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Anti-Cancer Agents Associated Diarrhea: Current Status and Prospects

Hao Wang[1,2], Zhansheng Jiang[3,4,5,6,7], Zhongsheng Tong[3,4,5,6]*

[1]Department of Breast Medical Oncology, Tianjin Cancer Hospital Airport Hospital, Tianjin 300000, China
[2]National Clinical Research Center for Cancer, China
[3]Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin 300000, China
[4]Tianjin's Clinical Research Center for Cancer, Tianjin 300000, China
[5]Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin, China
[6]Key Laboratory of Cancer Prevention and Therapy, Tianjin 300000, China
[7]Department of Integrated Traditional Chinese and Western Medicine, Tianjin Medical University Cancer Institute & Hospital, Tianjin 300000, China

***Corresponding author:** Zhongsheng Tong, tongzhongsheng@tjmuch.com

Abstract: Cancer stands as one of the major threats to human life. Ensuring the safety of drugs is paramount, and the impact of adverse reactions on patients' quality of life and prognosis should not be underestimated. Diarrhea is a common clinical adverse event, and despite the absence of specific anti-diarrhea drugs, there is a pressing need for improvement. This article aims to provide a valuable reference for researchers in clinical drug use and scientific tumor treatment. It summarizes recent advancements in drug mechanisms and adverse reactions, whether in preclinical research or clinical diagnosis and therapy.

Keywords: Diarrhea; Anti-cancer agent; Adverse reaction; Cancer; Treatment

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1. Introduction

Compared with traditional therapies, targeted and immunotherapy drugs demonstrate superior anti-tumor effects. However, the onset of diarrhea during cancer treatment may exacerbate patients' quality of life, diminish medication compliance, and, in extreme cases, pose life-threatening risks, leading to treatment interruption or cessation. This article reviews recent research and advancements in diarrhea associated with targeted and immunotherapy drugs in cancer treatment (**Tables 1** and **2**), aiming to serve as a valuable reference for researchers involved in the clinical use of drugs and assessment of patient prognosis.

2. Targeted therapy drugs

Targeted small molecule inhibitor anti-tumor drugs focus on key kinases in cell signal transduction pathways, controlling cellular signal transduction by managing enzymes. This control influences tumor growth, reproduction, and metastasis. Currently, the most widely applied clinical use involves small molecule targeted drugs for lung cancer, followed by breast cancer. These small molecule targeted drugs are categorized into tyrosine kinase inhibitors (TKIs) and serine/threonine kinase inhibitors.

2.1. Anti-HER2 targeted drugs

Human epidermal growth factor receptor-2 (HER2) is a transmembrane protein encoded by the oncogene *erbB2*. Amplification of the HER2 gene and overexpression of the HER2 protein occur in various solid tumors. Currently, drugs targeting HER2 include small molecule targeted drugs, TKIs, and specific monoclonal antibodies.

TKIs competitively bind to the intracellular adenosine triphosphate (ATP) binding domains of the epidermal growth factor family of receptor tyrosine kinases (ErbBs) due to their homological structure similar to ATP. The binding blocks downstream signals of HER2, inhibiting phosphorylation, ultimately hindering cancer cell proliferation and promoting apoptosis. Notably, TKIs, being small molecules, can penetrate the blood-brain barrier, proving effective in patients with central nervous system metastasis. Approved TKIs include lapatinib, neratinib, pyrotinib, etc. Lapatinib reversibly blocks EGFR and HER2, inhibiting downstream MAPK/ERK and PI3K/AKT pathways. Common adverse events primarily occur in the gastrointestinal tract, encompassing nausea, diarrhea, stomatitis, and indigestion. Pyrotinib, similar to neratinib, is an irreversible pan-ErbB2 receptor TKI that covalently binds to ATP binding sites in HER1, HER2, and HER4 kinase regions, inhibiting homodimers formation, blocking the downstream PI3K/AKT and RAS/RAF/MEK/ERK signaling pathways, thereby inhibiting tumor cell growth. Neratinib is an irreversible small-molecule pan-HER tyrosine kinase inhibitor of HER1, HER2, and HER4. The most frequent adverse events of pyrotinib and neratinib include gastrointestinal reactions, with diarrhea, nausea, abdominal pain, vomiting, decreased appetite, and indigestion being prevalent [1].

