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REVIEW ARTICLE

Effect of Tyrosine Kinase Inhibitors on Wound Healing and Tissue Repair: Implications for Surgery in Cancer Patients

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Abstract Small-molecule tyrosine kinase inhibitors (TKIs) represent a major advance in the treatment of certain forms of cancer. Unexpectedly, however, their use is associated with serious toxic effects on many vital organs and functions. Some of these effects, such as venous thromboembolism, haemorrhage, gastric perforation and a potential for impaired tissue healing, have direct implications for the safety of surgery in cancer patients. A number of currently approved TKIs are suspected or have been reported to impair wound healing but, understandably, there have been no formal pre- or post-approval clinical trials to evaluate the extent of the risk. Consequently, drug labels typically recommend discontinuation of the TKI concerned prior to elective surgery. In patients with gastric perforation, permanent discontinuation is advised. These recommendations, which are based on a precautionary principle, raise a dilemma, especially in patients with TKI-responsive tumours. This review focuses on the labelled potential of these novel antineoplastic agents to impair tissue repair and wound healing, and the evidence concerning the likely mechanisms involved. At present, because of the lack of formal clinical data, there are no evidence-based guidelines on the management of surgery in patients treated with TKIs. There is a need for a central registry of clinical outcomes following emergency surgery in cancer patients receiving TKIs and TKI-naïve matched controls. Analysis of outcomes data from such registries will assist in formulating guidelines on the management of elective surgery in TKI-treated patients. If TKIs are shown to significantly impair wound healing, patients receiving TKI therapy will require special monitoring and a collaborative approach between oncologists and surgeons for individualized reappraisal of the risk/benefit of the TKI treatment.

Key Points

A number of tyrosine kinase inhibitors (TKIs), predominantly those targeting angiogenesis, are recommended to be discontinued pre-surgery or in the event of impaired wound healing and/or gastric perforation. The labelled recommended courses of action are highly heterogeneous.

Molecular evidence linking angiogenesis with impaired wound healing and gastric perforations is less than secure. Rather, the evidence suggests a concerted role for a number of growth factors.

Discontinuation of a TKI in a patient with a TKI-responsive tumour presents a dilemma, since this course of action can adversely affect the disease control.

There is a pressing need for systematic collection of data, preferably by establishment of a registry of TKI recipients undergoing emergency surgery, in order that any causal association can be investigated and evidence-based guidelines can be formulated with respect to continued use of TKIs in the elective perioperative period.

The views expressed in this paper are those of the authors and do not necessarily reflect the views or opinions of their affiliates, any regulatory authorities or any of their advisory bodies.

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1 Introduction

The past decade has witnessed the approval of a number of small-molecule tyrosine kinase inhibitors (TKIs) for treatment of a variety of cancers (Table 1). As of 30 November 2013, a total of 22 antineoplastic TKIs had been approved by the US Food and Drug Administration (FDA), 19 of which had also been approved by the European Medicines Agency (EMA) [1, 2]. While these agents are generally well tolerated, they are also associated with serious toxic effects on the heart, lungs, liver, kidneys, thyroid, skin, blood coagulation, gastrointestinal tract and nervous system [3]. We have previously reviewed these novel agents with regard to their cardiovascular safety [4], hepatotoxicity [2] and on-target toxicities, which could serve as biomarkers of their efficacy [3]. An adverse safety profile of these agents is expected, since tyrosine kinases are widely distributed throughout the body, with specific and diverse functional roles in different organs. As a result, promiscuous inhibition of tyrosine kinases can be expected to give rise to undesirable effects at off-target sites.

Many uncommon but serious and potentially fatal adverse drug reactions associated with TKIs have been only poorly documented in clinical trials, and treatment of a larger number of less selected patients in routine oncological practice increases the likelihood of detecting toxicity [5–10]. For example, in October 2013, the FDA recommended (temporary) suspension of the marketing of ponatinib following an increasing frequency of reports of serious and life-threatening cardiovascular events in patients taking this drug [11]. The first TKI, imatinib, was approved in 2001 but, of the remaining 21 TKIs approved as of 30 November 2013, 13 (62 %) were approved during a brief period dating from April 2011 to November 2013 (see Shah et al. [1] for a partial list). Not surprisingly, therefore, even the postmarketing experience with their use also remains limited, especially in the setting of surgery.

In this review, we focus on the likelihood of the effects of TKIs on tissue repair and wound healing. First, we briefly summarize the prescribing information on the currently approved TKIs in this respect and then consider whether the molecular and biochemical evidence is robust enough to support the labelled recommendations. In view of the associated co-morbidities, patients with cancer are often frail and already face difficult recovery from surgery, compared with their otherwise healthy counterparts. Concurrent treatment with a TKI may further complicate their postoperative course and outcome if TKIs do indeed impair wound healing.

2 Impaired Wound Healing and Gastric Perforation Attributed to TKIs

2.1 Prescribing Information

For convenience, the prescribing information we typically refer to in this review is the FDA-approved labels for the TKIs, because these are the most detailed in their contents [12–33]. As shown in Table 2, the approved TKIs have been variously labelled as causing a number of adverse effects that are directly relevant in surgery. These include impaired wound healing, venous thromboembolism and haemorrhage, gastric perforation and fistulas. The rates of these effects are not precisely known and are not strictly comparable between different agents, because of differences in populations and the methodology used to assess the rates. Nevertheless, they are uncommon enough for the TKIs to be given regulatory approval for marketing.

2.1.1 Wound Healing

According to the drug labels, impaired wound healing is a potential risk following treatment with axitinib, cabozantinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib or vandetanib [13, 15, 25–27, 29, 30, 32]. In terms of frequency, there are no data on most of these agents, since no formal studies have been conducted to investigate the effect of any TKI on wound healing. However, complicated or impaired wound healing was not uncommon during clinical trials with axitinib (2 %) and cabozantinib (2 %). There was no indication that wound healing was affected by sorafenib monotherapy, but only 70 patients on sorafenib underwent surgical procedures, mainly minor. In clinical studies with vandetanib, a small number of patients had surgery while receiving the drug, but there were no reported wound healing complications.

