Review Article

Biological agents in gastrointestinal cancers: adverse effects and their management

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Abstract: Biological therapy comprises agents that by virtue of their unique mechanisms of action, are able to specifically incite a response against or target malignant cells. They differ from conventional chemotherapy with regard to mechanisms of action, indications and side effect profile. Biologic agents have revolutionized therapy for a number of malignancies. In the setting of gastrointestinal (GI) malignancies, agents targeting vascular endothelial growth factor (VEGF), human epidermal growth factor receptor 2 (Her2/Neu) and epidermal growth factor receptor (EGFR) have proven to be invaluable additions to chemotherapy. However, these agents bring with them a set of side effects attributable to their unique mechanisms of action. The anti VEGF agents—bevacizumab, aflibercept and ramucirumab, can result in renal and vascular complications such as hypertension, arterial thrombotic events (ATE), proteinuria and GI perforations. The anti EGFR agents classically cause dermatological toxicities, in addition to hypomagnesemia, which can be dose limiting for patients. Trastuzumab, a monoclonal antibody that targets Her2/Neu, is known to cause cardiotoxicity, especially when used with anthracyclines. Use of immunotherapy agents such as nivolumab is associated with the development immune related adverse events (irAEs). The use of these agents is expected to increase over the next few years and it is crucial that patients and practitioners are aware of their adverse effects and current management strategies. This review highlights the adverse events associated with the use of biologic and immunologic therapies in GI cancers, their incidence and current management strategies.

Keywords: Biological therapy; adverse effects; gastrointestinal cancer; VEGF inhibitor; EGFR inhibitors; immunotherapy

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Introduction

Gastrointestinal (GI) cancers constitute a wide spectrum of malignancies with wide variations in incidence, histopathological features, molecular characteristics and prognosis. Colorectal cancer is the 4th most common cancer in the United States, and the most common GI cancer. An estimated 134,490 new cases and 49,190 deaths attributable to CRC are expected in 2016. Despite major advances in the understanding of pathogenesis, epidemiology and treatment options, the 5-year survival stands at only 65.1%. The survival rates for other GI malignancies stand at similar or even lower rates—anal cancer (66.4%), gastric cancer (30.1%), esophageal cancer (18.4%) or pancreatic cancer (7.7%) (1).

Biologic therapy involves the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Monoclonal antibodies are laboratory produced antibodies

that bind to certain antigens on cancer cells. Over the past 30 years, the Food and Drug Administration (FDA) has approved biologics for a wide variety of conditions. In the setting of malignancy, they can kill cancer cells by inciting an immune response to the cancer (rituximab), inhibiting signals that suppress the patient's own immune response to the cancer (ipilimumab, pembrolizumab), affecting the tumor microenvironment or interfering with action of proteins or factors necessary for cancer growth [e.g., inhibition of vascular endothelial growth factor (anti-VEGF), inhibition of epidermal growth factor receptor (anti-EGFR)] (2,3). Monoclonal antibody therapy for GI cancers, though a recent advancement, is currently a well-established addition to chemotherapy to improve response rates and overall survival.

Multiple biologic therapies are approved for use in patients with GI cancers including agents targeting VEGF [bevacizumab, aflibercept in metastatic colorectal cancer (mCRC) and ramucirumab in metastatic colorectal and gastric cancer], agents targeting EGFR (cetuximab and panitumumab in mCRC without RAS mutations) and one agent targeting human epidermal growth factor receptor 2 (Her2/Neu) (trastuzumab in HER2 amplified, metastatic gastro-esophageal adenocarcinoma). In addition, several immunotherapy drugs are under intensive evaluation for GI cancer therapy in multiple early phase clinical trials (pembrolizumab, nivolumab, atezolizumab, durvalumab), and appear to be active in patients with microsatellite unstable tumors. These agents have adverse events that are distinct from the chemotherapeutic agents they are often combined with, depending on their target signalling pathway. This review aims to characterize the adverse events associated with use of biologic agents in GI malignancies, and summarize best practices for managing these adverse events.

