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Adverse events from targeted therapies in advanced renal cell carcinoma: the impact on long-term use

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The aim of this review is to help physicians tailor targeted treatments for advanced renal cell carcinoma to suit patient needs and ensure maximum overall duration of response to therapy by providing a summary of the frequency and time of onset of adverse events (AEs) and by raising awareness of AE profiles. A PubMed literature search was performed, and papers on targeted therapy-related AEs were reviewed. The frequency, severity and management of targeted therapy-related AEs are discussed. Manageable AEs commonly reported with all the approved targeted agents include: fatigue, gastrointestinal disorders (diarrhoea, nausea, vomiting), hypertension, skin and subcutaneous tissue disorders. Life-threatening AEs are less common than manageable AEs and are usually class specific. Data suggest that long-term treatment with well-established targeted agents does not result in increased or unexpected AEs. Caution is required with regard to the long-term use of newer targeted agents for which there are no long-term tolerability data or clinical experience. Studies have reported that the type and frequency of observed AEs associated with sequential tyrosine kinase inhibitor (TKI) use are similar to those reported in the literature for TKI monotherapy. Having an awareness of the AE profiles of targeted agents allows the development of effective management strategies. Generally, more extensive clinical experience has accumulated, and AE profiles are more predictable, for well-established targeted agents.

What's known on the subject? and What does the study add?
The side-effect of targeted agents is known.

The clinician should be aware of the side-effects of targeted agents and how to prevent/diminish them, particularly in sequential and combination therapies.

KEYWORDS

adverse events, renal cell carcinoma, targeted therapies

INTRODUCTION

Since the introduction of targeted therapy for the treatment of advanced renal cell carcinoma (RCC) the prognosis of this condition has improved. Six targeted agents (sorafenib, sunitinib, bevacizumab plus interferon (IFN), temsirolimus, pazopanib and everolimus) have now been approved for the treatment of RCC, and others will soon join the market. Although these treatments rarely result in a complete disease response, they do offer the possibility of stabilizing disease over a long period of time. Strategies that have been proposed for improving the overall duration of response to targeted therapy include combination therapy, dose escalation and using the available treatments in sequence. Each of these strategies may have the potential to increase the frequency, occurrence, duration and/or severity of treatment-related adverse events (AEs). In addition, prolonged treatment with targeted agents may result in the emergence of previously unidentified safety concerns. It is, therefore, ever more important to have a good understanding of the AE profiles of individual targeted agents: knowing what symptoms to look for and how to prevent and manage AEs. This can be a complicated task, with an expanding body of literature using various diagnostic methods and criteria to report the occurrence and characteristics of AEs. The perceived safety profile of treatments also changes as clinical experience grows after the approval of a therapy; the reported frequency of common AEs may increase as prescribing clinicians learn to recognize and manage AEs, and a wider range of rarer AEs may emerge over time.

The tyrosine kinase inhibitors (TKIs), sorafenib and sunitinib, both of which target the vascular endothelial growth factor (VEGF) pathway, were the first targeted agents to be approved for the treatment of RCC. With extensive clinical experience, the AE profiles for these two agents have now been well established [1–8]. The approval of sorafenib and sunitinib was followed by the approval of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus and the VEGF inhibitor bevacizumab (plus IFN) in 2007. The mTOR inhibitor everolimus and a third TKI, pazopanib (which also targets VEGF), are the latest targeted therapies to enter the market and therefore clinical experience with these agents is perhaps less well known and/or appreciated than the older agents. The present article aims to provide a summary of the frequency and time of onset of AEs associated with targeted agents, helping physicians to tailor treatments to suit patient needs and ensuring maximum overall duration of response to therapy.

EVIDENCE ACQUISITION

This was a non-systematic review, based on data from clinical trials, retrospective analyses and expanded-access programmes (EAPs) identified by an English-language literature search carried out in PubMed. The following search terms were used: therapy-related search terms: Nexavar, sorafenib, sorafenib

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TABLE 1 Dermatological toxicities reported in SmPCs, phase III trials and EAPs*

		Incidence of AEs, %													
		HFSR		Rash		Dry skin		Skin discolouration		Pruritus		Hair colour change		Alopecia	
		Grade													
	N	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
Sorafenib															
Phase III† [3]	451	33	6	41	1	13	0	–	–	17	<1	–	–	31	0
SmPC‡ [1]	451	19	4	28	<1	11	0	<1	–	17	<1	–	–	25	<1
EAP (EU-ARCCS) [13]	1145	56	13	33	5	–	–	–	–	11	<1	–	–	33	0
EAP (US-ARCCS)§ [4]	2504	–	10	–	5	–	<1	–	–	–	–	–	–	–	<1
Sunitinib															
Phase III [6]	375	29	9	24	1	21	<1	27	<1	–	–	20	0	12	0
SmPC‡ [2]	544	27	9	22	<1	20	<1	27	<1	7	<1	19	0	12	0
EAP [7]	4371	18	6	15	1	–	–	10	<1	–	–	–	–	–	–
Bevacizumab + IFN															
Phase III [14]	337	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SmPC‡¶ [9]	>3500	–	1–10**	–	–	≥10	–	≥10	–	–	–	–	–	–	–
Temsirolimus															
Phase III [15]	208	–	–	47	4	–	–	–	–	–	–	–	–	–	–
SmPC‡ [10]	208	–	–	42	5	11	1	–	–	19	1	–	–	–	–
Everolimus															
Phase III [16,17]	274	–	–	28	1	12	<1	–	–	12	<1	–	–	–	–
SmPC‡ [11]	274	1–10**	–	≥10	–	≥10	–	–	–	≥10	–	–	–	–	–
Pazopanib															
Phase III [18]	290	6	–	–	–	–	–	–	–	–	–	38	<1	–	–
US PI*‡ [12]	290	6‡	–	8	–	–	–	3	–	–	–	38	<1	8	–

