Literature Analysis of Adverse Effects Induced by Sunitinib

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Abstract

Objective To analyze adverse drug reactions (ADR) caused by sunitinib and provide reference for clinical safety. **Methods** The case reports of ADR related to sunitinib in six Chinese and English databases from 2006 to 2021 were searched to extract relevant data, and then statistical analysis was performed. **Results and Conclusion** A total of 147 articles were included, involving 156 cases and 283 adverse events. Adverse reactions occurred at the highest rate after 31 to 180 days of drug administration, and ADR involved organs/systems mainly in blood and lymphatic disorders (17.67%), gastrointestinal disorders (15.55%), and skin and subcutaneous tissue disorders (10.60%). The adverse effects caused by sunitinib involve multiple organs/systems throughout the body. Besides, there are many severe fatal cases. During clinical medication, patients should be monitored regularly, and drugs should be reduced or stopped timely when adverse reactions occur to reduce the risk of clinical medication.

Keywords: sunitinib; adverse drug reaction (ADR); literature analysis

Sunitinib (Sutent; Pfizer) is an oral multi-target tyrosine kinase inhibitor (TKI), and its targets include receptors of the vascular endothelial growth factor (VEGF) and the platelet-derived growth factor (PDGF) [1]. Sunitinib was approved by the FDA in the United States in January 2006, and was subsequently approved by National Medical Products Administration (NMPA) in China in November 2007. Current approved indications for sunitinib include imatinib-resistant gastrointestinal stromal tumor (GIST), inoperable advanced renal cell carcinoma (RCC), and unresectable, progressive pancreatic neuroendocrine tumor (pNET) [2].

Some side effects related to sunitinib include fatigue, nausea, rash, hand-foot syndrome, hypothyroidism, hypertension, anemia, leukemia and thrombocytopenia, involving multiple organs/systems. Sunitinib was included in the category of class B medical insurance in 2018, with a price drop of 67% and an increase of in the number of drug users. So far, many adverse drug reactions (ADRs) related to sunitinib have been reported. Then, we searched the case reports of ADR related to sunitinib from 2006 to 2021, and comprehensively analyzed the basic information of patients, the organ/system involved in adverse reactions, clinical manifestations and outcomes, so as to understand its mechanism and treatment method, and provide reference for monitoring the drug use and reducing the risks of clinical medication.

1 Data and methods

1.1 Search methods

To achieve the research objective, all case reports

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of ADR related to sunitinib were collected. Literature published from 1 January 2006 to 20 December 2021 was retrieved using a series of search terms such as sunitinib and case report in six databases, including CNKI, Wanfang, VIP, Embase, Web of Science and PubMed. The data were filtered with the following fields: (TI = (Sunitinib or Sutent) OR AB = (Sunitinib or Sutent)) AND (TI = (cause or adverse or side effect or case report or case series) OR AB = (cause or adverse or side effect or case report or case series)).

1.2 Inclusion and exclusion criteria

The obviously unrelated papers such as review, meta-analysis, animal model, and mechanism of action, were excluded manually after review of the titles and abstract. Literature with incomplete information, and other language (except in Chinese and English) was excluded after review of full text. Individual cases of ADR related to sunitinib were finally included. The literature screening was conducted by two researchers independently based on the exclusion criteria, and a third researcher reviewed it to ensure the quality of the screened literature.

1.3 Data extraction and analysis

Data on patient information, ADR information and correlation evaluation were extracted from the literature included in this study. If the author did not evaluate the correlation, it would be performed by researchers according to the Nobel assessment scale. The data were sorted out according to the medical dictionary for regulatory activities (MedDRA) version 24.0, and the severity of adverse reactions was assessed by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Then, the basic information, medication information and ADR were analyzed through Excel.

2 Results

2.1 Study data

A total of 7 270 papers was initially obtained in this study. To avoid multiple counts of the same literature, 3 261 duplicated papers were excluded through Endnote software, and 3 862 irrelevant papers were manually excluded. Finally, 147 papers were included, see Fig. 1.