Anti-angiogenic agents

Angiogenesis plays a critical role in the growth and spread of cancer, and requires the binding of signaling molecules, such as VEGF, to receptors on the surface of normal endothelial cells. Angiogenesis inhibitors interfere with various steps in this process. Bevacizumab is a recombinant humanized monoclonal antibody that targets VEGF-A, and was approved by the FDA in 2004 to treat mCRC as a combination with fluorouracil based regimens. Aflibercept was FDA approved in 2012 for use in combination with chemotherapy for mCRC. It is a recombinant, decoy receptor fusion protein, designed to target VEGF-A, VEGF-B and placental growth factor (4). Ramucirumab is a recombinant, monoclonal immunoglobulin G_1 antibody that binds VEGFR-2 and blocks the binding of VEGF-A, VEGF-C and VEGF-D (5). It was approved in 2014 for the treatment of advanced gastric or gastroesophageal junction carcinoma, either alone or in combination with paclitaxel, and subsequently in 2015 for second line therapy of mCRC patients, in combination with fluorouracil and irinotecan.

Adverse events often seen in association with use of anti-angiogenic agents are hypertension, proteinuria, thromboembolism, hemorrhage, delayed wound healing and increased wound complications and GI perforation.

Hypertension

Hypertension is a frequent adverse event attributable to the anti-angiogenic effects of VEGF inhibitors. Grade 3–4 hypertension is reported with a frequency of up to 17.4% in clinical trials evaluating combination of chemotherapy and anti-angiogenic agents (6-8). The development of hypertension is hypothesized to be due to reduced nitric oxide production and rarefaction of vessels (9,10). Hypertension in response to bevacizumab may also have a genetic component (11,12).

Hypertension can develop at any time during treatment, and can be dose related. All patients who are beginning therapy with angiogenesis inhibitors should have a formal cardiovascular risk assessment, including blood pressure (BP) monitoring at start of therapy and every 2–3 weeks thereafter as long as BP is stable (13). It is important to note that pre-existing hypertension is common in cancer patients (14), and this can worsen while on VEGF inhibitor therapy (15).

The goal of management is to keep the BP below 140/90 mmHg, and, in certain populations like diabetes mellitus or chronic kidney disease patients, below 130/80 mmHg. Drug therapy for VEGF inhibition induced hypertension includes usual anti-hypertensive agents. VEGF inhibition induced rise in BP dissipates after cessation of the drug. It is prudent to anticipate a fall in the BP upon cessation of VEGF inhibitor therapy and adjust the antihypertensive medications accordingly (16). VEGF inhibitors should not be initiated in patients with uncontrolled hypertension. Permanent discontinuation of therapy may be necessary if systolic BP is >200 mmHg or diastolic BP is >100 mmHg, hypertension is unmanageable with oral antihypertensive agents or in the event of hypertensive crisis (17,18).

Proteinuria

The incidence of all grade proteinuria attributable to angiogenesis inhibition is up to 63%, while the incidence of grade 3–4 proteinuria has been reported to be up to 7% (19). Proteinuria has been correlated with presence of hypertension and the dose of the VEGF inhibitor. All patients should be screened for proteinuria before initiation of therapy, along with BP monitoring and estimation of renal function. If there is no evidence of proteinuria, patients should have repeat screening before each cycle. If screening reveals grade 1+ proteinuria, then urinary protein excretion should be quantified using a spot urine protein/creatinine ratio or a 24-hour urine protein measurement (13).

Therapy should be discontinued for proteinuria >2 g/24 h or spot urine protein/creatinine ratio >2, until it returns to baseline (18). ACE inhibitors are a therapeutic option to combat proteinuria in addition to controlling rise in BP. A kidney biopsy may be necessary in cases of progressive renal disease, unexplained renal failure or nephritic syndrome to exclude other etiologies (13). Onset or relapse of minimal change disease in the setting of bevacizumab therapy has also been described (20,21).

Thromboembolic events

Addition of bevacizumab to standard chemotherapeutic options for GI malignancies increases the risk of arterial thrombotic events (ATE) but not that of venous thromboembolic events (22-24). An ATE can manifest as myocardial infarction, cerebrovascular accident, sudden cardiac death and transient ischemic attack (25).

This increased risk is likely related to the loss of and nitric oxide and prostacyclin production, which normally inhibit platelet aggregation. Inhibition of VEGF could cause defects in the endothelium that expose pro-coagulant phospholipids on the luminal membrane leading to thrombosis or hemorrhage (26). ATE have been reported to be more frequent in those with proteinuria. These drugs should be discontinued in anyone who experiences a severe ATE, while on therapy. These patients can receive full dose anticoagulation without any increased risk of grade ≥3 bleeding (18).