*–, not reported; AE, adverse event; ARCCS, advanced renal cell carcinoma sorafenib; EAP, expanded-access programme; HFSR, hand–foot skin reaction; IFN, inteferon; PI, prescribing information; SmPC, summary of product characteristics. *As pazopanib is not yet licensed in the EU, data from the US PI have been used. †All-causality AEs; ‡Drug-related AEs; §Published reports of the US-ARCCS do not include a listing of all grades of AE (only grade 2 and ≥3); ¶The SmPC for bevacizumab lists AEs reported across multiple clinical trials in patients with various malignancies. AEs are reported as very common (≥10%) or common (≥1–<10%); **Listed as palmar–plantar erythrodysaesthesia syndrome.*

tosylate, sunitinib, Sutent, sunitinib malate, temsirolimus, Torisel, bevacizumab, Avastin, Afinitor, everolimus, RAD001, Votrient, pazopanib; and disease-related search terms: renal cell carcinoma, RCC, metastatic RCC, renal cell cancer, kidney cancer. Original articles describing prospective or retrospective clinical studies and EAPs were included, and the references in review articles were reviewed for potentially relevant additional publications. Additional information was taken from the European summary of product characteristics (SmPC) for each of the agents under consideration.

EVIDENCE SYNTHESIS

MANAGEABLE ADVERSE EVENTS

Most of the AEs frequently associated with targeted therapy are not life threatening and can be managed with good prevention and symptomatic management strategies without the need to permanently discontinue treatment. There are many AEs associated with all of these agents, and they include fatigue, hypertension and diarrhoea. Agent-specific AEs have also been identified, including proteinuria, which is most often seen with bevacizumab plus IFN, hypothyroidism, most often seen with sunitinib, hand–foot skin reaction (HFSR), most often seen with sorafenib, hepatotoxicity most often seen with pazopanib and hyperlipidaemia most often seen with the mTOR inhibitors [1–4,6,7,9–18] (Tables 1–3).

If the patient is well informed about the AEs associated with individual targeted therapies and such AEs are detected sufficiently early, then their impact can be greatly minimized and they should not pose a barrier to continued long-term treatment in patients who respond well. For some patients (e.g. those in certain professions) the impact of some mild AEs may have a great impact on a patient's quality of life (e.g. taste disturbance in a chef, skin conditions in a musician). In such cases, unexpected AE onset and/or late detection may preclude symptomatic management necessitating temporary dose reduction or treatment discontinuation. In some cases, comorbidities such as diabetes and hypertension may also increase the risk of certain AEs. In addition, patient ethnicity and/or genetic predisposition may influence the AE profile of targeted therapy (though this is a subject beyond the scope of this review). To ensure early detection and optimal management of AEs to maximize patient benefits, it is important that the physician is aware of the range of manageable AEs associated with each agent, and that this information is effectively communicated to

TABLE 2 Gastrointestinal toxicities reported in SmPCs, phase III trials and EAPs*

		Incidence of AEs, %															
		Diarrhoea		Constipation		Nausea		Vomiting		Abdominal pain		Mucositis**		Stomatitis††		Dysgeusia	
		Grade															
	N	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
Sorafenib																	
Phase III† [3]	451	48	3	7	0	19	<1	12	1	5	<1	–	–	5	0	–	–
SmPC‡ [1]	451	38	2	6	0	16	<1	10	<1	–††	–	–	–	–§§	–	–	–
EAP (EU-ARCCS) [13]	1145	55	7	–	–	17	1	11	1	–	–	–	–	28	2	–	–
EAP (US-ARCCS)§ [4]	2504	–	2	–	–	–	1	–	–	–	1	–	–	–	1	1	0
Sunitinib																	
Phase III [6]	375	61	9	12	<1	52	5	31	4	11	2	26	2	30	1	46	<1
SmPC‡ [2]	544	60	7	15	<1	53	4	33	3	20	2	23	2	34	2	46	<1
EAP [7]	4371	44	5	13	<1	34	2	25	3	–	–	28	3	–	–	23	1
Bevacizumab + IFN																	
Phase III [14]	337	20	<3	–	–	–	–	–	–	–	–	–	–	–	–	–	–
SmPC‡¶ [9]	>3500	–	≥10	≥10	–	–	≥10	–	≥10	–	1–10	≥10	1–10	≥10	1–10	–	–
Temsirolimus																	
Phase III [15]	208	27	1	20	0	37	2	19	2	21	4	–	–	20	1	–	–
SmPC‡ [10]	208	27	1	20	0	37	2	19	2	21	4	19	1			–	–
Everolimus																	
Phase III [16,17]	274	17	1	–	–	18	<1	15	<1	–	–	17	<1	42	3	–	–
SmPC‡ [11]	274	≥10	–	–	–	≥10	–	≥10	–	1–10	–	–	–			–	–
Pazopanib																	
Phase III [18]	290	52	4	–	–	26	<1	21	2	11	2	–	–	–	–	–	–
US PI*‡[12]	290	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8	–

