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ORIGINAL ARTICLE

Adverse reactions of sorafenib, sunitinib, and imatinib in treating digestive system tumors

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Abstract

Background: This study was conducted to assess the adverse reactions caused by multi-target tyrosine kinase inhibitor treatment of gastrointestinal tumors.

Methods: We carried out a retrospective study of drug-related adverse reactions in 115 patients who were treated with sorafenib, sunitinib, and imatinib for primary hepatocellular carcinoma or gastrointestinal stromal tumors from October 2003 to March 2012 at the Peking University International Hospital.

Results: The total incidence of adverse reactions of sorafenib, sunitinib, and imatinib in patients with hepatocellular carcinoma and gastrointestinal stromal tumors was > 80%. The main adverse reactions of sorafenib were hypertension in 38 patients (33.3%) and diarrhea in 28 patients (24.4%). Sunitinib was associated with higher incidence and greater grade 3–4 toxicity. The common toxicities were skin color changes in 105 patients (90.9%), hand-foot skin reactions in 65 patients (54.6%), and leukopenia (63.6%), hypertension (22.7%), proteinuria (22.7%), liver function impairment (22.7%), and hypomagnesemia (27.3%). While imatinib was well tolerated, it was associated with the highest number of adverse reactions, including skin color change (55.6%) and edema (38.9%). Hypophosphatemia (4.4%) and hoarseness (2.2%) only occurred in the sorafenib treatment group.

Conclusions: The adverse reactions of multi-target tyrosine kinase inhibitor treatments are generally mild to moderate, and most patients can tolerate these without the need for further intervention. Some serious adverse reactions may be alleviated by discontinuing the drugs or by administering symptomatic treatment.

Introduction

Progress of tyrosine kinase-targeted therapeutic drugs has been steady in recent years. Currently, the multi-target tyrosine kinase inhibitors (TKIs) in clinical use include sorafenib, sunitinib, imatinib, erlotinib, and lapatinib.[1,2] Sorafenib prevents tumor growth by inhibiting the RAF/MEK/ERK signaling pathway. It also affects VEGFR and PDGFR by controlling tumor angiogenesis and, indirectly, tumor proliferation.[2] Clinical evidence has shown that sorafenib improves survival in primary hepatocellular carcinoma (HCC) patients by 10.7 months, and currently this drug is the standard treatment for primary HCC with acceptable toxicity.[3] Sunitinib is an oral multi-target TKI that inhibits multiple tyrosine kinase receptors associated with tumor growth and angiogenesis, such as VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα, PDGFRβ, and stem cell growth factor receptor (KIT). Sunitinib has been reported to prolong tumor progression (TTP) up to 27.3 weeks (vs. placebo 6.4 weeks) in patients that experience imatinib treatment failure.[4] Imatinib is a small molecule TKI for the treatment of gastrointestinal stromal tumors (GISTs), which binds to and inhibits the catalytic activity of receptor tyrosine kinases such as KIT, Bcr-Abl, α-PDGFR, and β-PDGFR, leading to anti-proliferative and apoptosis-inducing effects. Clinical studies have shown that adjuvant therapy with imatinib significantly improved survival (82%) and survival without recurrence in GIST patients.[5,6] Therefore, imatinib has become the standard first-line treatment for GIST,

Table 1 General characteristics of the 115 patients enrolled in the study

Characteristics	Imatinib	Sunitinib	Sunitinib	Sorafenib
Types	GIST	GIST	HCC	HCC
Case number	36	22	12	45
Age	56 (36–78)	52 (36–74)	57 (47–67)	57 (27–76)
Gender (%)				
Male	23 (63.9)	11 (50)	9 (75)	41 (91.1)
Female	13 (36.1)	11 (50)	3 (25)	4 (8.9)
Medication time	10.5 (1–81)	12.8 (2–24)	3.7 (0.5–17)	3 (0.6–21)

GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma.

both as postoperative adjuvant therapy and as treatment for recurrent metastases.[7]

