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REVIEW ARTICLE

Tyrosine Kinase Inhibitors: Their On-Target Toxicities as Potential Indicators of Efficacy

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Abstract Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of certain forms of cancers, raising hopes for many patients with otherwise unresponsive tumours. While these agents are generally well tolerated, clinical experience with them has highlighted their unexpected association with serious toxic effects on various organs such as the heart, lungs, liver, kidneys, thyroid, skin, blood coagulation, gastrointestinal tract and nervous system. Many of these toxic effects result from downstream inhibition of vascular endothelial growth factor or epidermal growth factor signalling in cells of normal organs. Many of these undesirable effects such as hypertension, hypothyroidism, skin reactions and possibly proteinuria are on-target effects. Since tyrosine kinases are widely distributed with specific functional roles in different organs, this association is not too surprising. Various studies suggest that the development of these on-target effects indicates clinically desirable and effective inhibition of the corresponding ligand-mediated receptor linked with oncogenesis. This is reflected as improved efficacy in the subgroup of patients who develop these on-target adverse effects compared with those who do not. Inevitably, issues arise with respect to the regulatory assessment of efficacy and risk/benefit of the TKIs as well as the clinical approach to managing patients who develop these effects. Routine subgroup analysis of efficacy data from clinical trials (patients with and without on-target toxicity) may enable more effective clinical use of TKIs since (i) discontinuing or reducing the dose of the TKI has a negative impact if the tumour is TKI-responsive; and (ii) it is usually possible to manage these undesirable on-target effects with conventional clinical approaches. Prospective studies are needed to investigate this proposition further.

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1 Introduction

Protein kinases have emerged as key pharmacological targets in the development of modern highly targeted drugs in oncology [1]. Phosphorylation of proteins by these kinases is an important activating mechanism in the communication of signals within a cell and regulation of cellular activity and function [1, 2]. Depending on their substrate specificity, these enzymes catalyze phosphorylation of tyrosine or serine/threonine, the three protein amino acids with a free non-carboxyl hydroxyl group. Tyrosine kinases are divided into two main families [2]. One family, referred to as receptor tyrosine kinases, consists of transmembrane receptor-linked kinases with a high affinity for many polypeptide growth factors such as vascular endothelial growth factor (VEGF) or epidermal growth factor (EGF), cytokines, and hormones which act as ligands of these receptors. The other family, referred to as non-receptor tyrosine kinases, consists of cytoplasmic proteins which lack transmembrane domains and are found in the cytosol, the nucleus and the inner surface of the plasma membrane. Many receptor tyrosine kinases are involved in oncogenesis, either due to gene mutation or chromosome translocation or simply by over-expression. In every case, the result is a 'gain-of-function' hyperactive kinase that induces an aberrant, ligand-independent, unregulated growth stimulus to the cancer cells. These findings provide

the pharmacological basis and impetus to the development of tyrosine kinase inhibitors (TKIs). We have previously summarized the physiological functions and clinical significance of these enzymes [3] but refer the reader to the reviews by others for a detailed understanding of this complex signalling system [1, 4–7]. No less than 16 small molecule TKIs have already been approved for clinical use in various cancers and many more are in the pipeline. The principal pharmacological targets of these TKIs have been summarized by us elsewhere [3].

Only a few of these agents, such as axitinib, bosutinib, erlotinib, gefitinib, ruxolitinib and vemurafenib, are selective enough for one or two receptor types but most of them target a variety of receptors. While these agents are generally well tolerated, clinical experience with them has highlighted their unexpected association with serious toxic effects on the heart, lungs, liver, kidneys, thyroid, skin, blood coagulation, gastrointestinal tract and the nervous system. Bleeding and thromboembolism are also associated with inhibitors of angiogenesis and result from endothelial dysfunction. Although the occurrence of haemorrhage and thromboembolism from the same drug may appear at first to be paradoxical, they are both underpinned by the same mechanisms. Within the microvasculature, there is an extremely tightly regulated balance of pro- and anti-coagulant proteins, platelet activating and inhibiting factors, and pro- and anti-fibrinolytic products [8, 9]. Disruption of this intricate balance could tip the system either way, promoting thromboembolism or haemorrhage.

Table 1 summarizes the cardiovascular risks associated with TKIs; we have previously reviewed some of these as well as the pharmacological properties of the 16 TKIs approved as of 30 September 2012 [3]. Tables 2 and 3 summarize the major non-cardiovascular adverse effects associated with these TKIs. For some TKIs, one or the other of these toxicities has proved to be a dose-limiting toxicity, thus limiting the ability to push up the doses to improve efficacy. Despite their toxicity profile, novel TKIs continue to be approved since they are effective, often highly so, in treating life-threatening conditions for which there are limited treatment options, if any in some cases. In a study comparing three groups of antineoplastic agents, the clinical benefit derived from recently approved antineoplastic drugs was found to be greater for targeted anticancer agents than for chemotherapeutic agents [10].

Protein kinases are so widely distributed and have such diverse physiological roles in various organs and body systems that their inhibition, unless highly selective for a particular ligand-mediated pathway *and* highly organ-specific, may be expected to have not only the desirable (efficacy) but also other undesirable (toxic) effects. For example, TKIs that target angiogenesis by inhibiting VEGF receptors (VEGFRs) are frequently associated with hypertension, haemorrhage and/or thrombosis [11, 12], whereas, in contrast, agents that inhibit EGF receptors (EGFRs) are more prone to induce diarrhoea or skin rash [13, 14]. Therefore, the efficacy and many toxic effects of TKIs are often intricately linked to each other; so much so that some of these on-target toxic effects such as hypertension, hypothyroidism or rash are believed to have a potential role as biomarkers of effective pharmacological inhibition of the target pathway and therefore clinically relevant antineoplastic activity. Other toxic effects such as haemorrhage or thrombotic events, although they may be on-target effects, are clearly unsuitable for this purpose.