*–, not reported; AE, adverse event; ARCCS, advanced renal cell carcinoma sorafenib; EAP, expanded-access programme; IFN, interferon; PI, prescribing information; SmPC, summary of product characteristics. *As pazopanib is not yet licensed in the EU, data from the US PI have been used; †All-causality AEs; ‡Drug-related AEs; §Published reports of the US-ARCCS do not include a listing of all grades of AE (only grade 2 and ≥3); ¶The SmPC for bevacizumab lists AEs reported across multiple clinical trials in patients with various malignancies. AEs are reported as very common (≥10%) or common (≥1%–<10%); **Mucositis or mucosal inflammation; ††Stomatitis or oral mucositis; ‡‡Pain (including mouth, abdominal, tumour and headache) is reported as very common (≥10%) across multiple clinical trials in patients with different tumour types; §§Stomatitis is reported as common (1–10%) across multiple clinical studies in patients with various malignancies.*

the patient when selecting and initiating treatment.

Fatigue

Fatigue is a very common AE of targeted therapy and is also a common comorbidity in cancer patients. In most cases, fatigue is probably associated with several contributing factors, which may include hypothyroidism, anaemia and dehydration. It has been suggested that hypogonadism during treatment with TKIs may also contribute to fatigue [19]. Because of its impact on quality of life, exacerbation of this symptom is often of high concern during cancer treatment. Patients with severe fatigue should be monitored for other causes that can be treated. Patient education and counselling may help reduce the impact of fatigue on quality of life by allowing patients to develop appropriate coping strategies. Guidelines from the National Comprehensive Cancer Network are available for managing cancer-related fatigue [20].

Skin and subcutaneous tissue disorders

Although most frequently associated with the TKIs and temsirolimus, dermatological AEs of one type or another occur with all the targeted agents. The reported frequency of common dermatological toxicities associated with individual targeted therapies is outlined in Table 1 [1–4,6,7,9–18]. HFSR and rash are the most common dermatological AEs of the TKIs, sorafenib and sunitinib, whereas temsirolimus is often associated with rash and pruritus. These conditions are the most common of all targeted therapy-related dermatological toxicities and share similar presentation characteristics in terms of symptoms and time of onset.

HFSR

Although not life-threatening, HFSR may range from minimal skin changes (grade 1) to painful ulcerative dermatitis (grade 3) [21]. A retrospective study of cutaneous AEs in 109 patients treated with sorafenib and 119 patients treated with sunitinib suggested that HFSR occurs early within the course of therapy at a median time to onset of 18.4 days with sorafenib, and 32.4 days with sunitinib after the start of therapy [22]. With

TABLE 3 Haematological disorders reported in SmPCs, phase III trials and EAPs*

		Incidence of AEs, %									
		Neutropenia		Thrombocytopenia		Anaemia		Lymphopenia		Leucocytopenia	
		Grade									
	N	All	3/4	All	3/4	All	3/4	All	3/4	All	3/4
Sorafenib											
Phase III† [3]	451	–	–	–	–	–	–	–	–	–	–
SmPC‡ [1]	451	1–10	–	1–10	–	1–10	–	≥10	–	1–10	–
EAP (EU-ARCCS) [13]	1145	–	–	–	–	–	–	–	–	–	–
EAP (US-ARCCS)§ [4]	2504	–	–	–	–	–	–	–	–	–	–
Sunitinib											
Phase III [6]	375	77	16	68	9	79	8	68	16	78	8
SmPC‡ [2]	544	16	10	16	8	12	4	4	2	8	3
EAP [7]	4371	9	4	16	6	10	3	–	–	–	–
Bevacizumab + IFN											
Phase III [14]	337	7	4	6	2	10	3	–	–	–	–
SmPC‡¶ [9]	>3500	–	≥10**	–	≥10	–	1–10	–	–	–	≥10
Temsirolimus											
Phase III [15]	208	7	3	14	1	45	20	–	–	6	1
SmPC‡ [10]	208	7	3	14	1	45	20	5	4	6	1
Everolimus											
Phase III [16,17]	274	11	0	5	1	25	7	42	15	26	0
SmPC‡ [11]	274	–	–	–	–	–	–	–	–	–	–
Pazopanib											
Phase III [18]	290	34	1	32	1	26	<3	31	4	34	1
US PI*‡ [12]	290	34	<2	32	<2	–	–	31	<5	37	0

*–, not reported; AE, adverse event; ARCCS, advanced renal cell carcinoma sorafenib; EAP, expanded-access programme; IFN, interferon; PI, prescribing information; SmPC, summary of product characteristics. *As pazopanib is not yet licensed in the EU, data from the US PI have been used; †All-causality AEs; ‡Drug-related AEs; §Published reports of the US-ARCCS do not include a listing of all grades of AE (only grade 2 and ≥3); ¶The SmPC for bevacizumab lists AEs reported across multiple clinical trials in patients with various malignancies. AEs are reported as very common (≥10%) or common (≥1–<10%); **Grade 3–5 febrile neutropenia is also very common (≥10%) [9].*

both agents, severe HFSR tended to develop earlier than mild HFSR.

