 1 | 8.0 (2.0-19) | NR | 1.6 (1.4-2.6) | 4.8 (3.0-8.4) | G3/4 27% |
| KEYNOTE59 | II | Pembrolizumab (<i>n</i> = 259) | 12 (8-16) | 27(21.7-32.9) | 2.0 (2.0-2.1) | 5.5 (4.2-6.5) | G3/4 18%; All-grade 60% |
| JAVELIN Gastric 300 | III | Avelumab (<i>n</i> = 185) | 2.2 (0.6-5.4) | 22 (16-29) | 1.4 (1.5-2.0) | 4.6 (3.6-5.7) | G3/4 9.2% |
| | | Chemotherapy (<i>n</i> = 186) | 4.3 (1.9-8.3) | 44 (37-52) | 2.7 (1.8-2.8) | 5.0 (4.5-6.3) | G3/4 32% |
| KEYNOTE61 PDL CPS ≥ 1 | III | Pembrolizumab (<i>n</i> = 196) | 16 (11-22) | NR | 1.5 (1.4-2.0) | 9.1 (6.2-11) | G3/4 25% |
| | | Paclitaxel (<i>n</i> = 199) | 14 (9.0-19) | NR | 4.1 (3.1-4.2) | 8.3 (7.6-9.0) | G3/4 35% |
| Hepatocellular carcinoma | | | | | | | |
| CHECKMATE40 | I/II | Nivolumab (dose-escalation) | 15 (6.0-28) | 58 (43-72) | NR | 15 (9.6-20) | G3/4 25% |
| | | Nivolumab (dose-expansion) | 20 (15-26) | 64 | 5.4 (3.9-8.5) | NR | G3/4 63% |
| KEYNOTE224 | II | Pembrolizumab (<i>n</i> = 169) | 18 (11-26) | 62 (52-71) | 4.9 (3.4-7.2) | 13 (10-16) | G3/4 25%; All-grade 73% |
| Biliary tract cancer | | | | | | | |
| KEYNOTE28 | I | Pembrolizumab (<i>n</i> = 24) | 17 (5.0-39) | 34 | NR | NR | G3/4 17%; All-grade 63% |
| Pancreatic cancer | | | | | | | |
| | II | Iplilimumab (<i>n</i> = 27) | 0 | 0 | NR | NR | NR |
| | I | Tremelimumab + gemcitabine (<i>n</i> = 34) | NR | NR | NR | 7.4 (5.8-9.4) | All-grade 94% |
| | Ib/II | Pembrolizumab + nab-paclitaxel (<i>n</i> = 17) | 18 | 76 | 9.1 (4.9-15.3) | 15 (6.8-23) | G3/4 71%; All-grade 100% |
| Colorectal cancer (dMMR) | | | | | | | |
| | II | Pembrolizumab (<i>n</i> = 10) | 40 (12-74) | 90 (55-100) | NR | NR | G3/4 41%; All-grade 98% |
| KHECKMATE 142 | II | Nivolumab (<i>n</i> = 74) | 31 (21-43) | 69 (57-79) | NR | NR | G3/4 20%; All-grade 70% |

DCR: Disease control rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression free survival; G: Grade; NR: Not reported; dMMR: Mismatch repair deficiency.

remaining 59 patients were not exposed to antibiotics. No significant difference was found in response rates and progression-free survival (PFS) between the two groups of patients. Subsequently, another two independent studies with larger sample sizes drew inconsistent conclusions. Indeed, Kaderbhai *et al*^[43] showed that in RCC patients, antibiotic use compared to no antibiotic use was associated with an increased risk of primary progressive disease (PD), shorter PFS, and shorter overall survival (OS). In NSCLC patients, antibiotic use was associated with similar rates of primary PD but

decreased PFS and OS. In a study by Routy, 69 out of 249 patients were prescribed antibiotics. PFS and OS were significantly shorter in the antibiotics-treated patients when all patients were combined. Furthermore, transplantation of fecal microbiota from patients who responded to ICIs into germ-free non-responders restored or enhanced the ICIs responsiveness. In univariate and multivariate Cox regression analyses, antibiotic use was found to be a predictor of resistance to PD-1 blockade, independent of classical prognostic markers in NSCLC and RCC^[44]. Gut microbiota composition analysis found that *A. muciniphila* was the most significantly associated bacteria with favorable clinical outcome, which increased the recruitment of CCR9+ CXCR3+ CD4+ T lymphocytes into tumor beds in an IL-12-dependent manner.

The different studies come to different conclusions, which may be due to a combination of several reasons. First, the duration time of antibiotic usage is different. Some studies allowed the use of antibiotics for 3 months before immunotherapy, while other studies used antibiotics for only 1 month before immunotherapy, and there is no unified standard. Second, the cancer type is different. RCC, melanoma, and NSCLC are more sensitive to ICIs. Third, all the studies were retrospective studies, which need to be further confirmed by randomized controlled clinical trials.

CONCLUSION

As is well-known, immunotherapy has become an important weapon in the treatment of GI tumors. However, it still lacks effective biomarkers. Besides, microbiota is known to influence the response to anticancer immunotherapy, and antibiotics have been proven to influence the occurrence and development of GI tumors. In this study, we reviewed a reasonable quantity of papers about the relationship between antibiotics and immunotherapy. Although few studies are directly related to GI tumors, the relevant studies suggest that antibiotics can affect the commensal microbiota and further affect the efficacy of immunotherapy. In a word, according to the current research evidence, it remains inconclusive that the relationship between antibiotics and immunotherapy is friend or foe, and we hope that more studies can focus on this area in the future.

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Table 3 Studies about antibiotics and immunotherapy

| | Research subjects | Tumor type | Patients No. | Research conclusion | Ref. |
|---|-------------------|--|--------------|--|---|
| 1 | Patients Mice | NSCLC/RCC/urothelial carcinoma Sarcoma/melanoma | 249 | ATB use presents a predictor of resistance to ICI | Routy <i>et al</i> ^[44] , 2018 |
| 2 | Patients | NSCLC | 74 | ATB use does not affect the efficacy of nivolumab | Kaderbhai <i>et al</i> ^[43] , 2017 |
| 3 | Patients | RCC/NSCLC | 360 | ATB use reduces clinical benefit from ICI | Derosa <i>et al</i> ^[45] , 2018 |
| 4 | Mice | Lymphoma/colon cancer/melanoma | | ATB treated mice respond poorly to CpG-oligonucleotide | Lida <i>et al</i> ^[42] , 2013 |
| 5 | Mice | | | ATB mice are resistant to cyclophosphamide | Viaud <i>et al</i> ^[41] , 2013 |

ATB: Antibiotics; ICI: Immune checkpoint inhibitor.

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