Though the current evidence to use low dose aspirin for prophylaxis of ATEs in patients receiving bevacizumab is limited, the concomitant use of bevacizumab, chemotherapy and aspirin does not appear to increase bleeding risk compared to chemotherapy plus aspirin alone. The decision to use aspirin for prophylaxis in patients receiving anti-angiogenic agents needs to be individualized based on risk factors and lack of contraindications to aspirin use (18,23).

Bleeding events

Anti-angiogenic agents can cause two distinct forms of bleeding—minor hemorrhage which is most commonly epistaxis, and major bleeding events including but not limited to GI, central nervous system, and vaginal bleeding, and hemoptysis.

Low grade mucocutaneous bleeding such as epistaxis does not usually require specific treatment and does not require treatment discontinuation.

A meta-analysis of nine studies utilizing bevacizumab for the treatment of colorectal cancer reported an overall incidence of grade 3–4 bleeding events of 1.8% (8). This was similar to the incidence reported by the Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study (2.2%; 95% CI, 1.6–2.9%). The majority of the events in the BRiTE study were GI or rectal bleeds.

To minimize the risk of severe bleeding in the setting of bevacizumab therapy, it is imperative that patients be evaluated for potential risk factors for bleeding (27). Bevacizumab should not be administered to patients with serious hemorrhage or recent hemoptysis and should be discontinued upon development of any serious bleeding event. Similarly, aflibercept should be avoided in patients with a bleeding diathesis or that receiving full dose anticoagulation (28).

GI perforation

In a meta-analysis of 33 randomized controlled trials utilizing bevacizumab, the incidence of GI perforation was reported to be 1.1% (95% CI, 0.8–1.5%) with an overall incidence of bevacizumab-associated GI perforation related mortality (grade 5) of 8.8% (95% CI, 5.3–14.3%) (29). Both low and high doses of bevacizumab are associated with increased risk of GI perforation, and the risk has been reported to be dose dependant (30). A similar rate of GI perforation has been reported with aflibercept (1.9%, 95% CI, 1.0–3.8%) with a mortality of 10.8% (95% CI, 4.1–25.5%) (31).

Possible mechanisms of GI perforation include limitation of blood flow to the GI tract leading to bowel infarction and perforations (30).

Patients at higher risk for perforation should be

identified prior to initiation of therapy, such as those with history of diverticulitis or peptic ulcer disease, radiation exposure, obstruction, recent endoscopy and multiple previous surgeries. If perforation is detected, prompt surgical assessment is necessary along with bowel rest, fluid resuscitation and intravenous broad spectrum antibiotics. A single centre study of patients who developed perforation while on bevacizumab revealed that the majority (79%) of patients were successfully managed non-operatively (32). However these decisions need to be individualized based on severity and clinical presentation.

Postoperative wound healing complications

The BRiTE study reported a 4.4% (95% CI, 2.7–6.2%) incidence of postoperative wound healing complications in patients who underwent a surgical procedure within 90 days of the last dose of bevacizumab (25). Among the listed complications were wound dehiscence, wound bleeding and wound infections.

VEGF is involved in three physiological responses to tissue injury necessary for wound healing—vasodilation, increased vascular permeability and angiogenesis. Blocking of these essential responses by VEGF inhibitors is believed to be the cause of delayed wound healing and predisposition to complications for patients on these agents (33-35).

It is currently recommended that bevacizumab, ramucirumab and aflibercept be discontinued at least 4–6 weeks prior to elective surgery and therapy should not be resumed for at least 4 weeks after major surgery, until the surgical wound is completely healed (36).

Neutropenia and thrombocytopenia

Aflibercept in combination with folinic acid, fluorouracil, irinotecan (FOLFIRI) has displayed a higher incidence of neutropenic complications (febrile neutropenia and neutropenic infections) than FOLFIRI plus placebo (37,38). In the ramucirumab versus placebo in combination with second-line FOLFIRI in patients with mCRC that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE) trial, ramucirumab in combination with FOLFIRI had a 38% incidence of grade 3–4 neutropenia compared to 24% in FOLFIRI/placebo (39). The ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW) trial also reported higher incidence of neutropenia (41% *vs.* 19%) and leukopenia (17% *vs.* 7%) in ramucirumab treated groups compared to controls (40).

