Tyrosine kinase inhibitors and mammalian target of rapamycin inhibitors related to cardiac toxicity

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Abstract

Background

Tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors (mTORIs) are emerging as one of the most commonly used targeted chemotherapeutic agents in cancer treatment. As with any other medication, adverse effects are not uncommon, especially cardiac adverse effects. Given the improved survival with the use of these medications, it is anticipated that primary care providers are going to manage them and deal with the adverse effects they developed from using these medications more frequently.

Aim

We reviewed comprehensively the cardiovascular adverse effects of the oral TKIs and mTORIs. In addition, we offered the current recommendations regarding management of these cardiovascular adverse effects to help the primary care providers manage these side effects.

Methods and Materials

A formal literature review of PubMed and ClinicalTrials.gov using the following terms: "sunitinib, sorafenib, pazopanib, temsirolimus, and everolimus" was used, with only phase 2 and 3 clinical trials in English language and published up to April 5, 2013 were consider in this review article.

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Results

We found that hypertension is the most commonly reported adverse effect with the use of TKIs. Pazopanib was associated with the highest incidence of hypertension. 32% of the patients who received pazopanib developed grade 1/2 hypertension and 6% developed grade 3/4 hypertension. The use of oral mTORIs was associated more with endocrinological derangements including hypertriglyceridaemia and hyperglycaemia, especially with everolimus usage.

Conclusion

It is not uncommon to see cardiac adverse effects with the usage of oral TKIs and mTORIs.

Keywords

Oral TKIs, mTORIs, adverse effects, cardiac

Introduction

It is estimated now that two thirds of patients diagnosed with cancer today will experience at least 5-year survival [1]. This rise in cancer survivors has created new challenges to the primary care providers and internists as they deal more often with patients who are on oral chemotherapy including oral TKIs and mTORIs. In this review article, we will discuss the cardiac toxicity of three oral small molecule TKIs, which are sunitinib, sorafenib, and pazopanib as well as the mTORIs, temsirolimus and everolimus. In addition, we will tailor this review to help the primary care providers and internists manage these side effects.

In the era of targeted cancer chemotherapy, TKIs and mTORIs have been one of the most commonly used targeted chemotherapies. These novel medications play a key role in the transmission of growth, differentiation, and migration and apoptotic signals. However, the use of these agents is not without limitations, including the development of resistance, the financial cost and adverse effects associated with the use of these drugs.

Methods and Materials

A formal literature review of PubMed and Clinical-Trials.gov using the following terms: "sunitinib, sorafenib, pazopanib, temsirolimus, and everolimus" was done. And only phase 2 and 3 clinical trials in English language completed and published up to April 5, 2013 were considered in this review article.

The TKIs (pazopanib, sorafenib, sunitinib)

There are two classes of tyrosine kinases, receptor tyrosine kinases (extracellular) and cellular tyrosine kinases (intra-cytoplasm or intra-nuclear). Fifty-six receptor tyrosine kinases are expressed, which can be subdivided into 19 families (AATYK, ALK, AXL, DDR, EGFR, EPH, FGFR, INSR, MET, MUSK, PDGFR, PTK7, RET, ROR, ROS, RYK, TIE, TRK and VEGFR family). In addition, 32 cellular tyrosine kinases are expressed, which can be subdivided into 11 families (ABL, ACK, CSK, focal adhesion kinase (FAK), FES, FRK, JAK, SRC-A, SRC-B, TEC and SYK family) [2]. See table 1.

Sunitinib works as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3), stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 (FLT3), colony stimulating factor 1 receptor (CSF1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib is currently approved for the treatment of gastrointestinal stromal tumour (GIST) after disease progression on or intolerance to imatinib mesylate, advanced renal cell carcinoma (RCC), and progressive well-differentiated pancreatic neuroendocrine tumors (pNET) in patients with unresectable locally advanced or metastatic disease [3].