There is a lack of prospective data for the assessment of management strategies for treating HFSR. Some patients require symptomatic management strategies while others require dose reduction followed by re-escalation or temporary dose interruption. Some of the symptomatic management strategies that are available include: carrying out baseline skin assessments and advising patients to remove calluses and hyperkeratotic areas before treatment and wear soft, comfortable shoes and socks and use cushioning (to avoid friction and rubbing) [23–27]. HFSR may also be treated with moisturizing creams although urea-containing creams should be used sparingly on hyperkeratotic areas [23–25,28,29]. Whilst it is believed that these measures can minimize symptoms, HFSR is the AE that most commonly results in dose reduction as symptoms can sometimes progress to a degree of discomfort that interrupts activities of daily living [1,26,30]. However, HFSR is a manageable toxicity if detected early and addressed via symptomatic treatment or dose modifications/interruptions as outlined above. Recommendations for temporary treatment interruption and/or dose modification in sorafenib therapy are outlined in Table 4.

Rash. In its mildest form, targeted therapy-associated rash may appear as a macular or papular eruption (grade 1) whereas at grade 4, rash presents as a generalized exfoliative, ulcerative or bullous dermatitis [21]. Skin discolouration (yellowing) usually appears during the first 6 weeks of therapy and normally fades and then disappears after drug discontinuation [31]. Pruritus (itching) may accompany dry skin or rash [30]. The application of topical, moisturizing skin emollients for symptomatic relief of rash, dry skin and pruritus is recommended.

Gastrointestinal disorders

A range of gastrointestinal AEs, such as diarrhoea, dysgeusia, nausea and vomiting, are commonly reported with all the currently available targeted therapies (Table 2). These AEs rarely lead to treatment discontinuation and can generally be managed using pharmacological intervention and dietary modifications. Although generally minor, gastrointestinal AEs can be serious in elderly patients, rapidly leading to serious dehydration if left uncontrolled [32]. There are published clinical guidelines on the management of cancer treatment-related diarrhoea (although these are not specific to targeted therapy or to patients with RCC) [33,34].

TABLE 4 Dose modifications recommended for managing sorafenib-related HFSR [1]

Skin toxicity grade	Occurrence	Suggested dose modification
Grade 1 (numbness, dysaesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activity)	Any occurrence	Institute supportive measures immediately and continue sorafenib
Grade 2 (painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities)	First occurrence	Institute supportive measures and consider a decrease in the dose of sorafenib to 400 mg daily for 28 days If toxicity returns to grade 0–1 after dose reduction, increase sorafenib to full dose after 28 days If toxicity does not return to grade 0–1 despite dose reduction, interrupt sorafenib for a minimum of 7 days, until toxicity has resolved to grade 0–1 When resuming treatment after dose interruption, resume sorafenib at a reduced dose of 400 mg daily for 28 days If toxicity is maintained at grade 0–1 at reduced dose, increase sorafenib to full dose after 28 days.
	Second or third occurrence	As for first occurrence, but upon resuming sorafenib, decrease dose to 400 mg daily indefinitely
	Fourth occurrence	The decision whether to discontinue sorafenib should be made based on clinical judgement and patient preference
Grade 3 (moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living)	First occurrence	Institute supportive measures and interrupt sorafenib for a minimum of 7 days until toxicity has resolved to grade 0–1 When resuming sorafenib after dose interruption, do so at reduced dose of 400 mg daily for 28 days If toxicity is maintained at grade 0–1 at reduced dose, increase sorafenib to full dose after 28 days
	Second occurrence	As for first occurrence, but upon resuming sorafenib, decrease dose to 400 mg daily indefinitely
	Third occurrence	The decision whether to discontinue sorafenib should be made based on clinical judgement and patient preference

Hypertension

Hypertension has a high incidence among some targeted treatments, occurring in 26–30%, 26–34% and 40% of patients receiving sunitinib, bevacizumab plus IFN, and pazopanib, respectively [2,6,9,14,18]. Hypertension is also commonly reported in patients receiving sorafenib (12–17%) [1,3], everolimus (1–10%) [11] and temsirolimus (7%) [10]. The management of hypertension is important in preventing the development of more serious conditions, such as chronic renal failure and cardiac events. Pre-treatment screening and control of blood pressure is recommended before initiating treatment with bevacizumab plus IFN, sunitinib or pazopanib [2,9,12]. Frequent blood pressure monitoring is also essential in patients treated with these agents and is advisable for all patients treated with targeted agents [2,9,18,35,36]. When hypertension occurs, it should be treated promptly with appropriate antihypertensive agents. In patients who develop severe hypertension that is not controlled with medical management, temporary interruption of targeted therapy is recommended [2]. Once hypertension is appropriately controlled, targeted treatment may be resumed [1,2,9].

Haematological disorders

The reported frequencies of common haematological disorders associated with targeted therapies are summarized in Table 3. Haematological disorders require laboratory tests for accurate diagnosis. While many of these AEs may go undetected at an early stage, leading to an escalation in severity before intervention, some are accompanied by symptoms that may help their identification. Common symptoms of thrombocytopenia include bruising, nosebleeds and/or bleeding gums. European guidelines recommend that thrombocytopenia should be treated with prednisolone and by ceasing any medication that may be responsible for causing the AE unless vitally indicated [37]. Another haematological disorder, afebrile neutropenia, can be managed with temporary treatment interruption. Febrile neutropenia, on the other hand, is a life-threatening condition that warrants prompt treatment interruption [27].

Anaemia, which is often accompanied by weakness, fatigue and general malaise, is most common in patients receiving everolimus (Table 3) [38]. It is important that anaemia is diagnosed and treated early, as patients with severe anaemia may develop symptoms such as palpitations, angina, intermittent claudication, fatigue and symptoms of heart failure. In severe cases of anaemia, treatment options range from the administration of recombinant erythropoietin to blood transfusion [39].