The adverse reactions resulting from molecular targeted therapy differ from those of traditional chemotherapy. In the first prospective randomized phase 3 study of sequential TKI therapy, Eichelberg *et al*. reported the efficacy and safety in patients with metastatic renal cell carcinoma who had undergone sequential treatment of sorafenib followed by sunitinib (So-Su) versus sunitinib followed by sorafenib (Su-So).[8] The most common treatment-emergent adverse drug reactions (ADRs) were diarrhea, hand-foot skin reactions, hypertension, and fatigue for first-line sorafenib; and diarrhea, fatigue, hypertension, and nausea for first-line sunitinib. GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract. Imatinib followed by sunitinib and regorafenib is the standard sequence of treatment for advanced disease. However, there is insufficient data regarding ADRs in Chinese GIST and HCC patients treated with TKIs. Further studies may provide a reliable reference for physicians administering targeted drug treatment. In this study, the primary endpoint was improvement in progression-free survival (PFS) after the administration of So-Su versus Su-So, assessed from randomization to progression or death during second-line therapy. Secondary endpoints included overall survival (OS) and safety. This report summarizes data regarding ADRs in primary HCC and GIST patients treated with TKIs.

Methods

A total of 115 patients with GIST and HCC who underwent TKI therapy from October 2003 to March 2012 were enrolled. Treatment modalities were as follows: imatinib: GIST first-line therapy, 400 mg orally, 1/day; sunitinib: unresectable GIST after imatinib treatment failure or intolerable recurrent metastases, 50 mg orally, 1/day for four weeks, with a drug holiday of two weeks, or 37.5 mg orally, 1/day continuously; and sorafenib: primary HCC, at 0.4 g orally, 2/day. If toxicity occurred during the treatment process, the dosage was adjusted appropriately according to the degree of ADR. Adverse reactions were evaluated according to National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0 using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Comparison between the two groups was based on χ^2 or Fisher's exact tests. Statistical significance was designated as $P < 0.05$. The Ethics Committee of the International Hospital of Peking University approved this study, and all patients signed informed consent before treatment.

Results

Patient characteristics

A total of 115 patients were enrolled, including 36 GIST cases treated with imatinib, 34 HCC and GIST cases treated with sunitinib, and 45 HCC cases treated with sorafenib. The age of the patients ranged from 26 to 78 years (median 55). The average duration of treatment was three months (from March to May 2005 in most cases) (Table 1).

Adverse reactions of molecular targeted therapy according to disease

Hepatocellular carcinoma

In HCC patients treated with sorafenib ($n = 45$) or sunitinib, incidences of ADRs were 86.6% and 83.3%, respectively, and were primarily mild to moderate. The common ADRs in the two groups were hand-foot skin reactions, hypertension, diarrhea, rash, and liver function impairment. Hand-foot skin reactions (53.3% vs. 16.7%; $P = 0.04$) and diarrhea (24.4% vs. 16.7%; $P = 0.03$) were more common in the sorafenib than the sunitinib group, respectively. By contrast, incidences of nausea and vomiting (33.3% vs. 4.4%; $P = 0.02$), yellowing of the skin (50% vs. 0%; $P < 0.01$), and myelosuppression (58.3% vs. 22.2%; $P = 0.02$) were significantly higher in the sorafenib than the sunitinib group, respectively. In the sunitinib group, there was a higher proportion of ≥ grade 3 adverse events (AEs). One patient died of drug-related cerebral

