REVIEW

Treatment-related gastrointestinal toxicities and advanced colorectal or pancreatic cancer: A critical update

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Abstract

Gastrointestinal toxicities (GIT), including oral mucositis, nausea and vomiting, and diarrhea, are common side effects of chemotherapy and targeted agents in patients with advanced colorectal cancer and pancreatic cancer. Being often underreported, it is still difficult to precisely establish their burden in terms of both patient's quality of life and cancer care costs. Moreover, with the use of more intensive upfront combination regimens, the frequency of these toxicities is rapidly growing with a potential negative effect also on patient's outcome, as a result of dose reductions, delays or even discontinuation of active treatments. Thus, identifying patients at higher risk of developing GIT as well as an optimal management are paramount in order to improve patient's compliance and outcome. After the description of the main treatment-induced GIT, we discuss the current knowledge on the pathophysiology of these side effects and comment the scales commonly used to assess and grade them. We then provide a critical update on GIT incidence based on the results of key randomized trials conducted in patients with metastatic colorectal cancer and advanced pancreatic cancer.

Key words: Gastrointestinal toxicities; Oral mucositis; Diarrhea; Colorectal cancer; Pancreatic cancer

Core tip: Although extremely frequent, treatment-related gastrointestinal toxicities in patients with advanced colorectal cancer and pancreatic cancer are often underreported. As such, it is difficult to establish to what extent such toxicities affect both patient quality of life and cancer care costs. In our work we describe the main gastrointestinal toxicities as well as their pathophysiology and grading scales. Finally, based on the results of the main randomized clinical trials, we provide a critical update on their incidence with both chemotherapeutic agents and novel targeted drugs.

INTRODUCTION

Gastrointestinal toxicities (GIT), including oral mucositis, nausea, vomiting, dyspepsia, diarrhea, and constipation are common adverse events of antineoplastic treatments. These side effects are frequently associated with classical chemotherapy drugs, although their rate of occurrence may vary according to treatment schedule[1]. Of all toxicities associated with cancer therapy, from a patient's perspective GIT are the most bothersome and consistently challenge patients' ability to tolerate cancer care[2].

Overall, the incidence of GIT is rising with the introduction of novel drugs and the adoption of more intense association regimens that combine polichemotherapy with targeted agents. At the same time, the vision of the gastrointestinal tract has markedly changed. The alimentary tube is no longer considered a compartmentalized anatomic tract divided in oral, gastric, small bowel and large bowel segments. Rather, it is now studied as an anatomic continuous in which the underpinning pathobiological phenomena such as mRNA TNF expression[3] may lead or contribute to concurrently emerging disturbances in different sites[4]. This concept is in line with the current approach in which regimen-related toxicities do not occur as solitary events, but present as cluster and may be holistically integrated with other common pathological pathways[5].

The assessment of GIT is largely dependent on clinician assignment of a grade based on a range of criteria established by various instruments. For describing toxicities (adverse events) associated with particular drug or radiation therapy regimens, the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE)[6] is probably the most commonly used. The periodic modification of CTC (now in its fourth version) makes longitudinal comparisons of studies difficult, as the criteria used to delineate severity scores have been inconsistent. A number of other grading systems have been used, often for specific components of GIT, with varying success. Aside from describing the toxicities of particular treatment regimens, scoring instruments play critical roles as research tools to assess the efficacy of toxicity interventions and as clinical guides for nursing interventions[7]. Finding a scoring instrument, which is easy to use and replicate, has clinical meaningfulness and is easily understood by all users has been challenging.

Notably, the health and economic burden of GIT associated with cancer treatments is significant[8]. Often treatment-related GIT toxicities result in unplanned medical consultation, emergency room visits, support infusion, gastrostomy placement and hospitalization leading to increased resource use and cost[9,10]. Furthermore, since management options for a number of GITs is limited, these toxicities may necessitate cancer treatment dose reduction or discontinuation thereby limiting optimum tumor control. In this review we summarize the scope of distinctive oral and gastrointestinal side effects of both standard chemotherapy regimens and novel agents used in colorectal and pancreatic cancers.