Table 1. **A list of the oral TKI with their taget receptors and the currently approved targeted tumors**

TKI	Tyrosine kinase target	Neoplasm (s) targeted
Sunitinib	PDGFRα, PDGFRβ, VEGFR1, VEGFR2, VEGFR3, KIT, FLT3, CSF1R, and RET	GIST RCC pNET
Sorafenib	KIT, FLT3, RET, VEGFR-1, VEGFR-2, VEGFR-3, PDGFRβ CRAF, BRAF, and mutant BRAF	of unresectable hepatocellular carcinoma, and advanced RCC
Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα and -β, FGFR -1 and -3, KIT, ITK, Lck, and c-Fms	RCC soft tissue sarcoma

Sorafenib works as an inhibitor of KIT, FLT3, RET, VEGFR-1, VEGFR-2, VEGFR-3, PDGFRß, CRAF, BRAF, and mutant BRAF. Sorafenib is currently approved for the treatment of unresectable hepatocellular carcinoma and advanced RCC, and other trials for thyroid and brain tumours are underway [4].

Pazopanib works as an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFRα and PDGFRß, fibroblast growth factor receptor (FGFR) -1 and -3, KIT, interleukin-2-inducible T-cell kinase (ITK), lymphocyte-specific protein tyrosine kinase (Lck), and transmembrane protein receptor tyrosine kinase (c-Fms). Pazopanib is currently approved for the treatment of patients with advanced RCC, and advanced soft tissue sarcoma who have received prior chemotherapy [5].

The mTORIs (everolimus, temsirolimus)

The mTORIs, including temsirolimus and everolimus, have seen a rapid rise in use for targeted chemotherapy [6]. Mammalian target of rapamycin (mTOR) is one of several kinases that are receptors involved in complex molecular pathways including those of cellular metabolism, growth, and proliferation. Initially discovered as an antibiotic, rapamycin was found to have immunosuppressing effects, shown to inhibit cellular proliferation and cell cycle progression. Continued research and development has led to development of additional mTORIs, which affect the same pathways, particularly with T-cell proliferation and with regard to cancer therapy, showing benefit with increased apoptosis of tumour cell lines and with diminishing tumour vascular angiogenesis [7].

Both temsirolimus and everolimus work in the same manner, all based off the initial immunosuppressive qualities noted of rapamycin, a novel antibiotic isolated from bacteria harvested from the island of Rapa Nui. Rapamycin was found to arrest cell growth and additional studies showed extensive immunosuppressive qualities, which led to creation of analogues that target the mTOR pathway, one that is instrumental in cell proliferation and growth [7]. It has been found that this mTOR pathway is often dysregulated in human diseases, such as diabetes, obesity, depression, and certain cancers. These mTOR inhibitors bind to kinases and portions of this pathway, limiting angiogenesis (helpful in particularly vascular tumours) as well as inhibiting cellular proliferation.

Everolimus has been approved for the treatment of advanced kidney cancer after failure with approved TKIs; subependymal giant cell astrocytomas associated with tuberous sclerosis not amenable to surgery; pancreatic neuroendrocine tumors not amenable to

surgery; breast cancer in receptor positive, HER2-negative patients in conjunction with exemestane; and in prevention of organ rejection in both renal and liver transplant. Temsirolimus has been approved for use in advance RCC.

Cardiac toxicity

Cardiotoxicity is not uncommon side effect of targeted cancer chemotherapy. Commonly seen cardiac toxicities include: left ventricular (LV) dysfunction, hypertension, QTc prolongation, myocardial ischaemia, arrhythmia and peripheral oedema.

The NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) was the adverse effects grading system in almost all the trials we reviewed. CTCAE classify the severity of adverse events (AEs) in 5 grades. In general, grade 1 encompasses mild AEs, grade 2 – moderate, grade 3 – severe, grade 4 – life-threatening or disabling, grade 5 – death related to AEs, respectively. Table 2 shows the definition of each cardiac AE observed with the use of the oral TKIs and mTORIs [8].

Sunitinib

LV ejection fraction (LVEF) / CHF

In the study for the use of sunitinib in patients with GIST [9], 11% of patients on sunitinib developed decline in LVEF; 59% of these patients required intervention with dose reduction and addition to anti-failure treatment; compared to 3% on placebo. In the same study, 2 (out of 209) patients on sunitinib and 2 patients on placebo died of sudden cardiac arrest. In a recent study by Demetri *et al.* [10], one patient experienced CHF (grade 2) who was managed clinically with anti-failure treatment.

In the study for the use of sunitinib in patients with RCC, 27% of patients on sunitinib developed decline in their LVEF (grade 1 and 2). Two patients (<1%) developed grade 3 CHF while on sunitinib [11]. Two phase 2 clinical trials, each reported grade 3 CHF in one patient out of total 38 patients [12] and 53 patients [13].