*TABLE 5 Potentially life-threatening AEs reported in SmPCs**

	Occurrence of potentially life-threatening AEs			
Targeted agent	Very rare	Uncommon (<1%)	Common (1–10%)	Very common (>10%)
Sorafenib [1]	–	Reversible posterior Leukoencephalopathy Hypertensive crisis Cardiac ischaemia/infarction† Gastrointestinal perforation	–	Haemorrhage
Sunitinib [2]	–	Haematological events† Cardiovascular events† Venous thromboembolic events† Pancreatic events† Hepatobilary events† Gastrointestinal perforation†	–	Haemorrhagic events†
Bevacizumab + IFN [9]	Hypertensive encephalopathy†	–	Cardiac failure Thromboembolism Haemorrhage Gastrointestinal perforation†	–
Temsirolimus [10]	Hypersensitivity/infusion reactions	Intracerebral bleeding† Bowel perforation Pericardial effusion (fluid around the heart)	Pneumonitis† Renal failure† Inflammation of the lungs Pleural effusion (fluid around the lungs) Problems with wound healing	–
Everolimus [11]	–	–	–	Non-infectious pneumonitis† Infections†
Pazopanib* [12]	–	Gastrointestinal perforation† Gastrointestinal fistula†	Arterial thrombotic events† Haemorrhage†	Severe hepatotoxicity†

*–, not reported; AE, adverse event; PI, prescribing information. IFN, interferon; SmPC, summary of product characteristics. *As pazopanib is not yet licensed in the EU, data from the US PI have been used; †Fatal outcomes reported in SmPC (including post-marketing).*

Bleeding and wound-healing complications

As patients with RCC may undergo surgery after or during treatment with targeted therapies, the risk of bleeding is an important consideration when prescribing treatment. Haemorrhagic events are frequently associated with agents targeting the VEGF pathway and have been reported (at any grade) in more than 10% of patients treated with sunitinib [2,6], sorafenib [1], bevacizumab plus IFN [9,14] and pazopanib [12,17]. Generally, these bleeding events are mild and manageable, with epistaxis being the most frequently reported. However, severe haemorrhage, with some fatal outcomes, has been reported with all these agents [1,2,9,12,14], and with temsirolimus [10].

Wound-healing complications have been reported for patients receiving bevacizumab plus IFN, and it is recommended that treatment with bevacizumab plus IFN is stopped for at least 6 weeks before surgery and not resumed for at least 28 days or until adequate wound healing has taken place [9,40]. No formal studies with TKIs on wound healing have been conducted, but as a precaution it is generally recommended that treatment should be interrupted in patients undergoing major surgery [1,2,10,18,41]. For the TKI, pazopanib, for example, it is recommended that treatment should be stopped at least 7 days before scheduled surgery [12]. Wound-healing complications have been reported, although not frequently, in patients receiving temsirolimus and caution is advised when using either of the approved mTOR inhibitors in the perisurgical period [10,11].

Endocrine and metabolic disorders

As with haematological disorders, endocrine disorders require laboratory tests for accurate diagnosis. Symptoms of endocrine disorders such as hyperglycaemia, fatigue and weight loss might also be confused with general cancer-related symptoms, leading to late diagnosis and treatment.

Hyperglycaemia. In phase III studies, hyperglycaemia occurred in 41% of patients treated with pazopanib (grade 3/4 in <1%) [18], 26% of patients treated with temsirolimus (grade 3/4 in 11%) [10,15], and 8% of patients treated with everolimus (grade 3 in 4%) [16]. There are no reports of hyperglycaemia in clinical trials of sorafenib, sunitinib or bevacizumab plus IFN in patients with RCC [1,2,9]. However, the SmPC for bevacizumab states that across multiple studies, grade 3/4 hyperglycaemia occurred with at least a 2% difference compared with the corresponding control groups [9]. Optimal glycaemic control is recommended before starting a patient on temsirolimus and everolimus, and serum glucose levels should be monitored periodically during treatment

[10,11]. Treatment of hyperglycaemia may require an increase in the dose of, or the initiation of, insulin and/or hypoglycaemic agent therapy [10].

Hypothyroidism. Like hyperglycaemia, symptoms of hypothyroidism include fatigue and dry itchy skin. Hypothyroidism has been extensively described in patients treated with sunitinib. While the incidence of hypothyroidism in the sunitinib phase III study was reported as 14% (grade 3/4 in 1%) [2], a recent analysis of other studies suggested that the incidence may be 50% or higher. Monitoring of thyroid function is recommended before and during sunitinib therapy [2]. Hypothyroidism was also observed in the pazopanib phase III study (all grades in 7%) [18] and proactive monitoring of thyroid function is also suggested during treatment with this agent [18]. No hypothyroidism was reported in the sorafenib phase III study. One small retrospective study identified biochemical hypothyroidism in seven of 39 (18%) patients treated with sorafenib [42]. Some authors suggest that thyroid monitoring is warranted with sorafenib; however, the association between sorafenib and hypothyroidism has not been confirmed and there is no recommendation for monitoring in the sorafenib SmPC. Targeted therapy-induced hypothyroidism can generally be managed with levothyroxine replacement therapy according to treatment guidelines [43] and should not require any dose reduction or interruption.