GIT IN ADVANCED COLORECTAL CANCER PATIENTS

Colorectal cancer (CRC) is the third most frequent cancer in men, after lung and prostate cancer, and is the second most frequent cancer in women after breast cancer. It accounts for 8% of new cancer cases in the United States, and is responsible for 8% to 9% of the estimated cancer deaths in the United States in 2014[11]. The therapeutic options available for the treatment of metastatic CRC have significantly increased over the last decade. Together with advances in surgical techniques, combination therapy of irinotecan and oxaliplatin with 5-fluorouracil and the introduction of novel drugs targeting epidermal growth factor receptor (EGFR) (cetuximab and panitumumab) or vascular endothelial growth factor (VEGF) (bevacizumab, aflibercept, regorafenib, and ramucirumab) have led to a median survival times now approaching 30 mo[12-15]. Furthermore, increasing numbers of trials testing novel drugs have all expanded the treatment options. However, the addition of such targeted agents to standard regimens has often led to increased rates of gastrointestinal side effects.

GIT associated with standard cancer therapy regimens are very common and often clinically significant, though varying in severity[16,17]. Moreover, it is well known that treatment-related side effects involving the gastrointestinal tube such as oral mucositis and dysgeusia, nausea and vomiting, and diarrhea may often occur together and share a similar biological etiology. Mucositis is probably the most extensively studied toxicity of the gastrointestinal tract and it refers to cancer regimen-related mucosal damages, which can either occur in the oral cavity, *i.e.,* oral mucositis or stomatitis, or in lower regions of the gastrointestinal tract. The usual presentation of oral mucositis includes erythema and/or ulceration of the mucosa, whereas gastrointestinal mucositis usually presents with pain, bloating, diarrhea, nausea and vomiting. As a result, mucositis is associated with considerable morbidity, diminished quality of life as

well as negative health and economic outcomes[18-20].

Similar to many other cancer treatment-related toxicities, GIT tends to be reported only when severe cases occur. Consequently, the incidence of this side effect is largely underestimated and often inconsistent, ranging from as low as 30% to almost 100% when all grades of mucositis are considered. Therefore, identification of subjects at higher risk as well as optimal management of this side effect can lead to better treatment tolerance, improved quality of life and more appropriate resource allocation. Mucositis risk depends on therapy-related factors such as the type of cancer drug administered, the regimen used, its dosage and schedule, and patient-related factors such as gender, age, baseline comorbidities and tumor diagnosis. Interestingly, also genomic plays a relevant role in the risk of developing oral mucositis[21,22], as well as the disruption of composition and function of the host-microbiota local environment[23,24].

Amongst the chemotherapeutic agents commonly used for patients with metastatic CRC, 5-FU and irinotecan are the two drugs with the highest risk for oral and gastrointestinal mucositis, respectively. In addition, multiple cycles of chemotherapy also seem to play an important role as risk factor for oral mucositis, mainly as a result of a cumulative effect, and the risk for GIT may increase when more intensive treatments such as FOLFOXIRI are used. Female gender results associated with higher risk of developing severe mucositis, as suggested by the results of clinical trials conducted in CRC patients treated with 5-fluorouracil[7,25,26].

Genomic determinants of GIT are associated with genes governing both drug metabolism [pharmacokinetic (PK)] and its pathobiology. An example of a PK-related pharmacogenomic marker of toxicity risk is the catabolic enzyme, dihydropyrimidine dehydrogenase (DPD) that plays a critical role in 5-FU metabolism. Insufficient DPD activity results in toxic levels of 5-FU and is associated with increases in both hematologic and non-hematologic toxicities[27]. DPD activity is affected by at least two variants of the DPYD gene, DPYD*2A and D949V. Additional DPYD variants have been uniquely described in African Americans[28,29]. As a consequence, a FDA-approved test to assess DPD activity is commercially available.

Improved understanding of the pathogenesis of GIT has led to opportunities to assess its variable risk among patients. For example, oxidative stress, which is responsible of reactive oxygen species (ROS) formation, typically occurs after the administration of chemotherapy and eventually leads to tissue damage. Preclinical studies showed that changes in the expression of genes of with single-nucleotide polymorphisms involved in the metabolism of reactive oxygen species were associated with increased risk of mucositis[7,30].

