Research progress on common adverse events caused by targeted therapy for colorectal cancer (Review)

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Abstract. As targeted drug therapy is increasingly applied in the treatment of colon cancer, understanding and managing the adverse reactions of patients is becoming increasingly important. The present review examines the mechanisms of and adverse reactions to the most commonly used targeted drugs for colon cancer, and discusses methods of coping with these adverse reactions. Approved targeted drugs for metastatic colon cancer include monoclonal antibodies targeting vascular endothelial growth factor (VEGF), including bevacizumab, ziv-aflibercept and regorafenib, and monoclonal antibodies targeting epithelial growth factor receptor (EGFR), including cetuximab and panitumumab. The present review assesses the major adverse effects of these drugs and methods of dealing with reactions to them. VEGF inhibitors primarily result in cardiovascular and kidney problems. Meanwhile, EGFR receptor inhibitors are frequently reported to cause rashes, diarrhea and hypertension, and are reviewed from the point of view of resulting electrolyte disturbances.

Contents

1. Introduction

Colorectal cancer is one of the most common malignancies globally (1-3). According to statistics by the World Health Organization, ~1.2 million new cases of colorectal cancer were identified globally in 2008 (3). Each year, >0.6 million patients succumb to mortality due to colorectal cancer, either directly or indirectly. The incidence of this malignancy is increased among males compared with females. Furthermore, the risk of colorectal cancer increases with age. For example, the median onset age for colorectal cancer in developed countries is 70 years. In the USA, colorectal cancer ranks third in terms of incidence and mortality (2). In China, colorectal cancer ranks fifth in terms of incidence (4,5).

Approximately 20% of all cases with colorectal cancer are stage IV (tumor, node and metastasis staging system; www.nccn.org/patients) at the first diagnosis, and the 5-year survival rate of these cases is only 13% (4,6-8). Chemotherapy is the main treatment for metastatic and local late-stage colorectal cancer; however, the toxicity and adverse side effects maybe intolerable for patients with a poor prognosis (9). In comparison, targeted therapy is associated with improved compliance, decreased toxicity and fewer side effects in addition to improved prognosis (10,11).

However, increasingly, adverse events associated with targeted therapy have been reported in previous years (12-15). At present, the approved targeted drugs for metastatic colorectal cancer include monoclonal antibodies targeting vascular endothelial growth factor (VEGF) and those targeting the epidermal growth factor receptor (EGFR). The representatives of the first category include bevacizumab, ziv-aflibercept and regorafenib; and those of the second category include cetuximab and panitumumab. The present review assesses the adverse events and the corresponding treatments following the use of these two categories of targeted drugs.

2. VEGF inhibitors

VEGF promotes angiogenesis. There are five ligands of VEGF (Fig. 1), as follows: VEGFA, VEGFB, VEGFC, VEGFD and placental growth factor (PlGF). Additionally, there are three receptors of VEGF: VEGFR1, VEGFR2 and VEGFR3, and 2 common receptors, neuropillin 1 and neuropillin 2. VEGFR1 binds to VEGFA, VEGFB and PlGF; VEGFR2 binds to VEGFA, VEGFC and VEGFD. VEGFR2 is considered to be the receptor involved in regulating angiogenesis, whereas VEGFR1 and VEGFR3 are involved in the chemotaxis of monocytes,

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survival of hematopoietic stem cells and formation of lymphatic vessels (16). VEGF inhibitors mainly function by blocking VEGF ligands. For example, bevacizumab inhibits the binding of VEGFA to VEGFR2, while ziv-aflibercept functions by intercepting the binding of VEGFA, VEGFB and PlGF (17-20).

The common adverse events arising from the use of VEGF inhibitors are outlined below.

Hypertension

Mechanism of occurrence. VEGF induces the synthesis of nitric oxide synthase via endothelial cells and results in the release of nitric oxide, a notable vasodilator (21). The blocking of VEGF-associated signaling pathways may decrease the secretion of nitric oxide synthase and result in hypertension (22,23). A previous study suggested that VEGF inhibitors induce hypertension by altering the rennin-angiotensin-aldosterone system (24). Another study hypothesized that VEGF inhibitors decrease the microvessel density of the internal organs in patients with hypertension, thus decreasing the blood flow rate and resulting in hypertension (25).