Blood lipid disorders. Hyperlipidaemia, hypercholesterolaemia and hypertriglyceridaemia can all contribute to the onset of cardiovascular disease. These AEs may be of particular concern to those patients who already have risk factors for developing cardiovascular disease (e.g. elderly patients). Blood lipid disorders are especially common AEs of the mTOR inhibitors temsirolimus and everolimus, with hyperlipidaemia reported to occur in 27% of patients treated with temsirolimus and at an incidence of ≥1/10 in patients treated with everolimus [10,11]. Strategies for managing blood lipid disorders include initiating or increasing the dose of lipid-lowering agents; serum cholesterol and triglycerides should be tested before and during treatment with temsirolimus [10].

Proteinuria. Proteinuria has been reported in patients receiving bevacizumab, with an incidence of 0.7–38% across multiple clinical trials [9]. In phase III studies, grade 3/4 proteinuria was seen in 7–15% of patients treated for RCC with bevacizumab plus IFN, however, in most cases proteinuria was not associated with renal dysfunction and permanent discontinuation of therapy was rarely required [9,14,44]. The risk of proteinuria is increased by uncontrolled hypertension. Monitoring of proteinuria is recommended before and during therapy with bevacizumab plus IFN [9]. In the phase III study of pazopanib, proteinuria was reported in 9% of patients and led to discontinuation of treatment in two (<1%) patients [12]. The US prescribing information for pazopanib recommends baseline and periodic urine analysis [12]. With both bevacizumab and pazopanib, therapy should be permanently discontinued in patients who develop grade 4 proteinuria (nephrotic syndrome) [9,12]. There are no reports of proteinuria in patients treated in clinical studies with temsirolimus, everolimus, sorafenib or sunitinib, although cases of proteinuria and rare cases of nephrotic syndrome have been reported through post-marketing experience with sunitinib [2].

LIFE-THREATENING ADVERSE EVENTS

Some AEs associated with targeted agents are life threatening (Table 5). Practitioners need to be aware of these events even if the frequency is relatively low so that they can monitor their patients appropriately to be sure to identify any serious conditions as early as possible. The chances of encountering rarer AEs may increase with longer duration of therapy. Generally, such events are associated with a specific agent or class of agents, e.g. non-infectious pneumonitis and infections are associated with the mTOR inhibitors everolimus and temsirolimus, whereas haemorrhagic and cardiac events are associated with the VEGF-targeted inhibitors (bevacizumab and the TKIs) and hepatotoxicity appears to be specific to pazopanib.

Pneumonitis

Non-infectious pneumonitis (also known as interstitial lung disease or intra-pulmonary disease) is a well-known class effect of the mTOR inhibitor rapamycin derivatives, including everolimus and temsirolimus. In a phase II study of everolimus in patients with RCC, grade 1/2 pneumonitis was reported in 12/39 patients (31%) and grade 3 pneumonitis in 7/39 patients (18%) [45]. In a phase III study, the incidence was lower, with non-infectious pneumonitis of any grade reported in 14% of patients treated with everolimus (grade 3/4 in 4%) [16]. However, a single-centre retrospective examination of radiographic chest images from patients included in this study identified interstitial changes at week 8 in 14/39 patients (36%) receiving everolimus treatment [46]. Similarly, in the temsirolimus phase III study, the reported incidence of non-infectious temsirolimus-induced pneumonitis was 2% (4/208 patients) [10], whereas a retrospective review of computed tomography scans identified temsirolimus-induced pneumonitis in 52/178 patients (29%) [47]. In both studies, the majority of cases appeared within the first 8 weeks of treatment and were asymptomatic. Where clinical symptoms of pneumonitis did occur, these were usually cough or dyspnoea. Most patients were successfully managed with dose interruptions and dose reductions. One patient in the temsirolimus phase III study and one patient in the everolimus retrospective review discontinued treatment [15,46].

In the absence of symptoms, non-infectious pneumonitis need not be a cause for treatment interruption, but severe and fatal outcomes related to mTOR-induced pneumonitis have been reported [10,11]. Temsirolimus- or everolimus-treated patients presenting with non-specific respiratory signs and symptoms, such as hypoxia, pleural effusion, cough or dyspnoea, should be assessed for non-infectious pneumonitis, and dose interruption until resolution of symptoms should be considered. For more severe symptoms, treatment discontinuation and high-dose steroids may be appropriate [10,11]. In addition, it is essential that appropriate diagnostic measures, including bronchoscopy, are taken to exclude an infectious origin or other causes of symptoms [48]. This is particularly important given the risk of opportunistic infection with mTOR inhibitors.

Infections

The mTOR inhibitors, everolimus and temsirolimus, have dose-dependent immunosuppressive properties and can therefore predispose patients to infections. In the temsirolimus phase III study, infections were reported in 27% of patients (grade 3/4 in 5%) receiving temsirolimus vs. 14% (grade

3/4 in 4%) in the control arm [15]. In the everolimus phase III study, infections were reported in 13% of patients (grade 3/4 in 4%) vs. 2% (grade 3/4 in 0%) in the control arm [16]. In one case, severe candidial sepsis, complicated by acute respiratory failure, was fatal [38]. Prescribers should be aware of this increased risk, and should ensure that any pre-existing infections are adequately treated before initiation of mTOR inhibitor therapy and that patients are monitored for signs and symptoms of infection. As noted in the previous section, it is particularly important that patients with pulmonary infiltrates/symptoms are rigorously assessed for signs of infection, owing to the potential overlap between pulmonary infections and non-infectious pneumonitis (which may mandate very different management strategies). A diagnosis of invasive systemic fungal infection should prompt immediate and permanent discontinuation of everolimus [11].