The pathogenesis of GIT is a complex process involving five different predictable phases, which is usually initiated by direct cell damage from chemotherapy. DNA damage, ROS formation and the subsequent death of the basal epithelial cells lead to the release of endogenous damage-associated pattern molecules (CRAMPs) which, in turn, trigger the innate immune response[31] as well as several other pathways involved in the production of pro-inflammatory cytokines. The nuclear factor Kappa-B (NF-κB) pathway is probably one of the most extensively investigated[32,33] and its activation eventually translates into signal amplification with local recruitment of inflammatory cells[34]. Development of symptomatic deep ulcerations, which can be easily colonized by oral bacteria, may lead to an extension of the mucosal damage itself. Healing usually occurs in the last stage with a complete restitutio ad integrum.

Similar to oral mucositis, gastrointestinal mucositis is a complex process, a result of both direct and indirect injury leading to crypt cell death, breakdown of the mucosal barrier and lastly to mucosal inflammation. Rapidly dividing cells are particularly sensitive to many cytotoxic chemotherapeutic agents, thus the GI tract is extremely vulnerable. The first abnormality detected in human small intestine on day 1 after chemotherapy is an increase of the rate of cells switching to apoptosis. Such phenomenon is then followed by a reduction in crypt length as well as villus area and mitotic index, reaching a nadir on day 3. Interestingly, the rate in apoptosis not always correlates with the severity of mucositis. Finally, on day 5 after chemotherapy a rebound hyperplasia usually leads to a gradual normalization of the tissue and to re-epithelialization[18].

Chemotherapy-induced diarrhea is most commonly reported with fluoropyrimidines and irinotecan, and this potentially dangerous side effect often needs to be aggressively managed[35]. Both drugs can cause acute damage of the intestinal mucosa leading to loss of epithelium. As a result, the increased amount of fluids that transits from the small bowel to the colon exceeds the absorptive capacity of the colon, finally resulting in diarrhea[36,37]. Moreover, while delayed-onset irinotecan-associated diarrhea appears to be multifactorial with both cytokine and direct toxic inflammatory-mediated effects on the intestinal mucosa as well as an alteration of the motility[38], the early-onset diarrhea is cholinergically mediated. Occurring in 45%-50% of patients, during or within several hours of drug infusion, such diarrhea seems to be caused by the structural similarity of the drug with acetylcholine. Moreover it is often accompanied by other symptoms of cholinergic excess such as abdominal cramping, rhinitis, lacrimation and salivation[37]. A number of clinical studies have demonstrated the role of UGT1A1 genotyping as a potential marker for CPT-11 toxicity[39], which may also correlate with severe hematological toxicity[40]. Once again, CRC patients exposed to multiple chemotherapy cycles may be at higher risk

for chemotherapy-induced diarrhea[41]. Obviously, the potential of the primary tumor to contribute to GI symptoms cannot be overlooked.

Little evidence is currently available on chemotherapy-induced esophageal mucositis mainly because most of the symptoms associated with esophageal mucositis are usually attributed to gastroesophageal reflux disease or to both viral and fungal infections. However, the effect of chemotherapy on esophageal epithelium has been described before and it appears that chemotherapeutic agents damage the dividing and differentiating cells, leading to a thin and ulcerated epithelium[42]. Similarly, modest information exists about mucositis of the stomach. Overall, gastrointestinal mucositis can be debilitating and in some cases also life-threatening: as a matter of fact, volume depletion can lead to acute renal failure, electrolyte disorders and metabolic acidosis.

With both irinotecan and oxaliplatin classified as moderate emetogenic cytotoxic drugs, nausea and vomiting can also be a relevant issue in patients with CRC treated with such agents[43]. Chemotherapy-induced vomiting and nausea can greatly affect patient's quality of life with subsequent poor compliance to chemotherapy. As a matter of fact, such symptoms not only can lead to metabolic disorders, anorexia and decline of the patient's performance status, but they can also be responsible for discontinuing potentially useful anticancer treatments[44,45]. Similarly to oral mucositis, the risk of nausea and vomiting depends on various factors including the type of drug administered, its dosage, schedule and route of administration as well as the patient's age, sex and his/her past medical history[44-46]. The role of pharmacogenomics in the occurrence and intensity of nausea and vomiting has not been fully unrevealed and deserves further studies.