In the context of drug toxicity, the terms ‘on-target’ and ‘off-target’ require an explanation. ‘On-target’ toxicity occurs due to primary pharmacological effects of a drug, whereas ‘off-target’ toxicity occurs due to secondary pharmacological effects of a drug. In the context of TKIs, ‘on-target’ toxicity occurs when the tyrosine kinase target regulating cancer cell survival and/or proliferation (and therefore a target for antineoplastic therapeutic effect) also serves an important role in normal function at a remote site, and its inhibition leads to an undesirable effect. ‘Off-target’ toxicity occurs when a TKI leads to toxicity via inhibition of a kinase (or any other mechanism) not intended to be a target of the drug [2]. Therefore, in this review, we refer to a toxic or an adverse effect as an ‘on-target’ effect if it is (i) at a site that is remote from the intended site of effect, *and* (ii) due to the same pharmacological mechanism that is also responsible for the therapeutic effect.

The purpose of this review is to provide an overview of easily measured or diagnosed on-target adverse effects that may have a potential role as biomarkers of efficacy and to provide evidence-based data regarding the mechanism that underpin these effects and evidence linking the induction of these undesirable effects to efficacy.

2 On-Target Toxicities due to Inhibition of Vascular Endothelial Growth Factor Receptors

There is now compelling evidence to indicate that induction of hypertension or hypothyroidism by a VEGFR inhibitor denotes adequate pharmacological inhibition of VEGFR and therefore is a predictor of its improved efficacy. In this section, we discuss the evidence that supports this notion.

2.1 Systemic Hypertension

Hypertension is likely a downstream consequence of disruption or inhibition of VEGFR-mediated angiogenesis. Vascular endothelium is physiologically a highly active tissue, secreting vasodilators such as nitric oxide and

Table 1 Cardiovascular toxicity of approved tyrosine kinase inhibitors (TKIs)[a] [reproduced from Shah et al. [3], with permission from Springer International Publishing AG 2013. All rights reserved]

Drug	Hypertension	Pulmonary hypertension	Bleeding	Venous thrombosis	Pulmonary embolism	Arterial thrombosis	CHF/LV dysfunction	QT liability[b]	Effusions/ oedema
Axitinib	■		■	■	■	■			
Bosutinib							■		■
Crizotinib					■			■	■
Dasatinib		■	■	■	■	■	■		■
Erlotinib				■		■			
Gefitinib								?[d]	
Imatinib			■			■			■
Lapatinib							■	■	
Nilotinib						■	■	■[c]	■
Pazopanib	■		■	■	■	■	■	■	
Regorafenib	■		■			■			
Ruxolitinib									
Sorafenib	■		■	■		■	■	■	
Sunitinib	■		■	■	■	■	■	■	■
Vandetanib	■		■			■	■	■[c]	
Vemurafenib								■	■

This table has been compiled with information contained in the US FDA-approved labels of these 16 TKIs (for details, see references 17–32)

[a] No inferences should be drawn from this table on the incidence of these events

[b] Authors' evaluation of the QT liability

[c] Boxed warning

[d] Data not certain enough to draw any conclusions on QT-liability of gefitinib

prostacyclin, and stimulation of VEGFR results in reduction of blood pressure. It is therefore not surprising that hypertension is the most frequently observed toxicity associated with TKIs (such as axitinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib) that potently inhibit VEGFR, especially the VEGFR2. Vascular rarefaction from impaired angiogenesis, resulting in an increased peripheral resistance, has also been proposed as an alternative mechanism for TKI-induced hypertension. However, this pathogenic mechanism does not explain the rapid onset of hypertension so often observed, and its amelioration on discontinuation of treatment, with a VEGFR inhibitor. Other studies, however, have suggested that a contributory role of vascular rarefaction cannot be discounted [15]. The cumulative incidence of hypertension (systolic blood pressure [SBP] $\geq$160 mmHg or diastolic blood pressure [DBP] $\geq$100 mmHg) following treatment with pazopanib is 28 %, 44 % and 57 % by days 9, 22 and 29, respectively [16]. This time-related increase in frequency likely supports the role of both mechanisms.

Incidence of hypertension, based on approved labelling, associated with VEGFR inhibitors is typically in the order of 20–30 % but may be higher with some agents such as pazopanib and axitinib (about 40 %) [17–33]. A meta-analysis of 10 trials that included 3154 patients treated with vandetanib, the majority with thyroid and lung cancers, reported summary incidences of all-grade and high-grade hypertension of 24.2 % and 6.4 %, respectively, but the incidence of all-grade hypertension across these 10 trials ranged from 4.2 % to 39.6 % [34]. The incidences of all-grade and high-grade hypertension also varied with tumour type treated, being higher in patients with medullary thyroid cancer than with non-small-cell lung cancer (NSCLC), and being higher with longer treatment duration in medullary thyroid cancer [34].

A number of studies have reported an association between TKI-induced hypertension and efficacy. Following a retrospective analysis of data from four studies of patients with metastatic renal cell carcinoma (RCC) who were treated with sunitinib, Rini et al. [35] reported better outcomes among patients who had sunitinib-induced hypertension defined by maximum SBP. For patients with and without hypertension, objective response rates (ORR) were 54.8 % versus 8.7 %, respectively, median progression-free survival (PFS) 12.5 months versus 2.5 months, respectively, and overall survival (OS) 30.9 months versus 7.2 months. Similar results were obtained when comparing patients with versus without sunitinib-induced hypertension defined by maximum DBP. A retrospective analysis by George et al. examined correlations between sunitinib-associated hypertension

Table 2 Serious non-cardiovascular effects of approved tyrosine kinase inhibitors (TKIs)[a]