2.1.2 Gastric Perforation

Spontaneous gastric perforation has been reported during clinical trials in patients treated with axitinib (1 %), cabozantinib (3 %), pazopanib (1 %), regorafenib (0.6 %) or sorafenib (1 %) [13, 15, 25, 27, 29]. A number of these patients developed fistulas (such as gastrointestinal and tracheal-oesophageal) and some had a fatal outcome. The label for cabozantinib carries a boxed warning regarding its potential to cause gastric perforation, fistulas and haemorrhage [15]. Non-gastrointestinal fistulas, including tracheal-oesophageal fistulas, were reported in 4 % of cabozantinib-treated patients. Two (1 %) of these were fatal. Serious gastrointestinal perforation (with a fistula) occurred in one ponatinib-treated patient 38 days post-

Table 1 Principal pharmacological targets and indications for currently approved tyrosine kinase inhibitors (TKIs)

TKI	FDA approval date	Principal pharmacological targets[a]			Approved indication(s)[b]
		VEGFR	EGFR (HER1)	Others	
Afatinib	12 July 2013		[e]	HER2, HER4	Non-small-cell lung cancer
Axitinib	27 January 2012	[e]		PDGFR, KIT	Renal cell carcinoma
Bosutinib	4 September 2012			BCR-ABL, SRC	Chronic myeloid leukaemia
Cabozantinib[c]	29 November 2012	[e]		HGFR/MET, RET, KIT, FLT3	Medullary thyroid cancer
Crizotinib	26 August 2011			HGFR/MET, ALK	Non-small-cell lung cancer
Dabrafenib	29 May 2013			BRAF	Melanoma with BRAF mutation(s)
Dasatinib	28 June 2006			BCR-ABL, PDGFR, SRC, KIT	*Chronic myeloid leukaemia*
					Acute lymphoblastic leukaemia
Erlotinib	18 November 2004		[e]		*Non-small-cell lung cancer*
					Pancreatic cancer
Gefitinib	5 May 2003		[e]		Non-small-cell lung cancer
Ibrutinib[d]	13 November 2013			BTK	Mantle cell lymphoma
Imatinib	10 May 2001			BCR-ABL, PDGFR, FLT3, KIT	*Chronic myeloid leukaemia*
					Acute lymphoblastic leukaemia
					Hypereosinophilic syndrome
					Myelodysplasia or proliferation
					Gastrointestinal stromal tumour
Lapatinib	13 March 2007		[e]	AKT, HER2	HER2-positive breast cancer
Nilotinib	29 October 2007			BCR-ABL, PDGFR, KIT	Chronic myeloid leukaemia
Pazopanib	19 October 2009	[e]		PDGFR, KIT	*Renal cell carcinoma*
					Soft tissue sarcoma
Ponatinib	14 December 2012	[e]		BCR-ABL, PDGFR, SRC, KIT, FLT3	Chronic myeloid leukaemia
Regorafenib	27 September 2012	[e]		BRAF, PDGFR, KIT	*Colorectal cancer*
					Gastrointestinal stromal tumour
Ruxolitinib	16 November 2011			JAK	Myelofibrosis
Sorafenib	20 December 2005	[e]		BRAF, PDGFR, FLT3, KIT	*Renal cell carcinoma*
					Hepatocellular carcinoma
					Medullary thyroid cancer
Sunitinib	26 January 2006	[e]		PDGFR, SRC, FLT3, KIT	*Gastrointestinal stromal tumour*
					Renal cell carcinoma
					Pancreatic neuroendocrine tumours
Trametinib[c]	29 May 2013			MEK1 and MEK2	Melanoma with BRAF mutation(s)
				BRAF	
Vandetanib	6 April 2011	[e]	[e]	SRC	Medullary thyroid cancer
Vemurafenib	17 August 2011			BRAF	Melanoma with BRAF mutation(s)

AKT protein kinase B, *ALK* anaplastic lymphoma kinase, *BCR-ABL* tyrosine kinase from oncogenic transcript from fusion of the Abelson1 gene and the breakpoint cluster region gene, *BRAF* member of the Raf (rapidly accelerated fibrosarcoma) kinase family of serine/threonine-specific protein kinases, *BTK* Bruton's tyrosine kinase, *EGFR* epidermal growth factor receptor, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *FLT3* Fms-related tyrosine kinase 3, *HER* human epidermal growth factor receptor, *HGFR/MET* hepatocyte growth factor receptor kinase, *JAK* Janus kinase, *KIT* mast/stem cell growth factor receptor, *MEK* mitogen-activated extracellular kinase, *PDGFR* platelet-derived growth factor receptor, *RET* rearranged during transfection, *SRC* sarcoma, *VEGFR* vascular endothelial growth factor receptor

[a] The pharmacological potency of a TKI at the targets listed varies widely, and the list is not all inclusive. A blank cell indicates that the TKI does not target VEGFR or EGFR

[b] The indications that are italicized are the initially approved indications

[c] Still under review by the EMA as of 30 November 2013

[d] Not yet submitted to the EMA as of 30 November 2013

[e] Target of the corresponding TKI

Table 2 Surgically-relevant labelled major effects of tyrosine kinase inhibitors (TKIs)

TKI	Impaired wound healing	Gastric perforation	Venous thromboembolism	Haemorrhage
Afatinib				
Axitinib	[a]	[a]	[a]	[a]
Bosutinib				
Cabozantinib	[a]	[a]	[a]	[a]
Crizotinib				
Dabrafenib				
Dasatinib			[a]	[a]
Erlotinib		[a]	[a]	
Gefitinib				
Ibrutinib				
Imatinib		[a]		[a]
Lapatinib				
Nilotinib				
Pazopanib	[a]	[a]	[a]	[a]
Ponatinib	[a]	[a]	[a]	[a]
Regorafenib	[a]	[a]		[a]
Ruxolitinib				
Sorafenib	[a]	[a]	[a]	[a]
Sunitinib	[a]	[a]	[a]	[a]
Trametinib				[a]
Vandetanib	[a]			[a]
Vemurafenib				

[a] Corresponding adverse effect reported in the label [12–33]. A blank cell indicates that the effect is not listed in the label

cholecystectomy [26]. The labels for erlotinib and imatinib also include gastrointestinal perforation (including fatalities) as a complication associated with their use [19, 22]. Patients receiving concomitant antiangiogenic agents, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs), or who have a prior history of peptic ulceration or diverticular disease, are reportedly at increased risk [19].

2.1.3 Haemorrhagic and Thromboembolic Events

The association between these events and use of a TKI can also be difficult to establish. Postoperatively, many patients are placed on thromboprophylaxis, making it difficult to determine if the bleeding is TKI-induced or due to thromboprophylaxis. Conversely, frail patients are generally at greater risk of thromboembolism because they have restricted mobility. However, in controlled clinical studies, haemorrhagic events (not uncommonly with a fatal outcome) were reported frequently during treatment with axitinib, cabozantinib, dasatinib, imatinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib or vandetanib [13, 15, 18, 22, 25–27, 29, 30, 32]. The frequencies often varied depending on the indication studied and between studies in the same indication. In broad terms, the frequencies of all haemorrhagic events combined were in the range of 10–40 %. Serious or severe events, which included cerebral haemorrhage, haematuria, hemoptysis, lower gastrointestinal haemorrhage and melena, were relatively much less frequent (ranging from 1 to 5 %). Bleeding events with certain TKIs, such as dasatinib and ponatinib, were often associated with severe thrombocytopenia. Although the occurrence of haemorrhage and thromboembolism from the same drug may seem paradoxical, they are both believed to be underpinned by the same mechanisms. Within the microvasculature, there is an extremely tightly regulated balance of pro- and anticoagulant proteins, platelet-activating and -inhibiting factors, and pro- and anti-fibrinolytic products [34]. TKI-induced disruption of this intricate balance could tip the balance either way, thereby promoting either thromboembolism or haemorrhage.

