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Managing toxicities and optimal dosing of targeted drugs in advanced kidney cancer

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Abstract

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The toxicities of new, targeted drugs may diminish their effectiveness in advanced kidney cancer if those toxicities are not recognized and properly addressed early in patient treatment. Most of the drug-related toxicities in advanced kidney cancer are manageable with supportive care, obviating a need for long interruptions, dose reductions, or permanent discontinuation of the treatment.

Keywords: Sunitinib, sorafenib, temsirolimus, toxicity, side effects, management

1. INTRODUCTION

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Sunitinib, sorafenib, temsirolimus, and bevacizumab are new drugs used in treatment of advanced kidney cancer [1–4], together with another emerging agent, everolimus [5]. By targeting healthy tissues, these drugs cause toxicities that can lead to delay, dose reduction, or discontinuation of the drug treatment. When such disruptions occur early on, the potential benefit to the patient of these new agents is lost.

The use of targeted agents in a less selected patient population outside of clinical trials can certainly be challenging, but experience to date shows that most of the toxicities associated with the new agents are manageable. The data about the toxicities of sunitinib and sorafenib outside of clinical trials in expanded-access programs are reassuring [6,7]. In the present review, we describe the recommended doses of the new drugs and the management of common toxicities of drugs used in advanced kidney cancer.

2. INHIBITORS OF KINASES: SUNITINIB AND SORAFENIB

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Sunitinib and sorafenib target tyrosine kinases, including vascular endothelial growth factor receptors (VEGFRs) [8]. The humanized monoclonal antibody bevacizumab inhibits vascular endothelial growth factor A (VEGFA), but is not discussed in this review. (It is not approved for use in advanced kidney cancer in Canada.)

2.1. Recommended Treatment Schedules and Dose Adjustments

2.1.1. Sunitinib From the drug label [9], the starting dose for sunitinib is 50 mg orally once daily with or without food, in a 4-weeks-on, 2-weeks-off regimen. Standard dose modification in 12.5-mg steps is recommended. If more than 2 dose reductions are required, discontinuation of therapy should be considered. Recovery to acceptable levels of toxicity must occur to allow sunitinib continuation. Re-escalation to the previous dose schedule can be considered in the absence of grade 3 or greater hematologic toxicity, or in the absence of grade 2 or greater non-hematologic toxicity. The drug label recommends permanent discontinuation of sunitinib in the rare case of congestive heart failure, pancreatitis, or hepatic failure.

Clinical studies excluded patients with a serum creatinine in excess of 2 times the upper limit of normal (ULN), and so caution is recommended in the presence of severe kidney impairment. No dose adjustment is required for Child–Pugh class A or B hepatic impairment, but sunitinib has not been studied in severe (Child–Pugh class C) liver impairment. Clinical studies excluded patients with aminotransferase levels in excess of 2.5 times the ULN or, if a result of liver metastases, in excess of 5 times the ULN [9].

Based mostly on clinical experience and very limited data from early-phase clinical trials [10,11], alternative regimens of sunitinib might be considered: either a 2-weeks-on, 1-week-off regimen, or continuous daily dosing with 37.5 mg. However, efficacy confirmation for these latter regimens is lacking.

2.1.2. Sorafenib The recommended dose of sorafenib is 400 mg orally twice daily without food (at least 1 hour before or 2 hours after a meal). When dose reduction is required, the dose may be reduced to 400 mg once daily, and further to 400 mg once every other day. An alternative, more gradual reduction is to use one dose of 200 mg while the second dose is maintained at 400 mg (600 mg daily total); reduction to 400 mg daily can then follow if toxicity persists.

Permanent discontinuation should be considered in the unlikely events of bleeding that requires medical intervention or of gastrointestinal perforation. Temporary interruption should be considered in patients undergoing major surgical procedures and in whom cardiac ischemia or infarction occur; in the latter setting, permanent discontinuation can be considered. No dose adjustment is necessary in patients with kidney impairment who are not undergoing dialysis (patients on dialysis have not been studied). Mild and moderate (Child–Pugh A and B) liver impairment may reduce plasma levels of sorafenib, but the optimal dose of sorafenib in hepatic impairment has not been established [12].

