REVIEW ARTICLE

Drug Safety 2009; 32 (9): 717-734
0114-5916/09/0009-0717/$49.95/0

Benefit-Risk Assessment of Sunitinib in Gastrointestinal Stromal Tumours and Renal Cancer

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Abstract

Sunitinib is a novel, oral, multi-targeted tyrosine kinase inhibitor with antiproliferative effects against cancer cells and antiangiogenic properties. Sunitinib was recently approved for the first-line treatment of patients with advanced renal cell carcinoma (RCC) and for the treatment of patients with gastrointestinal stromal tumours (GIST) after disease progression or intolerance to imatinib therapy. The main purpose of this benefit-risk assessment

is to review data on sunitinib efficacy along with its toxicity in patients with GIST and RCC. Sunitinib demonstrates a high level of efficacy with acceptable tolerability using either the 50 mg daily oral dosing for 4 weeks every 6 weeks or a continuous daily administration schedule at a lower dose. Hypertension and asthenia appear to be the most common adverse effects with sunitinib. Diarrhoea, anorexia, disgeusia, stomatitis and skin toxicity are other clinically relevant toxicities. Fatigue may, at least in part, be related to the development of hypothyroidism during sunitinib therapy. Skin toxicity consists of bullous lesion in the soles and palms that may require treatment discontinuation for a few days and/or dose reduction. Thyroid hormone levels should be monitored during treatment with sunitinib, with the occurrence of clinical signs of hypothyroidism needing treatment with levothyroxine sodium. Hypertension usually requires standard antihypertensive therapy and treatment discontinuation is less frequently necessary. Mild neutropenia and thrombocytopenia usually require no intervention. A decrease in left ventricular ejection fraction is a rare but potentially life-threatening complication. Although usually well tolerated, sunitinib needs to be administered cautiously with medical follow-up in patients with cancer to prevent, avoid and treat adverse effects in order to improve patient compliance. Its established antitumor activity requires attempting to maintain the highest tolerable dose in individual patients. Current oral formulations allow physicians to modulate dosages (between 25 and 50 mg/day) and/or schedules (4 weeks on, 2 weeks off or continuous administration) to optimize the benefit-risk profile of sunitinib in individual patients.

Tyrosine kinase inhibitors currently approved for use in patients with solid tumours include imatinib, erlotinib, gefitinib, sorafenib and sunitinib. These agents compete with adenosine triphosphate for binding within the intracellular domain of various wild-type and/or mutated receptor tyrosine kinases. Kinase inhibitors represent a new paradigm in anticancer therapy, and the focus of this review is sunitinib, a multi-targeted tyrosine kinase inhibitor with potent antiangiogenic effects and direct antitumor activities. 'Multi-targeted' agents (e.g. imatinib, sorafenib and sunitinib) that block several kinases were aimed to achieve a broader spectrum of activity than single-target inhibitors (e.g. erlotinib and gefitinib) and conventional cytotoxic chemotherapy.[1] The efficacy of sunitinib has been demonstrated in patients with advanced renal cell carcinoma (RCC) and in gastrointestinal stromal tumours (GIST) refractory or intolerant to imatinib.[2,3] On the basis of these results, sunitinib received US FDA approval in January 2006 and EU approval in January 2007 for these indications.[4] Furthermore, considering its mechanism of action, sunitinib may not be restricted to its current approved indications but may also further benefit patients with a broad number of tumour types. This review focuses on the efficacy and safety data of sunitinib in GIST and RCC and is aimed at balancing the benefits and risks for physicians involved in the treatment of patients with such diseases.

1. Mechanism of Action

Sunitinib is an oral oxindol, multi-targeted tyrosine kinase inhibitor, which demonstrates both antiangiogenic and antitumour activities due to selective inhibition of vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet-derived growth factor receptor (PDGFR)-α and -β, KIT, FMS-like tyrosine kinase 3 (FLT3), RET and colony stimulating factor 1 receptor (CSF-1R). In biochemical and cell-based assays, sunitinib was found to be a potent inhibitor of VEGFR-2

and PDGFR-β.[5] The inhibition of other tyrosine kinases by sunitinib was predicted to benefit specific types of cancer patients. For example, KIT is activated and/or mutated in GIST,[6] FLT3 may be mutated in acute myeloid leukaemia,[7] RET is often mutated in neuro-endocrine tumours[8] and CSF-1R is dysregulated in metastatic breast cancer.[9] *In vitro* metabolism studies demonstrated that sunitinib was primarily metabolized by cytochrome P450 (CYP) 3A4, resulting in formation of a major, pharmacologically active *N*-desethyl metabolite, SU012662. This metabolite was shown to be equipotent to the parent compound in biochemical tyrosine kinase and cellular proliferation assays, acting toward VEGFR, PDGFR and KIT.[10] Pharmacokinetic data indicated good oral absorption, no 'food effect' and a long half-life (>40 hours) allowing administration of one single daily dose for this agent.[11] The approved dosing regimen for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST is 50 mg/day for 4 weeks followed by 2 weeks off the treatment, given in repeated 6-week cycles (4/2 schedule). A continuous daily dosing regimen of sunitinib at 37.5 mg/day is also frequently used in patients with RCC and GIST.[12-15]

2. Toxicology Data

In vitro, sunitinib inhibited the growth of cell lines driven by vascular endothelial growth factor (VEGF), stem cell factor and platelet-derived growth factor (PDGF), and induced apoptosis of human umbilical vein endothelial cells at concentrations >50 ng/mL, which was selected to be the target concentration for clinical applications.[15] Pharmacokinetic data from animal studies consistently showed that plasma concentrations of sunitinib plus the active metabolite (SU012662) in the range 50–100 ng/mL were capable of inhibiting phosphorylation of PDGFR-β and VEGFR-2, thus inhibiting cell proliferation.[16-19] Based on the promising preclinical antitumor activity, safety data in animals and early results in phase I clinical studies in patients with acute myeloid leukaemia and solid tumours, the recommended oral dose of sunitinib was 50 mg daily for 4 weeks followed by 2 weeks off.

In a phase I study, 28 patients received dosages ranging from 15 to 59 mg/m^2 (ranging from 50 mg every other day to 150 mg/day).[20] Dose-limiting toxicities as measured by common toxicity criteria (CTC) and reported at the maximum tolerated doses of >42 mg/m^2 (>75 mg/day) were fully reversible grade 3 fatigue, grade 3 hypertension and grade 2 bullous skin toxicity. Therefore, the dose was recommended to be 30 mg/m^2 (50 mg/day). At this dose, toxicities were sore mouth, oedema and thrombocytopenia. Hair discoloration and yellow coloration of the skin were observed at doses >30 mg/m^2 (50 mg/day). Pharmacokinetics indicate that potentially active target plasma concentrations >50 ng/mL can be achieved with moderate inter-patient variability and a long half-life compatible with a single daily dosing.