Drug	Myelosuppression	Hypersensitivity and skin reactions	Pneumonitis	Hepatotoxicity	Hypothyroidism	GI perforation	Others
Axitinib	■			■	■	■	
Bosutinib	■	■		■			Renal failure
Crizotinib	■		■	■			Neuropathy
Dasatinib	■						Neuropathy
							Renal failure
Erlotinib		■	■	■		■	Renal failure
							Corneal effects
Gefitinib		■	■	■			
Imatinib	■	■		■	■		Renal failure
Lapatinib		■	■	■[b]			
Nilotinib	■	■	■	■			Neuropathy
							Renal failure
Pazopanib	■	■		■[b]	■	■	
Regorafenib	■			■[b]	■	■	
Ruxolitinib	■						
Sorafenib	■	■	■	■	■	■	Neuropathy
							Renal failure
Sunitinib	■	■		■[b]	■	■	Renal failure
Vandetanib	■	■	■		■		
Vemurafenib		■		■			Neuropathy
							Uveitis/Iritis
							Cutaneous squamous cell carcinoma
							New melanoma

This table has been compiled with information contained in the US FDA-approved labels of these 16 TKIs (for details, see references 17–32)

GI Gastrointestinal

[a] No inferences should be drawn on the incidence of these events from this table

[b] Boxed warning

and antitumor efficacy ($N = 319$) and safety ($N = 1565$) across three advanced gastrointestinal stromal tumour (GIST) studies [36]. Blood pressure was measured on days 1 and 28 of each treatment cycle at a minimum, and patient subgroups with and without hypertension (maximum SBP ≥140 mmHg and/or DBP ≥90 mmHg) were compared using Cox proportional hazards models. Landmark analyses were performed to evaluate associations between early hypertension and efficacy endpoints as well as adverse events. They reported that sunitinib-associated hypertension correlated with improved ORR, time to tumour progression, PFS and OS. However, incidences of hypertension-related adverse events were low and similar between groups, although incidences of cardiovascular adverse events were somewhat higher in patients with hypertension. Another retrospective analysis [37] of 230 patients (112 with RCC, 59 with thyroid cancer, 30 with lung cancer and 29 with melanoma) treated with axitinib showed that patients with DBP ≥90 mmHg had a significantly lower relative risk of death than those with DBP <90 mmHg (adjusted hazard ratio [HR] 0.55 [95 % CI 0.39–0.77]; $p < 0.001$). In patients with DBP ≥90 mmHg, the relative risk of progression was also lower (HR 0.76 [95 % CI 0.54–1.06]; $p = 0.107$) and ORR was significantly higher (43.9 % vs. 12.0 %; $p < 0.001$). In an 8-week landmark analysis, median OS (25.8 vs. 14.9 months) and median PFS (10.2 vs. 7.1 months) were greater for patients in the ≥90 mmHg group [37]. Adverse events were otherwise similar between groups. In patients with advanced hepatocellular cancer (HCC) who were treated with sorafenib, patients who had documented hypertension while on treatment had significantly better OS (18.2 vs. 4.5 months) [38].

Although the data are lacking or insufficient, it seems reasonable to conclude that hypertension may also be correlated with antineoplastic efficacy of other VEGFR inhibitors. This association of hypertension with inhibition

Table 3 Other frequent or non-serious adverse reactions reported with approved tyrosine kinase inhibitors (TKIs)[a]

	Diarrhoea	Vomiting	Proteinuria	Arthralgia/ Myalgia	Photosensitivity	Pruritus	Skin/hair depigmentation	Others
Axitinib	■	■	■					
Bosutinib	■	■		■		■		Dysgeusia
Crizotinib	■	■						Visual
Dasatinib	■							
Erlotinib	■	■		■				
Gefitinib	■	■				■		
Imatinib	■	■		■				
Lapatinib	■	■						
Nilotinib	■	■		■		■		
Pazopanib	■	■	■				■	Dysgeusia
Regorafenib	■	■	■					Dysphonia
								Dysgeusia
								Alopecia
Ruxolitinib								
Sorafenib	■		■					Alopecia
Sunitinib	■	■	■	■			■	Dysgeusia
Vandetanib	■	■	■		■			
Vemurafenib	■	■		■	■	■		Alopecia

This table has been compiled with information contained in the US FDA-approved labels of these 16 TKIs (for details, see references 17–32)

[a] No inferences should be drawn on the incidence of these events from this table

of VEGFR and its potential application as a biomarker of efficacy is further supported by the report that the VEGF-634CC genotype is associated with substantially decreased frequency and duration of sunitinib-induced hypertension compared with the VEGF-634GG genotype in patients with RCC [39]. Often this difference in efficacy is sufficiently striking in that it is observed even in small studies. For example, in a study of a total of 36 patients with metastatic RCC treated with sunitinib, development of hypertension ($n = 22$) was associated with better tumour response, longer PFS and OS compared with no hypertension [40].

2.2 Hypothyroidism

Thyroid dysfunction associated with TKIs spans a range of abnormalities, including hypothyroidism, thyroiditis and hyperthyroidism, but hypothyroidism is by far the most common of these. Hypothyroidism can be clinically overt or subclinical. It has been reported in preapproval clinical trials with axitinib, imatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib. According to approved labelling, the incidence ranges from about 4–5 % with pazopanib and regorafenib to as high as 32 % with vandetanib [26, 27, 31]. Among patients with normal baseline thyroid function, Clemons et al. [41] reported hypothyroidism in 15 (44 %) of 34 patients treated with sunitinib and 6 (27 %) of 22 patients treated with sorafenib. Daimon et al. [42] reported the incidence of thyroid dysfunction, which tended to be higher in patients treated with axitinib (6 of 6 = 100 %) than in those treated with sunitinib (9 of 15 = 60 %) or sorafenib (6 of 12 = 50 %). According to Torino et al. [43], retrospective studies indicate that sunitinib can induce hypothyroidism in 53–85 % of patients, and in prospective studies this complication has been reported in 36–71 % of patients. Sorafenib has been reported to be responsible for hypothyroidism in 18 % of patients with metastatic RCC. Biochemical hypothyroidism (as determined by the rise in serum thyroid-stimulating hormone [TSH] level) may be even more common. Monitoring of thyroid function tests at baseline and periodically thereafter is recommended. Although hypothyroidism seems to be reversible in the majority of patients, some patients develop irreversible thyroid damage requiring long-lasting thyroid hormone replacement therapy [44].