2.2. Drug Metabolism and Dose Modifications

Sunitinib and sorafenib are metabolized primarily by cytochrome P450 (CYP) 3A4 in the liver, and sorafenib additionally undergoes glucuronidation by uridine glucuronyl transferase 1A9 and by being a competitive inhibitor of CYP2B6 and CYP2C8 isozymes [9,12]. Concomitant use of medications that substantially affect these metabolizing enzymes should be avoided (Tables I and II). The dose of sunitinib should be reduced to a minimum of 37.5 mg if strong CYP3A4 inhibitors must be co-administered and possibly increased to a maximum of 87.5 mg if strong CYP3A4 inducers must be co-administered (Table I). Sorafenib seems not to have any clinically significant pharmacokinetic interactions with strong CYP3A4 inhibitors, but if a strong CYP3A4 inducer must be co-administered, an increase of the sorafenib dose should be considered [12].

TABLE I

Agents that interact with cytochrome P450 3A4

TABLE II

Agents that interact with cytochrome P450 2B6 and cytochrome P450 2C8[a]

2.3. Common Toxicities

The most commonly reported clinical toxicities are constitutional, gastrointestinal, hypertensive, and skin-related; the most common laboratory toxicities are lymphopenia, neutropenia, thrombocytopenia, anemia, elevated lipase, and hypophosphatemia [1,2]. In pivotal randomized clinical trials (RCTs), severe—that is, grades 3 and 4—toxicities were reported in two thirds of patients on sunitinib [1] and in more than one third of patients on sorafenib [2].

3. TEMSIROLIMUS

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Temsirolimus is a potent, highly specific inhibitor of the mammalian target of rapamycin (mTOR). It inhibits cell proliferation, cell growth, survival pathways, and tumour angiogenesis [13]. Everolimus (RAD001) is an orally administered mTOR inhibitor currently under review by Health Canada.

3.1. Recommended Treatment Schedule and Dose Adjustments

The recommended dose of temsirolimus in advanced kidney cancer is a flat dose of 25 mg infused over 30–60 minutes once weekly. Before each administration of temsirolimus, patients should receive intravenous (IV) H_1 antihistamine—for example, IV diphenhydramine 25–50 mg 30 minutes before temsirolimus. If hypersensitivity occurs, the infusion should be stopped for at least 30–60 minutes and resumed at a slower rate approximately 30 minutes after IV administration of an H_2 antihistamine—for example, IV famotidine 20 mg or ranitidine 50 mg [14]. If a severe hypersensitivity reaction occurs, re-challenge with temsirolimus is contraindicated.

Temsirolimus should be held in the presence of an absolute neutrophil count below 1000/μL, a platelet count below 75,000/μL, or any other grade 3 or greater toxicity. Once toxic effects have resolved to grade 2 or lesser, temsirolimus can be restarted at 20 mg or 15 mg weekly, but no lower. No data on dosing in patients with kidney and hepatic impairment are available [14].

3.2. Drug Metabolism and Dose Modifications

Temsirolimus is metabolized by CYP3A4, and strong inducers and inhibitors should not be co-administered (Table I). If a strong CYP3A4 inhibitor or inducer must be co-administered, the dose of temsirolimus should be reduced to 12.5 mg weekly or cautiously increased to 50 mg weekly respectively. If the strong CYP3A4 inhibitor is discontinued, a 1-week washout period should elapse before temsirolimus is re-instituted at the dose level previously used [14].

3.3. Common Toxicities

The most common clinical toxicities of temsirolimus are constitutional and skin-related; the most common laboratory toxicities are hyperglycemia, hypertriglyceridemia, hypercholesterolemia, hypophosphatemia, and hematologic toxicities. In a pivotal RCT, the most common severe toxicities were anemia (13%), hyperglycemia (9%), asthenia (8%), and hypertriglyceridemia (3%) [15]. Rare but fatal cases of nonspecific interstitial pneumonitis have been reported in phase I and II trials in patients with advanced kidney cancer on temsirolimus [16]. Most temsirolimus-related toxicities can be managed medically or with supportive care without a need for interruption or dose reduction.