Sunitinib has demonstrated time-dependent and dose-dependent antiproliferative effects in various human cancer cell lines, and in several human xenograft models, including renal, breast, lung, melanoma and epidermoid carcinoma.[16] Furthermore, antitumour activity was observed in numerous tumour types including RCC, GIST, neuro-endocrine tumours, non-small-cell lung cancer, sarcoma other than GIST, thyroid cancer and melanoma in phase I and early phase II clinical studies.[20,21] Objective responses were observed in six patients with cancer, including RCCs, neuro-endocrine tumours, a GIST and an unknown primary adenocarcinoma. At higher doses (>42 mg/m^2 or >75 mg/day), tumour responses were often associated with reduced intratumoral vascularization and central tumour necrosis, eventually resulting in organ perforation or fistula. Based on this phase I trial, the recommended dose of sunitinib was 50 mg/day for 4 weeks every 6 weeks.[20] The good responses observed in patients with RCC and GIST yielded further phase II/III evaluations in patients.

3. Benefit of Sunitinib in the Treatment of Renal Cell Carcinoma (RCC)

RCC accounts for 3% of all adult cancer. About one-third of patients have distant metastases at presentation. A total of 20–40% of patients treated by nephrectomy for localized disease develop

metastatic disease.[22] Approximately 50% of patients with metastases at presentation will survive less than 1 year and 10% will survive for over 5 years.[23] RCC is usually highly resistant to chemotherapy and radiotherapy. Standard first-line treatment for metastatic disease was immunotherapy with interferon-alpha and/or interleukin-2, achieving 6–20% response rates.[24] RCC displays several histological types, the most common being clear-cell RCC, accounting for 75% of cases.[25]

3.1 Mechanism of Action in RCC

RCCs are strongly associated with inactivation of the von Hippel-Lindau (VHL) gene. The VHL gene is involved in the hypoxia-inducible pathway.[26] Specifically, the VHL gene product ubiquitinates the hypoxia-inducible factor (HIF)-1α transcription factor, leading to its proteasomal degradation.[27] Physiologically, the HIF-1 complex (a heterodimer composed of α and β subunits) regulates the expression of several genes in response to hypoxic stress.[28] Human cells respond to hypoxic conditions through a series of pathways, many of which are mediated by HIF-1. In addition to regulation by the VHL complex, HIF-1 activity is regulated by growth factor and cell-adhesion pathways. HIF-1 binds to a variety of additional transcription cofactors, forming a pre-initiation complex of proteins that ultimately activate transcription of hypoxia-inducible genes, including those encoding VEGF (leading to angiogenesis), EGFR (leading to cell growth) and PDGF, and leads to increased production of erythropoietin.[29] Phenotypically, RCC is a highly vascular tumour, with increased levels of VEGF expression, and growth could be stimulated by factors produced through the HIF-1 pathway. Consequently, the inhibition of VEGF and PDGF signalling pathways by sunitinib may reverse, in part, the physiological consequences of losing VHL protein function and may inhibit tumour progression.

3.2 Efficacy in RCC

Approval for the sunitinib RCC indication was based on two consecutive, independent, open-label, phase II studies in patients with cytokine-refractory metastatic RCC (mRCC).[30,31] In the first study (n = 63), the objective response rate (ORR) was 40%, and 27% of patients had stable disease for at least 3 months. Median time to disease progression (TTP) was 8.7 months and median overall survival (OS) was 16.4 months.[30] The second study (n = 105) confirmed these results, with an ORR of 34%, 29% stable disease lasting at least 3 months, and a median progression-free survival (PFS) of 8.3 months.[31] Pooling data from these two phase II studies, a median PFS of 14.8 months was observed in responding patients compared with 7.9 months for patients experiencing stable disease as best response to treatment.

In addition, a phase III trial was launched comparing single agent sunitinib with interferon (IFN)α as first-line treatment for patients with mRCC.[2] A total of 750 treatment-naive patients with clear-cell mRCC were randomized to receive either oral sunitinib (n = 375) or subcutaneous IFNα (n = 375). Median PFS, the primary study endpoint, was significantly longer for the sunitinib group (11 months) than for the IFNα group (5 months), with a hazard ratio (HR) for disease progression of 0.42 (95% CI 0.32, 0.54; $p < 0.001$). Sunitinib was also associated with a significantly higher ORR than IFNα (31% vs 6%; $p < 0.001$). The PFS benefit with sunitinib compared with IFNα was observed across all prognostic subgroups examined. This ORR was exceptional compared with other first-and second-line treatments for mRCC (ORR ≤20%) such as IFNα or cytotoxic chemotherapy.[31] Supporting the important role of VEGF/VEGFR inhibitors in the control of tumour angiogenesis in RCC, a phase III trial assessing IFNα in combination with bevacizumab (a monoclonal antibody directed toward VEGF) reported comparable median PFS data (10.2 months compared with 5.4 months for IFNα/placebo [HR 0.63; $p < 0.001$]).[32] Recently, a population-based study evaluated the impact of sunitinib on OS in the treatment of patients with mRCC and reported that the introduction of first-line sunitinib was associated with a doubling of OS compared with patients treated with IFN alone. This benefit

extended to patients with poor Memorial Sloane-Kettering Cancer Center prognostic profiles.[33] Moreover, a study evaluating surgical parameters and perioperative complications in 44 patients treated with targeted molecular therapies, such as bevacizumab, sunitinib and sorafenib, before cytoreductive nephrectomy or resection of retroperitoneal RCC recurrence, and comparing them with a matched patient cohort who underwent upfront surgical resection, reported that preoperative administration of targeted molecular therapies is safe, and does not increase surgical morbidity or perioperative complications in patients treated with cytoreductive nephrectomy or resection of recurrent retroperitoneal RCC.[34]

4. Benefit of Sunitinib in the Treatment of Gastrointestinal Stromal Tumour (GIST)

Approximately 85% of patients with GIST display activating mutations of *KIT*. Others may have amplification of non-mutated *KIT*. Another 5–7% of patients have activating mutations of *PDGFR*.[35-37] Current standard of care for unresectable or malignant GIST is imatinib, an inhibitor of ABL, KIT and PDGFR.[38] Approximately 12–14% of patients have primary resistance to imatinib.[39,40] Furthermore, more than 40% of patients who initially responded to imatinib develop secondary imatinib resistance after a median of 18–26 months of treatment.[41]