We can conclude from the above studies that the incidence of symptomatic decline in the EF, i.e. CHF, with the use of sunitinib is low. We recommend obtaining a baseline evaluation of EF if patients have any history of cardiac dysfunction. If patients develop any symptoms they can be managed with beta-blockers, diuretics, and ACE inhibitors. Metoprolol is safer as compared with carvedilol which may require monitoring of therapy as sunitinib may increase level of carvedilol. Lisinopril, enalapril and also losartan are all safe with sunitinib.

Table 2. **The NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) classification of the cardiac AE observed with the use of oral TKIs and mTORIs**

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Prolonged QTc interval	QTc >0.45–0.47 second	QTc >0.47–0.50 second or ≥0.06 second above baseline	QTc >0.50 second	QTc >0.50 second with life-threatening signs or symptoms (e.g., arrhythmia, congestive heart failure (CHF), hypotension, shock syncope) or torsade de pointes	Death
Atrial fibrillation (AF)	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously within normal limits (WNL); intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously	Life-threatening consequences (e.g., hypertensive crisis)	Death
LV systolic dysfunction	Asymptomatic, resting ejection fraction (EF) <60–50%; shortening fraction (SF) <30–24%	Asymptomatic, resting EF <50–40%; SF <24–15%	Symptomatic CHF responsive to intervention; EF <40–20% SF <15%	Refractory CHF or poorly controlled; EF <20%; intervention such as ventricular assist device, ventricular reduction surgery, or heart transplant indicated	Death
Limb oedema	5–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting oedema	>10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with activities of daily living	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death

Follow-up echocardiogram in 3–6 months based on symptom progression is recommended.

QT interval

Sunitinib related QT prolongation is a dose dependent and may lead to torsade de pointes. Upon reviewing all the phase 2 and 3 studies of sunitinib use, one study had one patient who developed electrocardiogram (ECG) QT prolongation without any clinical sequel [14]. The other one, 4 patients developed grade 1 prolonged QT; 2 patients developed grade 2; 2 patients developed grade 3. None of them developed torsade de pointes [15].

Incidence of clinically significant QT prolongation is very low (0.1%) with sunitinib use. It is recommended to have a baseline ECG prior to initiation. Patients with baseline QTc prolongation should be monitored closely. In patients with no prior abnormality we do not monitor QTc in our practice.

Hypertension

In a large randomized study of patients with RCC, who received sunitinib, 34% experienced hypertension. 13% of total patients developed grade 3 or more hypertension [11].

In the study for the use of sunitinib in GIST, grade 3 hypertension was reported in 4% of patients on sunitinib compared to none on placebo [9].

In the study for the use of sunitinib in pNET, 27% of patients experienced hypertension. Grade 3 hypertension was reported in 10% of total patients on sunitinib. Dose reduction or treatment delay controlled blood pressure (BP) in 80% of patients with hypertension in the RCC study and 86% of patients with hypertension in the pNET study [16].

The reported incidence of hypertension as an adverse effect to the use of Sunitinib was variable among the phase 2 and 3 clinical trials that we reviewed with the incidence of grade 1/2 ranging from (3–71)%. The incidence of grade 3 ranging from (0–17)% and no reported cases of grade 4 or 5. Please refer to figure 1. These patients who developed hypertension while on sunitinib were treated with standard antihypertensive therapy and strict surveillance with weekly visits and early intervention of hypertension [10,11,13,15, 17–29].

Significant number of patients developed hypertension while on sunitinib. Hypertension was treated with standard antihypertensive therapy and strict surveillance with weekly visits and early intervention
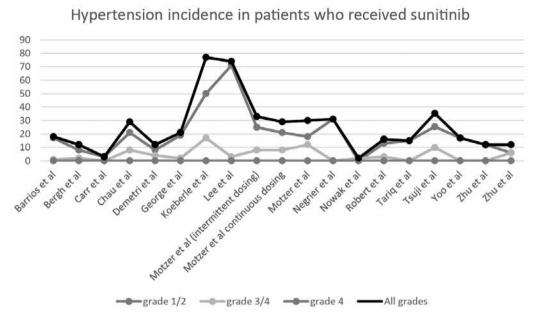
Figure 1. A line-graph diagram showing the incidence of hypertension in paitents who received sunitinib as reported in the phase 2 and 3 clinical trials that we reviewed

of hypertension. None of the patients on sunitinib developed grade 4 or 5 hypertension.