Monoclonal antibody drugs mainly include trastuzumab and pertuzumab. Trastuzumab can bind to the HER2 extracellular domain IV region, and pertuzumab can bind to the HER2 extracellular domain II region, inhibiting homodimer and heterodimer formation, and blocking downstream signal generation. As HER2 domains II and IV are opposite to each other, trastuzumab and pertuzumab can complement each other, and the combined use enhances efficacy but also increases the incidence of gastrointestinal side effects and diarrhea.

Antibody-drug conjugates (ADCs) represent a new class of anti-tumor-targeted drugs combining monoclonal antibodies and chemical drugs. Ado-trastuzumab, also known as T-DM1, is the first approved drug in China that is conjugated with trastuzumab and maytansine derivatives and is connected through a non-reducing thioether linker. T-DM1 releases active cytotoxins into cells through endocytosis, inhibiting cell growth and proliferation signaling, thereby killing tumor cells. It serves as the second-line treatment after trastuzumab failure for HER2-positive metastatic breast cancer. T-DM1 exhibits excellent pharmacokinetic characteristics and low toxicity, with common adverse reactions including fatigue, nausea, and musculoskeletal pain [2].

2.2. CDK4/6 inhibitors

Cyclin-dependent kinase (CDK) plays a pivotal role in cell cycle regulation. Uncontrolled retinoblastoma tumor suppressor protein (Rb) phosphorylation, mediated by CDK4/6, is a key factor in tumor growth. CDK4/6 inhibitors act on the cell cycle, selectively inhibiting CDK4/6 kinases to block the transition from the G1 to

S phase. They control cell division in the G1 phase and target multiple key nodes in the estrogen signaling pathway, exerting a synergistic anti-tumor effect and preventing unrestricted cell proliferation.

Palbociclib and ribociclib are both employed in the initial endocrine therapy for hormone receptor (HR)-positive, HER2-negative (HR+/HER2-) locally advanced or metastatic breast cancer, with neutropenia being the most common adverse event. Dalpiciclib is suitable for treating HR+/HER2- recurrent or metastatic breast cancer that has progressed after endocrine therapy, especially when combined with fulvestrant (estrogen receptor antagonist). Notably, no serious gastrointestinal adverse reactions have been reported. In China, abemaciclib is the only CDK4/6 inhibitor approved for early-stage breast cancer patients, demonstrating the highest incidence of diarrhea. This may be attributed to abemaciclib inhibiting calcium/calmodulin-dependent kinase II, which is involved in intestinal motility, and inhibiting CDK9, thereby modifying the cascade reaction mediated by glycogen synthesis kinase 3 [3].

2.3. EGFR inhibitors

Mutations in the kinase domain of epidermal growth factor receptor (EGFR) serve as oncogenic drivers in adenocarcinoma, a subset of non-small cell lung cancer (NSCLC). Upon binding to its ligand, the EGFR monomer undergoes dimerization, leading to tyrosine autophosphorylation. This initiates downstream signaling pathways, including RAS/RAF/MEK/ERK MAPK and PI3K/AKT/mTOR pathways, participating in the regulation of cell proliferation, migration, survival, and anti-apoptotic response.

First-generation EGFR TKIs, such as gefitinib, erlotinib, and icotinib, reversibly bind to EGFR and inhibit the binding of ATP to the tyrosine kinase domain. This inhibits autophosphorylation of EGFR receptor tyrosine, further inhibiting downstream signaling. Erlotinib exhibits the highest incidence of diarrhea, often reaching grade 3 and above. Most cases of gefitinib can be resolved without medication or with self-medication. Icotinib is less toxic and better tolerated, with most cases graded as 1 or 2, resolving without special treatment. Continuous treatment with first-generation EGFR TKIs typically leads to drug resistance, often involving T790M mutations. To address this, second-generation irreversible EGFR TKIs such as afatinib and dacomitinib were developed, offering enhanced and sustained inhibition of tumor cells. However, due to their non-selectivity, they present relatively high severity and incidence of rash and diarrhea.

The third generation of small molecule EGFR TKIs selectively bind to Cys797, targeting EGFR T790M and EGFR gene-sensitive mutations. Among them, osimertinib, an irreversible EGFR TKI, effectively treats resistance to previous-generation targeted drugs. Still, it lacks inhibitory activity against EGFR wild-type, resulting in a 44.0% incidence of full-grade diarrhea. Ametinib and fumetinib, independently developed in China, exhibit better gastrointestinal safety data than similar drugs, with a lower incidence of diarrhea. Despite promising therapeutic effects, third-generation EGFR TKIs face the challenge of acquired resistance. The development of fourth-generation drugs for widespread and effective treatment of EGFR-mutated tumors resistant to previous generations remains a scientific challenge [4].