2.2 Regulatory Recommendations on TKI Therapy in Candidates for Surgery

Since individual circumstances may vary widely, prescribing information cannot be expected to provide any guidance regarding surgery in an emergency setting when the surgery is critical and the TKI cannot be discontinued for long enough to be eliminated from the body. Table 3 summarizes the labelled recommendations for use of eight TKIs suspected to impair wound healing regarding their

Table 3 Summary of regulatory recommendations concerning use of tyrosine kinase inhibitors (TKIs) prior to surgery[a]

TKI[b]	Half-life (h)	Monitoring recommendations
Axitinib	2.5–6.1	Stop treatment at least 24 h prior to scheduled surgery
Cabozantinib	55	Stop treatment at least 28 days prior to scheduled surgery
Pazopanib	31	Treatment should be stopped at least 7 days prior to scheduled surgery
Ponatinib	12–66	Interrupt therapy for at least 1 week prior to major surgery
Regorafenib	28 (parent) 25–51 (metabolite)	Treatment should be stopped at least 2 weeks prior to scheduled surgery
Sorafenib	25–48	Temporary interruption is recommended in patients undergoing major surgical procedures
Sunitinib	40–60 (parent) 80–110 (metabolite)	Temporary interruption is recommended for precautionary reasons in patients undergoing major surgical procedures
Vandetanib	450	The appropriate interval between discontinuation of vandetanib and subsequent elective surgery required to avoid the risks of impaired wound healing has not been determined

[a] Physicians should check the latest labels [12–33] for detailed recommendations on dose modifications before elective surgery

[b] The other 14 TKIs are not labelled as causing impaired wound healing

Table 4 Summary of regulatory recommendations concerning use of tyrosine kinase inhibitors (TKIs) and gastric perforation[a]

TKI[b]	Monitoring recommendations
Axitinib	Use with caution in patients at risk of gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula periodically throughout treatment
Cabozantinib	Monitor for symptoms of gastrointestinal perforation or fistula. Discontinue cabozantinib in patients with perforation or fistula
Erlotinib	Permanently discontinue treatment in patients who develop gastrointestinal perforation
Imatinib	No recommendation on the course of action (despite the effect being listed)
Pazopanib	Monitor for signs and symptoms of gastrointestinal perforation or fistula
Ponatinib	No recommendation on the course of action (despite the effect being listed)
Regorafenib	Permanently discontinue regorafenib in patients who develop gastrointestinal perforation or fistula
Sorafenib	In the event of gastrointestinal perforation, discontinue sorafenib
Sunitinib	No recommendation on the course of action (despite the effect being listed)

[a] Physicians should check the latest labels [12–33] for detailed recommendations on dose modifications in patients with gastric perforation

[b] The other 13 TKIs are not labelled as being associated with gastric perforation

use in patients scheduled for elective surgery [13, 15, 25–27, 29, 30, 32]. However, in the postoperative situation, in the presence of advanced cancer, drug-induced impaired wound healing and organ perforation can be notoriously difficult to diagnose and manage, particularly in immunocompromised patients. More worrying from a clinical perspective, however, is the recommendation that since there is limited clinical experience regarding the timing of re-initiation of therapy following a major surgical intervention, the decision to resume TKI therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery. Such judgments clearly call for collaboration between the surgeon and the oncologist treating the patient. It is also recommended that therapy should be discontinued in patients with wound dehiscence.

Table 4 summarizes the labelled recommendations for use of nine TKIs in patients who develop gastric perforation or a fistula [13, 15, 19, 22, 25–27, 29, 30]. The prescribing information for these nine TKIs is highly heterogeneous, ranging from caution during use of the TKI in patients at risk to advice to monitor patients for symptoms of gastric perforation. In the event of perforation, there is no specific recommendation on the course of action for some TKIs, whereas permanent discontinuation is advised for others. Clinically, however, many elderly cancer patients are treated chronically with steroids or NSAIDs, which lead to gastric ulcers and perforation, making it difficult to establish causality between these events and use of a TKI.

Potentially, these recommendations could have a significant negative impact on a patient with a TKI-responsive

tumour. The interval between the last dose of a TKI and surgery is typically determined by the half-life of the TKI concerned. Generally, an interval equivalent to five half-lives is adequate for almost complete elimination of the drug from the body. Whereas an agent such as axitinib has a half-life in the range of 2.5–6 h, some TKIs such as cabozantinib, sorafenib and vandetanib have very long half-lives [4]. Two dilemmas clearly present themselves: (1) is there any evidence-based information to recommend discontinuation of TKIs before elective surgery; and (2) if so, is it the case that emergency surgery in patients receiving a TKI may be expected to have an inferior surgical outcome, compared with such surgery in patients not receiving a TKI?

The answers to these questions are important; therefore, we briefly review the evidence of adverse effects of tyrosine kinase inhibition on wound healing and tissue repair (see below). Before discussing small-molecule TKIs, we begin by discussing the effects of bevacizumab, which is the most widely studied drug with respect to its effects on wound healing and tissue repair.

3 Effect of Bevacizumab on Healing and Tissue Repair

Bevacizumab is a highly specific monoclonal antibody, which binds vascular endothelial growth factor (VEGF)-A, thereby preventing it from interacting with the VEGF receptor (VEGFR). It is indicated for the treatment of a number of cancers such as colorectal, lung and renal cancers. It is typically given in combination with other chemotherapeutic agents such as 5-fluorouracil, irinotecan or oxaliplatin. The US label for bevacizumab includes a boxed warning concerning induction of gastrointestinal perforation in up to 2.4 % of patients (the majority within the first 50 days of therapy), haemorrhage and the potential for wound healing complications [35]. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with metastatic colorectal cancer who underwent surgery during the course of bevacizumab treatment was 15 %, compared with 4 % in patients who did not receive this drug [35]. A recent report indicated that bevacizumab induced spontaneous intestinal perforation in 3 (2.1 %) of the 143 patients [36]. The label recommends discontinuation of bevacizumab following gastrointestinal perforation and discontinuation at least 28 days prior to elective surgery. It is also recommended that bevacizumab therapy should not be initiated for at least 28 days after major surgery and until the surgical wound is fully healed. Bevacizumab has also been reported to induce perforation of nasal septum [37, 38].

The monoclonal antibodies cetuximab and panitumumab are specific inhibitors of epidermal growth factor (EGF) receptor (EGFR) and are indicated for various malignancies. Despite their extensive use, there is no evidence of either of them being associated with gastrointestinal perforation, wound healing complications or haemorrhage [39–41].