4. MANAGEMENT OF TOXICITIES

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4.1. Fatigue

Fatigue has been reported in 51% and 37% of patients on sunitinib and sorafenib respectively; severe fatigue occurred in 5%–7% of patients [1,2]. In a RCT of sorafenib, patients with advanced kidney cancer on sorafenib did not experience significantly more fatigue than did patients on placebo [2].

Fatigue may be associated with hypothyroidism, anemia, depression, or dehydration, all of which can be addressed. Thyroid hormone replacement therapy benefited 50% of patients who developed overt hypothyroidism on sunitinib [17], indicating that other mechanisms causing fatigue are at play in these patients. Physical activity is effective in the management of cancer-related fatigue [18], and patients should be counselled to do some light exercise, if appropriate. In severe fatigue, treatment should be interrupted and the dose reduced (Table III).

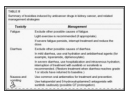

TABLE III

Summary of toxicities induced by anticancer drugs in kidney cancer, and related management strategies

4.2. Gastrointestinal Toxicity

4.2.1. Diarrhea In RCTs, diarrhea occurred in 53% and 43% of patients on sunitinib and sorafenib respectively; severe diarrhea occurred in 2%–5% of patients [1,2].

Mild diarrhea (an increase of up to 6 stools daily over baseline) can be managed by oral hydration and antidiarrheal agents (for example, loperamide or diphenoxylate) alone. In severe diarrhea, patient should be hospitalized for IV hydration; treatment with sunitinib and sorafenib should be discontinued until diarrhea is grade 1 or stools have returned to baseline, when treatment can be restarted at a lower dose. During an episode of diarrhea patients should be counselled to avoid the use of stool softeners, laxatives, antacids, and a fibre-rich diet. Other causes of diarrhea, such as antibiotics, infectious gastroenteritis, partial intestinal obstruction, and radiation-induced enteritis should be excluded (Table III).

4.2.2. Nausea and Vomiting Nausea and vomiting occurred, respectively, in 44% and 24% of patients on sunitinib and in 23% and 16% on sorafenib; severe nausea and vomiting occurred in 6% of patients only [1,2].

Common antiemetics can be used, including prophylactically, to relieve nausea and vomiting. Antiemetics such as haloperidol and 5-hydroxytryptamine3 antagonists can be associated with QT interval prolongation [19] and should be used cautiously in combination with sunitinib (see “Cardiotoxicity” later in this article).

Any constipation should be corrected (Table III).

4.3. Skin Toxicity

Skin toxicity typically occurs in the first few weeks of treatment with sunitinib and sorafenib [20,21]. Various skin changes may be observed, including hand–foot syndrome (HFS).

The most clinically significant skin toxicity, HFS, may lead to dose modification or discontinuation of treatment. Discontinuation of treatment in skin toxicities should be considered after the fourth occurrence of a grade 2 skin toxicity or the third occurrence of a grade 3 skin toxicity [12].

In a pooled analysis, HFS occurred in 19% (5% severe) of patients on sunitinib [22]. No reports of HFS have been seen with temsirolimus. Pre-existing hyperkeratosis confers a predisposition for HFS, and preventive manicure and pedicure are recommended. Topical treatment with keratolytics such as urea 40% cream, tazarotene 0.1%, or topical fluorouracil showed a beneficial effect in a small series of patients with HFS induced by sunitinib or sorafenib [23]. Moisturizers, shock absorbers, and topical corticosteroids have been found useful by many. Patients should be encouraged to avoid tight-fitting shoes and friction and to apply cream containing urea to the hands and feet daily throughout therapy. In the cases of severe HFS, treatment should be interrupted until recovery to grade 1, and the dose at resumption should be reduced (Table III).