4.1 Efficacy in GIST

An open-label, multicentre, phase I/II study of sunitinib in 97 patients with GIST showing progression or intolerance under imatinib mesylate therapy confirmed the safety of the recommended dose for sunitinib as 50 mg daily for 4 weeks with 2 weeks off.[42] Median time to progression was 7.8 months, and median OS was 19.8 months. Thirty-two patients (33%) had partial response or stable disease lasting for more than 6 months. Encouraging phase I/II results were confirmed in a double-blind, placebo-controlled, phase III trial in which 312 GIST patients with documented imatinib resistance or intolerance were randomized in a 2 : 1 ratio to receive sunitinib (n = 207) or placebo (n = 105).[3] The trial was unblinded early when the planned interim analysis, conducted after the first 149 cases of Response Evaluation Criteria In Solid Tumors (RECIST)-defined disease progression or death, revealed a significantly longer TTP in the sunitinib group (median 27.3 weeks; 95% CI 16.0, 32.1) than in the placebo group (median 6.4 weeks; 95% CI 4.4, 10.0); the HR for progression was 0.33 (95% CI 0.23, 0.47; $p < 0.0001$). Sunitinib treatment also significantly improved OS (HR 0.49; 95% CI 0.29, 0.83; $p = 0.007$). With respect to objective tumour response, 7% of patients in the sunitinib group achieved a partial response, 58% exhibited stable disease and 19% had progressive disease, compared with rates of 0%, 48% and 37%, respectively, in the placebo group. Of 59 patients in the placebo group who crossed over to sunitinib after disease progression, six patients (10%) subsequently achieved a partial remission. Novel statistical analysis of long-term survival to account for crossover in a phase III trial of sunitinib versus placebo in advanced GIST after imatinib failure confirmed the long-term OS benefit provided by sunitinib versus placebo to patients with imatinib-resistant/intolerant GIST in this phase III study. Indeed, a conventional analysis showed that OS converged in the two treatment groups (sunitinib median 74.7 weeks, 95% CI 61.4, 85.7; placebo 64.9 weeks, 95% CI 45.7, 98.4; HR 0.82; $p = 0.128$) as expected, given the crossover design. However, rank preserved structural failure time analysis yielded an estimated median OS for placebo of 36.0 weeks (95% CI 25.9, 51.0), revealing a significant sunitinib-treatment effect (HR 0.46; $p < 0.0001$) comparable to that of the blinded phase.[43]

A large, recent, open-label study with 1097 patients with advanced imatinib-resistant/intolerant GIST ineligible for other sunitinib trials,[44] showed that median estimated TTP was 37 weeks (95% CI 35, 44) and OS was 73 weeks (95% CI 66, 92) with 64% of patients alive in the overall population. In patients aged <59 years (n = 528; 68% alive), median OS was 92 weeks versus 64 weeks in patients >59 years (n = 562; 60% alive).

Among factors predictive of the response, a poster study suggests that circulating soluble KIT may be regarded as a potential surrogate marker for TTP in GIST studies and that a change in soluble KIT levels may predict TTP and OS.[45] Another recent study showed that the clinical activity of sunitinib after imatinib failure is significantly influenced by both primary and secondary mutations in the predominant pathogenic kinases, which has implications for the optimization of treatment of patients with GIST. Clinical benefit (partial response or stable disease for ≥6 months) with sunitinib was observed for the three most common primary GIST genotypes: *KIT* exon 9 (58%), *KIT* exon 11 (34%) and wild-type *KIT*/*PDGFR*-α (56%). PFS was significantly longer for patients with primary *KIT* exon 9 mutations ($p = 0.0005$) or with a wild-type genotype ($p = 0.0356$) than for those with *KIT* exon 11 mutations. The same pattern was observed for OS. PFS and OS were longer for patients with secondary *KIT* exon 13 or 14 mutations (which involve the *KIT*-adenosine triphosphate binding pocket) than for those with exon 17 or 18 mutations (which involve the *KIT* activation loop). Biochemical profiling studies confirmed the clinical results. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant GIST.[46]

5. Adverse Effects of Sunitinib

At the recommended dose of 50 mg daily for 4 weeks, sunitinib displays manageable and reversible adverse events (AEs). The majority of AEs reported in patients receiving sunitinib in clinical studies were mild to moderate in severity and generally consistent across indications.[2] (figure 1).

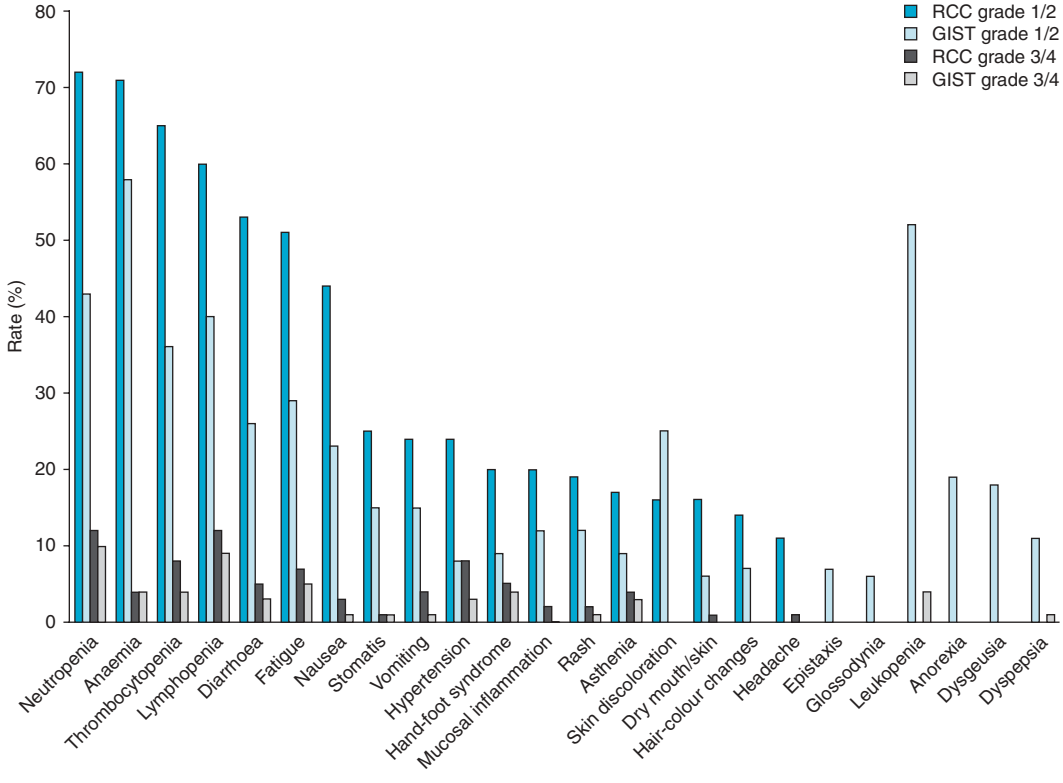

Fig. 1. Rates of grade 1–2 vs grade 3–4 toxicities of sunitinib in gastrointestinal stromal tumour (GIST) and in renal cell carcinoma (RCC).