Vomiting is a result of a multistep pathway which is controlled by the brain and is usually triggered by afferent impulses to the vomiting center, located in the medulla, originating from the chemoreceptor trigger zone, pharynx and gastrointestinal tract (*via* vagal afferent fibers) and cerebral cortex. Once the vomiting center is adequately stimulated, efferent impulses are sent to the salivation center, abdominal muscles, respiratory center and cranial nerves and vomiting occurs[47-49]. Chemotherapeutic agents as well as their metabolites usually lead to the activation of neurotransmitter receptors located in the chemoreceptor trigger zone, vomiting center and GI tract. The main neuroreceptors involved in the emesis are the serotonin (5-hydroxytryptamine) and dopamine receptors, which are targeted by many antiemetic agents[49]. Nausea and/or vomiting induced by chemotherapy are usually classified as acute, delayed, anticipatory, breakthrough or refractory. The timing of occurrence is the main difference between the acute-onset and the delayed-onset with nausea and/or vomiting occurring before and after 24 h from the administration of the drug, respectively. Anticipatory

nausea and/or emesis occurs before patients receive chemotherapy and is usually associated with a negative past experience with chemotherapy. Finally, breakthrough emesis refers to vomiting that occurs despite prophylactic treatment. The frequency of chemotherapy-induced vomiting, as mentioned before, depends on many factors but primarily on the ematogenic potential of the specific chemotherapeutic agents. The most recent MASCC and ESMO treatment guidelines follow the Grunberg classification for intravenous agents, which defines 4 different risk levels of vomiting: high emetic risk where 90% or more of patients experience acute emesis, moderate emetic risk, 30% to 90% of patients experience acute emesis, low emetic risk, 10% to 30% of patients with acute emesis and minimal emetic risk with fewer than 10% of patients experiencing acute emesis[50].

Rectal cancer patients who undergo chemoradiation may also suffer from proctitis, a treatment-induced proctopathy consisting in a painful epithelial damage to the rectum, usually associated with minimal or no inflammation. Based on the timing of symptoms, radiation proctitis can be classified as acute if it occurs during or within six weeks of radiation therapy or as chronic if it has a more delayed onset[51]. Risk factors include the dose of radiation, area of exposure, method of delivery as well as patient-related factors such as inflammatory bowel disease. Once again, specific polymorphisms of genes involved in the disease pathogenesis may be associated with greater risks for toxicity. For example, VEGFR2 H427Q QQ genotype was significantly associated with increased severe upper gastrointestinal tract mucositis[52].

The general pathobiology for proctitis is similar to other stratified squamous mucosa. While acute proctitis is a consequence of the direct mucosa damage form radiation exposure, chronic proctitis results from progressive epithelial atrophy and fibrosis associated with chronic mucosal ischemia and obliterative endarteritis. The main symptoms of acute radiation proctitis include diarrhea, tenesmus, urgency and mucus discharge; severe bleeding is usually more common in chronic proctitis. Occasionally patients may also develop symptoms of obstructed defecation due to strictures such as constipation and rectal pain.

Finally, another common gastrointestinal toxicity is dysgeusia; transient alteration in taste often leads to reduced appetite as well as low energy intake and weight loss. The chemotherapeutic agents that have been most associated with taste alterations include irinotecan, oxaliplatin, fluorouracil and gemcitabine[53]. These drugs may affect taste by stimulating taste receptors particularly when they are secreted in saliva. Dysgeusia often persists after drug clearance due to damage to the taste buds.

Clinical assessment of GIT

A number of scales are available to assess the severity of GIT. In general, toxicity of each area of the GI

Table 1 Oral mucositis grading scales					
CTCAE version 4.03			**Grade**		
	1	2	3	4	5
Description	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
WHO			**Grade**		
	0 (none)	I (mild)	II (moderate)	III (severe)	IV (life-threatening)
Description	None	Oral soreness, erythema	Oral erythema, ulcers, solid diet tolerated	Oral ulcers, liquid diet only	Oral alimentation impossible

CTCAE: Common Terminology Criteria for Adverse Events version; WHO: World Health Organization.

tract is graded independently. For oral mucositis the World Health Organization (WHO) scale (Table 1) or the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (Table 1) are among the most frequently used. While NCI-CTCv4 is limited to pain and ability to eat, the WHO scale combines both functional and objective (erythema and ulceration) assessments and probably provides a more complete indication of the severity of the condition. Gastrointestinal mucositis as well as nausea and vomiting are usually graded based on CTCAE scale. The severity of chemotherapy-induced diarrhea for instance, is based on the number of stools per day or increase in stoma output compared to baseline, as well as on the need for hospitalization and the effect on self-care activities. Similarly, vomiting is graded from 0 to 5 based on number of episodes per day and the need for hospitalization or total parental nutrition.