The precise mechanism or pathway involved in TKI-induced hypothyroidism is not known and a number of mechanisms (off- and on-target) have been suggested to explain this unexpected effect [43]. In this respect, it is worth bearing in mind that hypothyroidism was reported in 35 % of 281 cancer patients receiving immunotherapy with interleukin (IL)-2 alone, although moderate or severe hypothyroidism requiring thyroid hormone replacement occurred in only 9 % of these patients [45]. Hypothyroidism

was related to duration of IL-2 therapy and was not associated with clinical response. In an earlier study of 111 euthyroid patients with cancer who were receiving IL-2-based immunotherapy, primary hypothyroidism developed in 32 % during immunotherapy and 14 % after immunotherapy [46]. Three patients required levothyroxine. Elevated titres of antithyroglobulin and antithyroid microsomal antibodies were detected after treatment in 9 % and 7 %, respectively, of all patients without prior antibody abnormalities. This raises the possibility of an immune mechanism.

Wong et al. [47] have shown that in vitro, sunitinib had antiperoxidase activity that was about one-fourth the potency of propylthiouracil. Following a detailed study of 24 patients treated with sunitinib, Mannavola et al. [48] reported significant variations in ^{123}I uptake. Absence of thyroid autoimmunity, lack of a preceding transient hyperthyroidism and normal ultrasound pattern led them to conclude that the underlying mechanism is an impaired iodine uptake. Abdulrahman et al. [49] have shown that sorafenib enhances T4 and T3 metabolism, and suggested that in addition to any effects on thyroid vasculature, enhanced peripheral metabolism of thyroid hormone, likely by activity of type 3 de-iodinase, may contribute to hypothyroidism during therapy with these drugs. This observation has also been confirmed by Kappers et al. following treatment with sunitinib [50].

In vitro and in vivo studies have demonstrated that VEGF and VEGFR messenger RNA and protein are expressed in normal thyroid follicular cells. This is mediated in part by TSH [51]. Makita et al. [52] provided evidence that sunitinib induces hypothyroidism by reducing blood flow via capillary regression and constriction. ^{99m}Tc scintigraphy and ultrasonographic studies also suggest that sunitinib-induced hypothyroidism may occur frequently and may be a consequence of thyroiditis with transient thyrotoxicosis and that the marked decrease in thyroid size due to reduced capillary blood flow induced by VEGFR inhibition may cause delayed and/or permanent hypothyroidism [53]. In a Computed tomography (CT) scan study of 21 patients (9 receiving sorafenib and 12 receiving sunitinib) who developed hypothyroidism (as defined by raised TSH levels), thyroid gland was reduced in size to 89 ± 16 % after 3 months, 81 ± 21 % after 6 months, 71 ± 21 % after 9 months and 68 ± 21 % after 12 months, whereas the patients without hypothyroidism maintained a thyroid size of 90 ± 12 % even after 12 months ($p = 0.0030$) [54]. Among the patients with hypothyroidism, those treated with sunitinib tended to show greater reduction in thyroid size than those treated with sorafenib (59 ± 23 % vs. 79 ± 13 %, after 12 months).

Riesenbeck et al. [55] studied 31 patients who received sorafenib and 52 who received sunitinib. Twenty-one of the 66 (31.8 %) evaluable patients developed hypothyroidism during treatment (8 were treated with sorafenib and 13 with sunitinib). Abnormal TSH values occurred during the first 4 weeks of therapy in most (76.2 %) of these patients. Hypothyroidism was associated with a longer PFS (16.0 ± 0.8 months vs. 6.0 ± 0.8 months, $p = 0.032$). Hormone replacement with levothyroxine did not have an influence on survival. In multivariate analyses, hypothyroidism was an independent prognostic parameter ($p = 0.01$). Schmidinger et al. [56] reported subclinical hypothyroidism in 30 patients (36.1 %) within the first 2 months after initiating treatment with sorafenib or sunitinib. There was a statistically significant correlation between the occurrence of subclinical hypothyroidism during treatment and ORR (hypothyroid patients vs. euthyroid patients: 28.3 % vs. 3.3 %, respectively; $p < 0$ .001) and the median duration of survival (not reached vs. 13.9 months, respectively; HR 0.35; 95 % CI 0.14–0.85); $p = 0.016$). In multivariate analysis, development of subclinical hypothyroidism was identified as an independent predictor of survival (HR 0.31; $p = 0.014$). In the study by Clemons et al. referred to earlier [41], there was a statistically significant difference in the PFS between patients who developed hypothyroidism while receiving treatment compared with those who did not (18.2 vs. 10.1 months; $p = 0$ .01).

2.3 Proteinuria

Proteinuria has been reported following therapy with axitinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib. Its incidence varies with the agent, different studies and the patient population studied, ranging from isolated cases on sunitinib, just under 10 % on pazopanib and vandetanib to as high as 25 % with regorafenib (after adjusting for placebo rates). The interval to onset of proteinuria is not well characterized but Robinson et al. [57] have reported development of hypertension and proteinuria within 3 days and 2 weeks, respectively, of treatment with cediranib, an investigational VEGFR inhibitor. Only 35 % of 20 women who developed grade 3 hypertension developed proteinuria. In terms of severity, grade 3 proteinuria was a dose-limiting toxicity in a phase I trial of KRN951, another investigational VEGFR inhibitor [58] and in pre-approval trials proteinuria sometimes led to discontinuation of therapy with pazopanib.