All patients should have a baseline complete blood count and differential prior to initiation of therapy as well as prior to each cycle. If neutrophil count falls below 1.5×10^9/L, therapy should be delayed until recovery to above 1.5×10^9/L (28).

EGFR inhibitors

The EGFR inhibitors cetuximab and panitumumab are approved for use in patients with RAS wild type mCRC. Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds to the extracellular domain of human EGFR, competitively blocks the binding of EGF and inhibits downstream signal transduction (41). Panitumumab is a fully human IgG2 anti-EGFR monoclonal antibody (42,43). The major toxicities reported for these agents are mucocutaneous, diarrhea, hypomagnesemia, and infusion reactions.

Mucocutaneous toxicity

One of the major adverse events of therapy with an anti EGFR agent is skin toxicity, which can manifests in several forms. The incidence of any grade skin toxicity during therapy with cetuximab or panitumumab ranges from 80–95%, and grade 3–4 toxicities ranges from 6–10% (44-49). Papulopustular rash and xerosis have even been studied as prognostic markers of response to therapy in patients treated with cetuximab or panitumumab (50). Skin rash is mostly mild-to-moderate in severity and requires therapeutic intervention in about one third of patients. Although the skin rash is self-limiting and usually resolves without scarring upon discontinuation of anti-EGFR therapy, the condition can negatively affect treatment compliance and quality of life (QOL). In addition to leaving skin vulnerable to superinfection, skin rash can lead to dose modification or treatment discontinuation, thus potentially affecting the overall clinical benefits of this form of therapy.

The basal layer of the epidermis has strong expression of EGFR which contributes to epidermal growth, wound healing and inhibition of differentiation. Inhibition of EGFR leads to impaired growth and migration of keratinocytes as well as inflammatory chemokine expression by these cells. This leads to inflammatory cell recruitment and cutaneous injury, resulting in toxicities seen with

cetuximab or panitumumab (51).

Prophylactic measures have been evaluated as means to decrease the incidence or severity of skin reactions in response to anti-EGFR therapy. The skin toxicity evaluation protocol with panitumumab (STEPP) was the first prospective trial designed specifically to compare pre-emptive with reactive treatment for EGFR-inhibitor mediated skin toxicity. Patients receiving panitumumab in addition to FOLFIRI were randomly assigned to receive either pre-emptive treatment (daily skin moisturizer, sun-screen, 1% hydrocortisone cream, and doxycycline 100 mg twice daily, from 24 hours before their first dose of panitumumab through week 6) versus reactive treatment, after development of skin toxicity. The study revealed a significantly lower (29% *vs.* 62%) incidence of ≥ grade 2 skin toxicities during the 6-week period of therapy, coupled with lower rates of QOL impairment in the pre-emptive treatment group (52). A meta-analysis of 13 studies using anti-EGFR therapy for solid tumors revealed a 26% absolute difference in incidence of high grade acneiform skin rash when prophylactic antibiotics (tetracyclines) were used for several weeks prior to start of the anti EGFR therapy (53). *Table 1* outlines the major mucocutaneous toxicities associated with cetuximab or panitumumab use, their reported incidence rates and optimal management strategies.

Hypomagnesemia

Hypomagnesemia is a common side effect of therapy with anti-EGFR agents. A recent systematic review reported the incidence of cetuximab related hypomagnesemia to be 35–100% for all grade and 1.7–27% for grade 3–4 (65). The incidence of grade 3–4 hypomagnesemia with panitumumab has been reported to be 4%, with an all grade incidence of 28.9–85.7% (65,66). Incidence of hypomagnesemia appears to be related to the duration of treatment. In a Belgian study with 98 mCRC patients treated with anti-EGFR therapy, 97% experienced a progressive decline in magnesium levels with a median time to onset of hypomagnesemia of 99 days (range, 12–639 days) (67). The incidence has been reported as 5% within 3 months, 23% within 3–6 months and 47% with greater than 6 months of treatment with cetuximab (68).

Hypomagnesemia can lead to cardiovascular (arrhythmias, hypertension, cardiomyopathy), neuromuscular (weakness, confusion, tetany, agitation, tremors) or behavioural (depression, delirium, psychosis) complications (69). Hypocalcemia can be associated as a result of hypomagnesemia induced parathyroid hormone resistance.