3.1 Non-clinical Evidence of the Effect of Bevacizumab on Wound Healing

There is a substantial body of non-clinical evidence to suggest that bevacizumab impairs wound healing and is associated with a high incidence of gastrointestinal perforation. Below, we summarize two representative studies.

Application of bevacizumab topical eye drops at 1.0, 1.5, 2.5 or 5 mg/mL delayed healing of the rabbit corneal epithelium. Cell cultures growing under high concentrations of bevacizumab showed a delay in the proliferation of corneal epithelial and fibroblast cells [42]. Bevacizumab eye drops inhibited corneal wound healing in rats. Kim et al. [43] reported that after corneal epithelial damage, VEGF and nerve growth factor (NGF) increased normally in rat corneas. In contrast, when VEGF was inhibited by bevacizumab eye drops, the wound healing rate was decreased, and NGF was also downregulated.

3.2 Clinical Evidence of the Effect of Bevacizumab on Wound Healing

A number of studies have investigated the effect of bevacizumab on outcomes in surgical patients [43–51]. From their meta-analysis of 13 nonrandomized studies (with a total of 1,431 participants), Li et al. [52] concluded that there was no difference in overall morbidity and severe complications between the bevacizumab (+) group and the bevacizumab (−) group (43.3 versus 36.8 %, $p = 0.06$; 17.1 versus 11.4 %, $p = 0.07$; respectively). Bevacizumab-related complications, including wound complications and thromboembolic/bleeding events, were also similar in the bevacizumab (+) group and the bevacizumab (−) group (14.4 versus 8.1 %, $p = 0.21$; 4.1 versus 3.8 %, $p = 0.98$; respectively). However, these studies were all retrospective, and in all of the patients who were included, bevacizumab had been discontinued for some time before surgery. For example, in the three most recently reported studies, the median time from the end of systemic treatment to surgery for liver resection was 59 days (33–181 days) for the chemotherapy-alone group and 62 days (44–127 days) for the chemotherapy-plus-bevacizumab group in one study [49], and the interval from the last dose of bevacizumab to surgery was at least 5–6 weeks in the other two studies [50, 51]. At present, there appears

to be a lack of consensus on the optimal time interval between discontinuation of bevacizumab and surgery. Some investigators have reported higher rates of postoperative complications in patients who received bevacizumab within 8 weeks preceding surgery [45, 53], whereas others [46, 47] have failed to confirm this. All of the investigators have emphasized the need for confirmatory prospective studies before any firm conclusions are drawn.

The risk of impaired wound healing seems to be limited to preoperative use of bevacizumab. Since the FDA approved bevacizumab for recurrent glioblastoma, its use has increased in this patient population. Clark et al. [54] reported that significantly more patients who received preoperative bevacizumab developed healing complications than patients who did not receive it (35 versus 10.0 %, $p = 0.004$). In contrast, postoperative bevacizumab (started after a median of 43 days [range 22–65 days] after the second or third craniotomy) was associated with a 6 % rate of impaired healing, which was not significantly different from the rate in non-bevacizumab-treated controls ($p = 1.0$).

The duration of preoperative bevacizumab treatment (in weeks) did not influence healing (odds ratio 0.98, $p = 0.55$). More healing complications occurred in patients receiving preoperative bevacizumab than in non-bevacizumab-treated controls before the third craniotomy (44 versus 9 %, $p = 0.03$).

4 Effect of Small-Molecule TKIs on Healing and Tissue Repair

4.1 Non-clinical Evidence of the Effect of TKIs on Wound Healing

Although there are hardly any published clinical studies on the effects of small-molecule TKIs on wound healing and tissue repair, a few non-clinical studies have been reported.

Roman et al. [55] reported that semaxanib, an inhibitor of VEGFR, did not impair wound healing despite decreasing tissue perfusion and microvascular density in a wound-healing model in rats. Studies in knockout mice and preclinical toxicology studies showed that the major targets of toxicity following inhibition of EGFR are the skin and gastrointestinal tract. This suggests that EGFR inhibitors may also influence wound healing and gastrointestinal ulcer healing rates. In an elegant study, Kaftan et al. [56] investigated the effect of topical erlotinib, an EGFR inhibitor, on healing of experimental bilateral tympanic membrane perforation in rats. A solution of erlotinib (10 mg/mL) was applied to one tympanic membrane of each animal, and the vehicle only (in the control group) was applied to the other side daily for 12 consecutive days, followed by weekly observation for a total of 30 days. The mean healing period was found to be 12.1 days in the group with erlotinib and 6.4 days in the control group. There were corresponding differences in the histological parameters between the erlotinib group and the control group. In another study, the same investigators showed that both erlotinib (11.8 days) and cetuximab (9 days) prolonged healing latencies, compared with a reference value (7 days), and differences were observed in the histological parameters of the two groups [57]. The investigators concluded that although inhibition of EGFR does not lead to a persistent perforation, spontaneous perforation in patients receiving long-term treatment with EGFR inhibitors may be possible in patients with pre-existing tympanic membrane pathology. Indeed, there is a report of bilateral tympanic membrane perforation following long-term treatment with erlotinib [58]. The same group reported that inhibition of fibroblast growth factor (FGF) receptor (FGFR)-1 by its specific inhibitor, SU5402, also inhibited healing of tympanic membranes in a dose-dependent manner [59]. This observation suggests a role of multiple growth factors in wound healing.

We reviewed the pre-approval pharmaco-toxicological evaluation reports prepared by the FDA [60] and the EMA [61] for information on non-clinical evidence concerning the effects of approved TKIs on wound healing and tissue repair. There was no information available in the regulatory evaluations of axitinib, cabozantinib, pazopanib, ponatinib, regorafenib and sorafenib, despite the warnings in the prescribing information. For sunitinib, its potential effect on wound healing was evaluated in female SKH1 mice orally administered 40 and 80 mg/kg for up to five consecutive weeks [62]. On day 6, a full-thickness incision was made on the back of each mouse, which was then sealed with nylon sutures. Subsequently, the strength of the healed wounds was evaluated on days 13, 20 and 34. Mice treated with 40 mg/kg/day had wound tensile strength comparable to control, at all time points evaluated. Transient treatment-related effects were observed in mice treated with 80 mg/kg/day, corresponding to a 40 % decrease in wound tensile strength on day 20.

For vandetanib, the regulatory evaluation report included a study by Ko et al. [63], which had determined the effects of vandetanib on wound healing in Balb/c mice by measuring breaking strength in a murine model of cutaneous wound healing. Mice were administered 0, 50 or 100 mg/kg/day of the drug by oral gavage once daily, starting 7 days before wounding. The wound consisted of two (2 cm) full-thickness horizontal incisions made through the dorsal skin of the mouse through the panniculus carnosus. Treatment with vandetanib or the vehicle was continued for a total of 14 or 35 days until 7 or

28 days after wounding, respectively, when the breaking strength of the wounded skin was measured. The results indicated that the wound breaking strength was dose-dependently decreased in mice treated with vandetanib compared with controls at both 7 and 28 days after wounding. Histological examinations showed that vandetanib-treated mice had a qualitative reduction in the degree of fibrosis and epithelial proliferation at the wound site, compared with controls; however, vandetanib had no effect on microvasculature density.