GIT associated with specific treatment regimens

The current management of metastatic CRC involves various active drugs, given either in upfront combination or as single agents in later treatment lines. Although curative rates remain low for patients with advanced disease, the median overall survival has dramatically improved with modern treatments. Upfront 5FU-based doublet regimens with irinotecan or oxaliplatin combined with bevacizumab are currently widely used, and these combinations are usually associated with significantly increased rates of gastrointestinal mucositis compared to those previously reported (Table 2). Recently, the Italian phase 3 TRIBE study has randomized untreated patients with metastatic CRC to receive either FOLFOXIRI in combination with bevacizumab or FOLFIRI plus bevacizumab[13], with significant overall survival improvement for patients enrolled in the experimental arm (31 mo *vs* 25.8 mo, HR = 0.79). It came as no surprise, however, that the better outcome results were associated with increased toxicity as the overall safety profile, mainly in terms of GIT, was significantly worse for the triplet compared with the FOLFIRI plus bevacizumab arm. Severe or life-threatening grades of diarrhea were reported in 10.6% of patients enrolled in the FOLFIRI plus bevacizumab arm and in 18.8% of

those randomized to the FOLFOXIRI plus bevacizumab arm (*P* = 0.01). Similarly, stomatitis was described in 8.8% of patients treated with the triplet *vs* 4.3% (*P* = 0.048).

Results of the randomized CRYSTAL study showed that the upfront addition of cetuximab to FOLFIRI improved median OS of patients whose tumors did not have mutations at KRAS codons 12 and 13[54,55]. In KRAS wild-type patients, median PFS was 9.9 mo for those exposed to cetuximab *vs* 8.7 mo in those receiving FOLFIRI alone (HR = 0.69, 95%CI: 0.56-0.97, *P* = 0.012). Median OS was also significantly improved in the arm containing cetuximab (23.5 mo *vs* 20.0 mo, HR = 0.79, 95%CI: 0.67-0.94, *P* = 0.009). As expected, the safety profile showed a 50% increase of the frequency of grade 3 and grade 4 diarrhea which occurred in 15.7% of the patients allocated to the cetuximab arm *vs* 10.5% of those enrolled in the standard arm. Similarly, the PRIME trial compared the combination of FOLFOX plus panitumumab with FOLFOX alone, in patients with metastatic CRC who did not receive any prior treatment[56]. The study met its primary endpoint (PFS) in the KRAS wild-type population, with a median PFS for FOLFOX combined to panitumumab of 9.6 mo *vs* 8.0 mo for the FOLFOX alone arm (HR = 0.80, 95%CI: 0.66-0.97, *P* = 0.02). The addition of the monoclonal antibody, however, resulted in a significantly increased rate of diarrhea (18% *vs* 9%) and mucositis (9% *vs* < 1%).

FIRE 3 and CALGB 80405 were designed to assess whether cetuximab or bevacizumab was a more effective partner for doublet chemotherapy in the first-line treatment in patients with KRAS exon 2 wild-type metastatic CRC. In the European FIRE-3trial, patients were randomly assigned to receive FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab. Although no differences were noted in terms of response or PFS, median OS was significantly longer in the FOLFIRI plus cetuximab group (HR = 0.77, *P* = 0.017)[12]. By contrast, the US-based randomized phase 3 trial CALGB 80405, which compared first-line cetuximab or bevacizumab in combination with FOLFOX or FOLFIRI, failed to show a difference in terms of survival between

Table 2 Frequency of gastrointestinal toxicities in metastatic colorectal cancer: results from main recent clinical trials