Although it is easily measurable, proteinuria as an adverse effect of TKIs is not as well-characterized as some of their other effects. It is likely a mechanism-based toxicity resulting from inhibition of VEGFR [59]. The pathogenic mechanism of proteinuria in patients receiving anti-VEGF therapy is complex and has been reviewed by others [60–62]. The mechanism likely involves multiple

pathways and, when present, hypertension also plays an aggravating role. Podocytes (the glomerular visceral epithelial cells) play a central role in maintaining the selective filtration barrier of the renal glomerulus. Glomerular podocytes produce large amounts of VEGF during fetal development as well as during adulthood. Production of VEGF (by podocytes) is required for health and maintenance of the adjacent glomerular endothelium [59]. Nephrin is a transmembrane protein that is one of the major components of the slit membrane of podocytes, and it has an important role in maintaining its structure. Accumulating evidence suggests that in vivo nephrin associates with VEGFR2, and that nephrin-VEGFR2 interaction is a direct interaction occurring through VEGFR2 and nephrin cytoplasmic domains. Nephrin-VEGFR2 interaction is modulated by tyrosine phosphorylation of both cytoplasmic domains [63]. The role of nephrin is emphasized by the fact that glomerular nephrin under-expression is one of the mechanisms of the proteinuria induced by anti-angiogenic agents [64] and that ACE inhibitors have been shown to induce re-expression of nephrin in diabetic nephropathy [65] and improve endothelial function [66].

This mechanism, albeit complex, linking VEGFR inhibition with proteinuria, suggests that efficacy of TKIs may correlate with the occurrence of proteinuria; however, there are no published studies to substantiate this.

3 On-Target Toxicity due to Inhibition of Epidermal Growth Factor Receptors

3.1 Skin Reactions

Although a number of TKIs are associated with skin reactions, sometimes with a fatal outcome, the agents more prone to induce these are erlotinib, gefitinib, imatinib, sorafenib and vandetanib. These effects can range from simple rash to potentially fatal reactions such as bullous exfoliative dermatitis, Stevens–Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme and, exceptionally, anaphylaxis. However, acneiform rash is the most frequent skin toxicity induced by EGFR inhibitors. Their onset is usually within 2–4 weeks of initiating therapy. Depending on the drug, their incidence ranges from about 20 % to 75 %, usually grade 1 or 2 in severity. More severe forms are less frequent but sufficiently common as to warrant vigilance and discontinuation of therapy. In a meta-analysis of nine studies that included a total of 2961 patients treated with vandetanib, the summary incidences of all-grade and high-grade rash were 46.1 % and 3.5 %, respectively [67]. Lapatinib-associated skin reactions appear to differ clinically from those associated with other EGFR inhibitors in both frequency and severity. [68]. Most lapatinib-induced events developed between days 1 and 14 of starting treatment, with a median duration of 29 days. Three percent of these led to lapatinib dose reduction, 7 % resulted in dose interruption and 1 % led to drug discontinuation. Reported incidences of individual less severe skin reactions in association with sorafenib and sunitinib have been summarized by others [69, 70].

Skin toxicity is believed to be related to the inhibition of EGFR in the skin, which is crucial for the normal development and physiology of the epidermis. It is also believed to be a class effect of EGFR inhibitors [13]. Gefitinib and erlotinib are both metabolized primarily by cytochrome P450 (CYP) 3A4 but CYP1A1 also plays a major role in the metabolism of erlotinib and CYP2D6 provides a significant alternative pathway for the elimination of gefitinib. Suzumura et al. have recently reported that the frequency of skin rash is significantly higher in gefitinib-treated (but not erlotinib-treated) patients with reduced CYP2D6 activity compared with those with CYP2D6 normal activity [71], although available evidence does not suggest an association between both total and unbound gefitinib steady-state plasma trough concentrations and the development of skin rash [72]. The pathophysiology of skin toxicity has not been fully elucidated, but the leading hypothesis is that the keratinocytes of the basal layer of the epidermis react to EGFR inhibition by secreting cytokines that trigger an inflammatory response that eventually causes loss of skin barrier protection and secondary skin infections involving mainly the hair follicles [73]. Patients who have received radiotherapy prior to EGFR inhibitor administration tend not to develop a rash during erlotinib therapy over those areas of skin exposed to prior irradiation [74]. One explanation for this is that this may be a result of depletion of EGFR-expressing cells or that it may represent alterations in the microvasculature in the skin covering irradiated areas.

Presence and severity of skin rash is reportedly associated with improved clinical efficacy in patients receiving EGFR inhibitors, although the reasons for this association are not fully understood. Data reviewed by Pérez-Soler [75, 76] indicate that rash severity was highly significantly associated with survival in patients with NSCLC receiving erlotinib; median survival in patients with no rash was 46.5 days compared with 257 days in those with grade 1 rash ($p < 0.0001$) and 597 days in those with grade 2–3 rash ($p < 0.0001$). Similarly, for the combined NSCLC, head and neck cancer and ovarian cancer studies, median survival in patients with no rash was 103 days compared with 191 days in those with grade 1 rash ($p = 0.0001$) and 266 days in those with grades 2–4 rash ($p = 0.0001$). Data from one large phase III study (single agent in NSCLC, $n = 444$ in the erlotinib group and $n = 229$ in the placebo group) showed that the presence of rash strongly correlated