2.4. ALK inhibitors

Anaplastic lymphoma kinase (ALK) belongs to the receptor tyrosine kinase (RTK) superfamily and is encoded by the *ALK* gene. The fusion of the *ALK* gene and echinoderm microtubule-associated protein-like 4 (EML4) gene is a crucial driver gene in NSCLC. Ligand binding to the ALK receptor induces intracellular kinase domain dimerization and downstream kinase signal transduction. This process inhibits the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK MAPK pathways, ultimately restraining tumor proliferation.

The first-generation inhibitor, crizotinib, targets ALK, c-ros oncogene 1 (ROS1), and c-MET tyrosine

kinases. It binds to the EML4-ALK fusion protein domain, inhibiting downstream pathways and resulting in a diarrhea incidence rate of 55.84% [5]. Second-generation inhibitors, ceritinib, alectinib, and brigatinib, primarily target crizotinib-resistant ALK-positive NSCLC, with an efficacy of approximately 20, 10, and 12 times higher than crizotinib, respectively [5-7]. The most prevalent adverse events observed with first- and second-generation ALK inhibitors were low-grade gastrointestinal toxicities such as nausea, vomiting, and diarrhea [8]. Differences in the toxicity patterns were observed in these 4 inhibitors, with more visual disorders with crizotinib, more dysgeusia with crizotinib and alectinib, more gastrointestinal and hepatic toxicities with ceritinib, and more respiratory complications with brigatinib. Ensartinib, a potent second-generation TKI, had a higher risk of nausea (36%), vomiting (26%), and diarrhea (11.0%) [9]. Lorlatinib, a third-generation highly selective ALK/ROS1 dual-target inhibitor with strong blood-brain barrier penetration, commonly induces hypercholesterolemia (81%) and hypertriglyceridemia (60%), with a 28% incidence of diarrhea [10].

2.5. ROS1 inhibitors

ROS1 fusion/rearrangement is a common mutation in NSCLC, representing a proto-oncogene highly expressed in various tumor cell lines. Gene rearrangement keeps the tyrosine kinase region activated, initiating signaling pathways, such as MAPK/ERK, PI3K/AKT, JAK/STAT3, and SHP1/2. These pathways control cell proliferation, survival, and metastasis. Due to homology in the kinase region and ATP-binding site, most ALK inhibitors (except alectinib) can effectively inhibit the proliferation of ROS1-positive cell lines [11].

Cabozantinib targets multiple tyrosine kinases, including ROS1, vascular endothelial growth factor receptor (VEGFR), MET, and rearranged during transfection (RET). It is used to treat advanced and metastatic medullary thyroid cancer, though it leads to multiple gastrointestinal adverse events. In a phase II trial, the high-grade diarrhea incidence rate was 58%, with an overall diarrhea incidence of 7% [12]. Entrectinib can effectively treat ROS1-rearranged NSCLC because it can permeate the brain barrier and is particularly effective against brain metastasis. The most common adverse reactions are fatigue, constipation, dizziness, diarrhea, etc. [13]. Repotrectinib, a new generation ROS1 and tropomyosin receptor tyrosine kinase (TRK) TKI inhibitor, exhibits 90 times the potency of crizotinib. Common adverse events include dizziness (49%), dysgeusia (48%), and constipation (20%), but there are no reported cases of diarrhea incidence [14]. Taletrectinib is used to treat adult patients with advanced or metastatic ROS1-positive NSCLC who have not received ROS1 inhibitor treatment or have previously received crizotinib treatment. Results from the Phase I study of patients with advanced solid tumors in the United States showed that the most common treatment-related adverse events were nausea (47.8%), diarrhea (43.5%), and vomiting (32.6%) [15].

2.6. MET inhibitors

c-MET, encoded and synthesized by the mesenchymal-epithelial transition factor (MET), is a receptor tyrosine kinase that binds to hepatocyte growth factor (HGF). Upon binding and phosphorylation, it regulates kinase activity, eliciting various effects in the cytoplasm. These factors activate downstream signaling pathways, promoting cell proliferation, migration, angiogenesis, and invasion. Normally expressed, the c-MET pathway promotes tissue differentiation and repair; however, abnormal expression or regulation can stimulate the proliferation and metastasis of tumor cells.

Crizotinib is a type Ia MET TKI and a highly selective competitive inhibitor for the ATP-binding site of the RTK. Capmatinib, tepotinib, and savotinib are categorized as type Ib MET TKIs, while cabozantinib is considered a type II MET TKI. Capmatinib, the first targeted therapy drug for MET14 metastatic NSCLC, demonstrated a low incidence of gastrointestinal adverse events in the phase II GEOMETRY mono-1 study.