Hypomagnesemia should be suspected in patients who develop chronic diarrhea, arrhythmias, refractory hypokalemia or hypocalcemia during therapy with cetuximab or panitumumab (69). Electrolytes should be monitored periodically for 8 weeks after completion of anti-EGFR therapy. *Table 2* outlines the management of hypomagnesemia.

Diarrhea

In EGFR monotherapy trials, the incidence of grade 3–4 diarrhea has been 1–2%. This incidence increased to 28% in trials combining cetuximab with chemotherapy (44,72-75). A 2015 meta-analysis of 18 studies and 13,382 patients revealed a 66% increased risk of developing grade 3–4 diarrhea while on treatment with cetuximab or panitumumab in combination with chemotherapy compared to chemotherapy alone (RR, 1.66; 95% CI, 1.52–1.80) (76). The reported overall incidence of grade 3–4 diarrhea was 18%, compared to 11% in the control arm. The same meta-analysis also reported a significantly higher risk of mucositis in patients receiving panitumumab or cetuximab as part of their therapy (RR, 3.44; 95% CI, 2.66–4.44). The incidence of severe mucositis was 8% in the experimental arm and 2% in the control arm.

Patients should be provided education for symptoms of severe diarrhea, dehydration and electrolyte disturbances at the start of treatment. Management of diarrhea includes bowel rest, hydration, electrolyte repletion, and anti-motility agents such as loperamide and diphenoxylate once infection is ruled out. Hospitalization may be necessary in cases of severe dehydration, fever, neutropenia, or nausea and vomiting that prevents oral hydration (77). Admitted patients should receive intravenous fluid resuscitation, anti-diarrheal agents such as loperamide or octreotide as well as electrolyte supplementation as needed (78). Orally administered, topically active corticosteroid budesonide is active in loperamide resistant chemotherapy induced diarrhea (79,80).

Infusion reactions

The incidence of severe infusion reactions in mCRC patients treated with cetuximab is 3.5–7.5% and with panitumumab <3% (55). The lower incidence with panitumumab as compared with cetuximab is likely due to panitumumab being a fully humanized antibody (81). The mechanisms of infusion

Table 1 Major mucocutaneous toxicities associated with use of anti-epidermal growth factor receptor therapy with optimal management strategies

Skin toxicity	Incidence	Description	Management
Papulopustular rash	60–80% (any grade); 5–20% (≥ grade 3) (54)	Erythematous inter- and intra-follicular papules and pustules commonly affecting sun exposed areas of the body	Mild pustular/papular eruption with little or no symptoms—topical 2% clindamycin plus 1% hydrocortisone in lotion base b.i.d till resolution of rash
			Moderate pustular or papular eruption, moderately symptomatic, may or may not interfere with daily life—treatment for mild PLUS oral minocycline 100 mg b.i.d or doxycycline 100 mg b.i.d for minimum 4 weeks and continuing for the duration of treatment as long as the rash is symptomatic. Scalp lesions—topical 2% clindamycin plus triamcinolone acetonide 0.1% in equal parts of propylene glycol and water until resolution
			Severe extensive, painful intolerable rash that interferes with daily life: (I) panitumumab—withhold drug till toxicity improves to ≤ grade 2; (II) cetuximab—withhold treatment for 1 week. PLUS above mentioned therapies for mild and moderate lesions. If improvement seen—dose re-escalation. If no improvement—discontinue anti EGFR agent. [Adapted from BC cancer agency protocol for EGFR skin rash, (55,56)].
Xerosis	Up to 35%, more common in elderly and patients with history of atopic eczema (57,58)	Excessive dryness of skin characterised by diffuse fine scaling. Can progress to chronic asteatotic eczema—pruritic dry cracked fissured skin with irregular scaling. Can predispose to staphylococcal or herpes infections	Emollients and moisturizing creams. Antihistaminics for pruritus. Pregabalin may help with pruritus associated with cetuximab (59). Fissures—treat with emollients. Seal fissures with cyanoacrylate or flurandrenolide tape that delivers high potency steroids and protects against mechanical trauma (60). Systemic or topical antibiotics if infection
Paronychia	10–15% (55)	Erythematous painful inflammation of the nail fold, brittle slow growing nails with candida or secondary bacterial infection, periungual abscesses (61)	Minocycline or doxycycline 100 mg BID. Non-infected painful paronychia can be treated with potent topical steroids, combined with antiseptic soaks and topical antibiotics (61). Severe cases—local nail steroid injections or nail fulguration (62)
Telangiectasia and hyperpigmentation	–	Small dilated blood vessels. Fading of telangiectasia results in hyperpigmented patches. Usually a result of photosensitivity on sun exposed parts	Sun protection for prevention—SPF 30 broad spectrum sun screen, avoiding outdoor activities between 11 am to 4 pm, barrier sun protection such as clothing and hats
Hair changes	–	Hirsutism—excessive hair growth; hypertrichosis of the face; fine, brittle or curly scalp hair; trichomegaly of the eyelashes	Hair changes generally resolve within a month of discontinuing treatment
Ocular adverse events—blepharitis, conjunctivitis, increased lacrimation	15% (63)	Inflammation of the meibomian glands along the lid margins, inflammation of the conjunctiva, redness, itching, pain (63)	Warm compress; eyelid scrub; topical antibiotics (64)