with OS. This correlation increased with rash severity grade: grade 1 versus no rash (HR 0.41; $p < 0.001$) and grade ≥2 versus no rash (HR 0.29; $p < 0.001$). Similar results were observed for PFS. Disease control (complete response + partial response + stable disease) seemed to increase with the presence and severity of rash [77]. In one pharmacogenetic study of EGFR polymorphisms, the T allele of −216G/T was associated with significantly higher rates of stable disease/partial response ($p = 0.01$) and also with a significantly higher risk of gefitinib-related rash/diarrhoea ($p = 0.004$) in a multivariate model [78]. In a study of sorafenib in the treatment of HCC, the tumour control rate was 48.3 % in patients who developed skin toxicity versus 19.4 % in patients without cutaneous side effects, and the median time to progression was 8.1 months in the group of patients with skin toxicity versus 4.0 months in those without skin toxicity [79]. In a meta-analysis of 17 prospective trials and 7 retrospective case series [80], skin rash was found to be an independent predictive factor for survival (HR 0.30; $p < 0.00001$) and progression (HR 0.50; $p < 0.00001$) in NSCLC patients treated with anti-EGFR TKIs. In addition, patients who developed grade 2–4 rash were more likely to respond to treatment compared with patients with no rash (42 % vs. 7 %). The result for survival meta-analysis appeared to be similar for gefitinib and erlotinib. A retrospective study of pancreatic cancer patients who received combination gemcitabine and erlotinib also reported longer OS in association with high-severity rash in erlotinib-treated pancreatic cancer patients [81]. In another analysis of efficacy of erlotinib in 184 patients, of whom 124 had skin rash at 1 month, it was determined that median PFS in patients who were observed with rash during the treatment was 3.0 vs. 1.2 months in patients with no rash ($p < 0.001$). The corresponding data for OS, ORR, PFS at 1 month and OS at 1 month were 13.9 vs. 5.8 months ($p < 0.001$), 17.4% vs. 3.3% ($p = 0.001$), 2.9 vs. 1.1 months ($p = 0.027$) and 13.8 vs. 9.9 months ($p = 0.082$), respectively [82]. Mita et al. evaluated the antineoplastic activity of erlotinib in patients with advanced NSCLC in whom the dose was increased until a maximal level of tolerable skin toxicity was reached and characterized its pharmacokinetics and pharmacodynamics [83]. Dose escalation to 200–475 mg/day was feasible in 38 (90 %) of the 42 patients. Median PFS was 2.3 months (95 % CI 1.61–4.14) across all patients but was 3.5 months and 1.9 months, respectively, for patients who did and did not experience the target rash (HR 0.51; $p = 0.051$). Neither the rash severity nor the response correlated with erlotinib exposure. A recent meta-analysis of 33 eligible trials involving 6,798 NSCLC patients treated with EGFR-inhibiting TKIs, using various severities of rash as markers of outcome, has reported that skin rash not only predicts the clinical response (higher ORR and disease control rates) but also serves as a prognostic factor (longer PFS and OS). All these outcomes were significantly better in the rash group than in the no-rash group [84].

It is worth cautioning that other factors may influence the predictive value of skin reactions. For example, skin toxicity has been consistently linked with higher response rates and longer survival among patients with metastatic colorectal cancer who have been treated with cetuximab [85], whereas patients without rash appear to have a poor outcome. However, subsequent studies of outcomes by *KRAS* status showed that cetuximab dose escalation did not increase response in patients with tumours carrying a mutant *KRAS* gene [86] but there was evidence of improved response rate in those carrying the wild-type *KRAS* gene [87]. In an earlier study, *KRAS* status was an independent prognostic factor associated with OS and PFS, whereas skin toxicity was only associated with OS [88].

4 Implications for the Assessment of Efficacy, Therapeutic Dose and Risk/Benefit

Regulatory authorities frequently undertake or request analyses of efficacy (and safety) by subpopulations. The variables usually include baseline demographics such as age, sex, ethnicity, geographic region and disease characteristics such as baseline disease severity, previous therapy and, as it relates to TKIs, presence of specific mutations. Subgroup analysis by ethnicity revealed that the ORR to gefitinib was much higher in the Japanese patients (27.5 %) compared with the Caucasian patients (10.8 %) [89]. Further analysis of the data revealed this inter-ethnic difference to be due to a higher frequency of activating mutations of the EGFR tyrosine kinase domain in the Asian populations. However, in general, such analyses have rarely yielded sufficiently reliable information relevant to optimizing therapy during the post-approval period, and regulatory authorities require prospective confirmatory trials to demonstrate effects observed in subgroup analysis. Although the notion of on-target side effects of drugs is all too well-known (e.g. excessive anticoagulation following warfarin or hypotension and oedema following calcium channel blockers [CCBs]), these exaggerated effects occur at the intended site and are predictable. They serve no useful purpose as markers of efficacy; rather they indicate unnecessarily high plasma concentrations of the drug resulting from inappropriate dose or drug interactions. In contrast, unpredictable on-target effects of TKIs discussed above occur at sites remote from that intended for therapeutic purpose and are indicative of effective (generalized) inhibition of the pharmacological target that translates into clinical efficacy at the intended site of action.

Regulatory submission of sorafenib included an analysis of the relationship between hypertension and efficacy based on investigator-assessed PFS data from one of the studies [90]. PFS in sorafenib-treated patients was analysed by presence or absence of hypertension in cycle 1. Post-baseline hypertension (defined as SBP $\geq$160 mmHg) was reported in 170 sorafenib-treated patients and 73 patients receiving placebo. Median PFS in these patients was 224 (with hypertension) and 139 days (without hypertension) in sorafenib-treated patients, and 172 and 78 days, respectively, in placebo-treated patients. Trough sorafenib concentration data were evaluable in only 67 patients of the 451 treated with sorafenib. Pharmacokinetic exposure and hypertension adverse events reported from one study (study 11213) were also presented (but not displayed in the regulatory assessment report). Measurements of circulating concentration of VEGF and a number of circulating active peptides and hormones were also performed at baseline and after 3 weeks of therapy. There were no significant changes in the levels of these vasoactive, renal and angiogenic factors, and there was no correlation of levels of these factors with blood pressure, thus mitigating their use as biomarkers of efficacy. Pazopanib data submitted for regulatory approval included an analysis of the relationship between steady-state trough plasma pazopanib concentrations and the probability of the occurrence of a study-specific definition of hypertension [91]. The trough plasma pazopanib concentration at which there was a 50 % probability of observing hypertension was 15.3 μg/mL. Pazopanib decreased soluble VEGFR2, a marker for VEGFR inhibition, in a concentration-dependent fashion.