Table 2 Adverse reactions after administration of molecular targeted therapy

	All adverse effects			¾ adverse effects		
Reaction	Sunitinib *N* = 12	Sorafenib *N* = 45	*P*	Sunitinib *N* = 12	Sorafenib *N* = 45	*P*
Fatigue	4 (33.3)	11 (24.4)	0.80	0	5 (11.1)	0.57
Hand and foot skin reactions	2 (16.7)	24 (53.3)	0.04	0	4 (8.9)	0.57
Hypertension	3 (25.0)	15 (33.3)	0.84	0	2 (4.4)	1.00
Rash or scaling	2 (16.7)	5 (11.1)	0.98	0	2 (4.4)	1.00
Loss of appetite	1 (8.3)	4 (8.9)	1.00	1 (8.3)	1 (2.2)	0.89
Nausea, vomiting	4 (33.3)	2 (4.4)	0.02	1 (8.3)	0	0.21
Diarrhea	2 (16.7)	11 (24.4)	0.03	0	1 (2.2)	0.40
Liver damage	4 (33.3)	2 (4.4)	0.85	2 (16.7)	1 (2.2)	0.93
Thrombocytopenia	7 (58.3)	10 (22.2)	0.02	2 (16.7)	4 (8.9)	0.80
Leukopenia	7 (58.3)	3 (6.6)	< 0.001	3 (25.0)	1 (2.2)	0.25
Granulocytopenia	9 (75)	3 (6.6)	< 0.001	3 (25.0)	0	0.01
Anemia	2 (16.7)	0	0.21	0	0	—
Skin yellow dye	6 (50)	0	< 0.001	0	0	—
Taste change	2 (16.7)	0	0.21	0	0	—
Bleeding	1 (8.3)	0	0.21	1 (8.3)	0	0.21
Stomach ache	0	4 (8.9)	0.57	0	0	—
Loss of hair	0	4 (8.9)	0.57	0	0	—
Hoarse voice	0	2 (4.4)	1.00	0	0	—
Hypophosphatemia	0	1 (2.2)	1.00	0	0	—
Proteinuria	0	1 (2.2)	1.00	0	0	—
Fever	0	1 (2.2)	1.00	0	0	—

hemorrhage during sunitinib treatment. Yellowing of the skin (50%) and taste changes (16.7%) only occurred in the sunitinib treatment group, while hypophosphatemia (4.4%) and hoarseness (2.2%) only occurred in the sorafenib treatment group. Other ADRs are shown in Table 2.

Gastrointestinal stromal tumors

There was a total 58 patients with GISTs, including 36 patients treated with imatinib and 22 treated with sunitinib. Both drugs were well tolerated with mostly mild to moderate ADRs, and no serious ADRs occurred. The most common ADRs in the imatinib treatment group were: skin color change (55.6%), fatigue (16.7%), and edema (38.9%), with a low incidence of other AEs (Table 3). Compared to imatinib, there were more AEs in the sunitinib group, and the most common were: skin color change (90.9%), hand-foot skin reactions (54.6%), and leukopenia (63.6%). The incidence of other AEs was also higher in the sunitinib compared to the imatinib group: hypertension (22.7% vs. 0%; $P = 0.01$), hypomagnesemia (27.3% vs. 0%; $P < 0.01$), and proteinuria (22.7% vs. 0%; $P < 0.001$), respectively. These AEs were generally tolerable, with the dose in two patients reduced because of recurrence of grade 3 hand-foot skin reactions and thrombocytopenia. Hypothyroidism was only associated with sunitinib treatment, at an incidence of 27.3% (Table 3).

Discussion

Differences in adverse reactions between targeted drug and cytotoxic chemotherapeutic treatments

With the wide clinical application of molecular targeted therapies, adverse reactions associated with such therapies have been the subject of recent research. In general, ADRs have been reported to be mild and the tolerable, and with characteristics different to those associated with chemotherapy.[9,10] Adverse reactions resulting from traditional chemotherapy usually manifest as nausea, vomiting, loss of appetite, diarrhea and other digestive system reactions, leukopenia, neutropenia, anemia, thrombocytopenia and other myelosuppressive reactions, oral mucositis, fatigue, hair loss, and hand-foot and other skin changes. These adverse reactions are reported to occur in targeted therapy, but at significantly lower intensity and can be alleviated by continued treatment.[2,6,11–14] Rare adverse reactions resulting from chemotherapy, such as skin color changes, rash, hypertension, water and sodium retention, and bleeding, are also known to occur in targeted therapy, but at higher incidence rates than with chemotherapy.[15,16]

Skin color changes to the hands and feet occurring as a result of targeted drug administration (such as sorafenib and sunitinib), referred to as the hand-foot skin reaction (HFSR), also occur after the administration of