Skin rash associated with sunitinib, sorafenib, and temsirolimus usually presents as low-grade maculopapular or seborrheic dermatitis [15,24] that rarely requires treatment interruption or dose reduction. Urea-containing lotions may be helpful if the skin is very dry. The dermatitis can be managed with the use of fragrance-free moisturizers and topical clindamycin or corticosteroids (hydrocortisone 1% cream, for instance) [15,24]. In more severe cases, systemic antibiotics (for example, orally administered doxycycline) can be used. Seborrheic-like rash with scaly areas can be treated with topical antifungals or steroids. Often, patients can attempt a re-escalation of the drug if a lower dose has been well tolerated for a period of time (Table III).

4.4. Hypothyroidism

In observational studies with sunitinib, up to 85% of patients developed biochemical hypothyroidism, and approximately one quarter of all patients showed signs or symptoms of hypothyroidism that needed treatment [17,25]. In contrast, in one observational study with sorafenib, biochemical hypothyroidism occurred in 18% of patients, and only 3% of patients had clinically significant hypothyroidism [26]. Sunitinib-induced hypothyroidism may develop in the first few weeks after initiation of treatment and can quickly become severe [17,27]. Rarely, hyperthyroidism may precede development of hypothyroidism in patients on sunitinib [9].

With both sunitinib and sorafenib, thyroid-stimulating hormone should be measured at baseline. The measurement should be repeated every 2 months with sunitinib, but only if symptoms and signs of hypothyroidism occur with sorafenib. The current recommendation is that overt and subclinical hypothyroidism should be treated [28]. With recognition and proper treatment of hypothyroidism, no dose modification of sunitinib and sorafenib should be required (Table III).

4.5. Hypertension

In two recent meta-analyses of prospective clinical trials, 21% (7% severe) of patients on sunitinib and 23% (6% severe) of patients on sorafenib developed arterial hypertension [29,30]. Untreated arterial hypertension may be important in the exacerbation of myocardial damage [31]. This hypothesis is supported by animal studies, which show that inhibition of VEGFR signalling promotes transition from compensatory cardiac hypertrophy to heart failure in response to pressure overload [32,33].

Patients receiving sunitinib or sorafenib should be monitored closely for hypertension, which should be treated if necessary. Patients should be encouraged to monitor and record blood pressure daily at home. The objective of treatment is to normalize blood pressure (resting level below 140/90 mmHg). Standard hypertensive therapies are recommended [34]; vasodilatators appear to be the most effective. Optimal choices are drugs not metabolized by the CYP system in the liver—for example, lisinopril and quinapril, temisartan and valsartan, atenolol and hydrochlorothiazide [35]. Antihypertensive drugs that are substrates of CYP3A4—for example, enalapril, losartan, nifedipine, and amlodipine—are not ideal, but can be used cautiously. The CYP3A4 inhibitors such as verapamil and diltiazem should be avoided [35]. In severe hypertension (above 200 mmHg systolic or above 110 mmHg diastolic), treatment should be temporarily interrupted until hypertension is controlled; it can then be restarted at a lower dose. Uncontrolled hypertension should be controlled before sunitinib or sorafenib is started. Patients with known hypertension will likely need assessment or dose adjustments to their antihypertensive drugs, or both. With proper management of hypertension, it is unlikely that interruption, dose reduction, or discontinuation of treatment will be required (Table III).

4.6. Cardiotoxicity

Recent small observational studies showed symptomatic cardiac disease in 15%–18% of patients treated with sunitinib or sorafenib [36,37]. Ongoing adjuvant trials will provide a definitive answer about the cardiotoxicity of these drugs; however, in everyday clinical practice, caution is already recommend concerning this possible toxicity. Sunitinib prolongs the QT interval in a dose-dependent manner, an effect that can occasionally lead to ventricular arrhythmias (less than 1% of cases) [9].