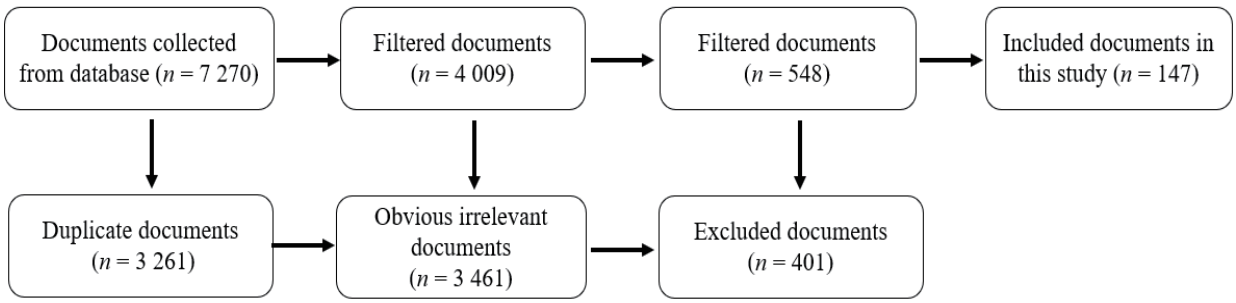


Fig. 1 Flow chart of literature screening

2.2 Basic information of patients

A total of 156 patients were enrolled in this study, including 87 males (55.77%) and 69 females (44.23%), with a ratio of 1.26 : 1. To clearly demonstrate the age of patients, eight age groups were divided and listed in Table 1. The analysis revealed that the number of patients aged 61−70 was the largest, accounting for 35.90%, while patients (> 60 years old) accounted for 53.85%, and patients (< 40 years old) accounted for 6.41%. The average age of the patients was 60, which showed that the drug was mostly used in the elderly.

Table 1 Sex and age distribution of the patients

Age	Male	Female	Total	Percent (%)
11−20	0	2	2	1.28
21−30	0	2	2	1.28
31−40	2	4	6	3.85
41−50	13	7	20	12.82
51−60	25	17	42	26.92
61−70	34	22	56	35.90
71−80	13	14	27	17.31
81−90	0	1	1	0.64
Total	87	69	156	100

2.3 Medication information

2.3.1 Cause of administration

Current approved indications for sunitinib include GIST, RCC, and pNET. The analysis revealed that 22 patients were off label uses, and the causes of administration included liver cancer, lung cancer and soft tissue sarcomas. Sunitinib was mainly used for the treatment of renal cell carcinoma, accounting for 66.03%, followed by gastrointestinal stromal tumors accounting for 16.03%. The specific distribution of medication reasons is shown in Fig. 2.