Table 3 Adverse reactions in gastrointestinal stromal tumor patients after administration of molecular targeted therapy

	All adverse effects			¾ adverse effects		
Reaction	Imatinib *N* = 36	Sunitinib *N* = 22	*P*	Imatinib *N* = 36	Sunitinib *N* = 22	*P*
Fatigue	6 (16.7)	9 (40.9)	0.41	0	0	—
Edema	14 (38.9)	6 (27.3)	0.37	1 (2.8)	0	1.00
Rash	3 (8.3)	4 (18.2)	0.48	1 (2.8)	0	1.00
Hair loss	0	1 (4.6)	0.38	0	0	—
Hand and foot skin reactions	0	12 (54.6)	<0.001	0	3 (13.6)	0.05
Skin color change	20 (55.6)	20 (90.9)	0.01	0	0	—
Hair pigmentation	1 (2.8)	7 (31.8)	0.01	0	0	—
Appetite loss	4 (11.1)	3 (13.6)	1.00	0	0	—
Nausea, vomiting	1 (2.8)	0	1.00	0	0	—
Taste diminishes	1 (2.8)	2 (9.1)	0.66	0	0	—
Stomach ache	1 (2.8)	0	1.00	0	0	—
Diarrhea	2 (5.6)	4 (18.2)	0.28	0	1 (4.6)	0.38
Leukopenia	4 (11.1)	14 (63.6)	<0.001	0	2 (9.1)	0.62
Thrombocytopenia	4 (11.1)	7 (31.8)	0.11	1 (2.8)	1 (4.6)	1.00
Anemia	0	6 (27.3)	0.34	0	1 (4.6)	0.38
Headache	1 (2.8)	0	1.00	0	0	—
Thyroid function reduction	0	6 (27.3)	0.00	0	0	—
Bleeding	0	3 (13.6)	0.05	0	0	—
Hypertension	0	5 (22.7)	0.01	0	0	—
Liver damage	0	5 (22.7)	0.01	0	1 (4.6)	0.38
Pancreas damage	0	1 (4.6)	0.38	0	0	—
Proteinuria	0	5 (22.7)	0.01	0	1 (4.6)	0.38
Hypomagnesemia	0	6 (27.3)	0.00	0	0	—
Hypokalemia	0	1 (4.6)	0.38	0	0	—

chemotherapy drugs (such as capecitabine, fluorouracil, and doxorubicin), known as the "hand-foot syndrome" (HFS).[3,17,18] HFSR and HFS may occur in the palms and soles of the feet, accompanied by tenderness, and alleviation of symptoms occurs after drug withdrawal.[14,19,20] HFSR manifests mainly as excessive keratinization around the erythema, while HFS shows symmetrical sensory abnormalities, erythema, and edema. These syndromes also show histologically distinct features.[2,21] Although the mechanisms are unclear, both may be associated with the simultaneous inhibition of the PDGFR and VEGFR pathways and a decline in the capacity of the skin to repair.

Both targeted drugs and chemotherapy may lead to bone marrow suppression and hepatotoxicity, although a distinct feature of chemotherapy is that bone marrow suppression usually occurs in the first five to seven days of treatment, and reaches a peak at 10–14 days. Leukopenia, neutropenia (> grade 3), and mild to moderate thrombocytopenia and anemia are common features of both syndromes, and require a subcutaneous injection of granulocyte colony-stimulating factor to support treatment. A higher incidence of bone marrow suppression-related inhibition of the *c-Kit* gene has been associated with sunitinib, sorafenib, and other multi-target drugs. Because the c-Kit protein is widely expressed in hematopoietic progenitor cells, it plays an important role in hematopoiesis. Bone marrow suppression higher than grade 3 rarely develops after the administration of targeted drugs, but mild leukopenia, neutropenia, and thrombocytopenia occur and may be alleviated by oral medication. Individual patients with repeat grade 3 bone marrow suppression may require cessation of treatment or dosage reduction to induce tolerance. Compared with sorafenib, sunitinib treatment is reported to show a higher incidence of liver damage (22.7%–33.3% vs. 4.4%, respectively). GIST patients with poor liver function reserve need to be closely monitored while on sunitinib treatment. Sorafenib is recommended for HCC patients with A-grade liver function Child–Pugh scores, although caution is recommended for use in B-level patients.[22]