Incidence. Kabbinavar *et al* (26) reported the results of a phase II clinical trial. The incidence of stage III hypertension was 2.9% following intravenous administration of fluorouracil alone. When fluorouracil was combined with bevacizumab, the incidence of hypertension increased to 60%. It was noteworthy that all recruited patients were aged >65 which may have affected drug metabolism. However, for the same population, the combined use of bevacizumab and S-1 resulted in an incidence of hypertension of 11% (27). The most notable limitation of this previous study was the small cohort size, in that only 56 patients were included.

As to the choice of targeted drugs, a previous meta-analysis (28) revealed that the overall incidence of hypertension was 42.4% in patients receiving ziv-aflibercept treatment; among them, the incidence of advanced hypertension was 17.4%. The overall incidence of hypertension was 23.6% following the use of bevacizumab, and the incidence of advanced hypertension was 7.9%. The overall incidence of hypertension was 44.4% for patients who were administered regorafenib, and the incidence of advanced hypertension was 12.5%. Another previous meta-analysis study (29), focusing on the adverse events occurring subsequent to bevacizumab treatment for non-small cell lung carcinoma, indicated that the incidence of hypertension was 19.55%, while that of advanced hypertension was 6.95%. This discrepancy between these previous studies may be due to the differing cancer types. Overall, VEGF inhibitors result in hypertension, particularly amongst elderly patients (30). Another population-based study revealed that the risk of hypertension induced by VEGF inhibitors was higher among those with a previous history of hypertension (31). Thus, VEGF inhibitors maybe used, but with caution, for patients with a previous history of hypertension.

Clinical treatment. The following principles should be followed in order to prevent and treat hypertension induced by VEGF inhibitors (32,33): i) Blood pressure monitoring should be performed for patients treated using VEGF inhibitors at least once every 2-3 weeks, and frequency of monitoring should be increased during treatment. ii) VEGF inhibitors should not be administered unless blood pressure is properly controlled. iii) If hypertension was once induced or aggravated by VEGF inhibitors for the patient, blood pressure monitoring should be continued even subsequent to the cessation of VEGF inhibitor treatment. iv) Any antihypertensive drugs may be used, however, the angiotensin converting enzyme inhibitor is considered to be the superior drug, as it may prevent or treat other side effects arising from treatment with VEGF inhibitors, namely, proteinuria.

Proteinuria

Mechanism of occurrence. Proteinuria is another side effect resulting from the use of VEGF inhibitors. If the protein content in the urine is >300 mg/dl, this usually indicates proteinuria (34-39). Proteinuria caused by the use of VEGF inhibitors is asymptomatic (34) without obvious pathological changes of the kidney (35). As to the mechanism of occurrence of proteinuria, a previous study (36) proposed the intervention of a podocyte-derived VEGF signal axis. However, the glomerular podocytes may constitutively express VEGF and activate VEGFR2 on glomerular vascular endothelial cells, thus establishing and maintaining basic liver functions (36,37).

Incidence. The incidence of proteinuria appears to be dependent on the dose of VEGF inhibitors and the severity of hypertension (38,39). Generally speaking, VEGF inhibitors are more likely to induce hypertension compared with proteinuria. As demonstrated by a previous meta-analysis (40,41), the relative risk (RR) caused by VEGF inhibitors was 3.46 and that of proteinuria was 2.51 compared with the control group. Another meta-analysis included 6,882 cases from a total of 33 clinical trials, and the results revealed that the incidence of proteinuria was 18.7% among patients receiving VEGF inhibitor treatment and the incidence of advanced proteinuria (grade 3 or above) was 2.4% (42).

Clinical treatment. Prior to the use of VEGF inhibitors, screening for proteinuria should be performed. For patients that are negative for proteinuria, only screening is required prior to each treatment; for patients that are positive for proteinuria, evaluation by physicians in nephrology is required if the treatment with VEGF inhibitors is to be administered and the treatment should be highly individualized (43,44).

However, no standards have been established so far for the treatment of proteinuria caused by VEGF inhibitors. According to US Food and Drug Administration guidelines (44), anti-angiogenic drugs should be disused if protein content in the urine >2 g/24 h. Furthermore, if hypertension is induced by VEGF inhibitors and complicated by proteinuria, ACEI and angiotensin receptor blockers are often used for the effect of decreasing the level of protein in the urine and protecting the blood vessels (34).

Other adverse events. Other side effects caused by VEGF inhibitors include hemorrhage (45), diarrhea (46), cardiovascular events including myocardial infarction, thromboembolism, stroke and heart failure (47), gastrointestinal perforation (48), hand-foot syndrome (49) and reversible encephalopathy (50). Symptomatic treatments are usually adopted for these events. However, these events experience low incidence rates (41).