Baseline and periodic assessment of electrocardiogram and left ventricular ejection fraction (LVEF) should be considered in patients receiving sunitinib or sorafenib, especially in those with a history of heart disease. Every patient with new symptoms of peripheral edema, dyspnea, chest pain, or dizziness (although these symptoms are common in progressing cancer *per se*) should be assessed for cardiac disease. In the presence of congestive heat failure, sunitinib and sorafenib should be discontinued, and appropriate standard therapy for heart disease should be started. The dose of sunitinib or sorafenib should be interrupted or reduced in patients without clinical symptoms of congestive heart failure but with a LVEF of less than 50% or more than 20% below baseline [9]. Sunitinib should be used cautiously in patients with a known history of QT prolongation, in those who are using CYP3A4 inhibitors or drugs that are known to prolong QT, and in those with electrolyte disturbances [9] (Table III).

4.7. Interstitial Pneumonitis

Interstitial pneumonitis is a potentially life-threatening toxicity of temsirolimus, and patients, especially those with a history of lung disease, should be monitored for it. In patients with radiographic changes of interstitial pneumonitis but no symptoms (for example, dry cough, dyspnea, fever), treatment with temsirolimus can continue, but these patients should be followed closely. In patients with symptoms of interstitial pneumonitis, lung imaging and pulmonary function tests should be performed. Where mild

symptoms are present, temsirolimus may be temporarily interrupted until symptoms resolve. In cases with severe symptoms, temsirolimus should be discontinued, and treatment with high-dose steroids (for example, 1 mg/kg prednisone) should be started. Tapering of the steroid dose should be considered if gradual improvement in symptoms and pulmonary function tests occur [15,16] (Table III).

4.8. Hyperglycemia

Fasting blood sugar should be tested before and regularly during treatment with temsirolimus [15]. Hyperglycemia may manifest as excessive thirst, increased urination, and blurred vision; if untreated, it may lead to coma. Management of hyperglycemia may include diet, orally administered agents for glycemic control (metformin, for instance), and insulin, if required [15] (Table III).

4.9. Hyperlipidemia

Serum cholesterol and triglycerides should be measured at baseline and regularly every 1–2 months during treatment with temsirolimus. If levels are elevated, a diet with reduced saturated fats and addition of lipid-lowering agents could be considered. Pravastatin is the only statin that is not a substrate of CYP3A4; it is the safest option in combination with temsirolimus [35]. However, use of lipid-lowering medications may not be practical in this advanced cancer population. When triglyceride levels exceed 1000 mg/dL (11.3 mmol/L), the risk of triglyceridemia-induced pancreatitis is high, and in patients without hepatic and renal insufficiency, fibrates (for example, gemfibrozil and fenofibrate) can be considered [38]; otherwise, interruption of treatment is recommended (Table III).

4.10. Hematologic and Other Laboratory Toxicities

A complete blood count should be obtained at the beginning of each treatment cycle. If grades 1 and 2 hematologic toxicities (hemoglobin not lower than 8 g/dL, leucocyte count not lower than 2000/mm^3, and platelet count not lower than 50,000/mm^3) are present, treatment can be continued at the same dose level. If grade 3 toxicity is present, the dose should be held until toxicity reaches grade 2 or lower, at which time treatment can be resumed at the same dose. If grade 4 toxicity is present, the dose should be held until toxicity reaches grade 2 or lower, at which time treatment can be resumed at a reduced dose. For symptomatic anemia, blood transfusions without treatment interruption and dose reduction may be offered.

Serum lipase and amylase should be followed, and consumption of alcohol should be discouraged if these parameters become elevated. In RCTs, clinical pancreatitis developed in only 3 patients (fewer than 1%) on sorafenib [12]. A diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values [12]. If a patient develops clinical symptoms of pancreatitis, sunitinib or sorafenib should be held while the symptoms are investigated (Table III).

Phosphate levels should be monitored before each treatment cycle, and in hypophosphatemia, oral phosphate replacement (that is, 1 tablet of sodium acid phosphate twice daily with meals) should be considered (Table III).

5. CONCLUSIONS

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Patients with advanced kidney cancer need to be closely monitored for the development of drug-related toxicities. Development of drug-related toxicities (even at mild and moderate levels) should be vigorously managed with supportive measures to prevent interruptions of treatment, dose reductions, and eventual development of life-threatening complications.

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