The non-clinical evidence reviewed above suggests that EGFR may have a greater role than VEGFR in influencing wound healing, and that multiple growth factors, rather than any one single factor, may be involved. On balance, however, the evidence is not conclusive enough and at best points to an effect at very high exposures.

4.2 Clinical Evidence of the Effect of TKIs on Wound Healing

The clinical evidence is largely anecdotal, consisting of case reports from pre-approval clinical trials and post-approval clinical use. An exhaustive search of the PubMed database, using a variety of search terms, revealed a remarkable paucity of published clinical reports on the effect of TKIs on wound healing. What little evidence exists is sufficient to raise question marks concerning any improvement in the risk/benefit of discontinuing a TKI before surgery, especially in a patient with a TKI-responsive tumour.

Investigators reporting a small, retrospective study in patients with metastatic renal cell cancer (mRCC) suggested that discontinuation of sunitinib or sorafenib therapy may actually be risky in terms of progression with new metastases and potential complications [64]. In a later study, the same investigators showed that following discontinuation of TKI therapy in 36 patients with mRCC, recurrence was observed in 24 patients (66.7 %). Re-exposure to the TKI was effective in 86.9 % of these cases [65]. In another small study in patients with mRCC, discontinuation of TKI therapy 2 weeks before surgery, following a median treatment period of 17 weeks, was associated with an increased incidence and severity of intraoperative adhesions [66]. Govindan et al. [67] described four instances in which patients underwent surgical procedures (emergency laparotomy, internal fixation of bony metastasis and drainage of a labial abscess followed by laparotomy) while receiving gefitinib 250 mg once daily for management of advanced non-small-cell lung cancer. There was no evidence of an adverse effect on wound healing. Apart from this single report, we were unable to locate any other published reports concerning the effects of TKIs on non-ophthalmic surgical complications.

Johnson et al. [68] reported the case of a 79-year-old woman who presented with a persistent corneal epithelial defect while undergoing treatment with erlotinib for lung cancer. Within 2 weeks of her discontinuing erlotinib treatment, the abrasion healed and had no recurrence. Ibrahim et al. [69] also reported a case of a 60-year-old female, who presented with sudden onset of painless loss of vision in one eye due to a perforated corneal ulcer, following 3 months of treatment with gefitinib for metastatic adenocarcinoma of the lung. Gefitinib was stopped, and the patient went on to have a corneal graft surgery but post-operatively developed corneal graft melting. Animal studies have suggested that the corneal effects of gefitinib may be irreversible [70]. Saint-Jean et al. [71] reported on ten eyes in five patients during treatment with systemic EGFR inhibitors; four patients were receiving erlotinib for end-stage lung carcinoma, and one patient was receiving panitumumab for end-stage colorectal cancer. Multiple epithelial defects were observed in all ten eyes, corneal melting and thinning were observed in three eyes in two patients, two eyes in one patient presented with lower lid ectropion, and two eyes in two patients presented with corneal perforation, both requiring penetrating keratoplasty.

5 Evidence of the Roles of VEGF and EGF in Wound Healing

The potential role of growth factors in wound healing is best illustrated by recombinant platelet-derived growth factor (PDGF). This agent has been approved by the FDA for treatment of lower-extremity diabetic neuropathic ulcers with adequate blood supply and which have extended into the subcutaneous tissue or beyond [72].

However, examination of Tables 1 and 2 reveals that nine of the ten TKIs (imatinib being the exception) that are labelled as being potentially associated with impaired wound healing and/or gastrointestinal perforation are active at VEGFR and/or EGFR. The suspected association is stronger for TKIs that are active at VEGFR than for those that are active at EGFR. Below, therefore, we summarize the pathophysiology of wound healing and the evidence of a role of growth factors, especially VEGF and EGF, in wound healing and tissue repair.

5.1 Pathophysiology of Wound Healing

The process of wound healing consists of three overlapping phases, which consist of blood clotting and inflammation, formation and proliferation of new tissue and, finally, tissue remodelling. Each of these three phases is associated with a complex cascade of cellular and biochemical

responses, resulting in release of growth factors, cytokines, hormones and low molecular weight mediators from the serum and from degranulating platelets. Briefly, normal wound healing is characterized by formation of fibrovascular granulation tissue, which contains fibroblasts, collagen and blood vessels.

The first phase is characterized by invasion, within minutes, by various inflammatory cells. Platelets and neutrophils arrive first because of their abundance in the circulation, followed by monocytes and lymphocytes. These cellular elements secrete a broad spectrum of cytokines and growth factors, which attract cells from the wound edge and from the circulation. The second phase of wound healing, the formation of new tissue, is initiated by migration of keratinocytes of the injured epidermis and hair follicles, followed by proliferation of these cells at the wound edge. Depending on the effectiveness of angiogenesis and new vessel formation, the vascular component appears as early as day 3 after wounding. The third phase of wound repair is the tissue remodelling phase, when the epidermis returns to its normal thickness through re-differentiation of keratinocytes. Most of the invading cellular components, including most of the inflammatory cells, undergo apoptosis, but persistence of fibroblasts may result in formation of hypertrophic scars and keloids. The entire process ultimately results in healing of the wound, typically within 2 weeks. In the vast majority of surgical procedures, nearly all acute wounds heal by an orderly and timely process, with recovery of strength and integrity similar to those of normal skin. Prolonged inflammation such as that observed following bacterial infection frequently results in severe tissue damage, which delays the healing process and may cause excessive scarring or even malignant transformation of cells at the wound site. Impaired healing in patients with risk factors such as old age, diabetes or inadequate circulation often results in a chronic wound.