We recommend use of metoprolol, amlodipine, lisinopril, losartan or hydrochlorthiazide based on physician choice. Therapy can be titrated as required. Dose reduction for hypertension is usually not required unless adequate antihypertensive are not able to control BP adequately.

Other reported cardiac AEs

No reported AF or hyperlipidaemia were reported with sunitinib use [12–15,17–22,24–36]. Peripheral oedema grade 1 and 2 was ranging between 13–55% in phase 2 and 3 studies [17,20,22].

In summary, the total number of patients from all the trials we reviewed and reported AEs were 2,795. These who developed hypertension grade 1/2 were 377 patients (13%) and these who developed hypertension grade 3/4 were 129 patients (5%). And none developed grade 5. In regard to the development of reduction in EF, 84 patients (3%) developed grade 1/2, and 14 patients (0.5%) developed grade 3/4, and none developed grade 5. 13 patients (0.5%) developed grade 1/2 clinical CHF, 2 developed grade 3/4, and one patient (~0%) developed grade 5 (Table 3).

Pazopanib

LVEF/CHF

In the study for the use of pazopanib in soft tissue sarcoma (STS) [37], LV dysfunction occurred in 11% of patients on pazopanib. One percent of patients on pa-

Table 3. **A table showing the pooled data from all the sunitinib trials we reviewed. A total of 2,795 patients developed AEs. It is evident that hypertension grade 1/2 is the most common observed cardiac AE from the use of sunitinib**

	Grade 1/2		Grade 3/4		Grade 5	
	n	%	n	%	n	%
Hypertension	377	13	129	5	0	0
Reduction in EF	84	3	14	0.5	0	0
Clinical CHF	13	0.5	2	~0	1	~0

zopanib in the STS trial had CHF. 88% of patients with LV dysfunction treated with pazopanib in the STS trial had concurrent hypertension which may contribute to the worsening LV function in patients at risk.

Though overall incidence of symptomatic LV dysfunction is low we recommend to carefully monitoring patients on pazopanib for clinical signs or symptoms of CHF in addition to obtaining a baseline and periodic evaluation of LVEF in patients at risk of cardiac dysfunction including previous anthracycline exposure, and patients with history of coronary artery disease or CHF.

Beta-blockers (metoprolol, carvedilol), ACE inhibitors (lisinopril, enalapril), angiotensin II receptor blocker (ARB) (losartan), diuretics (hydrochlorothiazide (HCTZ)) and calcium channel blockers (Norvasc) are generally safe to use in these patients and do not interact with pazopanib adversely.

QT interval

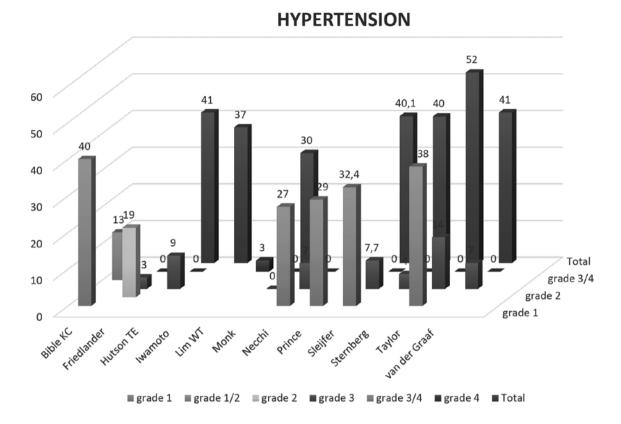In the studies for the use of pazopanib in RCC [38–42], QT prolongation was identified on routine ECG moni-

Figure 2. A 3D-column graph showing the incidence of hypertension in paitents who received pazopanib as reported in the phase 2 and 3 clinical trials that we reviewed

toring in 2% of patients. Torsades de pointes occurred in less than 1% of patients who received pazopanib.

In the randomized RCC and STS trials [37–46], 1% (3/290) of patients and 0.2% (1/240) of patients respectively, who received pazopanib had post-baseline values between 500 to 549 msec. Post-baseline QT data were only collected in the STS trial if ECG abnormalities were reported as an adverse reaction. None of the 268 patients who received placebo on the two trials had post-baseline QTc values more than 500 msec.