Common adverse events include edema, nausea, vomiting, etc., with a diarrhea incidence of 18% [16]. Tepotinib, a potent and highly selective MET inhibitor, exhibited peripheral edema as the most common treatment-related adverse event in patients with *Met*ex14-skipping advanced/metastatic NSCLC in the VISION phase 2 nonrandomized clinical trials [17]. Savolitinib, the first oral highly selective MET inhibitor approved in China, showed gastrointestinal adverse events in a phase I study on advanced solid malignant tumors. These events were primarily nausea (58%), fatigue (38%), vomiting (33%), and diarrhea (13%) [18].

2.7. BRCA inhibitors

Breast cancer susceptibility genes (*BRCA1* and *BRCA2*) are tumor suppressor genes significantly associated with hereditary ovarian cancer and breast cancer. The translated proteins from these genes play a crucial role in repairing double-stranded DNA breaks and regulating cell growth. Mutations in *BRCA* genes can result in the loss of tumor suppression. Poly ADP ribose polymerase (PARP) inhibitors can impede the repair of DNA single-strands. Tumor cells containing *BRCA* mutations, lacking BRCA-encoded proteins, are unable to repair DNA double-strand breaks through homologous recombination, ultimately leading to tumor cell death. PARP inhibitors function through synthetic lethality, exploiting specific vulnerabilities within the cell without inducing apoptosis.

Olaparib, a PARP inhibitor, has demonstrated significant clinical activity in *BRCA*-mutated ovarian cancer. It inhibits DNA single-strand repair, inducing cancer cell death. The most common gastrointestinal adverse events include nausea, vomiting, and diarrhea, with a diarrhea incidence of 22.1% [19]. Niraparib, an oral selective inhibitor of PARP-1 and PARP-2 nuclear proteins, exhibited common gastrointestinal adverse reactions, including nausea, vomiting, constipation, and loss of appetite, in the phase III trial of NOVA [20]. Rucaparib strongly affects PARP-1, PARP-2, and PARP-3, with the most common gastrointestinal adverse events being nausea, vomiting, constipation, and diarrhea [21].

2.8. VEGFR inhibitors

Vascular endothelial growth factor receptor (VEGFR) is a tyrosine kinase receptor. The autophosphorylation of specific residues in its structure transmits signals to other signaling effectors. It is involved in many signal transductions necessary for angiogenesis and cell migration and plays a vital role in the induction pathway, including VEGFR1, VEGFR2, and VEGFR3. The autocrine function of VEGF in tumor cells leads to high expression of VEGF and VEGFR, promoting the formation of new blood vessels in tumors. Targeted inhibitors reduce the expression of VEGF and VEGFR, block signal transduction pathways, and deplete blood VEGF produced by tumor cells, thus cutting off the blood supply and inhibiting angiogenesis.

Sorafenib and lenvatinib are first-line oral multikinase inhibitors approved for treating advanced hepatocellular carcinoma (HCC). A meta-analysis found that sorafenib was associated with a higher incidence of diarrhea and hand-foot syndrome, whereas lenvatinib had an increased occurrence of adverse events such as hypertension, proteinuria, fatigue, decreased appetite, and weight loss [22]. Fruquintinib, a highly selective inhibitor of tumor angiogenesis, primarily targets VEGFR1/2/3. The Phase III FRESCO study indicates the main gastrointestinal adverse events include abdominal pain, discomfort, and diarrhea [23]. Anlotinib, a new small molecule multi-target TKI with anti-tumor angiogenesis and growth inhibitory effects, is suitable for locally advanced patients who have progressed or relapsed after receiving at least two types of systemic chemotherapy or treatment of NSCLC. The Phase III clinical trial ALTER0303 shows that the main gastrointestinal adverse events include diarrhea, oropharyngeal pain, and oral mucositis [24].