Hypertension is also a common ADR associated with antiangiogenic drugs, and in this study the incidence was 22–33.3%. TKI-induced hypertension may be associated with impaired angiogenesis. Targeted drugs, such as sorafenib and sunitinib, may damage endothelial cell function, increase VEGF levels, and change nitric oxide metabolism; on the other hand, the decrease in microvascular density and blood vessel surface area increases peripheral vascular resistance. Hypertension responds well to the angiotensin-converting enzyme inhibitor (ACEI) class of

antihypertensive drugs. Therefore, blood pressure should be monitored regularly during molecular targeted therapy, and ACEIs and non-dihydropyridine calcium antagonists should be administered as needed.

Hypothyroidism only occurred in patients administered sunitinib, probably because it promotes thyroid follicular apoptosis and thyroid inflammation. The occurrence of this ADR correlated positively with medication duration. The incidence of thyroid dysfunction in the sunitinib group was 27.3%, and the earliest occurrence, detected during routine thyroid monitoring, was within the first 10 months of treatment. Thyroid dysfunction was treated with thyroid tablets, which did not interfere with sunitinib treatment. Therefore, baseline thyroid function should be recorded in GIST patients before sunitinib treatment is administered, followed by thyroid stimulating hormone examination every two to three months post-treatment.

Similarities and differences in adverse reactions caused by different targeted drugs

In this study, adverse reactions resulting from sorafenib, imatinib, and sunitinib administration included weakness, diarrhea, hypertension, hand-foot skin reactions, rash, and other ADRs consistent with those reported in the literature.[7,12,23,24] The type and extent of ADRs among several types of targeted drugs were different. Adverse reactions experienced after sunitinib administration occurred more frequently and at greater intensity in both HCC and GIST patients, possibly because sunitinib inhibits a large number of signaling pathways.[7] However, the incidence and severity of ADRs in HCC and GIST patients were different, which may be related to the mildness of disease, and longer disease and sunitinib treatment duration in GISTs.[7,23]

Targeted drugs also cause hepatorenal toxicity, as indicated by a 40–60% increase in AST/ALT during sunitinib treatment; a black box warning of fatal hepatic failure has been mandated by the United States Food and Drug Administration (FDA) in this regard. The reported incidence of liver damage after imatinib administration is not high (6–12%), but liver failure has been reported in 3–6% of patients with grade 3–4 liver damage. As a result, the FDA has recommended monitoring liver function during treatment. Sorafenib-induced liver damage is reported in 21–25% of cases, but liver failure has not yet been reported; therefore, relevant FDA recommendations do not include monitoring of liver function. The incidence of sunitinib-related liver function abnormalities in this study was 22.7–33.3%, which is slightly lower than that reported in the literature;[25] 4.4% of patients undergoing sorafenib treatment were reported to show liver damage, while 36 patients undergoing imatinib treatment did not show liver damage, consistent with incidence rates reported in the literature. Therefore, GIST patients with poor liver function reserve should be closely monitored for liver function during sunitinib treatment. Sorafenib is recommended for HCC patients with A-grade liver function Child–Pugh scores, although caution is recommended for its use in B-level patients.

In summary, sorafenib, sunitinib, and imatinib have anti-tumor efficacy in HCC and GIST, and are associated with specific adverse reactions, such as hand-foot skin reactions and hypertension. Generally, drug tolerability was acceptable, and the incidence of grade 3 or higher serious ADRs in this study was low. Appropriate prevention and treatment measures may maximize the benefits of molecular targeted therapy. Rare serious adverse reactions, such as cardiotoxicity and bleeding, should be taken seriously.

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Disclosure

No authors report any conflict of interest.

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