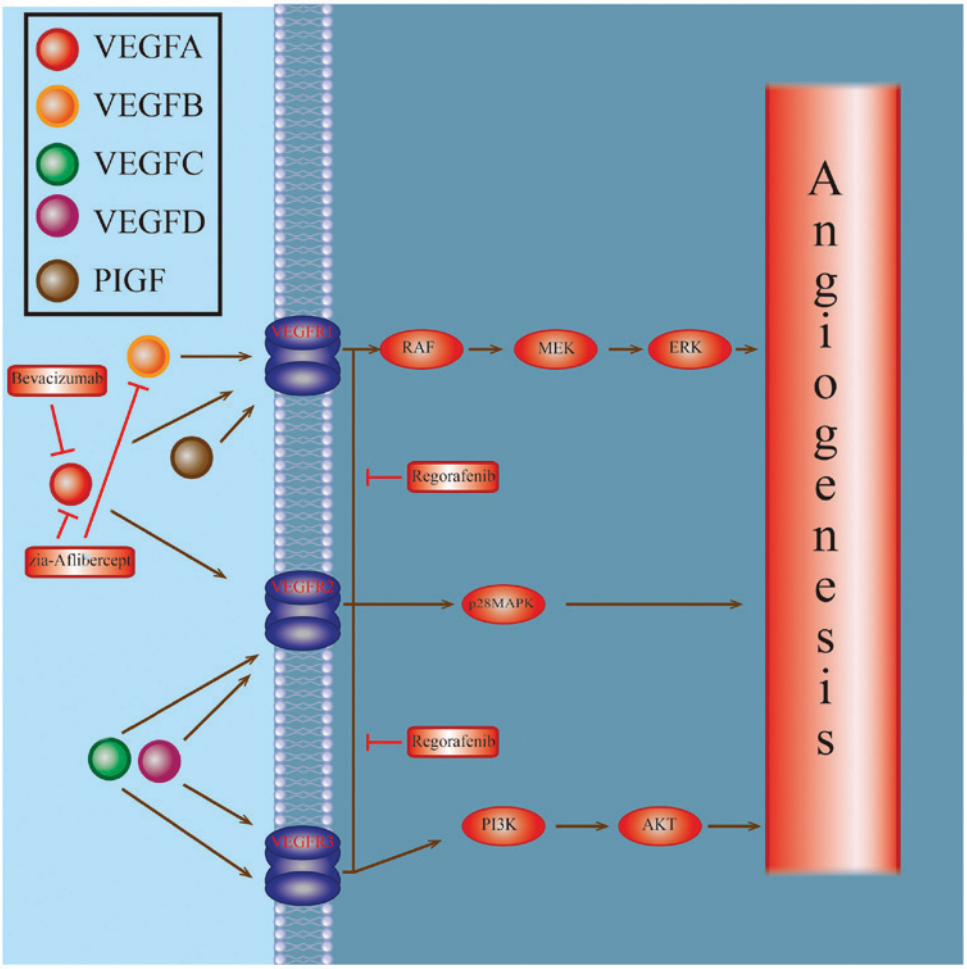

Figure 1. Anti-angiogenic mechanism of bevacizumab, ziv-aflibercept and regorafenib. Bevacizumab binds to VEGFA and interrupts its interaction with VEGFR1 and 2. In addition to VEGFA, ziv-aflibercept binds to and interrupts the function of VEGFB and PlGF. Regorafenib is an oral diphenylureamulti-kinase inhibitor that targets angiogenic (VEGFR1-3), stromal and oncogenic receptor tyrosine kinases. VEGFR, vascular endothelial growth factor receptor; PIGF, placental growth factor; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B.

3. EGFR tyrosine kinase inhibitors

The EGFR signaling pathway is one of the first pathways discovered to be involved in the targeted therapy of tumors (Fig. 2). This pathway affects the proliferation, differentiation, migration and apoptosis of cells (51,52) and usually demonstrates abnormal expression and activation in various solid tumor types (52-54). The common adverse events associated with EGFR tyrosine kinase inhibitors (TKIs) are outlined below.

Hypomagnesemia

Mechanism of occurrence. EGF is a hormone that regulates Mg^{2+} reabsorption in the kidney by activating the Mg^{2+} channel transient receptor potential cation channel subfamily M member 6 (55). EGFR TKIs antagonize the reabsorption, leading to hypomagnesemia (55).