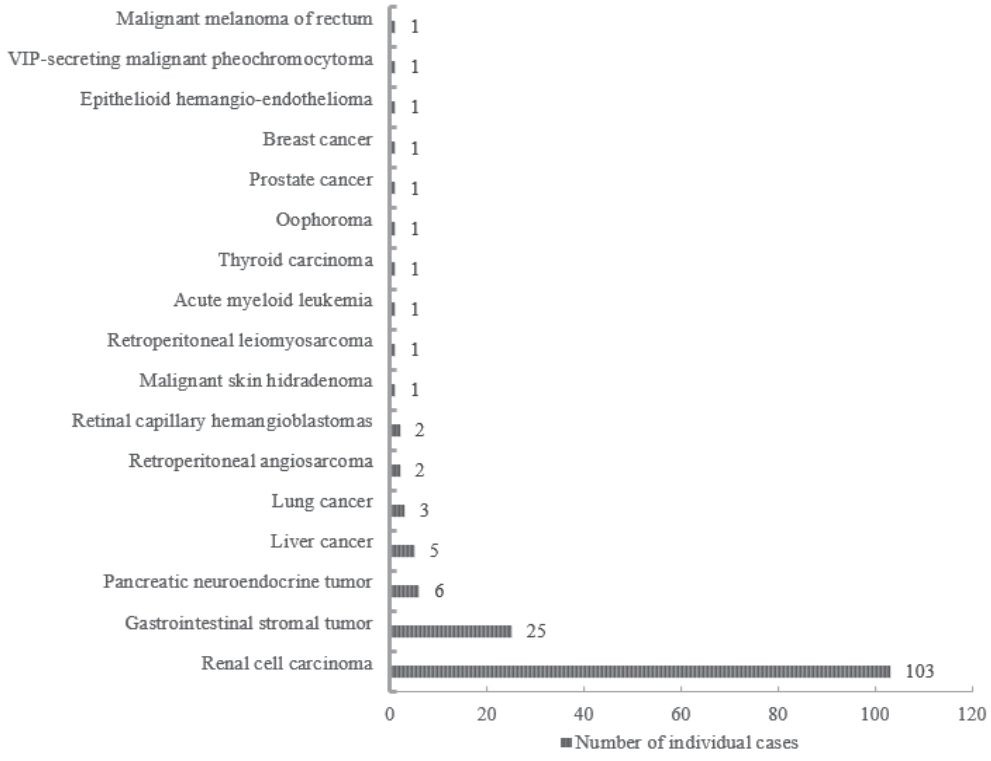


Fig. 2 Cause of administration

2.3.2 Dosage of administration

The recommended dosage of sunitinib for GIST and RCC is 50 mg/day, and the course of treatment is 4 weeks, then the drug is stopped for 2 weeks (Schedule 4/2). The recommended dosage for pNET is 37.5 mg/day continuously without a schedule off-treatment period [3]. The analysis revealed that the dosage of administration in 45 patients was less than the recommended dosage due to individual safety and tolerance. Three patients took an overdosage with an maximum dose of 400 mg/bid (400 mg twice daily). The specific dosage is shown in Table 2.

Table 2 Dose of administration

Dosage (mg/d)	Number of cases	Percent (%)
50	99	63.46
37.5	32	20.51
25	8	5.13
50, then reduced to 37.5	7	4.49
37.5, then reduced to 25	3	1.93
400	1	0.64
200	1	0.64
62.5	1	0.64
50	1	0.64
50, then reduced to 25	1	0.64
25	1	0.64
12.5	1	0.64
Total	156	100

2.4 ADR information

2.4.1 Occurrence time of ADR

Sunitinib was used for GIST and RCC for 4 weeks on and 2 weeks off (Schedule 4/2). But when it was used for pNET, there was no withdrawal. ADR related to sunitinib occurred on the day of medication to 1 445 days. Among them, the incidence of ADR was the highest after 31−180 days of administration, accounting for 28.98%, followed by 15−30 days of administration, accounting for 26.50%. The specific occurrence time of ADR is shown in Table 3.

Table 3 Occurrence time of ADR

Occurrence time of ADR (d)	Number of cases	Percent (%)
1−7	22	7.77
8−14	71	25.09
15−30	75	26.50
31−180	82	28.98
180−365	22	7.77
> 365	11	3.89
Total	283	100

2.4.2 Organ/system and clinical manifestation of ADR

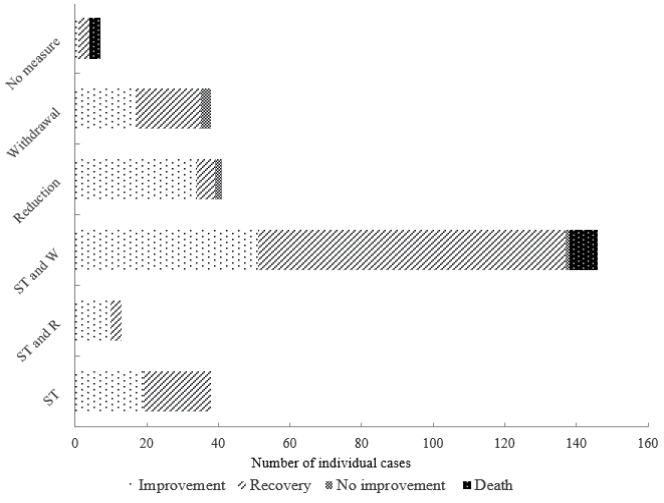
A total of 283 ADRs was included in this study. The analysis revealed that there were 21 organs/systems involved. Among them, blood and lymphatic disorders was the organ/system with the highest incidence, accounting for 17.67%. The main clinical manifestations were thrombocytopenia, leucopenia, neutropenia, and anemia, followed by gastrointestinal disorders and skin and subcutaneous tissue disorders, and its clinical manifestations were diarrhea and hand-foot syndrome (Table 4).