EGFR, epidermal growth factor receptor.

Table 2 Management of hypomagnesemia due to anti-epidermal growth factor receptor agents

Grade	Definition (CTCAE 2010)	Management
1	1.2 mg/dL to < lower limit of normal	Usually asymptomatic—does not require replacement therapy (68,70,71)
2	<1.2–0.9 mg/dL	Oral supplementation may be ineffective due to diarrhea. Weekly intravenous treatment with magnesium sulphate 4 g. Can consider weekly monitoring without supplementation for asymptomatic patients (55,68,70)
3	<0.9–0.7 mg/dL	Replacement therapy is essential as there is increased risk for cardiac arrhythmias. Usually requires intravenous magnesium sulphate 6–10 g twice a week
4	<0.7 mg/dL	Daily supplementation may be necessary (55). Temporary discontinuation of the EGFR inhibitor may be necessary until the magnesium levels are within normal range (68,70)

EGFR, epidermal growth factor receptor.

and hypersensitivity reactions to the two antibodies may differ, and cases of successful treatment with panitumumab after severe hypersensitivity to cetuximab, as well as vice versa, have been described (82-84).

The administration of corticosteroids (dexamethasone or hydrocortisone) with antihistaminics (diphenhydramine) prior to cetuximab infusion reduces the incidence of infusion reactions, without limiting efficacy (85).

Anti-HER2 agents (trastuzumab)

Based on results from the Trastuzumab for Gastric Cancer (ToGA) trial (86), trastuzumab was approved by the FDA in 2010 in combination with cisplatin and a fluoropyrimidine in patients with Her2/Neu amplified metastatic gastric or gastroesophageal junction adenocarcinoma. Prior to this, trastuzumab had been extensively used in breast cancer, hence its toxicity profile was well characterized much before approval for use in GI malignancies.

In the ToGA trial, there were no significant differences in the incidence of grade 3–4 adverse events upon addition of trastuzumab, except for diarrhea (9% in trastuzumab plus chemotherapy *vs.* 4% in chemotherapy alone). Additionally, the incidence of grade 3–4 cardiac adverse events was also found to be similar in the two groups (6% in both). Four patients in the trastuzumab/chemotherapy group had cardiac events versus nine patients in the chemotherapy alone group. The incidence of cardiac dysfunction, defined as a ≥10% drop in left ventricular ejection fraction (LVEF) to an absolute value <50%, was 5% in the trastuzumab plus chemotherapy arm versus 1% in the chemotherapy alone arm (86).

The cardiotoxicity of trastuzumab in breast cancer is known to be accentuated when given concurrently with an anthracycline. Concomitant use of trastuzumab and anthracycline (epirubicin) containing regimens in gastric cancer should be avoided. In a large meta-analysis of over 29,000 women, severe cardiotoxicity associated with trastuzumab was seen in 3% of patients (87). Similar to prior studies, the meta-analysis demonstrated an increased rate of severe cardiotoxicity when anthracyclines and trastuzumab were used together versus trastuzumab alone (2.9% versus 0.9%).