Incidence. A previous meta-analysis study (56) revealed that the incidence of hypomagnesemia due to the use of cetuximab or panitumumab was 17%, and that of advanced hypomagnesemia was 3.5%. Compared with cetuximab, the risk of hypomagnesemia with the use of panitumumab was increased (57). The incidence of hypomagnesemia was positively correlated with the treatment duration. Another previous study (58) revealed that the incidence of hypomagnesemia due to the use of cetuximab for metastatic colorectal cancer was 6-47% (with a treatment duration of 3-6 months). Another two meta-analyses (59) focusing on cetuximab revealed that the incidence of grade 3 and 4 hypomagnesemia were 3.9 and 5.6% with cetuximab, respectively. The relative risk of grade 3 and 4 hypomagnesemia with combined chemotherapy was 8 and 4.75, respectively (60).

Clinical treatment. Hypomagnesemia is negatively associated with age, potentially due to the easier loss of Mg^{2+} (61,62). Furthermore, severe hypomagnesemia may lead to changes in muscle strength (including cramps, muscle weakness and ataxia), heart lesions (including coronary spasms, arrhythmia and long Q-T syndrome) and psychotic symptoms (including epilepsy, insanity, depression and anxiety) (63). These symptoms are easily confused with paraneoplastic syndrome (64). Thus, an electrolyte test is recommended prior to treatment, particularly for elderly patients, together with reexamination once every 2-4 weeks.

For grade 1 hypomagnesemia, which is usually asymptomatic, no interventions are recommended clinically (65).