Table 4 Organ/system and clinical manifestation

Organ/system	Clinical manifestation	Number of cases	Percent (%)
Blood and lymphatic systems	Thrombocytopenia (20), leucopenia (9), neutropenia (4), thrombocytopenic purpura (4), hemoglobin decrease (3), haemolytic anaemia (3)	50	17.67
Gastrointestinal system	Diarrhea (10), acute pancreatitis (5), bowel perforation (4), pneumatosis cystoides intestinalis (3), nausea (3), oral mucositis (3)	44	15.55
Skin and subcutaneous tissue	Hand-foot syndrome (12), erythema (4), rash (2), decrustation (2), leukocytoclastic vasculitis (2)	30	10.60
Nervous system	Reversible posterior leukoencephalopathy syndrome (9), hyperammonemic encephalopathy (4), Guillain-Barre syndrome (4)	19	6.71
Endocrine system	Hypothyroidism (14), thyrotoxicosis (2)	19	6.71
Renal and urinary systems	Nephrotic syndrome (4), renal failure (4), allergic interstitial nephritis (2)	15	5.30
Hepatobiliary system	Acute cholecystitis (6), liver dysfunction (3), liver failure (2), liver dysfunction (2), jaundice (1)	14	4.95
Others	Hypertension (14), weakness (9), osteonecrosis of the jaw (7), fever (4), heart failure (4), hypoglycemia (4),	92	32.51
Total		283	100

2.4.3 Treatment measures and outcome of the ADR

Of the 283 ADRs in this study, patients in 159 cases stopped or reduced administration and took symptomatic treatment measures after the occurrence of the ADRs, and patients in 79 cases only stopped or reduced administration. Among them, patients in 6 cases did not improve after taking measures for adverse reactions, and patients in 3 cases died without taking any measures after the adverse reactions, as shown in Fig. 3.



Note: ST – Symptomatic treatment; ST and R – Symptomatic treatment and reduction; ST and W – Symptomatic treatment and withdrawal.

Fig. 3 Treatment measures and outcome of the ADR

2.4.4 ADR association evaluation

283 adverse events were scored according to the Naranjo Adverse Drug Reaction Probability Scale. The score was made by the author. If the authors did not evaluate the ADR, the score was performed by researchers according to the Nobel assessment scale. The results showed that the score for 132 adverse events was 3−4, indicating a possible association of the event with sunitinib. Meanwhile, the score for 150 adverse events was 5−8, indicating a probable association of the event with sunitinib. And the score for one adverse event was 9, indicating a highly probable association of the event with sunitinib, as shown in Fig. 4.