None of the clinical trials we reviewed reported prolonged QT internal. This may be attributed to the fact that these studies didn't report AEs with incidence less than 10% unless they were grade 4 or 5.

Until we get more post marketing studies for pazopanib, we recommend periodic monitoring with on-treatment ECGs and electrolytes (magnesium, potassium).

Hypertension

In the study for the use of pazopanib in RCC [42], hypertension occurs early in the course of treatment (40% of cases occurred by day 9 and 90% of cases occurred in the first 18 weeks). Approximately 40% of patients who received pazopanib experienced hypertension. Grade 3 hypertension was reported in 4%

to 7% of patients receiving pazopanib. Approximately 1% of patients required permanent discontinuation of pazopanib because of uncontrolled hypertension.

The incidence of hypertension in the phase 2 and 3 studies we reviewed was similar to the incidence of hypertension in a company-sponsored study [42] as shown in figure 2.

Hypertension is a significant AE to the use of pazopanib. Therefore we recommend to treat patients with standard antihypertensive therapy. Drugs, considered safe with pazopanib, are lisinopril, HCTZ, amlodipine and metoprolol. Patients should be monitored closely early during start of treatment and then with BP check at every visit. The side effect is generally considered to be reversible and BP may return to normal after cessation of therapy.

Other reported cardiac AEs

AF was reported in 6.7% in one trial [44]. Peripheral oedema was reported in 10% [39] in one study and in another 3% [47]. Chest pain was attributed to pazopanib usage. It was reported one patient with grade 1 chest pain and one patient with grade 3 chest pain [44]. 3% (1 patient) developed hyperlipidaemia in one trail [47], and 7 patients developed grade 1 hyperlipidaemia in another study [44].

In summary, the total number of patients who received pazopanib from all the trials we reviewed and reported AEs were 1,244. 400 patients (32%) developed hypertension grade 1/2 and 71 patients (6%) developed grade 3/4. None developed grade 5 hypertension.

Sorafenib

Hypertension

As seen in similar medications above, sorafenib most reported AE was hypertension. For example in one long-term study of patients from the TARGET trial, 95% of patients experienced some type of AEs and 25% experienced new-onset hypertension [48] (Table 4).

Table 4. **A table showing the pooled data from all the sorafenib trials we reviewed. A total of 2,625 patients developed AEs in the trials which reported hypertension and a total of 198 patients developed AEs in the trials which reported arrhythmias**

	Grade 1/2		Grade 3/4		Grade 5	
	n	%	n	%	n	%
Hypertension	364	13.8	103	4	0	0
Arrhythmias	11	5.5	0	0	0	0

In addition, as TKIs are often added to other chemotherapy regimens, one study showed a doubling of hypertension (12% vs. 6%) when this TKI was added to cisplatin and paclitaxel regimen in non-small cell lung cancer (NSCLC) [49].

Our recommendations are in line with treating hypertension with the use of the other TKIs. We recommend the use of metoprolol, amlodipine, lisinopril, losartan or hydrochlorthiazide based on physician choice and close monitoring with visits every 6–8 weeks until stable is prudent.

Arrhythmias

Another commonly reported AE of this medication was arrhythmias, typical seen as AF with an average incidence of 5.5% grade 1 or 2 (Table 4). A clinician will need to assess a multitude of factors, including hypertension and LV function (along the lines of Cha2DSVasc2) to determine if a patient will need anticoagulation.

Oedema

In the trials we researched with regard to sorafnib, there were relatively low rates of oedema as a reported AE. In only one trial, 3% of patients developed significant oedema edema which was thought to be secondary to medication use [50].

mTORIs

Cardiovascular side effects found in patients treated with mTORIs differed from those in the TKI population – anaemia, mucositis and rashes were commonly reported AEs and often endocrinological derangements were typical. Serum lipid profiles often worsened and hyperglycaemia was consistently an issue for many. In one study, dyslipidaemia was reported in nearly three-fourths of all patients [51].