Table I. Adverse events reported in at least 10% of patients treated with sunitinib in a randomized phase III study in metastatic renal cell carcinoma[2]

Adverse events	Toxicity frequency (%)	
(n = 375)	grade 1/2	grade 3/4
Non-haematological		
Fatigue	51	7[a]
Diarrhoea	53	5[a]
Skin discoloration	16	0
Nausea	44	3[a]
Anorexia	NS	NS[a]
Dysgeusia	NS	NS
Stomatitis	25	1[a]
Vomiting	24	4[a]
Hand-foot syndrome	20	5[a]
Rash	19	2
Asthenia	17	4[a]
Mucosal inflammation	20	2[a]
Dyspepsia	NS	NS
Hypertension	24	8[a]
Headache	11	1[a]
Hair-colour changes	14	0
Dry skin	16	1[a]
Haematological		
Anaemia	71	4
Neutropenia	72	12
Lymphopenia	60	12[a]
Thrombocytopenia	65	8[a]

a Grade 3 toxicity only.

NS = not stated.

The frequency of haematological and non-haematological adverse effects of sunitinib for patients with mRCC is summarized in table I, which is based on a published randomized phase III study of treatment-naive patients.[2] The most commonly reported treatment-related, non-haematological AEs include fatigue, gastrointestinal toxicities (diarrhoea, nausea, vomiting, stomatitis and dyspepsia), hypertension, skin discoloration and hand-foot syndrome. Most events were of grade 1 or 2 severity, with relatively few (<10%) grade 3 or 4 events (mainly fatigue, gastrointestinal toxicities, hypertension and hand-foot syndrome).

AEs for the phase III placebo-controlled trial in GIST[3] are summarized in table II. A recent open-label study carried out in patients with advanced imatinib-resistant/intolerant GIST ineligible for other sunitinib trials[44] showed that dose reductions occurred in 39% of patients and dose interruptions occurred in 57% of patients, 79% of them because of AEs. In this open-label study, the most common all-causality AEs were fatigue (48%), diarrhoea (45%) and nausea (35%). The most common grade 3 or higher AEs were fatigue (10%), abdominal pain (10%) and hand-foot syndrome (9.2%). Grade 3 or higher haematological AEs included anaemia (8%), neutropenia (8%) and thrombocytopenia (5%). Hypothyroidism occurred in 7% of patients, and 23% of patients had elevated creatinine levels (mostly grade 1/2). Congestive heart failure (CHF) was reported in <5% of patients.[44]

5.1 Gastrointestinal Adverse Effects

Data on the gastrointestinal adverse effects were extracted from clinical studies.[2,3,30,31]

5.1.1 Anorexia

Anorexia occurs in about 10–20% of patients undergoing sunitinib therapy, but rarely exceeds grade 2. Although anorexia rarely requires dose modifications, underlying causes should always be investigated, in particular, a potential relationship to coexisting hypothyroidism and gastrointestinal toxicities (e.g. taste changes, diarrhoea, stomatitis or nausea). Patient education about nutrition and consultation with a dietician is recommended to handle this toxicity and to optimize compliance.

5.1.2 Diarrhoea

Diarrhoea occurs in approximately 53% of patients with RCC undergoing sunitinib therapy and 26% of patients with GIST, but grade 3 or 4 toxicity is rare and observed in only 3–5% of cases. In contrast to chemotherapy-induced diarrhoea, which is usually continuous, sunitinib-induced diarrhoea can occur irregularly; days of diarrhoea are mixed with days of normal bowel movements. Dose reductions are rarely necessary for grade 1 and 2 toxicity. Grade 1 and 2 diarrhoea may be managed by oral hydration and oral anti-diarrhoeal agents such as loperamide, as

Table II. Adverse events in patients with gastrointestinal stromal tumours (GIST) that occurred at least 5% more frequently with sunitinib than with placebo in per-protocol population[3]

Adverse events	Toxicity frequency (%)	
(n = 202)	grade 1/2	grade 3/4
Non-haematological		
Fatigue	29	5[a]
Diarrhoea	26	3[a]
Skin discoloration	25	0[a]
Nausea	23	1[a]
Anorexia	19	0[a]
Dysgeusia	18	0[a]
Stomatitis	15	1[a]
Vomiting	15	1[a]
Hand-foot syndrome	9	4[a]
Rash	12	1[a]
Asthenia	9	3[a]
Mucosal inflammation	12	0[a]
Dyspepsia	11	1[a]
Hypertension	8	3[a]
Epistaxis	7	0[a]
Hair-colour changes	7	0[a]
Dry mouth	6	0[a]
Glossodynia	6	0[a]
Haematological		
Anaemia[b]	58	4[a]
Leucopoenia	52	4[a]
Neutropenia	43	10
Lymphopenia	40	9
Thrombocytopenia	36	4

a Grade 3 toxicity only.

b Anaemia is included in this table, despite a difference of <5% between the treatment groups, because of its frequency and clinical relevance in GIST.

needed. Treatment should be interrupted for grade 3 or 4 diarrhoea until diarrhoea is grade 1 or less, or has returned to baseline. Usually, diarrhoea resolves quickly in the 2-week break between cycles. The sunitinib dose should be reduced by one dose level (12.5 mg) in subsequent cycles in cases of grade 3 or 4 diarrhoea, based on the dose modifications made in sunitinib studies and recommendations given in the product monograph.[47] Patients can be advised to discontinue the use of stool softeners and fibre supplements, drink plenty of liquids, eat and drink often in small amounts, and avoid any other possible factors contributing to diarrhoea such as tobacco, spicy, fatty or high-fibre foods and caffeine.