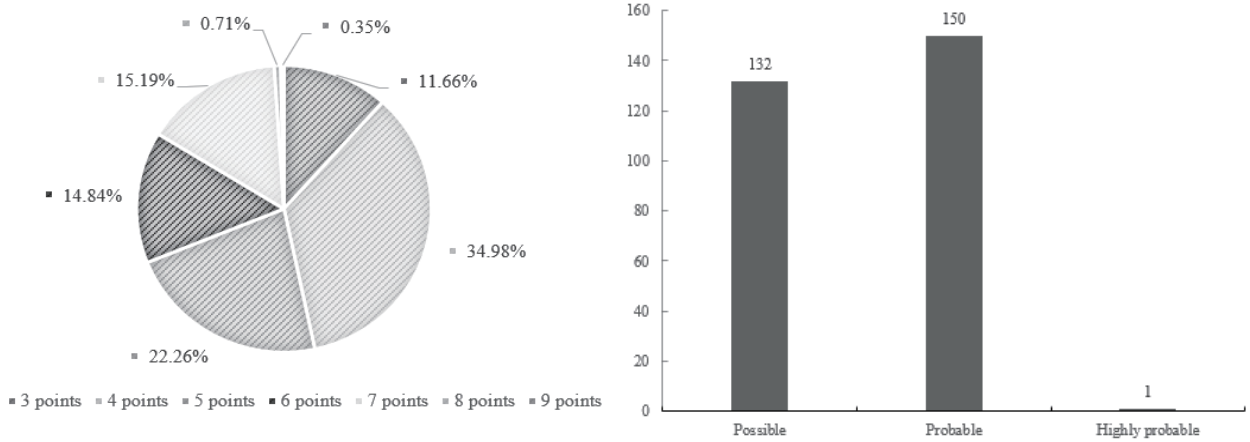


Fig. 4 ADR association evaluations

3 Discussion

In this study, case reports of sunitinib ADRs were screened. Then, basic information of patients, reasons for administration, dosage, occurrence time of ADRs, clinical manifestation of ADRs, treatment measures and outcome and association evaluation were studied. Specific analysis of important sections is detailed below.

3.1 Analysis of patient information

The gender difference in the patients was not significant. Patients (> 60 years old) accounted for 53.85%. Among them, the number of patients aged 61−70 was the largest, accounting for 35.90%, followed by patients aged 51−60, which may be due to the fact that GIST, RCC, and pNET often occur in middle and old aged patients [4]. Sunitinib and its main metabolites are mainly metabolized by the liver, 61% are excreted in feces and 16% by the kidney. However, liver and kidney function of the elderly has decreased, and gastrointestinal digestive and absorption functions are weak, resulting in slow metabolism of sunitinib. Therefore, the prolongation of drug half-life increased the incidence of ADRs.

3.2 Analysis of drug use

3.2.1 Reasons for administration

For the indications of sunitinib, 85.90% of patients took the drug according to the instructions. 22 patients were off label uses, and the reasons for administration included liver cancer, lung cancer and soft tissue sarcomas. Although some scholars or institutions have carried out clinical trials of sunitinib for the treatment of these diseases, it is not within the scope of indications for sunitinib labelling.

The results of a phase III trial of sunitinib versus sorafenib in advanced hepatocellular cancer revealed that patients' overall survival (OS) with sunitinib was significantly inferior to sorafenib, and sunitinib-treated patients reported more frequent and severe toxicity [5].

The results of a phase II trial evaluating the efficacy of sunitinib in small-cell lung cancer (SCLC) revealed that sunitinib was safe and effective in SCLC [6]. The results of a phase II study of sunitinib malate (SM) in subjects with soft tissue sarcomas revealed that sunitinib had therapeutic effects in liposarcoma, leiomyosarcoma, fibrosarcoma, and malignant fibrous histiocytoma [7]. So far, other studies have shown that sunitinib is active for thyroid, ovarian, breast, prostate, and melanoma, but the results need to be confirmed by more studies.

Therefore, sunitinib should not be recommended for the treatment of liver cancer due to the risk of severe toxicity. Sunitinib can be used to treat lung cancer, soft tissue sarcoma, thyroid cancer, breast cancer, prostate cancer under the premise of obtaining patient informed consent and there is no more other effective therapeutic schedule.

3.2.2 Dosage of administration

The analysis revealed that 68.59% of patients took the drug with the recommended dosage, and 45 patients were given less than the recommended dosage due to individual safety and tolerance. Three patients received an overdosage of 50 mg/bid, 200 mg/d, and 400 mg/bid respectively. However, the treatment of overdose with sunitinib is only a general supportive measure and there is no specific antidote. Therefore, the maximum dosage recommended by the instructions should be avoided in clinical practice.

In this study, some RCC patients used a 2/1 scheme (2 weeks on, 1 week off). As the first-line standard treatment regimen for patients with mRCC, with the recommended dose of sunitinib is 50 mg/d, a 4/2 scheme (4 weeks on, 2 weeks off). According to the published results, a 2/1 scheme showed comparable efficacy and reduced incidence of adverse effects compared with the 4/2 scheme for mRCC patients. However, there are some limitations in the number of patients studied, which needs to be further confirmed with more large sample randomized controlled studies.

3.3 ADR analysis

3.3.1 Occurrence time of ADRs

ADRs related to sunitinib can occur on the day of medication to 1 445 days, which means ADRs may occur immediately after medication, or there will be delay. Among them, the incidence of ADRs is the highest after 31−180 days of administration, accounting for 28.98%, followed by 15−30 days of administration, accounting for 26.50%. Therefore, more attention should be paid to the patients taking sunitinib after a week, and corresponding measures should be taken in time for any ADRs to ensure the safety of patients.