Table 1. Incidence of diarrhea in clinical trials of tyrosine kinase inhibitors [5-24]

Drug	Target	Diarrhea incidence	
		All levels	3 and above
Lapatinib	HER2	55.0	16.0
Pyrotinib		100	52.0
Neratinib [b]		95.0	39.8
Trastuzumab		67.0	8.0
Pertuzumab [b]		72.0	12.0
Ado-trastuzumab (T-DM1)		11.3	/
Palbociclib	CDK4/6	14.4	1.1
Ribociclib [b]		25.8	1.5
Dalpiciclib		15.0	/
Abemaciclib [a]		85.3	13.5
Gefitinib	EGFR	55.8	0.9
Erlotinib [a]		40.9	1.8
Icotinib [a]		9.5	7.4
Afatinib [a]		95.2	14.4
Dacomitinib [a]		87.0	8.0
Osimertinib		44.0	/
Ametinib	ALK, MET, ROS1	6.7	0
Fumetinib		6.7	0
Crizotinib		55.84	/
Ceritinib		51.82	6.36
Brigatinib	ALK, ROS1	37.0	/
Ensartinib		11.0	0
Lorlatinib		28.0	< 1
Entrectinib [a b]		33.5	2.6
Alectinib	ALK	11.84	/
Repotrectinib	ROS1	/	/
Taletrectinib		43.5	2.2
Tepotinib [a b]	MET	26.0	0.4
Capmatinib [b]		18.0	1.0
Savolitinib		13.0	0
Cabozantinib [b]	MET, ROS1, etc.	58.0	7.0
Olaparib	BRCA	22.1	1.1
Niraparib		19.1	0.3
Rucaparib		33.3	3.0
Lenvatinib [a]	VEGFR	39.0	4.0
Fruquintinib [a]		25.2	3.2
Anlotinib [a]		35.0	1.02
Sorafenib		53.2	7.3

[a] Instructions include safety data on adverse drug reactions and diarrhea; [b] Drugs not marketed in China. Abbreviations: HER, human epidermal growth factor receptor; CDK4/6, cyclin-dependent kinase 4 and 6; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; MET, mesenchymal-endothelial transition; BRCA, breast cancer gene; VEGFR, vascular endothelial growth factor receptor.

3. Immunotherapy

The goal of tumor immunotherapy is to reactivate anti-tumor immune cells and overcome the immune evasion mechanism employed by tumors. This approach can be categorized into immune checkpoint inhibitors, tumor vaccines, cellular immune cell therapy, and non-specific immune modulators. Among them, immune checkpoint inhibitors mainly include CTLA-4 inhibitors and PD-1/PD-L1 inhibitors with widespread clinical utilization.

In anti-tumor immunity, immune checkpoint molecules act as negative regulatory factors targeting T lymphocyte activation. Overexpression of immune checkpoints inhibits T cell activity, compromises immune function, and facilitates the immune escape of tumor cells. Immune checkpoint inhibitors (ICBs) aim to block immunosuppression and enhance anti-tumor T cell activity by targeting programmed cell death 1 (PD-1) / programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4), thus inhibiting tumor growth.

3.1. PD-1/PD-L1 inhibitors

PD-1 is coupled with PD-L1; phosphorylation of the receptor tyrosine inhibitory motif and receptor tyrosine conversion motif structure in the PD-1 cell membrane region recruits protein tyrosine phosphatase. In the cell membrane area, dephosphorylation occurs in the T cell antigen receptor and CD28 membrane domain, activating the first signal and co-stimulatory signal of T cells. This inhibits signal transmission to downstream proteins, blocking T-cell activation. PD-1 and PD-L1 inhibitors, binding to PD-1 on the surface of T cells and PD-L1 on the surface of tumor cells, respectively, disrupt the binding of the PD-1 receptor to the ligand of PD-L1/L2. This prevents the phosphorylation of the intramembrane motif of PD-1, eliminating immunosuppression in the signaling pathway. Consequently, suppressed T cells regain their recognition function of tumor cells, restoring immune system function and enhancing oncolysis involving cytotoxic T cells, leading to tumor cell death [25].

Anti-PD-1 monoclonal antibody drugs have a basic structure of IgG4. The IgG4 molecule, characterized by a short hinge region and unstable disulfide bonds, enables semi-molecular exchange between molecules. All anti-PD-1 monoclonal antibody drugs replace serine at position 228 of the core hinge motif with proline (S228P). This stabilizes the inter-chain disulfide bond, preventing fragment antigen-binding (Fab) segment exchange and overcoming unpredictability in efficacy and toxicity caused by instability [26].

Nivolumab, the world's first PD-1 inhibitor, received approval for marketing in China in 2018. Common side effects such as diarrhea and fatigue were observed. In the same year, China's first domestically produced anti-PD-1 monoclonal antibody, toripalimab, was approved for marketing to treat unresectable or metastatic melanoma that had failed previous systemic therapy. Subsequently, pembrolizumab, tislelizumab, etc., along with PD-L1 inhibitors such as atezolizumab and durvalumab, were successively employed in different forms and marketed for various tumor indications.