5.2 Evidence of the Role of VEGF in Wound Healing

The VEGF family comprises at least four members, including VEGF-A, VEGF-B, VEGF-C and VEGF-D. Of these, VEGF-A is highly specific for the growth of new blood vessels in adult physiological and pathological processes, and it has previously been found to be sufficient on its own to stimulate angiogenesis in quiescent vasculature. These ligands bind to and activate the tyrosine kinase receptors VEGFR-1 (also known as FLT1), VEGFR-2 (KDR) and VEGFR-3 (FLT4). Of these, VEGFR-2 is known to be the major signalling receptor, whereas VEGFR-1 is believed to function largely as a decoy receptor binding VEGF. Although VEGFR-1 binds VEGF-A tenfold more tightly than does VEGFR-2, this interaction alone has not been found to be sufficient to induce angiogenesis in blood vessels. Cellular responses to a wound result in release of VEGF, which induces angiogenesis. VEGF is unique for its effects on multiple components of the wound healing cascade, including collagen deposition and epithelialization. Transcription and secretion of VEGF are elevated in all forms of acute skin wounds, and it is produced by many cell types that participate in wound healing, including endothelial cells, fibroblasts, platelets, neutrophils and macrophages. VEGF also plays a role in mediating corneal nerve repair [73]. There is abundant evidence from animal studies to support a role of VEGF in wound healing, and some key features, as reviewed by Muller et al. [74], can be briefly summarized as follows:

- Expression of VEGF-A strongly increases upon skin injury—in particular, in keratinocytes and macrophages—but this is much less pronounced in animal models of poorly healing wounds.
- When antibodies neutralizing VEGF-A were applied to porcine wounds, there was impaired wound angiogenesis and formation of granulation tissue.
- There was a delay in wound healing in mice with keratinocyte-specific knockout of VEGF-A, and inhibition of VEGFR-2 function strongly reduced wound angiogenesis and granulation tissue formation. However, wound closure was not affected, demonstrating that a reduction in angiogenesis can be tolerated in normally healing animals.
- VEGF-B seems to be dispensable for wound healing, since incisional wounds generated in VEGF-B–deficient mice healed normally and angiogenesis was not affected.
- VEGF-D is expressed in the skin and upregulated following injury, but its loss in mice did not obviously affect the wound healing process, possibly because of compensation by VEGF-C.

For a detailed account of the role of VEGF in wound healing, the reader is referred to the reviews by Muller et al. [74] and Bao et al. [75].

5.3 Evidence of the Role of EGF in Wound Healing

In addition to the VEGF signalling system, a normally functioning EGF signalling system is also necessary in many tissues, including the skin and its appendages, for proper development and tissue homeostasis. The biological activities of EGF are mediated through four tyrosine kinase receptors, designated EGFR (HER1 or ErbB1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). EGFR (HER1) is highly expressed in different cell types of the healing wound—in particular, the keratinocytes. The latter also express HER2 and HER3, indicating that different

members of the EGF/EGFR families are involved in re-epithelialization. Current evidence indicates that injury induces several signalling pathways that involve EGF. For example, phosphoinositide-3 kinase (PI3K) is activated by the binding of ligands to cognate tyrosine kinase receptors. One of the downstream mediators of the activated PI3K signalling cascade is activated AKT (also known as protein kinase B). Using $AKT1^{-/-}$ and $AKT2^{-/-}$ mice, Somanath et al. [76] demonstrated that deficiency of AKT1, but not AKT2, results in impaired assembly of collagen in skin wounds and around the blood vessels.

EGF signalling also appears to modulate angiogenesis via upregulation of angiogenic factors, such as VEGF. Inhibition of the EGFR pathway has been shown to inhibit angiogenesis, tumour growth and metastasis [77]. A dysfunctional EGF system results in defective cellular proliferation and differentiation, one consequence of which is impaired wound healing.

Evidence of the role of EGF in wound healing is also derived primarily from animal studies of skin and corneal wounds. Some key elements from a wealth of evidence supporting the role of EGF in wound healing can be briefly summarized as follows:

- EGFR ligands are growth factors for keratinocytes, playing a central role in controlling proliferation of these cells.
- EGFR ligands also activate mesenchymal cells and stimulate fibroblast proliferation and angiogenesis.
- Diverse EGFR ligands are detected in wound fluid.
- Expression of EGFR transiently increases after wounding, indicating a role of the EGF network in healing of skin wounds.
- EGFR-knockout mice display a marked delay in wound repair as a result of impaired re-epithelialization and wound contraction.

In one multicentre study of the safety, ocular tolerance and efficacy of an ophthalmic solution of EGF for treatment of traumatic corneal epithelial defects in 104 patients, the mean epithelial healing time was significantly shorter in the EGF-treated group than in the placebo-treated group (44.17 versus 61.05 h; $p < 0.01$) [78]. The number of epithelial defects that were completely healed at 24, 48 and 72 h after the onset of treatment was significantly greater in the EGF-treated group. This was confirmed recently in a much larger study, which reported that EGF eye drops were very effective in treating acute heterogeneous corneal diseases, without significant adverse effects and with 86.8 % clinical efficacy [79].

For a more detailed account of the role of EGF in wound healing, the reader is referred to the reviews by Muller et al. [74], Schneider et al. [80], Yu et al. [81] and Márquez et al. [82].

5.4 Evidence of the Role of VEGF and EGF in Gastric Ulcers

Gastrointestinal ulcers can be viewed conceptually as internal wounds that resist normal healing processes. Tyrosine kinase ligands also play a role in induction and healing of gastric ulcers. Physiological activity of tyrosine kinases is 20- to 40-fold greater in the gastric mucosa than in the liver or pancreas, and age-associated changes in gastric mucosal proliferative activity are accompanied by parallel alterations in tyrosine kinase activity [83]. Increased tyrosine phosphorylation of proteins is necessary for physiological and pathological regeneration [84]. Regeneration of the gastric mucosa following a wound or an injury is controlled by a number of growth factors (such as EGF, PDGF and hepatocyte growth factor [HGF]), which coordinate proliferation and migration of cells after binding to specific receptors on the cell surface [85, 86]. During ulcer healing, SRC kinase is activated by the EGF cascade and regulates cell migration [87]. Animal studies have shown significantly increased phosphorylation of EGFR after ulcer induction and an increase in EGFR expression in the early stages of ulcer healing, localized in the epithelial cells of the ulcer margins and regenerating glands [88]. Use of NSAIDs and/or infection with *Helicobacter pylori* is a known risk factor for a gastric ulcer. NSAIDs reduce both basal and EGF-induced re-epithelialization by various molecular mechanisms, including reduced SRC activity [87]. These findings suggest that NSAIDs can directly affect the signalling pathways and cell cytoskeleton essential for re-epithelialization. *H. pylori* has been reported to upregulate tyrosine kinase signal transduction pathways, including SRC, EGFR and other factors following infection [89–91]. Reduction in EGF and EGFR levels in gastric tissues has been observed following eradication of *H. pylori* [92].

5.5 Relevance of TKI-Induced Clinical Inhibition of VEGFR and EGFR

Although the evidence summarized above is highly suggestive of a role of VEGF and/or EGF in wound and ulcer healing, there are certain inconsistencies with regard to the effects of pharmacological inhibition of these pathways on wound healing. Given the molecular pharmacology of wound healing, and the non-clinical evidence of the roles of VEGF and EGF in this process, it would be reasonable to expect clearer evidence of the adverse effects of TKIs on wound healing in clinical trials and following their routine clinical use. One explanation for the observed discrepancy may be the marked differences in exposure to the TKI in non-clinical studies and in patients in the clinical setting. Duan et al. [93] evaluated the effects of SU6668, an

inhibitor of VEGFR, PDGF receptor (PDGFR) and FGFR, on the healing of skin wounds in a murine incisional wound model and concluded that SU6668 at a fully efficacious dose of 100 mg/kg/day had no significant effect on the healing process and that inhibition of the receptors for VEGF, PDGF and FGF at levels necessary to inhibit tumour growth in mouse xenograft models does not affect the healing of incisional wounds in mice.