The incidence of cardiotoxicity in patients treated with trastuzumab specifically for GI malignancies is not currently characterized, but it is safe to assume that the risk is similar to patients with breast cancer. Trastuzumab associated cardiac toxicity manifests as left ventricular dysfunction, arrhythmias, hypertension, congestive heart failure or cardiomyopathy. Risk factors for cardiotoxicity with trastuzumab therapy are similar to those observed in the general population—pre-existing hypertension, smoking, diabetes, obesity, dyslipidemia, family history of cardiovascular disease, and personal history of coronary artery disease (87,88).

Patients should undergo a thorough cardiac assessment including baseline LVEF prior to initiation of therapy, and every 3 months during and upon completion of trastuzumab therapy. Trastuzumab should be held if there is a ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below the institutional limit of normal and ≥10% absolute decrease from pre-treatment value. If trastuzumab has been withheld for significant LV dysfunction, LVEF measurement should be repeated at 4-week intervals.

In the setting of metastatic gastric cancer, the most common (>10%) adverse reactions in the trastuzumab arm compared to control were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common reactions resulting in discontinuation of treatment were infection, diarrhea and febrile neutropenia.

Immunotherapy agents

Immunotherapy is fast emerging as an effective anti-neoplastic treatment, alternative to chemotherapy for a number of malignancies. Anti-CTLA-4 agents (ipilimumab) and anti-PD1 agents (nivolumab, pembrolizumab) are already approved for use in metastatic melanoma and non-small cell lung cancer (89-91). These results have paved the way for immunotherapy trials in GI malignancies including esophageal, gastric, pancreatic, hepatocellular, colorectal and anal cancer. Though these are not currently approved for use in any GI malignancy, more patients are receiving these agents on clinical trials, and given their unique toxicities, clinicians should be familiar with managing these adverse events.

Immune checkpoint inhibition with anti-CTLA-4 and anti-PD-1/PD-L1 agents triggers a number of autoimmune endocrinopathies affecting the pituitary, thyroid, adrenals, and endocrine pancreas. Autoimmune attacks on non-endocrine sites are also seen resulting in dermatological toxicity, colitis, pneumonitis, hepatitis or myocarditis (92-96). Patients receiving these agents should have regular thyroid function studies, CBC, liver function tests and metabolic panels at each treatment and at 6–12 weeks intervals for 6 months after completion of therapy (97). *Table 3* outlines the major immune related adverse events (irAEs) seen with immune checkpoint inhibitors, their incidence and management.

Other types of immunotherapies under further evaluation are tumor vaccines and adoptive cell transfer therapy (107). Adoptive cell transfer involves the administration of activated, tumor reactive, *ex vivo* expanded T cells to directly attack cancer cells. This requires a preparative chemotherapy for lymphodepletion which results in transient neutropenia and thrombocytopenia. Administration of active T cells can cause a cytokine release syndrome characterized by fever, tachycardia, oliguria, hypotension and multi-organ failure. Treatment usually involves supportive care with fluids and anti-inflammatory agents while awaiting spontaneous recovery (97). Administration of T-cells can result in autoimmunity as well, with the clinical manifestations depending on the intended target on the cancer cells. For example, when carcinoembryonic antigen was targeted for mCRC, severe life threatening colitis was seen (108).

An oncolytic virus based vaccine approved for metastatic melanoma—talimogene laherparepvec (TVEC)—also has a favourable toxicity profile, with the only ≥ grade 3 toxicity in >2% of patients being cellulitis (109), and is currently undergoing clinical trials in GI malignancies as well.

Conclusions

Biological agents are an indispensable addition to chemotherapy for GI malignancies leading to improved response rates and overall survival. However, the addition of these novel drugs brings forth a number of unique adverse events in addition to those already seen with combination chemotherapeutic regimens. It is important for the care team, including patients and their caregivers, surgeons, nurses, oncologists and primary care physicians to be able to recognize these adverse events to allow for prompt referral and optimal management and lower the risk of permanent sequelae.