Compared with chemotherapy, PD-1/PD-L1 inhibitors significantly reduce gastrointestinal risks, with a low risk of severe diarrhea and common mild adverse reactions such as diarrhea, nausea, vomiting, and constipation. Simultaneously, they increase the risk of all grades of colitis, with considerable heterogeneity in the incidence of diarrhea observed in clinical observations, particularly with higher rates of colitis.

3.2. Anti-CTLA-4 inhibitors

Cytotoxic T lymphocyte antigen 4 (CTLA-4) functions in the initial stages of the immune response. Blocking CTLA-4 allows cytotoxic T cells to infiltrate tumor cells and restricts the penetration of regulatory T cells (Treg) into the tumor microenvironment. This prevents Treg cells from inhibiting the activity of cytotoxic T cells, ultimately reversing tumor-induced T-cell dysfunction. CTLA-4 inhibitors act on Treg/T cells, depleting Treg

through antibody-dependent cell-mediated cytotoxicity (ADCC).

Ipilimumab, the world's first approved anti-CTLA-4 immune checkpoint inhibitor, significantly improves the overall survival rate of patients with unresectable/metastatic melanoma. Clinical experience analysis indicates that the most common adverse events include skin reactions, colitis, and diarrhea [27].

Table 2. Incidence of diarrhea in clinical trials of immune checkpoint inhibitors [25-27]

Classification	Drug name	Indications	Diarrhea incidence	
			All levels	≥ Level 3
PD-1	Nivolumab	NSCLC; SCCHN; EC or GEJC; GC or GEJC; MPM; ESCC	25%	1.5%
	Pembrolizumab	NSCLC; MM; SCCHN; EC; HCC; EC; MSI-H/ dMMR CRC; TNBC	12%	/
	Toripalimab	NSCLC; MM; NPC; UTUC	< 10%, ≥ 0.01%	/
	Sintilimab	HL; HCC; EC; GC or GEJC	< 10%, ≥ 0.01%	/
	Camrelizumab	HL; HCC; NSCLC; EC; NPC	< 10%, ≥ 0.01%	/
	Tislelizumab	HL; UTUC; NSCLC; HCC; MSI-H; ESCC; NPC; GC or GEJC	< 10%, ≥ 0.01%	/
	Penpulimab	HL; NSCLC	0.4%	0
	Putelimab	MSI-H/dMMR CRC	< 10%, ≥ 0.01%	/
PD-L1	Atezolizumab	ES-SCLC; CRC; NSCLC	> 10%	/
	Durvalumab	NSCLC; ES-SCLC	16.3%	0.6%
CTLA-4	Ipilimumab	MM; RCC; MSI-H/dMMR CRC	21%	5%

The safety data of adverse drug reactions and diarrhea are from the instructions. Abbreviation: NSCLC, Non-small cell lung cancer; ES-SCLC, extensive-stage small cell lung cancer; EC, esophageal cancer; GEJC, gastroesophageal junction cancer; SCCHN, squamous cell carcinoma of head and neck; GC, gastric cancer; EAC, esophageal adenocarcinoma; MPM, malignant pleural mesothelioma; ESCC, esophageal squamous cell carcinoma; HL, Hodgkin lymphoma; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; MM, melanoma; MSI-H, microsatellite instability-high solid tumor; dMMR, deficient mismatch repair; TNBC, triple-negative breast cancer; NPC, nasopharyngeal carcinoma; RCC, renal cell carcinoma; UTUC, upper tract urothelial cancer; ESCC, esophageal squamous cell carcinoma.

3.3. Bispecific antibody inhibitors

Bispecific antibodies (BsAbs) bind specifically to two antigens or two different epitopes of the same antigen. They function by bridging cells and receptors, mediating the formation of protein complexes. Bispecific antibodies have the unique ability to redirect specific immune effector cells, target multiple antigens, mediate the killing effect of immune cells, activate immune cell efficacy and endocytosis, exhibit stronger specificity and targeting, and reduce off-target toxicity [28].

Global research on anti-tumor BsAbs has entered a phase of rapid development and holds extraordinary prospects in clinical applications. However, current international clinical trials are primarily in their early-stage research, and fewer BsAb products have received approval for marketing [29]. Cadonilimab, China's first independently developed PD-1/CTLA-4 bispecific antibody approved for marketing, is used in the treatment of advanced cervical cancer. It can simultaneously block the interaction of PD-1 and CTLA-4 with their ligands, promoting tumor-specific T-cell immune activation and exerting a more potent anti-tumor effect [30]. According to its drug instructions, the overall incidence of diarrhea with cadonilimab was 12.6%, and the incidence of grade 3 and above diarrhea was 0.9%.