Dyslipidaemia

Dyslipidaemia whether elevated in cholesterol or in triglycerides was the most reported event and the percentage affected was marked (Tables 5 and 6). While non-pharmacological interventions such as weight loss in obese patients, aerobic exercise, avoidance of concentrated sugars and medications that raise serum triglyceride levels and strict glycaemic control in diabetics should be suggested as first-line therapy, these metabolic derangements are more likely to be drug-induced and often a pharmacological approach may be needed. While there is evidence that cardiovascular risk is diminished by the use of statins regardless of the elevated lipid type, with moderate to severe elevations in triglycerides (>500 mg/dL [5.7 mmol/L]), our recommendations would be to start a therapy with a fibrate or, possibly, use of fish oil, however fibrates seem to have improved microvascular outcomes in recent trials. Once patient's triglycerides have been brought down to more acceptable levels, a statin can be considered as dual therapy for the overall dyslipidaemia present and as a reduction of cardiovascular risk. Nicotinic acid is not recommended, given the risk of worsening glycaemic control, one of the very side effects of these medications.

Hyperglycaemia

In clinical use of mTORIs, patients are likely to have an increase in serum glucose, which may in turn result in the need to increase the dose or initiate insulin or an oral hypoglycaemic agent. Many of the reviewed studies showed a significant increase in elevated serum glucose (Tables 5 and 6). Clinicians should be aware of this and the myriad complications this may cause. Treatment with mTORIs may be prolonged and thus elevated blood glucose may require closer vigilance. Changes in dietary habits would be recommended and an increase in oral hypoglycaemic dosages or initiation of insulin may be necessary.

Conclusion

With the continued improvements in targeted cancer therapies and recently with much decreasing costs of

Table 5. **A table showing the pooled data from all the temsirolimus reviewed trials**

Temsirolimus	Grade 3/4		All	
	n (total number of patients who developed AEs)	%	n (total number of patients who developed AEs)	%
Hypercholesterolaemia	6 (498)	1.2	85 (498)	17
Hypertriglyceridaemia	20 (608)	3.2	125 (608)	20.5
Hyperglycaemia	32 (608)	5.2	111 (608)	18.2

Table 6. **A table showing the pooled data from all the everolimus reviewed trials**

Everolimus	Grade 3/4		All	
	n (total number of patients who developed AEs)	%	n (total number of patients who developed AEs)	%
Hypercholesterolaemia	0	0	633 (1943)	32.5
Hypertriglyceridaemia	2 (985)		480 (985)	49
Hyperglycaemia	66 (1174)	5	303 (1174)	26

certain therapies, the cost drops from $5,000/month to about $175/month [52]. A primary care provider will begin to see more patients using these medications and with improved survival only to have the more insidious 'daily' effects causing problems. Overall, hypertension was the most commonly reported adverse effect and clinicians will need to encourage closer monitoring and implement aggressive antihypertensive regimens for their patients (Table 7). With closer monitoring, the other effects such as bleeding risk, anaemia and thrombosis may be picked up on sooner and mitigated too much benefit for these patients.

Conflict of interest: None declared

References

1. Travis LB, Yahalom J. Cancer Survivorship. Preface. Hematol Oncol Clin North Am. 2008 Apr;22(2):xi-xii.

2. Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. Oncogene. 2000 Nov 20;19(49):5548-5557.

3. Blumenthal GM, Cortazar P, Zhang JJ, et al. FDA approval summary: sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors. Oncologist. 2012;17(8):1108-1113.

4. FDA approval summary: Sorafinib. 2011 [Internet]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021923s011lbl.pdf.

5. FDA approval summary: Pazopanib. 2012 [Internet]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022465s-010S-012lbl.pdf.

6. Gentzler RD, Altman JK, Platanias LC. An overview of the mTOR pathway as a target in cancer therapy. Expert Opin Ther Targets. 2012 May;16(5):481-9.

Table 7. **Table showing a monitoring and intervention plan summary for ae primary care provider to guide him/her when dealing with TKIs cardiac AEs**

Clinical follow-up	Sunitinib	Sorafenib	Pazopanib
CHF/Low LVEF	• baseline evaluation of EF if risk factor • monitor for clinical signs and symptoms of CHF	• baseline evaluation of EF if risk factor • monitor for clinical signs and symptoms of CHF	• baseline evaluation of EF if history or risk factors • monitor for clinical signs and symptoms of CHF
QT prolongation	• baseline evaluation monitoring with ECG and electrolytes based on symptoms	• not significantly reported	• baseline evaluation and periodic monitoring with ECG and electrolytes based on symptoms
Hypertension	• treated as needed with standard antihypertensive therapy • dose reduction or delay treatment as clinically warranted • strict surveillance with weekly visits • discontinue in hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction	• treated as needed with standard antihypertensive therapy • dose reduction or delay treatment as clinically warranted • strict surveillance with weekly visits • discontinue in hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction	• treated as needed with standard antihypertensive therapy • dose reduction or delay treatment as clinically warranted • strict surveillance with weekly visits • discontinue in hypertensive crisis or if hypertension is severe and persistent despite antihypertensive therapy and dose reduction

7. Dunlop EA, Tee AR. Mammalian target of rapamycin complex 1: signalling inputs, substrates and feedback mechanisms. Cell Signal. 2009 Jun;21(6):827-35.

8. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 2003 Jul;13(3):176-181.

9. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006 Oct 14;368(9544):1329-1338.

10. Demetri GD, Garrett CR, Schoffski P, et al. Complete longitudinal analyses of the randomized, placebo-controlled, phase III trial of sunitinib in patients with gastrointestinal stromal tumor following imatinib failure. Clin Cancer Res. 2012;18(11):3170-3179.

11. Barrios CH, Hernandez-Barajas D, Brown MP, et al. Phase II trial of continuous once-daily dosing of sunitinib as first-line treatment in patients with metastatic renal cell carcinoma. Cancer. 2012;118(5):1252-1259.

12. Kroiss M, Quinkler M, Johanssen S, et al. Sunitinib in refractory adrenocortical carcinoma: a phase II, single-arm, open-label trial. J Clin Endocrinol Metab. 2012;97(10):3495-3503.

13. Nowak AK, Millward MJ, Creaney J, et al. A phase II study of intermittent sunitinib malate as second-line therapy in progressive malignant pleural mesothelioma. J Thorac Oncol. 2012;7(9):1449-1456.

14. Chau NG, Hotte SJ, Chen EX, et al. A phase II study of sunitinib in recurrent and/or metastatic adenoid cystic carcinoma (ACC) of the salivary glands: current progress and challenges in evaluating molecularly targeted agents in ACC. Ann Oncol. 2012;23(6):1562-1570.

15. Koeberle D, Montemurro M, Samaras P, et al. Continuous Sunitinib treatment in patients with advanced hepatocellular carcinoma: a Swiss Group for Clinical Cancer Research (SAKK) and Swiss Association for the Study of the Liver (SASL) multicenter phase II trial (SAKK 77/06). Oncologist. 2010;15(3):285-292.

16. Blumenthal GM, Cortazar P, Zhang JJ, et al. FDA approval summary: sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors. Oncologist. 2012;17(8):1108-1113.

17. Bergh J, Bondarenko IM, Lichinitser MR, et al. First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study. J Clin Oncol. 2012;30(9):921-929.

18. Carr LL, Mankoff DA, Goulart BH, et al. Phase II study of daily sunitinib in FDG-PET-positive, iodine-refractory differentiated thyroid cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res. 2010;16(21):5260-5268.

19. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in the treatment of nongastrointestinal stromal tumor sarcomas. J Clin Oncol. 2009;27(19):3154-3160.

20. Lee JL, Ahn JH, Lim HY, et al. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. Ann Oncol. 2012;23(8):2108-2114.

21. Motzer RJ, Hutson TE, Olsen MR, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clini Oncol. 2012;30(12):1371-1377.

22. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clini Oncol. 2009;27(22):3584-3590.

23. Negrier S, Gravis G, Perol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. Lancet Oncol. 2011;12(7):673-680.

24. Robert NJ, Saleh MN, Paul D, et al. Sunitinib plus paclitaxel versus bevacizumab plus paclitaxel for first-line treatment of patients with advanced breast cancer: a phase III, randomized, open-label trial. Clin Breast Cancer. 2011;11(2):82-92.

25. Tariq Mahmood S, Agresta S, Vigil CE, et al. Phase II study of sunitinib malate, a multitargeted tyrosine kinase inhibitor in patients with relapsed or refractory soft tissue sarcomas. Focus on three prevalent histologies: leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma. International journal of cancer. Int J Cancer. 2011;129(8):1963-1969.

26. Tsuji Y, Satoh T, Tsuji A, et al. First-line sunitinib plus FOLFIRI in Japanese patients with unresectable/metastatic colorectal cancer: a phase II study. Cancer Sci. 2012;103(8):1502–1507.

27. Yoo C, Kim JE, Lee JL, et al. The efficacy and safety of sunitinib in korean patients with advanced renal cell carcinoma: high incidence of toxicity leads to frequent dose reduction. Jpn J Clin Oncol. 2010;40(10):980-985.