Cardiovascular events

Arterial hypertension can be seen with all targeted agents, however, it is more common with VEGF targeted therapies as discussed previously. Grade 3–4 hypertension occurs in ~3–4% of patients treated with sorafenib, bevacizumab plus IFN or pazopanib, 8–10.3% of patients receiving sunitinib and in 1% of patients treated with temsirolimus [1–3,6,9,14,18]. If left uncontrolled, hypertension can increase the risk of serious cardiovascular events.

Cardiac ischaemia/infarction. In the sorafenib phase III study, 5% of patients on sorafenib experienced cardiac ischaemic/infarct AEs, six of which were reported to be related to the study drug [3]. In the pazopanib phase III study, cardiac ischaemia/infarction was reported in 2% of patients, cerebral vascular accident in <1% of patients and transient ischaemic attack in 1% of patients [12,18]. In a phase II study of sunitinib in cytokine-refractory RCC, 1% of patients experienced treatment-related fatal myocardial infarction [2]. Indeed, patients who present with cardiac events <12 months before sunitinib administration are excluded from sunitinib clinical studies [2]. The SmPC for bevacizumab lists congestive heart failure (CHF) as a common (>1%) AE across studies in multiple tumour types [9], however, in phase III studies in patients with RCC, bevacizumab plus IFN was associated with CHF and cardiac ischaemia/infarction in <1% of patients [14,44]. This combination has been shown to result in an increased incidence of arterial thromboembolic events (including cerebrovascular accidents, transient ischaemic attacks and myocardial infarctions) compared with IFN alone [9,14]. In particular, patients aged >65 years, or those with a history of arterial thromboembolism, have an increased risk of developing arterial thromboembolic events on treatment with bevacizumab plus IFN [9].

Left ventricular ejection fraction. Cardiovascular events, such as a decline in left ventricular ejection fraction (LVEF) and decreased cardiac activity or cardiac failure, have been reported in patients receiving targeted therapies. Decline in LVEF has been reported in 2–21% of patients receiving sunitinib [2] and in 15.6% of patients receiving sorafenib [49]. QT interval prolongation (a condition that may lead to an increased risk of ventricular arrhythmias) is a rare AE that has been reported in 1% of patients treated with sunitinib (changes from baseline in excess of 60 ms [2]) and in approximately 2% of patients treated with pazopanib [12].

Close monitoring for clinical signs and symptoms of CHF is recommended in patients who are prescribed bevacizumab, sunitinib or pazopanib [2,9,12]. However, no clear evidence-based guidelines exist for cardiac monitoring of patients treated with targeted agents. More data, coupled with a multidisciplinary approach involving cardiologists and oncologists, are needed to formulate evidence-based management recommendations for treatment-induced cardiotoxicity in patients with RCC.

Gastrointestinal perforation

Gastrointestinal perforation is an uncommon but potentially fatal AE of all targeted agents, especially bevacizumab plus IFN treatment. The SmPC for sorafenib and sunitinib, and the US prescribing information for pazopanib, all report an incidence of gastrointestinal perforation with each of these agents of <1%, with few fatalities [1,2,12]. In phase III studies of bevacizumab plus IFN in patients with RCC, gastrointestinal perforation occurred at a frequency of 1% and one patient died as a result of bevacizumab-related gastric perforation [14,44]. Across multiple studies in patients with various malignancies, fatal gastrointestinal perforations have occurred in 0.2–1% of bevacizumab-treated patients, most frequently in those with colorectal cancer [9]. Caution is advised when using any of the VEGF-targeted agents in patients at risk for gastrointestinal perforation or fistula. Treatment should be permanently discontinued in patients who do develop gastrointestinal perforation.

Haemorrhage

Serious haemorrhage, generally tumour-related, is a potentially fatal complication of targeted therapies, and is particularly associated with bevacizumab treatment. Grade 3–5 haemorrhage was reported in 2–3% of patients in the phase III clinical trials of bevacizumab plus IFN in patients with RCC [14,44]. A similar frequency of haemorrhage, mostly tumour-related, was reported across multiple studies of bevacizumab treatment in other tumour types [9]. Following a severe CNS haemorrhage in one patient in a phase I study, patients with brain metastases have since been excluded from bevacizumab studies. In an exploratory, retrospective analysis of patients with various tumour types, grade 4 CNS bleeding was recorded in 3/91 (3%) bevacizumab-treated patients with brain metastases [9]. In the SmPC for bevacizumab, it is advised that at-risk patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab should be discontinued if intracranial bleeding occurs [9].

Serious haemorrhage is also a risk with the TKIs. In clinical studies of sunitinib and sorafenib, grade 3 or greater haemorrhage has been reported in approximately 2% of patients [1,2,50]. Fatal haemorrhage has been recorded during post-marketing experience with sunitinib [2]. In the phase III clinical study of pazopanib, 9/290 (3%) patients experienced serious bleeding events, including pulmonary, gastrointestinal and genitourinary haemorrhage, and four patients (1%) died as a result. Across clinical studies of pazopanib in RCC, 5/586 (1%) patients died from haemorrhagic events, which were cerebral or intracranial in two cases [12].