5.1.3 Nausea and Vomiting

The emetogenic potential of sunitinib is low in patients with RCC and GIST. Less than 5% of patients experience grade 3 or 4 vomiting, and only 15–25% experience grade 1 or 2 vomiting. Nausea seems to occur more frequently, but grade 3 or 4 nausea is rare. Common antiemetics can be used to relieve nausea and vomiting. If nausea or vomiting is expected, antiemetics can be given prophylactically before administration of sunitinib. However, particular care should be used when sunitinib is combined with antidopaminergic agents such as domperidone, or serotonin 3 receptor antagonists, such as granisetron, ondansetron and dolasetron, because they have been associated with QT/corrected QT (QTc) interval prolongation and torsade de pointes.[48]

5.1.4 Oral Changes, Stomatitis, Mucositis and Heartburn

A number of oral changes, including sensitivity, taste changes, dry mouth, stomatitis and mucositis may occur with varying frequency (10–30%). Dose adjustments or interruptions are seldom necessary. Symptoms usually resolve quickly within the 2-week break between therapy cycles, but tend to recur within subsequent cycles. The extent of oral changes may be correlated with the degree of oral care. Treatment for oral adverse effects includes alcohol-free mouthwashes, viscous lidocaine (lignocaine), nonperoxide toothpaste and lip creams or balms for cheilitis. Patients should be counselled to make an alcohol-free mouthwash with half a teaspoon of baking soda or salt in 1 cup of warm water and rinse several times a day. Dietary modifications, such as avoiding spicy foods, acidic foods, foods at extreme temperatures and alcoholic drinks, and eating soft foods, may be helpful. Antacids are recommended for the treatment of heartburn.

Patients may be counselled to brush their teeth gently after eating and at bedtime with a soft toothbrush, to use gauze instead of a brush,

and use baking soda instead of toothpaste if their gums bleed.

5.2 Hypothyroidism

The data described in this section were extracted from clinical studies.[2,3,30,31]

Hypothyroidism has been reported in patients receiving sunitinib as early as 1–2 weeks after the initiation of therapy.[49-52] Up to 85% of patients with RCC experienced abnormal thyroid results on one or more thyroid-function tests. Similar results have been reported in other published studies.[50-52] These abnormalities were consistent with hypothyroidism in all patients, frequently included elevation of thyroid-stimulating hormone (TSH) levels and were less commonly associated with decreased T3/T4 levels and free-thyroxine indexes. Thyroid abnormalities were detected relatively early in the treatment (median at cycle 2, with a wide range). Approximately 84% of patients with abnormal thyroid-function test results developed symptoms consistent with hypothyroidism such as fatigue, anorexia, oedema, fluid retention or intolerance to the cold. Thyroid hormone replacement benefited about 50% of the patients treated.[49] The incidence of hypothyroidism seems to increase progressively with the duration of sunitinib therapy. Although the mechanism for this complication is unknown, observations of preceding TSH suppression and subsequent absence of visualized thyroid tissue in some patients suggest that sunitinib may induce a destructive thyroiditis through follicular-cell apoptosis.[49,50] The incidence of hypothyroidism during sunitinib therapy is probably underestimated because, initially in trials, TSH level was not checked routinely. Recently, hypothyroidism (all grades) was reported in 7% of patients in an open-label study in GIST patients.[44]

Patients should be screened for the development of hypothyroidism with TSH measurements taken at baseline and then at intervals of 2–3 months. A low serum TSH level and mild symptoms suggesting thyroiditis-induced thyrotoxicosis may precede the onset of hypothyroidism, which may itself progress rapidly from mild to profound.[53] A regular surveillance of thyroid function is warranted for patients receiving sunitinib. Any abnormal TSH value or symptoms suggestive of hypothyroidism should prompt more thorough evaluation. Patients developing overt hypothyroidism should be treated with thyroid hormone replacement therapy. Treatment should be considered, even for patients with subclinical hypothyroidism because these patients are unlikely to achieve normal TSH levels without treatment. Typical levothyroxine sodium doses should allow for the normalization of TSH levels and resolution of symptoms.

5.3 Haematotoxicity

The data described in this section were extracted from clinical studies.[2,3,30,31] Sunitinib induces neutropenia and thrombocytopenia in about 50–70% of patients. Only 4–12% of patients develop grade 3 or 4 neutropenia or thrombocytopenia, and no cases of neutropenic fever have been reported so far. Blood counts usually recover quickly within the 2-week break between cycles of therapy. Complete blood counts should be done at the beginning of each treatment cycle for patients receiving treatment with sunitinib. If grade 3 or 4 neutropenia recurs, or if thrombocytopenia persists for at least 5 days, the dose of sunitinib should be reduced in the next scheduled cycle. Recommended dose reductions are given in table III.

Patients with neutropenic fever or infection should be seen and treated promptly, as the treating physician deems appropriate. Grade 3 or 4 lymphopenia and anaemia usually do not require dose modification. Erythropoietins or blood transfusions may be used at the discretion of the treating physician to treat anaemia. Patients should follow basic guidelines to minimize the risk of infections, including washing hands often and always after using the bathroom, and avoiding crowds and people who are sick. To minimize the risk of bleeding, patients should be counselled to avoid bruises, clean their noses by blowing gently, treat constipation if it occurs and, as indicated in section 5.1.4, brush their teeth gently with a soft toothbrush to avoid irritating the gums. Maintaining good oral hygiene

Table III. Recommended dose modifications for treatment-associated haematological and cardiac toxicities[a]

Grade 1	Grade 2	Grade 3	Grade 4
Haematological toxicity			
Continue at the same dose	Continue at the same dose level	Withhold dose until toxicity is grade ≤2, or has returned to baseline, then resume treatment at the same dose level	Withhold dose until toxicity is grade ≤2, then reduce the dose by 1 level and resume treatment
Cardiac toxicity			
Continue at the same dose	Continue at the same dose level, except in the event of LVEF <50% or >20% below baseline; non-urgent ventricular paroxysmal dysrhythmia requiring intervention. Withhold dose until toxicity is grade ≤1, then reduce dose by 1 level and resume treatment	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce the dose by 1 level and resume treatment	Discontinue sunitinib

a For treatment associated toxicities in sunitinib clinical trials (modified according to protocol A6181034).[2]

LVEF = left ventricular ejection fraction.

is important. Patients may avoid taking NSAIDs because they may increase the risk of bleeding.