It would, therefore, seem feasible and reasonable to analyse efficacy of TKIs by subpopulation of patients who do and who do not develop pre-defined on-target effects. Subgroup analysis by above toxicities is particularly helpful in optimizing TKI therapy since effective therapy is already available for hypertension and hypothyroidism. As long as the tumour itself is not resistant to TKI therapy, it may be possible to increase the dose of TKI in patients who tolerate higher doses without developing hypertension, hypothyroidism or skin reaction. If the tumour is resistant, it will not be known in advance whether failure of therapeutic response is due to tumour resistance or failure to achieve full pharmacological inhibition of the tyrosine kinase concerned. Therefore, before attributing failure to respond to tumour resistance, one will have to be sure that full inhibition has been achieved and this will require increasing the dose until on-target toxicity is manifest.

One recent editorial commented that the era of targeted therapy has added another dose-finding strategy to the classical maximum tolerated dose (MTD) strategy, namely determination of the optimum biologic dose (OBD). In contrast to MTD, which is based on appearance of (dose-limiting) toxicity, the recommended OBD will be determined by more rational, scientifically derived endpoints such as escalating doses (i) to reach a predefined pharmacologic parameter; (ii) until a target becomes saturated with the drug; or (iii) until a target-mediated biologic pathway is optimally altered [92].

Sponsors should also be encouraged to gather data on biomarkers in blood and tissues, and correlating these with pharmacokinetic and imaging studies. For example, results from phase I studies in Japanese patients [93, 94] have shown that thyroglobulin elevation was observed in all patients who continued treatment with axitinib for $\geq$3 months, and abnormal TSH correlated with exposure to axitinib ($r = 0.72$). Decrease in soluble VEGFR2 levels also correlated significantly with exposure to axitinib ($r = 0.94$). Imaging studies revealed a substantial decrease in tumour metabolic activity associated with axitinib.

Data submitted for regulatory approval of gefitinib provide valuable information concerning the regulatory dilemma [89, 95]. Two key trials had investigated the efficacy and safety of two doses (250 mg and 500 mg daily). In terms of efficacy, there was no significant difference between the two doses. Dosing with 250 mg/day or 500 mg/day of gefitinib demonstrated objective tumour response rates of 11.8 % and 8.8 %, respectively, and disease-related symptom improvement rates of 43.1 % and 35.1 %, respectively. Median PFS times were 59 days and 60 days, respectively. Median survival rates between the two dose groups were 185 days for the 250 mg/day group compared with 183 days for the 500 mg/day group. In terms of skin reactions, drug-related rash occurred in 43–47 % in the 250 mg/day dose group and in 53–69 % in the 500 mg/day dose group. Drug-related grade 3–4 rash was reported in < 0.5 % of patients in 250 mg/day dose group but in 2–5 % of patients in 500 mg/day dose group. Thus, although skin reactions were slightly more frequent with the higher dose, there was no difference in efficacy between the two doses. Inevitably, the question arises as to whether the dose should have been increased above 500 mg/daily.

MTD for gefitinib was established at 750 mg and 1000 mg. Tumour response was seen across a wide range of gefitinib doses between 150 mg and 800 mg. Clear dose-dependency was seen with respect to tolerability. Doses below 600 mg were accompanied by mild and readily reversible side effects, while 600 mg or higher doses yielded toxicity leading to treatment interruption and dose reductions.

Although both doses were well tolerated and most of the reported adverse events for gefitinib were Common Toxicity Criteria grade 1 or 2, dose reductions due to toxicity occurred in 0.5 % of patients in the 250 mg dose group versus 9.5 % of patients in the 500 mg dose group. There

were fewer drug interruptions due to adverse events in the 250 mg/day group than in the 500 mg/day group (15.1 % vs. 25.5 %) and fewer patients receiving the 250 mg/day dose withdrew due to drug-related adverse events.

5 Management of On-Target Toxicity

In terms of improving outcomes on therapy with TKIs in those patients who tolerate the therapy without any adverse effect, two issues arise. The first issue is whether increasing the dose until there is evidence of effective inhibition of the corresponding tyrosine kinase receptor is associated with better risk/benefit ratio. There are no data available at present to enable an evidence-based conclusion. In sorafenib studies submitted to the regulatory authorities, even in patients in whom hypertension was not reported as an adverse event, blood pressure tended to increase within the first 3 weeks of sorafenib therapy. Whether or not increasing the dose to induce hypertension with greater frequency or severity is beneficial is unclear. Data on axitinib did reveal evidence of an exposure-response relationship for several adverse events including hypertension and the sponsor proposed a sequential dose reduction from 5 mg to 3 mg to 2 mg twice daily for the management of hypertension [96]. Since dose reduction has been a typical approach to managing hypertension induced by anti-angiogenesis TKIs generally, a relationship almost certainly exists. The second issue is whether the dose should be reduced or maintained in those patients who develop grade 1–2 on-target toxicity. Available evidence would suggest that the dosing should be maintained without any reduction and the toxicity treated conventionally.

Hypertension caused by angiogenesis inhibitors is usually reversible and mostly managed successfully with standard medications [97]. The most commonly used antihypertensive agents are diuretics, ACE inhibitors (ACEIs), β-blockers, CCBs and angiotensin receptor blockers (ARBs). To evaluate optimal therapeutic approaches to prevent hypertension following VEGFR inhibition, Franklin et al. [98] characterized the dose-dependent effects of seven antihypertensive agents from three pharmacological classes on hypertension induced by ABT-869 in conscious telemetry rats. ABT-869-induced hypertension could be prevented and reversed with sub-therapeutic or therapeutic doses of antihypertensive drugs with a general rank order of ACEIs > ARBs > CCBs. Since many CCBs are metabolized by CYP3A4, which also metabolizes most of the TKIs [3], caution is required to prevent the risk of drug interactions. Izzedine et al. [99] have reviewed the published evidence and proposed an algorithm for the management of hypertension induced by angiogenic inhibitors. There is also evidence that angiotensin II is a powerful mitogen and promoter of angiogenesis, implying that treatment with ACEIs and ARBs may have a potential antineoplastic effect as well [100].