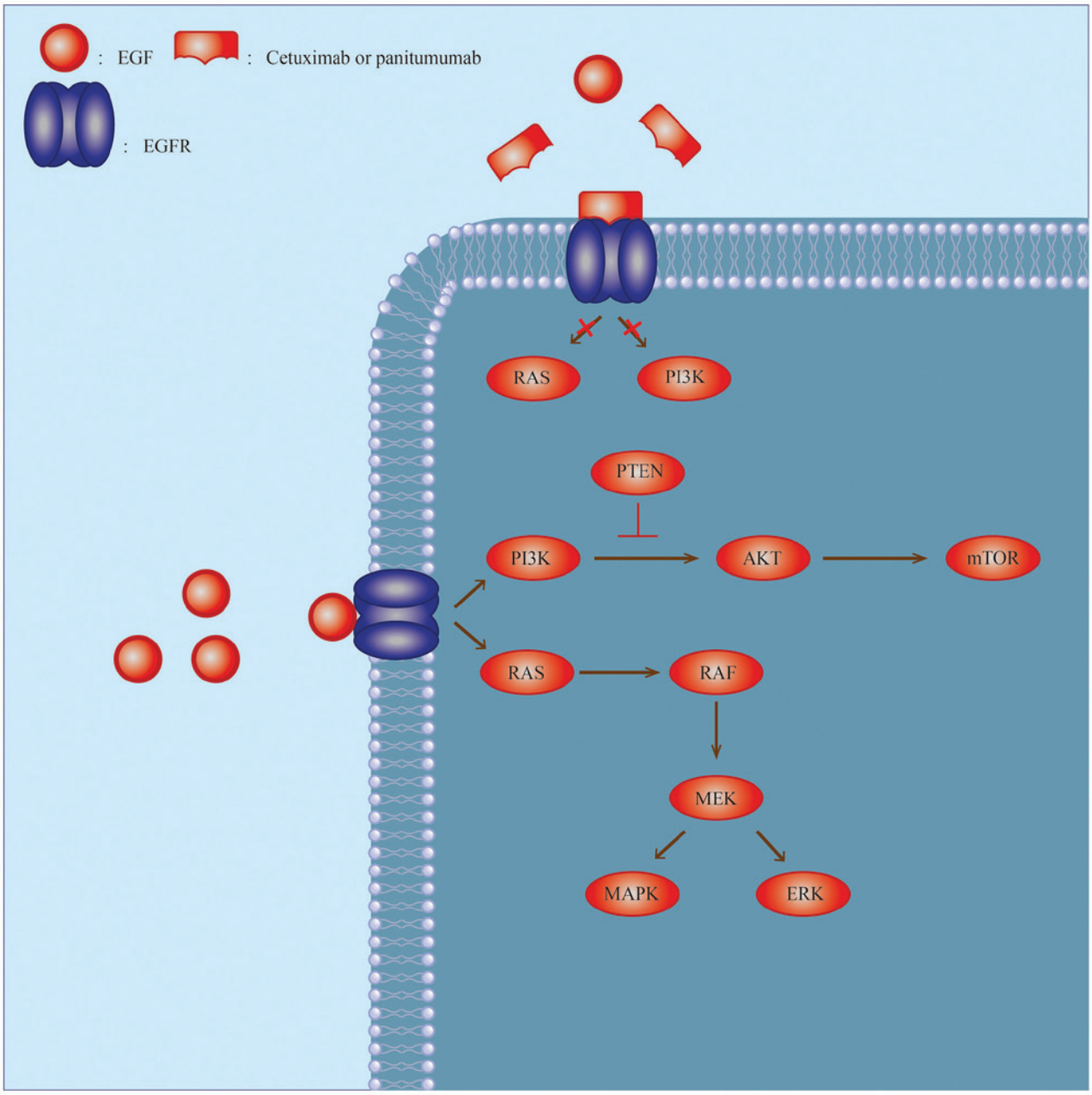

Figure 2. Potential mechanisms of resistance to EGFR-targeted therapy. Schematic representation of the monoclonal antibodies cetuximab/panitumumab and of the EGFR-mediated intracellular signaling pathways. EGFR, endothelial growth factor receptor; PTEN, phosphatase and tensin homolog; mTOR, mechanistic target of rapamycin; MEK, mitogen-activated protein kinase kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B.

For grade 2 hypomagnesemia or above, intravenous infusion of Mg^{2+} is usually required as oral administration, which may induce diarrhea (61).

Hypopotassemia

Mechanism of occurrence. At present, the underlying mechanism of hypopotassemia occurrence caused by EGFR TKI is not well understood. It is a generally held opinion that EGFR TKIs may cause nephrotoxicity (66). A previous study (67) revealed the function of inhibited Mg^{2+} channel TRPM-6 in this process. When hypomagnesemia occurs, increased K^+ is required for the repair of Na-K-adenosine triphosphatase. This may result in decreased renal potassium conservation and hence hypopotassemia.

Incidence. A previous meta-analysis (68) indicated that the incidence of hypopotassemia due to EGFR TKIs for patients with tumors was 14.5%. Notably, the incidence of grade 3/4 hypopotassemia in colorectal cancer treated by cetuximab and panitumumab was increased compared with that in other tumor types (RR for cetuximab, 2.19; RR for panitumumab, 3.30). Cisplatin is the preferred chemotherapeutic drug for many tumor types, but it may cause strong nephrotoxicity (69,70). Thus, this result requires a more specific explanation.

Clinical treatment. The treatment of hypopotassemia is not difficult clinically. Regular potassium tests are necessary during medication, and potassium may be infused if necessary.

If hypopotassemia is complicated by hypomagnesemia, Mg^{2+} infusion is necessary (71).

Other adverse events. The most common side effect of EGFR TKIs is a skin rash, which was one of the first identified side effects (72-76). A number of studies and literature reviews are focused on the topic of the skin rash caused by EGFR TKIs (77-79).

Other adverse events associated with EGFR TKIs are diarrhea (80), hypertension (81,82), transfusion reactions (83) and hepatotoxicity (84).

4. Conclusions

Targeted therapy has unique advantages in treating colorectal cancer, and the progression of this therapy is fueled by an enhanced understanding of the tumor types it aims to target at a genetic level (8,85-87). However, as targeting remains imprecise, certain adverse events are consistently reported (26-30,39,41,45-51). This is particularly true when the targeted therapy is combined with chemotherapy (27,28) Therefore, gaining a deeper understanding of the underlying mechanisms of the side effects occurring as a result of targeted therapy and identifying methods to treat them are highly prioritized. According to a previous study, the optimal method for coping with the side effects associated with targeted therapy is not to decrease the dosage, but through symptomatic treatment, which is capable of avoiding toxicity and adverse side effects (33). For example, VEGFR TKIs may cause hypertension, which may be prevented by proper preventive measures. The active control of blood pressure during targeted therapy can avoid damage of relevant target organs caused by hypertension and prevent progression of hypertension, as a medical consensus, ordinary patients with hypertension also require active control of blood pressure.

In conclusion, proficient understanding of the underlying molecular mechanisms of targeted drugs and the potential adverse events in addition to the proper treatments for these adverse effects is crucial for improving the prognosis of patients with cancer.

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Competing interests

The authors declare that they have no competing interests.

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