5.4 Hypertension

The data described in this section were extracted from clinical studies.[2,3,30,31] Hypertension seems to be a class effect of angiogenesis inhibitors.[54-57] Bevacizumab, sorafenib and sunitinib have been shown to increase blood pressure.[30,56,58] The exact pathogenesis by which sunitinib induces hypertension is not yet known. It has been speculated that tyrosine kinase inhibitors may exert hypertensive effects directly at the level of the vasculature through processes such as vascular rarefaction, endothelial dysfunction or altered nitrous oxide metabolism.[54,59] The appearance of hypertension, particularly grade 3, was associated with higher treatment response to sunitinib in mRCC.[60] The total incidence of hypertension was 23% (6% grade 3/4) in the open-label study in GIST.[44] Early and intensive antihypertensive therapy with the goal of maintaining sunitinib use may improve response rates in those patients.[60]

Patients receiving sunitinib should be monitored for hypertension and treated, as appropriate, with standard antihypertensive therapy, avoiding antihypertensive drugs that may potentially interact with CYP3A4, which could interact with sunitinib. Therapy for hypertension is often required only during the therapy phase and may be discontinued when patients are not taking the drug. The objective of treatment is to normalize blood pressure (resting rate <140/90 mmHg). Temporary suspension of sunitinib is recommended for patients with severe hypertension (>200 mmHg systolic or >110 mmHg diastolic). Treatment with sunitinib may be resumed once hypertension is controlled. Patients with uncontrolled hypertension should not be treated with sunitinib. Caution should be used if sunitinib is prescribed in combination with other drugs that also cause PR interval prolongation or peripheral oedema.[61-63] Pre-existing hypertension may require adjustment of antihypertensive medications during sunitinib therapy. Daily blood pressure monitoring at home and keeping records of blood pressure data in the patient's diary is also suggested for this patient population. Generally, no patient needs to discontinue sunitinib therapy because of hypertension, and dose reductions are rarely necessary.

5.5 Bleeding

Data on bleeding events described in this section were extracted from clinical studies and

the Sutent® product monograph.[2,3,30,31,47] Bleeding events and tumour haemorrhages have been reported in 26% of patients receiving sunitinib for mRCC. Epistaxis was the most common haemorrhagic adverse effect reported; less common bleeding events included rectal, gingival, upper gastrointestinal, genital and wound bleeding. Treatment-related haemorrhage of tumours has been observed in patients receiving sunitinib (2%). In the case of pulmonary tumours or metastases, this haemorrhage may be a severe life-threatening haemoptysis or pulmonary haemorrhage. A higher incidence of pulmonary haemorrhage has been observed in patients with lung cancer (8%). However, in patients with mRCC, severe grade 3 and 4 bleeding incidents are extremely rare (<1%). Assessment of haemoptysis should include serial complete blood counts, physical examination and, if indicated, imaging. Temporary discontinuation of sunitinib or dose interruption may be considered until the cause of haemorrhage is determined. Dose discontinuation for mild-to-moderate epistaxis may not be necessary and may be considered only if conventional measures have failed. In a recent surgical congress, the frequency of emergency operations during sunitinib therapy was reported to be higher (9.5%: three bowel perforations, one intraperitoneal bleeding) than during first-line therapy with imatinib (1.3%: two bowel perforations, one bleeding).[64] The authors suggested these cases may be related to more advanced and more resistant disease or direct mechanism of sunitinib action combining cytotoxic and antiangiogenic activities leading to dramatic tumour response. Tumour/bowel perforation and bleeding were shown to be especially important in GIST cases treated with sunitinib.

5.6 Cardiac Toxicity

Data on cardiac toxicity described here were extracted from clinical studies and the Sutent® product monograph.[2,3,30,31,47,65] Left ventricular dysfunction is an important cardiac adverse effect of sunitinib, although arrhythmias, including bradycardia, and PR and QT interval prolongation, have only rarely been observed (<1%). Caution is advised if QT/QTc or PR interval-prolonging agents are combined with sunitinib. Left ventricular dysfunction, which manifests as a decrease in left ventricular ejection fraction (LVEF), has been reported in up to 12% of mRCC patients receiving sunitinib, but symptomatic ventricular dysfunction (grade 3 or 4) was seen in only 1–2%. The clinical significance of these findings remains unknown because no difference in clinically symptomatic heart failure was observed between the two study groups in the pivotal phase III mRCC trial. Updated data indicate that 21% of sunitinib-treated patients experienced a decline in LVEF. This cardiotoxicity was reported to be reversible and without clinical sequelae; however, in a retrospective study among patients treated with sunitinib, 15% developed symptomatic grade 3/4 heart failure.[64] Moreover, in another recent study,[66] 6 of 224 (2.7%) patients who received sunitinib developed heart failure that resulted in substantial morbidity and, in some cases, mortality. Symptomatic heart failure occurred soon after initiation of sunitinib (mean onset: 22 days after initiation), was associated with a decline in cardiac function and elevations in blood pressure, and was not completely reversible in most patients, even after termination of sunitinib therapy. These observations suggested that sunitinib-associated heart failure may represent a potentially serious toxicity and underscore the need for careful monitoring of cardiac function and aggressive control of hypertension in these patients. Studies to elucidate potential mechanisms of heart failure and left ventricular dysfunction resulting from treatment with sunitinib are necessary to develop strategies for prevention and treatment of this complication.

A retrospective study[67] reviewed all cardiovascular events in 75 patients with imatinib-resistant, metastatic, gastrointestinal stromal tumours who had been enrolled in a phase I/II trial investigating the efficacy of sunitinib. The composite cardiovascular endpoint was cardiac death, myocardial infarction and CHF. The authors also examined the effects of sunitinib on LVEF and blood pressure and investigated potential mechanisms of sunitinib-associated cardiac effects by studies in isolated rat cardiomyocytes and in mice. Of

75 patients given repeating cycles of sunitinib in the phase I/II trial, eight (11%) had a cardiovascular event, and CHF was recorded in six (8%). Ten of 36 (28%) patients treated with the approved sunitinib dose had absolute LVEF reductions in ejection fraction of at least 10%, and seven of 36 (19%) had LVEF reductions of 15% or more. Sunitinib induced increases in mean systolic and diastolic blood pressure, and 35 of 75 (47%) individuals developed hypertension (>150/100 mmHg). CHF and left ventricular dysfunction generally responded to sunitinib being withheld and institution of medical management. Sunitinib caused mitochondrial injury and cardiomyocyte apoptosis in mice and in cultured rat cardiomyocytes. Left ventricular dysfunction might be due, in part, to direct cardiomyocyte toxicity, exacerbated by hypertension. Patients treated with sunitinib should be closely monitored for hypertension and LVEF reduction, especially those with a history of coronary artery disease or cardiac risk factors.[67]

Patients who have cardiac risk factors or a recent history of cardiac events (e.g. acute coronary syndrome, arterial bypass graft, symptomatic CHF, stroke or pulmonary embolism) should be monitored for clinical signs and symptoms of CHF, and evaluated for decreased LVEF while receiving sunitinib, including baseline and periodic evaluations of LVEF. For patients with LVEF <50% or >20% below baseline, the dose of sunitinib should be interrupted or reduced, regardless of clinical evidence of CHF (table III). In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. Blood pressure should be monitored more frequently for patients with a history of CHF because an increase can accentuate the clinical symptoms of CHF. For patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