Table 3 Major adverse effects associated with immune checkpoint inhibitor therapy and their management

Adverse event	Incidence and agents	Description	Management
Dermatological toxicities	34% of patients who received nivolumab, 39% of patients who received pembrolizumab (98), 47–68% of patients with ipilimumab (99)	Maculopapular rash, papulopustular rash, Sweets syndrome, follicular dermatitis, urticarial dermatitis, vitiligo, bullous pemphigoid, lichenous dermatitis (100)	Dermatological evaluation necessary for patients with atypical rash, lack of improvement with intervention, grade 3–4 lesions, or oral mucosal involvement. Serum testing for liver and kidney function, tryptase and IgE levels. Grade 1—continue immunotherapy, topical corticosteroids, oral antihistaminics for pruritus. Grade 2—oral prednisone 1 mg/kg/d, oral antihistaminics. If improves to ≤ grade 1, resume immunotherapy. After symptoms improve, taper steroids over ≥1 month. Discontinue immunotherapy if rash does not improve after 12 weeks from last dose. Grade 3–4—hold immunotherapy, oral prednisone 1 mg/kg/d, oral antihistaminics. If improves to ≤ grade 1, taper steroids over ≥1 month. If worsens, additional immunotherapy may be required (infliximab, mycophenolate mofetil, cyclophosphamide) (98)
Endocrine toxicities	Any grade endocrine toxicity in about 5–10% (101)	Hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency	Hypophysitis requires hormone replacement depending on specific deficiencies developed. Adrenocortical insufficiency can be treated with glucocorticoid replacement, adrenal crisis requires hospitalization, endocrinology consultation, intravenous corticosteroid replacement and fluid and electrolyte management. Hypothyroidism requires thyroid hormone replacement. Early thyroiditis may present with symptoms of hyperthyroidism which can be symptomatically managed with β-blockers. Most endocrinopathies can be successfully treated with hormone replacement, hence discontinuation of therapy is not usually required (101)
Hepatic toxicity	Incidence is ≤10% (102). Higher rates of grade 3–4 events have been reported when anti-PD-1 was combined with anti-CTLA-4 mAbs, or when ipilimumab was combined with dacarbazine (99)	Usually asymptomatic elevations in AST and ALT levels. Radiologically can appear as hepatomegaly, periportal edema, periportal lymphadenopathy (103)	Patients should have standard liver function tests, exclusion of viral and drug induced hepatitis and exclusion of malignancy. Grade 1—continue immunotherapy if asymptomatic, monitor LFTs routinely. Grade 2—withhold immunotherapy, oral prednisone 1 mg/kg/d, monitor LFT daily. If improves and LFT improves to ≤ grade 1, resume immunotherapy. After improvement, taper steroids over ≥1 month with weekly LFTs. Grade 3–4—discontinue immunotherapy, intravenous methylprednisolone, monitor LFTs daily. If no improvement, consider additional immunosuppression. Do not use infliximab as it can cause hepatotoxicity (98,99)
Pneumonitis	Incidence is ≤10% with anti-PD1/PD-L1 therapy (98). Development of sarcoidosis has also been reported with ipilimumab (104-106)	Acute interstitial pneumonia or acute respiratory distress type pattern on radiology	Investigations include high resolution CT scan, microbial assessment, bronchoscopy and pulmonary consultation as necessary. Grade 1—continue immunotherapy with monitoring for symptoms every 3 days. Repeat CT at every cycle. Grade 2—withhold immunotherapy. Daily monitoring. Oral prednisone 1 mg/kg/d. If improves to ≤ grade 1 within 3 days of supportive care, resume immunotherapy. Taper steroids over ≥ 1 month after improvement. Grade 3–4—discontinue immunotherapy, hospitalization, intravenous methylprednisolone, prophylactic antibiotics, consider additional immunosuppression. If improves to ≤ grade 1, taper steroids over ≥6 weeks (98)
Diarrhea/colitis	Diarrhea occurs in up to 44% of patients treated with ipilimumab, with an incidence of grade 3–4 diarrhea of 18% (99). With anti-PD-1 antibodies, incidence of all grade diarrhea is 6–16% and that of high grade diarrhea is 2.2% (102)	–	Rule out other causes like infection by stool studies. Endoscopy to confirm or exclude colitis may be needed in persistent diarrhea or ≥ grade 2. Grade 1—continue immunotherapy, symptomatic management, loperamide, electrolyte replacement. Grade 2—interrupt immunotherapy, symptomatic and supportive management, consider methylprednisolone and prophylactic antibiotics. Grade 3–4—discontinue immunotherapy, high dose corticosteroids. Prophylactic antibiotics. Additional immunosuppression may be required. If improvement seen, taper corticosteroids over >4 weeks (96,99)

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Footnote

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