Trials	Nausea		Vomiting		Diarrhea		Oral mucositis	
	Any grade	G3-G4	Any grade	G3-G4	Any grade	G3-G4	Any grade	G3-G4
Folfiri + cetuximab (FIRE-3 trial, Heinemann *et al*[12]. *Lancet Oncol* 2014)	45%	3%	22%	2%	46%	11%	38%	4%
Folfiri + bevacizumab (FIRE-3 trial, Heinemann *et al*[12]. *Lancet Oncol* 2014)	58%	5%	29%	3%	49%	12%	41%	3%
Folfiri + aflibercept (VELOUR trial, Van Cutsem *et al*[60]. *J Clin Oncol* 2012)	53.4%	1.8%	32.9%	2.8%	69.2%	19.3%	54.8%	13.8%
Regorafenib (CORRECT trial, Grothey *et al*[63]. *Lancet* 2013)	14%	< 1%	8%	1%	34%	7%	27%	3%
Folfoxiri + bevacizumab (Tribe trial, Loupakis *et al*[13]. *N Engl J Med* 2014)		2.8%		4.4%		18.8%		8.8%
Folfox + bevacizumab (Tribe trial, Loupakis *et al*[13]. *N Engl J Med* 2014)		3.2%		3.2%		10.6%		4.3%

the two targeted agents[57]. Both FIRE-3 and CALGB 80405 trial, however, showed a similar safety profile. The most common grade 3 or 4 adverse events in both treatment groups were diarrhea (11% of patients in the cetuximab arm and 14% in the bevacizumab arm for FIRE-3 trial, 11% of patients in the cetuximab arm and 8% in the bevacizumab arm for CALGB 80405). The frequency of stomatitis as well as nausea and vomiting was in line with previously reported results.

Even after protocol amendment because of safety-concerns, very high rates of severe diarrhea (35% of grade 3-4) were reported when the triplet regimen FOLFOXIRI was associated with panitumumab in 37 molecularly selected CRC patients enrolled in the TRIP study[58]. Accordingly, in the POCHER trial that exposed 42 unresectable metastatic CRC patients to cetuximab plus a chronomodulated combination of 5-Fluorouracil, oxaliplatin and irinotecan, grade 3 and 4 diarrhea occurred in 93% and 36% of patient before and after dose reduction[59].

Second-line chemotherapy also includes novel agents. Aflibercept, a multitarget antiangiogenic fusion protein, was combined to FOLFIRI in the multinational phase III trial VELOUR, showing significantly prolonged OS and PFS in pretreated advanced CRC patients compared with chemotherapy alone[60]. More grade 3 or 4 adverse events were reported in the aflibercept arm compared with the placebo arm. In particular, higher rates of severe diarrhea (19.3% *vs* 7.8%) and stomatitis/ulceration (13.7% *vs* 5%) were noted. Furthermore, diarrhea was one of the toxicities that most frequently led to chemotherapy discontinuation in the experimental arm. Ramucirumab is a novel VEGFR2 inhibitor already approved in pretreated patients with advanced gastric cancer[61]. The RAISE study compared FOLFIRI plus ramucirumab to FOLFIRI plus placebo in 1072 CRC patients who had failed first-line chemotherapy[62]. The trial met its primary endpoint showing a 2 mo increase in median OS (HR = 0.844, 95%CI: 0.73-0.97, *P* = 0.022). The combination of FOLFIRI and ramucirumab however

was associated with higher incidence of any grade stomatitis (30.8% *vs* 20.8%) and diarrhea (59.7% *vs* 51.5%) compared to FOLFIRI alone; of note, the rate of severe cases was not statistically different between treatment arms.

Regorafenib is a small tyrosine kinase inhibitor which has been approved in pretreated patients with advanced CRC based on the positive survival results of the double-bind, placebo-controlled phase III trial CORRECT trial[63]. The most common adverse events included GI toxicities of any grade, such as diarrhea (34% *vs* 8% in placebo arm), oral mucositis (27% *vs* 4%), nausea (14% *vs* 11%), constipation (8% *vs* 5%), and vomiting (8% *vs* 5%); furthermore diarrhea was also one of the most frequent regorafenib-related grade 3 or grade 4 adverse events. Since the combination of regorafenib and cetuximab could be a valuable strategy to overcome acquired resistance to EGFR-inhibitors[64], the gastrointestinal toxicity profile of the combination deserves to be further studied.