5.7 Fatigue

The data described in this section were extracted from clinical studies and the Sutent® product monograph.[2,3,30,31,47] Fatigue represents one of the most frequently encountered sunitinib-related adverse effects in RCC and GIST. Approximately 30–60% of patients complain about fatigue, although only 5–11% experience severe fatigue, which interferes with the activities of daily living (grade 3). A number of potential causes should be ruled out. Fatigue may be caused or exacerbated by underlying dehydration. Adequate fluid and nutritional intake should be ensured. Laboratory and clinical evaluations should be done to eliminate other possible causes of fatigue, such as hypothyroidism, anaemia or depression. Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function carried out before and during sunitinib treatment (every 2 months) and be treated according to standard medical practice (see also section 5.2). Thyroid hormone replacement can be used for patients with mRCC or GIST and thyroid abnormalities to improve hypothyroidism-related symptoms and possibly treatment tolerance.[40,68]

Anaemia may exist and can be identified by monitoring complete blood counts. Erythropoietic agents or blood transfusions may be used at the discretion of the treating physician. Depression may have an impact on the severity of fatigue. Fatigue improved in some patients who received antidepressants or methylphenidate.

Patients should be counselled to take naps or breaks, do light exercise, and should also be advised not to drive a car or operate machinery.

5.8 Skin Toxicity

Skin toxicity typically occurs after 3–4 weeks of treatment. A number of different skin changes may be observed, including hand-foot syndrome, changes in hair colour, skin rash, dry skin, skin discoloration, acral erythema and subungual splinter haemorrhages. Data on skin toxicity in the following three sections were extracted from clinical studies and the Sutent® product monograph.[2,3,30,31,47]

5.8.1 Hand-Foot Syndrome or Acral Erythema

Hand-foot syndrome presents as painful symmetric erythematous and oedematous areas on the palms and soles, commonly preceded or accompanied by paresthesias, tingling or

numbness.[69] Desquamation can occur in severe cases. Painful hyperkeratotic areas on pressure points surrounded by rings of erythematous and oedematous lesions, and painful bullous lesions, blisters or skin cracking can be noted (figure 2). Pre-existing hyperkeratosis of the sole seems to confer a predisposition for painful soles and functional consequences. Although this syndrome can sometimes clinically resemble the more classic chemotherapy-induced hand-foot syndrome or palmar-plantar erythrodysesthesia that can arise with fluorouracil, cytarabine, capecitabine or doxorubicin, most patients with sunitinib-induced hand-foot syndrome have more localized and hyperkeratotic lesions that are distinct from classic chemotherapy-induced hand-foot syndrome. In addition, patients may experience symptoms without significant morphological changes. The exact pathogenesis of this type of hand-foot syndrome is still unknown.

A recent study identified 12 patients developing hand-foot skin reaction (HFSR) on treatment with sorafenib (83%) or sunitinib (17%). The majority presented with grade 3 (75%). The authors concluded that there are unique clinicopathological characteristics of HFSR due to the multikinase inhibitors that correlate with the time of agent initiation.[70]

Management strategies for hand-foot syndrome (palmar-plantar erythrodysesthesia syndrome) include having a manicure and pedicure before treatment as a preventative measure, treatment interruptions and a shorter course (2 weeks) of therapy much more often than dose reduction. Treatment with topical agents that have keratolytic, antiproliferative and

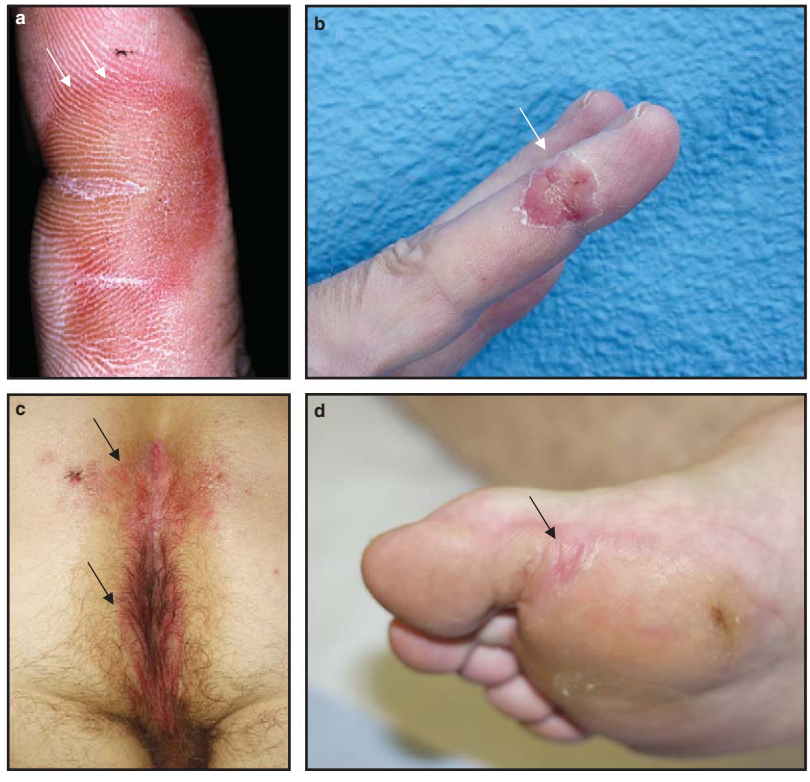

Fig. 2. Classical skin toxicity observed under sunitinib therapy. (**a**) Painful bullous lesion may occur in palms, soles and interphalangial flexion sections of fingers. (**b**) Bullous lesion may heal within a few days after treatment discontinuation. (**c**) Similar erythema and bullous lesion may occur in other parts of the body. (**d**) Sole lesions may also consist of hyperkeratosis.

anti-inflammatory properties were of benefit (for example, topical corticosteroids, such as betamethasone dipropionate cream or salicylic acid cream). Patients should decrease pressure on affected areas, staying off the feet whenever possible and avoiding friction or pressure to the hands. During treatment, shock absorbers may be used to relieve painful pressure points, and sandals seem to be helpful for some patients. Patients should be advised to avoid tight-fitting shoes and/or rubbing pressure on the hands and feet, heavy activity, tight-fitting jewellery and shaving off blisters. Patients should also be advised to wear loose-fitting clothes, clean their hands and feet with lukewarm water rather than hot water, and then gently pat dry and to apply a sunscreen and creams containing lanolin or urea to the hands and feet.