While use of bevacizumab is associated with a significant increase in the rates of impaired wound healing and gastric perforation [35], there is no evidence of this being the case with small-molecule TKIs (such as axitinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib and vandetanib), which inhibit the VEGF/VEGFR signalling pathway, albeit via different mechanisms. Nevertheless, these TKIs are labelled as carrying a risk of impaired wound healing. It seems reasonable to conclude that the label warnings have been guided, as a form of class labelling based on a precautionary principle, by the effects that are known to be associated with bevacizumab.

Likewise, there is also a similar discrepancy with regard to the EGFR pathway. Although cetuximab, a highly specific inhibitor of the EGFR pathway, was shown to delay healing of the tympanic membrane in animal studies [57], extensive clinical experience with this protein or panitumumab (another inhibitor of EGFR) has not led to any concerns regarding an adverse effect on wound healing. Nor has the extensive use of erlotinib and gefitinib, both also active inhibitors of the EGF signalling pathway, been noteworthy for similar effects. Indeed, there was no evidence of impaired wound healing in gefitinib-treated patients requiring emergency laparotomy [67]. There are only a handful of isolated reports of an adverse effect on the cornea, and the possibility of a tissue-specific effect cannot be discounted.

Thus, the possibilities (1) that the roles of VEGF and EGF are only peripheral or supportive; and (2) that other growth factor(s) may have a more pivotal role in wound healing merit further consideration.

6 Potential Role of Other Growth Factors in Wound Healing

Wound healing is clearly a more complex process than is currently understood, and it is now known that a whole range of signalling systems coordinate the process. This is demonstrated by analysis of growth factors, their receptors and downstream signalling components. Interestingly, and more importantly, similar molecular and cellular mechanisms appear to underlie tissue repair and oncogenesis, and experimental studies have provided strong evidence for the hypothesis that cancer may be viewed as an over-healing wound [94]. Ceelen et al. [95] have also drawn attention to close similarities between wound healing, inflammation and tumour growth, by tabulating the roles of various growth factors that are potentially involved in these processes. It is therefore intuitive that interventions that inhibit tumour growth may be expected to inhibit wound healing.

Chmielowiec et al. [96] demonstrated that HGF/c-Met signalling is essential for generation of the hyperproliferative epithelium in skin wounds. However, in the context of TKIs, it is interesting to note that both crizotinib and cabozantinib are inhibitors of HGF/c-Met signalling, yet only cabozantinib is associated with impaired wound healing and gastric perforation. Luo et al. [97] reported that HGF, HGF receptor (HGFR), EGF, VEGF and cyclooxygenase (COX)-2 are activated in the injured mucosa of patients with erosive oesophagitis, and speculated whether their activation might be involved in mucosal repair and ulcer healing of erosive oesophagitis. Most recently, Meyer et al. [98] showed that wound repair is severely delayed in mice lacking FGFR-1 and FGFR-2 in their keratinocytes. Notably, however, the FGF pathway does not seem to be the principal target of the currently approved TKIs that are labelled as inhibiting wound healing. Demidova-Rice et al. [99] have also emphasized the importance of platelets and various platelet-derived factors in wound healing. No doubt there are many other factors involved, and the reader is referred to more detailed reviews [74, 100]. Having reviewed the evidence of the roles of various factors such as PDGF, EGF, FGF, HGF/c-Met, insulin growth factor (IGF), VEGF, NGF and others in wound healing, Muller et al. [74] concluded that in most cases, the consequences of the loss of a single growth factor were relatively mild, suggesting redundancy or compensation, and that some growth factors seem to exert unique functions—the most remarkable example being HGF, since loss of its receptor on keratinocytes completely inhibited migration and proliferation of the receptor-deficient cells in wounded skin. They conclude that although extensive knowledge has been gained on the role of certain growth factors and their receptors in wound healing, there is still little information on the function of some other growth factors in this regard. Cazander et al. [101] have reviewed the evidence of the role of complement, whereas Miyamoto et al. [102] have highlighted a potential role of stem cell factor in wound healing.

7 Discussion

As stated earlier, TKIs that are active at VEGFR and/or EGFR are suspected to impair wound healing, and the suspicion is stronger for TKIs that are active at VEGFR than for those that are active at EGFR. However, it is

evident that no one single candidate pharmacological target stands out that can satisfactorily and consistently explain the current labelling of TKIs with respect to their effect on wound healing and, by inference, support the current recommendation to discontinue a TKI prior to surgery.

Temporarily withholding a medication, such as warfarin or a β-blocker, before surgery in otherwise healthy patients is a common practice and is guided by risk/benefit analysis based on sound pharmacological principles and clinical evidence.

The majority of TKIs are prescribed in a setting of advanced cancers in patients with limited life expectancy, and they have been approved for clinical use because they are effective, often highly so in a subset of patients. Clearly, different risk/benefit considerations apply when contemplating temporary or permanent discontinuation of a TKI in a patient with a TKI-responsive tumour. A direct corollary of the common mechanisms that underlie tissue repair and oncogenesis [93, 94] is that impaired wound healing is either confined to, or more likely in, those patients whose tumours appear to be responsive to treatment with TKIs. If so, the practice of stopping a TKI before surgery raises an even more acute dilemma. Wound healing is a complex process involving a cascade of various equally important growth factors, other than simply VEGF and EGF. The clinical evidence of an adverse effect of small-molecule TKIs on wound healing at clinical doses is at present tenuous, making it difficult to make an informed decision on whether it is advisable to discontinue their use before surgery.

8 Conclusions

A large number of TKIs are in development or under regulatory review, and their use is expected to increase markedly in the future. Recommendations in prescribing information are based on small sample sizes and often anecdotal cases without any formal clinical trials. As TKIs become used more widely, with expanding indications for each, their postmarketing safety profile will require careful monitoring, and their risk/benefit and prescribing recommendations may require regular re-assessment.

In the absence of any reliable and definite evidence at present, surgeons have to be guided by the recommendations in the prescribing information when elective surgery is contemplated. However, the situation is different when a patient on a TKI requires emergency surgery. In this setting, the long half-life of many TKIs would preclude waiting until the TKI is eliminated from the body. We believe that a registry should be set up to gather more reliable evidence concerning the outcomes of emergency surgery in patients treated with TKIs. Ultimately, analysis of outcomes data from such registries may facilitate the evolution of informed guidelines on the management of elective surgery in TKI-treated patients.