28. Zhu AX, Duda DG, Ancukiewicz M, et al. Exploratory analysis of early toxicity of sunitinib in advanced hepatocellular carcinoma patients: kinetics and potential biomarker value. Clin Cancer Res. 2011;17(4):918-927.

29. Zhu AX, Sahani DV, Duda DG, et al. Efficacy, safety, and potential biomarkers of sunitinib monotherapy in advanced hepatocellular carcinoma: a phase II study. J Clin Oncol. 2009;27(18):3027-3035.

30. Pan E, Yu D, Yue B, et al. A prospective phase II single-institution trial of sunitinib for recurrent malignant glioma. J Neurooncol. 2012;110(1):111-118.

31. Saylor PJ, Mahmood U, Kunawudhi A, et al. Multitargeted tyrosine kinase inhibition produces discordant changes between 99mTc-MDP bone scans and other disease biomarkers: analysis of a phase II study of sunitinib for metastatic castration-resistant prostate cancer. J Nucl Med. 2012;53(11):1670-1675.

32. Scagliotti GV, Krzakowski M, Szczesna A, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol. 2012;30(17):2070-2078.

33. Spigel DR, Greco FA, Rubin MS, et al. Phase II study of maintenance sunitinib following irinotecan and carboplatin as first-line treatment for patients with extensive-stage small-cell lung cancer. Lung Cancer. 2012;77(2):359-364.

34. Tong CC, Ko EC, Sung MW, et al. Phase II trial of concurrent sunitinib and image-guided radiotherapy for oligometastases. PLoS One. 2012;7(6):e36979.

35. Yi JH, Lee J, Lee J, et al. Randomised phase II trial of docetaxel and sunitinib in patients with metastatic gastric cancer who were previously treated with fluoropyrimidine and platinum. Br J Cancer. 2012;106(9):1469-1474.

36. Zurita AJ, George DJ, Shore ND, et al. Sunitinib in combination with docetaxel and prednisone in chemotherapy-naive patients with metastatic, castration-resistant prostate cancer: a phase 1/2 clinical trial. Ann Oncol. 2012;23(3):688-694.

37. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012;379(9829):1879-1886.

38. Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. Eur J Cancer. 2012;48(3):311-323.

39. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2010;28(3):475-480.

40. Powles T, Sarwar N, Jones R, et al. An indirect comparison of the toxicity of sunitinib and pazopanib in metastatic clear cell renal cancer. Eur J Cancer. 2012;48(17):3171-3176.

41. Rexer H. First-line therapy of advanced or metastasized renal cell cancer: open randomized phase III sequence study to examine the effectiveness and tolerance of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the first-line treatment of patients with advanced or metastasized renal cell cancer (SWITCH-2 - AN 33/11). Urologe A. 2012;51(5):724-726. German.

42. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061-1068.

43. Altorki N, Lane ME, Bauer T, et al. Phase II proof-of-concept study of pazopanib monotherapy in treatment-naive patients with stage I/II resectable non-small-cell lung cancer. J Clin Oncol. 2010;28(19):3131-3137.

44. Bible KC, Suman VJ, Menefee ME, et al. A multiinstitutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. J Clin Endocrinol Metab. 2012;97(9):3179-3184.

45. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol. 2009;27(19):3126-3132.

46. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012 May 19;379(9829):1879-1886.

47. Iwamoto FM, Lamborn KR, Robins HI, et al. Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02). Neuro Oncol. 2010;12(8):855-861.

48. Hutson TE, Bellmunt J, Porta C, et al. Long-term safety of sorafenib in advanced renal cell carcinoma: follow-up of patients from phase III TARGET. Eur J Cancer. 2010;46(13):2432-2440.

49. Scagliotti G, Novello S, von Pawel J, et al. Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(11):1835-1842.

50. Gupta-Abramson V, Troxel AB, Nellore A, et al. Phase II trial of sorafenib in advancedcancer. J Clin Oncol. 2008;26(29):4714-4719.

51. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. N Engl J Med. 2012;366:520-529.

52. UPDATE 1-Bayer loses landmark Indian drug case over Nexavar [Internet]. Available from: http://www.reuters.com/article/2012/03/12/natco-pharma-bayer-nexavar-idUSL5E8EC88S20120312.