5.8.2 Skin Rash

Generalized erythema, maculopapular or seborrheic dermatitis-like rashes have been reported with sunitinib therapy, the vast majority of which are grades 1 or 2.[71] Skin rashes caused by sunitinib rarely require dose reduction and the symptoms tend to decrease over time. Patients should be advised to use moisturizing skin lotions or creams often, particularly after showers or before bedtime. Urea-containing lotions may be helpful, particularly if the skin is very dry. Patients can use anti-itch formulas and antidandruff shampoos if they have itchy scalps or scalp discomfort. A recent study[72] suggested that the use of colloidal oatmeal lotion may be beneficial in controlling tyrosine kinase inhibitor-associated skin rash. Patients should avoid hot showers, use sun protection and wear loose-fitting cotton clothes. If their cases are severe, they may use topical therapies such as cortcicosteroid creams.

5.8.3 Changes in Skin or Hair Colour

Yellow discoloration of the skin caused by the yellow colour of the active drug and its metabolite is a common treatment-related AE of sunitinib therapy. Occurring in approximately 30% of patients, this adverse effect is reversible when treatment is discontinued. Yellow discoloration of the urine has been observed in conjunction with skin discoloration because of excretion of the drug and its metabolites.[20,47]

Hair depigmentation can occur after 5–6 weeks of treatment (2–3 weeks in men with facial hair), but this effect is reversible as early as 2–3 weeks after treatment is discontinued (figure 3). Successions of depigmented and normally pigmented bands of hair may correlate with on and off periods of treatment.

Sunitinib-induced hair depigmentation is thought to be caused by the blockade of KIT signalling and other receptors. KIT signalling is vitally important for both melanocyte proliferation or differentiation and proper pigment production.[73,74] Persistence of melanocytes associated with hair follicles on biopsies indicated that sunitinib did not affect the migration and survival of melanocytes. Experiments with mice suggest that sunitinib inhibits melanocyte function rather than their development or survival.[75]

6. Optimizing the Sunitinib Safety Profile

The approved sunitinib 4/2 dosing schedule was selected from among several others during phase I development because it had the most promising efficacy along with acceptable tolerability.[20] In general, the AEs reported during the clinical development of sunitinib have been mild to moderate in intensity and easily managed by dose reduction, dose interruption or standard supportive medical therapies.[2,3,30,31,47] Two phase II studies have investigated the safety and efficacy of an alternative continuous dosing schedule in patients with RCC or GIST.[14,15] Although a direct comparison cannot be made, the continuous dosing regimen seemed to be as well tolerated as the 4/2 schedule. Moreover, it provides the advantage of maintaining sustained anti-tumour activity and preventing tumour regrowth during the off-treatment period, which has been observed in some cases. An actualized study of 61 patients showed that continuous daily dosing of sunitinib appears to be a safe and potentially effective dosing strategy for patients with GIST after imatinib failure.

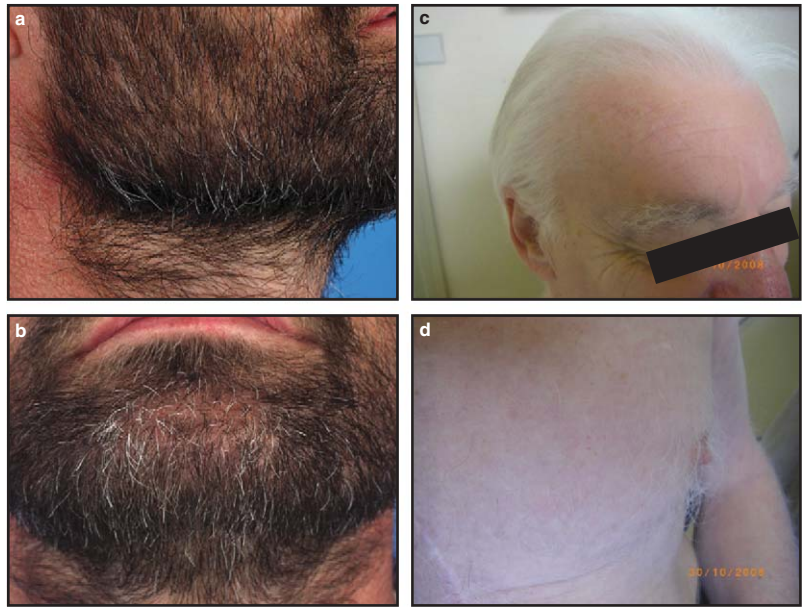

Fig. 3. Hair depigmentation under sunitinib therapy. Possibly reflecting exposure to sunitinib and inhibition of KIT in the skin, partial-to-total hair depigmentation may occur. This mainly occurs on facial hair because it grows more rapidly (**a** and **b**), but may also progressively affect the coloration of hair (**c**) and all body hair (**d**).

Continuous daily dosing was associated with constant drug exposure and a persistent pharmacodynamic effect.[76]

However, the response rate appears to be higher with the 4/2 schedule than with the continuous administration schedule, and may be explained by a dose-effect relationship for efficacy, which was confirmed by a recent exposure-response analysis in RCC, indicating that increased exposure to sunitinib was associated with clinical benefit.[77]

This may mean that in the future, physicians could adapt the dose of the drug and the schedule to balance safety and efficacy according to individual patient characteristics, tolerability[78] and tumour type (slow-growing tumours or tumours with rapid kinetics).

Interactions between sunitinib and other drugs are only partially known. Because of its metabolism by CYP3A4, a number of drugs can potentially interact with sunitinib. Clinical response and toxicity should not only be carefully observed when sunitinib is combined with either a CYP3A4 inducer or inhibitor and doses adjusted as necessary, but also when drugs coadministered interact with ABC transporters. A recent report has demonstrated that sunitinib blocks the function of the ABC transporters, P-glycoprotein (ABCB1) and ABCG2, which may also affect the bioavailability of these drugs.[79]

7. Conclusions

Patients receiving therapy with sunitinib should be monitored by a qualified physician experienced in the use of anticancer agents. Patients beginning treatment with sunitinib should be counselled about the potential for adverse effects related to their treatment and advised about how to identify them, and patients should be encouraged to monitor the status of their health on a regular basis and report any adverse effects to their healthcare team as soon as possible.

The challenge for the future is to ensure that the potential of multi-targeted agents is maximized by selecting the patient populations most likely to derive clinical benefit, by optimizing

the dose schedules used and by investigating multi-targeted therapies combined with other agents of the same type or with conventional chemotherapy and/or other treatment modalities.

Acknowledgements

No funding was received for the preparation of this benefit-risk assessment. Eric Raymond has been a consultant to and received honoraria from Pfizer Inc. Sandrine Faivre has received honoraria from Pfizer Inc. None of the other authors have any conflicts of interest relevant to the content of this benefit-risk assessment.

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