4. Treatment options and research progress

4.1. Analysis of diarrhea related to drug treatment

4.1.1. Targeted agents

An analysis of data from 42 randomized control trials (RCTs) revealed a significant increase in the risk of all-grade diarrhea and high-grade diarrhea in patients treated with HER2-targeted agents compared to controls. The likelihood of experiencing full-grade and high-grade diarrhea was 2.78 times and 4.89 times higher, respectively, than in the control group. It is believed that HER2 and EGFR expressed on the intestinal epithelial cell membrane can negatively regulate chloride secretion through synergistic effects via multiple pathways. Excessive chloride secretion may consequently lead to secretory diarrhea [31].

In addition, some studies proposed a potential role of ErbB in targeted drug-induced diarrhea. Overexpression of ErbB is associated with gastrointestinal-related cancers. ErbB1 can promote intestinal recovery, wound healing, cell survival, ion transport, and regulation and maintenance. Intestinal stem cells and ErbB drugs may cause direct damage to the gastrointestinal mucosa [32].

To summarize the mechanism of diarrhea caused by targeted drugs: TKIs can inhibit small intestinal epithelial cell signaling, induce endoplasmic reticulum stress, hinder cell proliferation and repair capabilities, and cause damage to small intestinal cell connections and atrophy. Patients with impaired immune function, either spontaneous or drug-induced weakening of gastrointestinal function, are prone to intestinal microbial infections and microflora disorders, leading to diarrhea. Disorders of ion channel transport in small intestinal epithelial cells can also cause diarrhea.

4.1.2. Immunotherapy drugs

Currently, the risk of immune-related colitis is more common during treatment with PD-1/PD-L1 inhibitors, while prominent gastrointestinal reactions are less frequent. These inhibitors, due to their mechanism of action, non-specifically activate the body's immune system, affecting organs throughout the body. Among the adverse reactions observed, gastrointestinal issues include diarrhea, nausea, constipation, etc. Research indicates that the longer a patient undergoes treatment with PD-1/PD-L1 inhibitors, the higher the likelihood of persistent gastrointestinal reactions.

Studies focusing on patients with NSCLC reveal that PD-1/PD-L1 inhibitor treatment increases the incidence of all-grade colitis (approximately four times) while decreasing the incidence of all-grade diarrhea. PD-1/PD-L1 inhibitors may induce colitis by disrupting the balance of auto-tolerance and causing an excessive release of inflammatory factors. However, across various studies, it is consistently observed that the risk of colitis is heightened, while the risk of diarrhea is reduced [33].

4.2. Diagnosis

Diarrhea stands as a crucial factor in adverse drug evaluation during cancer treatment. As defined by the World Health Organization (WHO), diarrhea involves the passage of loose or liquid stools three or more times a day or more frequently than normal. According to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, criteria for diarrhea severity encompass five levels.

Severe diarrhea can result in fluid loss and pose a life-threatening risk, particularly in young children, malnourished individuals, those who are immunocompromised, and patients with a severe prognosis. Hence, when patients manifest diarrhea symptoms, prompt identification and the provision of robust supportive care can enhance the patient's quality of life. The following conditions should be promptly assessed to facilitate subsequent treatment planning and decision-making [34]:

(1) Investigate the duration and frequency of diarrhea, stool characteristics, potential pathological mixtures, tumor type and stage data, anti-cancer treatment, comorbidities, and accompanying symptoms such as headache, abdominal pain, nausea and vomiting, fever, and rectal bleeding.
(2) Conduct a thorough skin and mucosal assessment to determine hydration status, along with abdominal and rectal examinations.
(3) Based on the clinical situation, conduct laboratory examinations, including blood cell count, ionogram, acid-base balance, biochemical examination, general examination, stool culture, and urinalysis.
(4) In selected cases, perform endoscopic or radiological examinations to evaluate the anatomical cause of diarrhea.
(5) Evaluate the patient's dietary characteristics and medication compliance.

5. Treatment

5.1. Dietary treatment

Currently, dietary symptomatic treatment of tumor-related diarrhea is empirical. Maximizing bowel movements until the diarrhea subsides is the initial priority. Subsequently, oral nutritional supplements consisting of isotonic, lean, and lactose-free drinks should be consumed to compensate for the loss of intestinal enzymes due to changes in intestinal villi and mucosa. If well tolerated, solids with minimal lactose, low fiber, low fat, low overall acidity, and no gastric irritants can be reintroduced. Patients should consume small meals frequently and avoid lactose, spicy foods, alcohol, caffeinated beverages, certain fruit juices, and foods high in fiber and fat.