3.3.2 Organ/system of ADR analysis

(1) Blood and lymphatic disorders. Among the 283 ADRs in this study, blood and lymphatic disorders was the organs/systems with the highest incidence. The main clinical manifestations were thrombocytopenia, leukopenia, neutropenia, thrombocytopenic purpura and anemia. Thrombocytopenia was one of the common ADRs of sunitinib, which had been reported in multiple literature. The cause of thrombocytopenia related to sunitinib was mainly myelosuppression. Thrombocytopenia was also reported to result from thrombotic microangiopathy. In addition, sunitinib may cause immune-mediated thrombocytopenia [8]. The decrease in white blood cells, neutrophils, and hemoglobin caused by sunitinib was mainly due to myelosuppression. Sunitinib-associated anemia had been hypothesized to occur via off-target inhibition of the stem cell growth factor c-Kit, leading to impaired erythrocyte maturation [9].

The blood and lymphatic disorders in this study relieved by withdrawal or symptomatic treatment, except for one patient who developed thrombocytopenia did not improve after reduced administration. Besides, two patients died of thrombocytopenia and neutropenia. Therefore, routine blood tests should be conducted regularly during

prolonged administration to prevent the above adverse events.

(2) Gastrointestinal disorders. The main clinical manifestations of gastrointestinal disorders were diarrhea, acute pancreatitis and bowel perforation, which also included other ADRs such as nausea, vomiting, mucositis, and dyspepsia. The mechanism of acute pancreatitis was unclear. It may include pancreatic ischemia associated with the antiangiogenic effect and a reduction in the protective effect of VEGF as well as the platelet-derived growth factor, which would increase the severity of pancreatitis [10, 11].

One of the patients who developed necrotizing pancreatitis during treatment with sunitinib died 4 weeks after admission. Sunitinib is likely to generate rapid tumor degeneration, as inhibition of VEGF significantly reduces capillary density within the small intestinal villi, leading to bowel perforation [12]. Therefore, the seriousness of such ADRs cannot be underestimated. If the patient has severe gastrointestinal symptoms during the administration, the drug should be stopped immediately to reduce the occurrence of serious ADRs.

(3) Skin and subcutaneous tissue disorders. The main clinical manifestations of ADRs involving skin and subcutaneous tissue disorders were hand-foot syndrome, erythema, rash, and decrustation. Hand-foot syndrome and rash were common ADRs of sunitinib. The mechanism of hand and foot syndrome is unclear, and it is believed that sunitinib targets receptors of VEGF and PDGF and damages capillaries, and the damaged vessels would suffer mechanical damage again during daily activities, resulting in hand and foot syndrome. Moreover, sunitinib may also cause hand-foot syndrome by suppressing PDGFR and c-Kit expressed in the sweat duct epithelium, thereby causing changes in the sweat duct pathophysiology [13].

This study did not involve life-threatening skin and subcutaneous tissue disorders, but such ADRs may have a negative impact on patients' feelings. Therefore, during clinical medication, doctors should pay attention to patients' skin changes, remind patients to strengthen skin care, and medical treatment can be applied if necessary.

(4) Nervous system disorders. Among the ADRs involving nervous system disorders in this study, 9 patients developed reversible posterior leukoencephalopathy syndrome (RPLS), which was improved or recovered after stopping drug use and symptomatic treatment. The pathogenesis of RPLS is not entirely clear but it appears to have been related to disordered cerebral auto regulation and endothelial dysfunction [14]. Several other mechanisms have also been proposed. Whatever the pathogenesis of RPLS is, it should be kept in mind that early diagnosis and timely treatment are the key to saving patients' lives. 4 cases had hyperammonemic encephalopathy (HE) in this study. In the absence of obvious liver disease, the patient had a sudden change in mental status with markedly increase of serum ammonia levels [15]. HE induced by sunitinib may be related to its anti-angiogenic effect. There were 4 patients who developed Guillain-Barre syndrome (GBS). GBS is an autoimmune-mediated disease. The mechanism may be related to the sunitinib-mediated inhibition of VEGFRs causing a corresponding increase in VEGF levels, which increases the numbers of B lymphocytes and immature myeloid cells resulting in GBS [16]. ADRs involving nervous system disorders are rare and can have a serious impact on patients' daily lives. Therefore, during clinical medication, doctors should pay attention to such rare ADRs.