Whether or not an increased TKI dose might lead to hypothyroidism (and, possibly, to an associated improvement in response) in patients who do not develop hypothyroidism at the standard dose is at present unclear. A diagnostic and therapeutic algorithm for the management of TKI-related hypothyroidism has been proposed by a number of investigators [43, 101]. Levothyroxine is the standard treatment for overt hypothyroidism and is recommended in some patients with subclinical hypothyroidism; overt or subclinical hypothyroidism per se does not justify the withdrawal of TKI therapy. Whether or not thyroid replacement therapy may adversely affect cancer-related clinical outcomes (PFS or OS) is also unclear at present. Concerns have been expressed that thyroid replacement therapy may permit tumour growth [56, 102] and prospective studies are necessary to investigate this risk. In the cohort of TKI-induced hypothyroid patients treated by Schmidinger et al. [56], levothyroxine treatment did not have an impact on outcome, but most of their patients had remained in a hypothyroid state despite replacement therapy.

Typically, the approach to managing skin reactions has been to reduce the dose or discontinue the TKI concerned. However, such strategies have a negative impact, especially if the tumour concerned is particularly responsive to the treatment concerned. Evidence linking the incidence and severity of skin toxicity secondary to EGFR inhibitors and survival is sufficiently compelling that careful assessment of the risk benefit is necessary before these agents are discontinued or their dose reduced in patients who develop these reactions.

Skin toxicity associated with TKIs is rarely life-threatening but may cause significant physical and psycho-social discomfort. Therefore, the objective of managing EGFR inhibitor-associated skin toxicity should be to minimize such detrimental effects without antagonizing the clinical efficacy of EGFR inhibitors. There is currently no evidence-based treatment or guideline to prevent or treat the EGFR inhibitor-associated skin toxicities although various expert panels have issued recommendations on a proactive, multidisciplinary approach that includes patient education and the use of a grade-based treatment algorithm [13, 103–107]. Oral isotretinoin with or without an antibiotic, which is widely used, has been reported to be highly effective [108–110]. There is optimism concerning the potential availability of highly specific treatment in the future. Preclinical data suggest that topical application of a potent phosphatase inhibitor, menadione (vitamin K3) can rescue inhibition of EGFR and downstream signalling molecules

in the skin of mice receiving the systemic EGFR inhibitor erlotinib or cetuximab [73]. The protective effect of menadione on human keratinocytes exposed to anti-EGFR agents seems to be mediated by oxidative stress, which in turn leads to phosphatase inhibition and shifts the state of the intracellular receptor to the activated phosphorylated state [111]. These effects are non-specific for the phosphatase involved in EGFR dephosphorylation and, therefore, may also be beneficial in treating the effects of other kinase inhibitors that also cause skin toxicity. A phase 1, multicentre, randomized, double-blind, placebo-controlled study of the safety, tolerability and systemic absorption of menadione topical lotion as an emergent and pre-emergent treatment for EGFR inhibitor-associated rash has been completed [112], while another clinical trial investigating menadione topical lotion in treating skin discomfort and psychological distress in patients with cancer receiving panitumumab, erlotinib or cetuximab is ongoing [113].

6 Conclusions

We have reviewed data that provide compelling evidence for the concept of 'on-target' toxicity that may serve as effective biomarkers of efficacy. Optimal use of this novel class of drugs requires identification of those patients who are likely to benefit. To this end, phase III clinical trial data submitted for regulatory approval ought to include subgroup analysis of efficacy in patients who develop on-target toxic effects. Data should also be gathered on evaluation of biomarkers in blood and tissues and correlating these with pharmacokinetic and imaging studies.

Recommending the use of on-target toxicity as a biomarker of efficacy is certain to raise challenges for the sponsors, regulators and clinical oncologists. For the sponsor, a drug cannot be considered ineffective until it can be demonstrated that it is ineffective, or not effective enough, despite achieving full inhibition of the target tyrosine kinase. The problem is that other off-target toxicity may prevail before this full inhibition is achieved. One option may be to continue increasing the dose in those patients who otherwise tolerate the drug well, in effect conducting a form of enrichment design study. For regulators and clinical oncologists, the practice of an open-ended dose schedule with no specified maximum dose and a recommendation to continue increasing the dose to induce a toxic effect are counter to normal practice, especially since the tumour may be intrinsically resistant (for example, presence of *KRAS* mutation and therapy with an EGFR inhibitor as discussed earlier) or an off-target effect that is otherwise mild and well tolerated may be aggravated (e.g. liver function tests). The clinical oncologist may have difficulty persuading patients to increase the dose until a skin reaction occurs. There is also the practical issue of monitoring the maintenance of full inhibition of the target kinase once the on-target toxicity is induced and treated adequately. Notwithstanding these challenges, it is clear that caution is required when discontinuing a potentially effective therapy simply because of apparent failure to observe a clinical response when the maximum recommended dose has been reached but possibly without full inhibition of the target enzyme.

Provided the patients are carefully monitored and correctly managed, there seems no obvious reason why it should not be possible to achieve anticancer efficacy and optimize risk/benefit in individual patients despite the development of hypertension, hypothyroidism or skin reactions. Prospective studies are needed to investigate whether continuing TKI therapy with concurrent treatment of on-target toxicity is more effective and is associated with improved clinical outcomes than discontinuing or reducing the dose of the TKI in patients who develop these on-target toxicities.

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