5.2. Drug treatment

For diarrhea related to molecular targeted therapy, immune preparations, and tumor vaccines, specific clinical drugs are not available. Therefore, chemotherapy is often employed to treat diarrhea. For instance, the initial dose of loperamide should be 4 mg, followed by 2 mg every 4 hours or after each unformed stool (not exceeding 16 mg/d). Loperamide should be discontinued after at least 12 hours without diarrhea. During radiation therapy, patients should continue taking standard doses of loperamide. If diarrhea persists after 24 hours of high-dose loperamide, a second-line antidiarrheal drug such as the natural somatostatin derivative octreotide, oral budesonide, or opium tincture should be considered. Octreotide can reduce intestinal corticosteroids, decrease gastro-pancreatic peptide secretion, and is effective in loperamide-refractory diarrhea. In cases of mild diarrhea caused by chemotherapy, it is recommended to use 100–150 μg of octreotide every 8 hours one day after loperamide. Severe diarrhea requires octreotide as first-line treatment, administered subcutaneously or intravenously every 8 hours [34].

5.3. Probiotics

Probiotics can alleviate all grades of diarrhea and enterocolitis caused by acute infection, antibiotics, chemotherapy, or radiotherapy. They can also reduce grades 3–4 diarrhea after irinotecan chemotherapy, allowing patients to decrease the use of antidiarrheal drugs. For example, the combination of live *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* can decrease the incidence of radiation-induced diarrhea and the need for antidiarrheal drugs [35].

5.4. Traditional Chinese medicine

Traditional Chinese medicine (TCM) classifies cancer treatment-related diarrhea as "diarrhea." Zhongzi Li's "Nine Methods for Treating Diarrhea," from the late Ming Dynasty and early Qing Dynasty, still provides

ideas for TCM syndrome differentiation and prescription selection for cancer treatment-related diarrhea. The chemical components of herbal formulas often act synergistically at multiple targets in the body, making them a valuable resource for developing multi-compound and multi-target therapies to control gastrointestinal toxicity. For example, baicalin and baicalein in Huangqin Decoction can protect the active autophagy of damaged intestinal epithelial cells and cancer cells, promoting the polarization of macrophages into the M2 phenotype, thereby alleviating ulcerative colon inflammation. These components are widely used to treat gastrointestinal syndromes with symptoms such as diarrhea, nausea, abdominal cramps, and vomiting [36]. Clinically, TCM often dialectically uses Chinese herbal formulas to treat cancer-related diarrhea. For those with spleen deficiency and a weak stomach, Shenling Baizhu Powder and Jianpi Recipe can be employed for treatment. Sishen Pills, Guifu Lizhong Pills, and others can be utilized for those with kidney yang deficiency [37]. Banxia Xiexin Decoction has shown efficacy in treating adverse reactions of diarrhea in patients with non-small cell lung cancer during chemotherapy, significantly reducing the frequency of grade 3 or above diarrhea [38].

6. Summary and outlook

With the ongoing development of modern medical technology and continuous updates in various treatment modalities, cancer patients now have more diverse treatment options. However, the challenges posed by tumor heterogeneity, individual patient differences, uncertainties in drug efficacy, and the unpredictability of adverse reactions persist. Researchers need a comprehensive understanding of the severity and diversity of drug-related diarrhea in different treatment options and should formulate treatment plans based on factors such as the patient's illness and medication compliance.

During the treatment process, close observation of adverse reactions is crucial. Prompt diagnosis and the implementation of symptomatic measures are essential when adverse reactions occur. When addressing drug-related diarrhea, clinicians should consider the clinical adaptability of anti-diarrheal drugs to avoid secondary harm.

While the mechanisms underlying drug-induced diarrhea, especially with targeted drugs and immunotherapy drugs, have been partially discussed, further research is needed to fully understand their effects and mechanisms. This knowledge is crucial for guiding clinical medication effectively.

In recent years, Chinese herbal medicine preparations have shown promise in various fields, displaying great development potential. More research in clinical practice can delve into the mechanisms and practical application of Chinese herbal medicine preparations in preventing diarrhea. This research will provide theoretical guidance for clinical applications and contribute to the ongoing progress in tumor treatment.

Disclosure statement

The authors declare no conflict of interest.

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