Finally, a number of MEK inhibitors have progressed into clinical trials and are currently under evaluation. The mitogen-activated protein kinase (MAPK) signaling pathways involve a family of protein kinase which play critical roles in regulation of many cellular activities such as cell proliferation, survival, differentiation and angiogenesis. MAPK pathway blockade through MEK inhibition can be an effective approach in patients with metastatic CRC. Amongst the MEK inhibitors currently under development, trametinib (GSK1120212), a potent small molecule inhibitor of MEK kinase, is the most extensively investigated. An early phase I trial of trametinib enrolled patients with advanced solid tumors, including patients with chemotherapy refractory advanced colorectal cancer. Dose-limiting toxicities included diarrhea[65].

In this area, the study of patients' immune genetics and inflammation to predict the risk of increased gastrointestinal toxicity has been suggested, but not fully elucidated[66,67].

GIT IN PATIENTS WITH ADVANCED PANCREATIC ADENOCARCINOMAS OR NEUROENDOCRINE CANCER

Pancreatic cancer is one of the deadliest among the solid malignancies, and pancreatic ductal adenocarcinoma (PDAC) accounts for over 95% of all cases diagnosed[68]. Most patients present with metastatic disease at the time of diagnosis and the goal of treatment is therefore palliative. Historically, gemcitabine was the standard of care for first-line treatment, since randomized studies combining gemcitabine with platinum, erlotinib[69] or capecitabine[70] only produced marginal clinical improvements. Recently, the French phase Ⅲ trial PRODIGE 4/ACCORD 11 showed that upfront FOLFIRINOX was superior to gemcitabine in patients with advanced pancreatic cancer, in terms of median OS (11.1 mo *vs* 6.8 mo, HR = 0.57), median PFS (6.4 mo *vs* 3.3 mo), and objective responses[71]. In the study, however, treatment-related GIT were significantly greater with FOLFIRINOX compared to gemcitabine group, mainly because of a higher incidence of grade 3 or 4 vomiting (14.5% *vs* 4.7%, *P* = 0.002) and diarrhea (12.7% *vs* 1.2%, *P* = 0.0001). While a three-drug antiemetic regimen is suggested to provide optimal control of nausea and vomiting[72], retrospective studies reassuringly suggest that a more conservative de-intensified schedule of the same triple regimen may be equally effective and less toxic[73]. The phase Ⅲ MPACT trial set the combination of gemcitabine plus nab-paclitaxel as a novel standard treatment option showing its superiority in terms of response rate, median PFS, and median OS compared to gemcitabine alone[74]. The safety analysis of the trial found that the combination was fairly tolerable, and although it was associated with more side effects than gemcitabine alone, the overall quality of life was improved[75]. Notably, the combination produced higher incidence of any grade diarrhea compared to gemcitabine (37% *vs* 13%) as well as more severe diarrhea (6% *vs* 1%)[76].

The development of novel anticancer agents, interfering with tumor's microenvironment or with the tumor cell itself, is also producing advances[77]. A randomized phase Ⅱ trial with gemcitabine and TH-302 (evofosfamide), a hypoxia-activated prodrug, showed potential therapeutic efficacy, increasing PFS by 2 mo[78]. Enrolled patients were randomized to gemcitabine alone or gemcitabine plus TH-302 at two different doses of 240 mg/m^2 or 340 mg/m^2. The combination regimen produced increased skin, mucosal and hematological toxicities. In particular, a higher incidence of all-grade stomatitis was reported for the combination compared to gemcitabine alone (18% for the lower TH-302 dose, 36% for the higher TH-302 dose, 7% for gemcitabine alone) although the cases of severe stomatitis were numerically similar among the treatment arms. MAESTRO, a phase Ⅲ randomized trial in which patients are randomized to gemcitabine alone versus gemcitabine plus TH-302 at the dose of 340 mg/m^2 is currently ongoing. The combination of gemcitabine and masitinib also produced interesting clinical results in a recent phase Ⅲ trial, although increased rates of nausea (58% *vs* 47%, *P* = 0.036) and vomiting (50% *vs* 37%, *P* < 0.001) were noted for the experimental arm[79].