Hepatotoxicity

Hepatotoxicity is a concern generally associated with the newer targeted agents; in phase III studies of the first five targeted agents to be approved, grade 3/4 increases in

serum liver enzymes were infrequent (≤4%) [1,2,9–11]. However, in the phase III clinical study of pazopanib, elevations in serum transaminases and bilirubin were commonly observed, with grade 3/4 elevations in serum alanine transaminase (ALT), serum aspartate transaminase (AST) and serum bilirubin occurring in 12%, 8%, and 3% of patients, respectively [18]. Across all studies investigating pazopanib monotherapy, concomitant elevations in serum bilirubin and serum ALT were recorded in 13/977 (1%) patients, and two patients died from disease progression and hepatic failure [12]. Hepatic function should therefore be monitored in patients treated with pazopanib. In clinical studies, the majority of liver transaminase elevations were seen within 18 weeks of treatment initiation. Regular monitoring of serum liver enzymes (every 4 weeks) is therefore recommended during the first 4 months, with testing continuing periodically thereafter. ALT elevations between three and eight times the upper limit of normal necessitate weekly monitoring. If ALT levels rise above 8 times the upper limit of normal, treatment should be interrupted until levels have returned to grade 1 or baseline. Persistently raised ALT, or concurrently raised ALT and bilirubin, warrant permanent discontinuation of pazopanib [12].

LONG-TERM EXPERIENCE WITH TARGETED AGENTS

As we gain experience with targeted agents we are moving towards longer duration of treatment with individual agents and with the sequential use of agents, therefore, understanding long-term safety profiles is important. As sorafenib and sunitinib were the first targeted agents to be approved for the treatment of RCC, there are published data assessing the long-term tolerability of these agents in clinical settings [4,5,7,8,13]. In the phase III study of sorafenib, long-term treatment over approximately 3 years did not result in the occurrence of new toxicities or in an increase in the overall incidence of treatment-related AEs [5]. Indeed, in terms of initial presentation, most AEs tended to develop in the early cycles of therapy and presented less frequently with each subsequent cycle; first presentations of HFSR, hypertension and diarrhoea were not reported after cycle 13, and first presentation of fatigue was not reported after cycle 15 [5]. The overall incidence of HFSR also decreased after the early cycles [5]. In other cases, AEs may become more apparent over time. For example, the initial safety reports from the phase III study of sunitinib did not mention hypothyroidism, whereas in the final analysis and in EAPs this proved to be a common AE [6,7,51]. It should also be noted, of course, that the frequency of other AEs, e.g. diarrhoea, tends to remain fairly consistent during long-term treatment and as such these events may require ongoing management.

Studies investigating the sequential use of sorafenib and sunitinib have reported that the types and frequencies of observed AEs are in line with those previously reported in the literature for targeted-agent monotherapy [17,52]. Furthermore, one study investigating the third-line use of sunitinib after failure on two other targeted therapies reported that no substantial new toxicities or significantly increased severity of previously experienced AEs were observed during sunitinib rechallenge [53].

Although bevacizumab has not been in use in patients with RCC for as long as sorafenib and sunitinib, it does have a long history of use in patients with cancer, having been approved for the treatment of colorectal cancer in 2004. The safety information in the SmPC for bevacizumab is based on a database of more than 3500 patients with various malignancies [9]. Thus, it is likely that even rare AEs attributable to bevacizumab would have emerged by now.

There are currently no long-term data for the tolerability of everolimus[1], temsirolimus, or pazopanib in RCC. It is therefore possible that the occurrence of some AEs may be underestimated in patients taking these therapies.

CONCLUSIONS

There are differences between the targeted agents that impact treatment selection for specific patients. As different patients have different comorbidities, it is important to carefully consider the AE profile of each targeted agent so as not to exacerbate pre-existing conditions. Also, decisions about how best to make use of the multiple targeted agents available must take account of any overlapping toxicities that could be exacerbated through either concomitant or sequential use. Most of the AEs associated with targeted therapies are not life threatening, and can be easily prevented and managed with early identification. AE prevention and management helps physicians to ensure that patients can adhere to their treatment schedule at an optimal dose, thus prolonging the duration of therapy while patients continue to experience stable disease. Having an awareness of 'rarer' AEs that may be life threatening ensures appropriate monitoring to alert physicians when a switch in therapy may be necessary. An awareness of possible variations in AE profile according to patient ethnicity may also help in this regard. Knowing what treatment-related AEs to expect allows for effective patient education and for management strategies to be put in place. Generally, with agents that have been available for longer, more extensive clinical experience has accumulated and the AE profiles are more predictable. For newer agents, such as everolimus and pazopanib, there is less clinical experience and, as yet, there are no long-term data. In these cases, caution is required with regard to potentially serious AEs, such as liver failure, until more extensive data are available.

[1]There are some long-term safety data for everolimus (Certican®) although these are for patients undergoing organ transplantation at a dose lower than that used to treat RCC. Common AEs of Certican® include: infections, cardiac disorders, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia, hypertension, lymphocoele, venous thromboembolism, leucopenia, thrombocytopenia, anaemia, coagulopathy and thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome.

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CONFLICT OF INTEREST

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Abbreviations: **IFN**, interferon; **AE**, adverse event; **TKI**, tyrosine kinase inhibitor; **VEGF**, vascular endothelial growth factor; **mTOR**, mammalian target of rapamycin; **EAP**, expanded access programme; **SmPC**, summary of product characteristics; **HFSR**, hand–foot skin reaction; **CHF**, congestive heart failure; **LVEF**, left ventricular ejection fraction; **ALT**, alanine transaminase; **AST**, aspartate transaminase; **RCC**, renal cell carcinoma.