(5) Endocrine disorders. In the ADRs involving the endocrine disorders, 14 patients suffered from hypothyroidism, 11 patients eventually were improved or recovered after stopping drug use and (or) symptomatic treatment, and one patient died. Hypothyroidism is one of the common adverse effects in patients treated with sunitinib. The potential mechanisms by which sunitinib might induce hypothyroidism include blockade of iodine uptake, destructive thyroiditis, and inhibition of peroxidase activity [17]. Regardless of the mechanism, regular monitoring of patients' thyroid function is essential during sunitinib treatment.

(6) Renal and hepatobiliary disorders. The main clinical manifestations of renal and urinary disorders were nephrotic syndrome and renal failure. VEGF

is important for maintaining normal glomerular endothelial function. However, sunitinib has anti-VEGFR effects, so patients having sunitinib therapy can ultimately develop proteinuria with nephrotic change and potentially impaired renal function [18]. Therefore, serum creatinine and proteinuria should be monitored immediately after sunitinib therapy, which can diagnose kidney disease early to avoid renal damage.

The main clinical manifestations of hepatobiliary disorders were acute cholecystitis, liver dysfunction, and liver failure. Although the mechanism of cholecystitis is uncertain, it is reported that sunitinib may play a role in the development of cholecystitis by inducing local endothelial injury and gallbladder ischemia [19]. Sunitinib is mainly metabolized by cytochrome CYP3A4. The half-life of sunitinib and its major metabolite are 40−60 h and 80−110 h, respectively. The accumulation of sunitinib and its major metabolite may contribute to hepatic toxicity. Therefore, liver function should be monitored regularly during drug use. When ADRs occur, targeted measures should be taken in time, and stopping drug use is required if necessary.

(7) Musculoskeletal and connective tissue disorders (osteonecrosis of the jaw). Notably, seven patients developed osteonecrosis of the jaw (ONJ) after taking sunitinib, among which, three patients were under a medication with both sunitinib and zoledronic acid. It assumes as a bisphosphonate (BP)-related adverse effect, and sunitinib may increase the risk of BP-induced ONJ. Sunitinib, as an anti-angiogenic drug, may induce ONJ by causing mucosal breakdown, angiogenesis disturbance and bone remodeling, especially in patients receiving BP therapy [20]. Therefore, we should be aware of this potential risk during clinical medication, regularly monitor the oral condition, and maintain oral hygiene of patients to minimize the risk of ONJ.

(8) Other disorders. Sunitinib-induced ADRs involve multiple organs/systems. In addition to the above disorders, sunitinib can also cause ADRs in other organs/systems, such as general disorders and administration site conditions (weakness, fever), infections and infestations (peritonitis, pyoderma gangrenosum), respiratory, thoracic, and mediastinal disorders (epistaxis, dyspnea, interstitial pneumonia), abnormal inspection indicators (elevated thyroid stimulating hormone levels, elevated liver enzymes, elevated serum creatinine, elevated transaminases) and psychiatric disorders, etc. Therefore, sunitinib can cause ADR in multiple organs/systems. During the clinical medication period, much attention should be paid to the health status of patients to detect and deal with ADRs in time.

4 Conclusion

Sunitinib is widely used in treating gastrointestinal stromal tumors, renal cell carcinoma, and pancreatic neuroendocrine tumors. At the same time, sunitinib can induce ADRs such as nausea, rash, hand-foot syndrome, hypothyroidism, thrombocytopenia and anemia, involving multiple organs/systems such as gastrointestinal disorders, skin and subcutaneous tissue disorders, blood and lymphatic disorders. Multiple ADRs related to sunitinib were severe, which may lead to death. Therefore, patient's condition should be monitored regularly during administration, and the administration should be reduced or stopped in time when ADRs occur, which can ensure patient safety.

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