Neuroendocrine tumors (PNET) represent approximately 2% of all pancreatic cancers. Due to their rarity and heterogeneity, the advances in their characterization and treatment have been slow, and a limited number of efficacious systemic treatments are currently available[80]. Large phase Ⅲ clinical trials have demonstrated that everolimus and sunitinib could significantly improve PFS in these patients. Everolimus belongs to mammalian target of rapamycin (mTOR) inhibitor. Aberrant signaling through the mechanistic mTOR pathway has been implicated in neuroendocrine tumorigenesis, and altered expression of mTOR pathway components has been observed in NETs. A randomized placebo-controlled phase Ⅲ study of patients with PNET demonstrated a significantly improved PFS with everolimus (11.0 mo *vs* 4.6 mo, HR = 0.35, 95%CI: 0.27-0.45)[81]. Among drug-related adverse events oral stomatitis, rash, diarrhea, and fatigue should be included. Aphthous-like oral stomatitis has been identified as one of the most common dose-limiting toxicities associated with the drug[82], and the pathogenesis of this side effect has been demonstrated peculiar[83]. GI toxicities are frequent, including stomatitis, diarrhea and vomiting, with most of them being grade 1 or 2, though some cases of stomatitis and diarrhea were grade 3 or grade 4.

Sunitinib is an oral multitarget tyrosine kinase inhibitor with antiangiogenic properties. Compared to placebo, sunitinib doubled median PFS from 5.5 to 11.4 mo when given continuously at the dose of 37.5 mg/d to patients with well-differentiated pancreatic NET enrolled in a multinational, randomized, double-blind, placebo-controlled phase 3 trial[84].

The GI toxicities associated with sunitinib were diarrhea, nausea, vomiting, dysgeusia and stomatitis; the majority of adverse events was grade 1 or 2 and easily managed wit appropriate medical therapy[85].

A comprehensive description or major GI toxicities of the above cited drugs are represented in Table 3.

CONCLUSION

Chemotherapy-induced gastrointestinal toxicities not only are a common problem in cancer patients but they often are clinically significant. Defining the epidemiology of these peculiar toxicities has always been compelling for many reasons including underreporting and differences in assessment techniques and scales. Overall, they remain a significant burden for patients undergoing systemic

Table 3 Frequency of gastrointestinal toxicities in advanced pancreatic cancer: results from main clinical trials

Trials	Nausea		Vomiting		Diarrhea		Oral mucositis	
	Any grade	G3-G4	Any grade	G3-G4	Any grade	G3-G4	Any grade	G3-G4
Gemcitabine + TH-302 (240 mg/m²) (Borad *et al*[78]. *J Clin Oncol* 2014)	39%	10%	24%	6%	28%	3%	18%	0%
Gemcitabine + TH-302 (340 mg/m²) (Borad *et al*[78]. *J Clin Oncol* 2014)	46%	5%	38%	8%	36%	4%	36%	0%
Sunitinib (Yao *et al*[81]. *N Engl J Med* 2011)	45%	1%	34%	0%	59%	5%	22%	4%
Everolimus (Raymond *et al*[84]. *N Engl J Med* 2011)			15%	0%	34%	3%	64%	7%
Folfirinox (PRODIGE 4/ACCORD11 trial, Conroy *et al*[71]. *N Engl J Med* 2011)			14.5%		12.7%			
Nab-paclitaxel + gemcitabine (MPACT trial, Von Hoff *et al*[74]. *N Engl J Med* 2013)					6%			

chemotherapy with or without targeted drugs, with potentially negative effects on both patient's outcome and cancer care costs. Moreover, the more aggressive upfront regimens often used nowadays in patients with metastatic colorectal cancer together with the introduction of novel targeted therapies are likely to worsen the issue. Improved understanding of the pathophysiology underlying gastrointestinal toxicities has allowed identifying patients at higher risk, developing new effective treatments to prevent or help the recovery from such disturbances and to provide symptomatic relief. Still, management of chemotherapy-induced gastrointestinal toxicities remains a major challenge with future studies needed in order to identify subjects who are genetically predisposed to develop severe GI side effects.

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