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References

1. Shah RR, Roberts SA, Shah DR. A fresh perspective on comparing the FDA and the CHMP/EMA: approval of antineoplastic tyrosine kinase inhibitors. Br J Clin Pharmacol. 2013;76:396–411.
2. Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf. 2013;36:491–503.
3. Shah DR, Shah RR, Morganroth J. Tyrosine kinase inhibitors: their on-target toxicities as potential indicators of efficacy. Drug Saf. 2013;36:413–26.
4. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarization (QT interval). Drug Saf. 2013;36:295–316.
5. Johnson JR, Ning Y-M, Farrell A, et al. Accelerated approval of oncology products: the Food and Drug Administration experience. J Natl Cancer Inst. 2011;103:636–44.
6. Seruga B, Sterling L, Wang L, et al. Reporting of serious adverse drug reactions of targeted anticancer agents in pivotal phase III clinical trials. J Clin Oncol. 2011;29:174–85.
7. Niraula S, Seruga B, Ocana A, et al. The price we pay for progress: a meta-analysis of harms of newly approved anticancer drugs. J Clin Oncol. 2012;30:3012–9.
8. Jonsson B, Bergh J. Hurdles in anticancer drug development from a regulatory perspective. Nat Rev Clin Oncol. 2012;9:236–43.
9. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst. 2009;101:1642–9.
10. Sherrill B, Kaye JA, Sandin R, et al. Review of meta-analyses evaluating surrogate endpoints for overall survival in oncology. Onco Targets Ther. 2012;5:287–96.
11. Food and Drug Administration. FDA drug safety communication (5 November 2013): FDA asks manufacturer of the leukemia drug Iclusig (ponatinib) to suspend marketing and sales. http://www.fda.gov/drugs/drugsafety/ucm373040.htm. Accessed 9 Nov 2013.
12. Food and Drug Administration. Gilotrif (afatinib) label approved on 12 July 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201292s000lbl.pdf. Accessed 10 Sep 2013.
13. Food and Drug Administration. Inlyta (axitinib) label approved on 27 January 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202324lbl.pdf. Accessed 10 Sep 2013.
14. Food and Drug Administration. Bosulif (bosutinib) label approved on 4 September 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203341lbl.pdf. Accessed 10 Sep 2013.

15. Food and Drug Administration. Cometriq (cabozantinib) label approved on 29 November 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203756lbl.pdf. Accessed 10 Sep 2013.
16. Food and Drug Administration. Xalkori (crizotinib) label approved on 24 February 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s003lbl.pdf. Accessed 10 Sep 2013.
17. Food and Drug Administration. Tafinlar (dabrafenib) label approved on 29 May 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202806s000lbl.pdf. Accessed 10 Sep 2013.
18. Food and Drug Administration. Sprycel (dasatinib) label approved on 7 October 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021986s009s010lbl.pdf. Accessed 10 Sep 2013.
19. Food and Drug Administration. Tarceva (erlotinib) label approved on 17 April 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021743s017lbl.pdf. Accessed 10 Sep 2013.
20. Food and Drug Administration. Iressa (gefitinib) label approved on 17 June 2005. http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021399s008lbl.pdf. Accessed 10 Sep 2013.
21. Food and Drug Administration. Imbruvica (ibrutinib) label approved on 13 November 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf. Accessed 18 Nov 2013.
22. Food and Drug Administration. Gleevec (imatinib) label approved on 31 January 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021588s035lbl.pdf. Accessed 10 Sep 2013.
23. Food and Drug Administration. Tykerb (lapatinib) label approved on 14 February 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022059s013lbl.pdf. Accessed 10 Sep 2013.
24. Food and Drug Administration. Tasigna (nilotinib) label approved on 1 May 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022068s012lbl.pdf. Accessed 10 Sep 2013.
25. Food and Drug Administration. Votrient (pazopanib) label approved on 15 November 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022465s013lbl.pdf. Accessed 10 Sep 2013.
26. Food and Drug Administration. Iclusig (ponatinib) label approved on 14 December 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf. Accessed 10 Sep 2013.
27. Food and Drug Administration. Stivarga (regorafenib) label approved on 27 September 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203085lbl.pdf. Accessed 10 Sep 2013.
28. Food and Drug Administration. Jakafi (ruxolitinib) label approved on 21 June 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202192s001lbl.pdf. Accessed 10 Sep 2013.
29. Food and Drug Administration. Nexavar (sorafenib) label approved on 14 October 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021923s012lbl.pdf. Accessed 10 Sep 2013.
30. Food and Drug Administration. Sutent (sunitinib) label approved on 16 November 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021938s021s022s023lbl.pdf. Accessed 10 Sep 2013.
31. Food and Drug Administration. Mekinist (trametinib) label approved on 29 May 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204114s000lbl.pdf. Accessed 10 Sep 2013.
32. Food and Drug Administration. Caprelsa (vandetanib) label approved on 9 October 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022405s003lbl.pdf. Accessed 10 Sep 2013.
33. Food and Drug Administration. Zelboraf (vemurafenib) label approved on 17 August 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429s000lbl.pdf. Accessed 10 Sep 2013.
34. Elice F, Rodeghiero F, Falanga A, et al. Thrombosis associated with angiogenesis inhibitors. Best Pract Res Clin Haematol. 2009;22:115–28.
35. Food and Drug Administration. Avastin (bevacizumab) label approved on 26 January 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125085s267lbl.pdf. Accessed 10 Sep 2013.
36. Borzomati D, Nappo G, Valeri S, et al. Infusion of bevacizumab increases the risk of intestinal perforation: results on a series of 143 patients consecutively treated. Updates Surg. 2013;65:121–4.
37. Fakih MG, Lombardo JC. Bevacizumab-induced nasal septum perforation. Oncologist. 2006;11:85–6.
38. Traina TA, Norton L, Drucker K, et al. Nasal septum perforation in a bevacizumab-treated patient with metastatic breast cancer. Oncologist. 2006;11:1070–1.
39. Food and Drug Administration. Erbitux (cetuximab) label approved on 4 March 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125084s242lbl.pdf. Accessed 10 Sep 2013.
40. Food and Drug Administration. Vectibix (panitumumab) label approved on 28 March 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125147s169lbl.pdf. Accessed 10 Sep 2013.
41. Fuloria J. Safety profiles of current antiangiogenic therapies for metastatic colorectal cancer. Onco Targets Ther. 2012;5:133–42.
42. Kim TI, Chung JL, Hong JP, et al. Bevacizumab application delays epithelial healing in rabbit cornea. Invest Ophthalmol Vis Sci. 2009;50:4653–9.
43. Kim EC, Lee WS, Kim MS. The inhibitory effects of bevacizumab eye drops on NGF expression and corneal wound healing in rats. Invest Ophthalmol Vis Sci. 2010;51:4569–73.
44. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol. 2005;91:173–80.
45. D'Angelica M, Kornprat P, Gonen M, et al. Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. Ann Surg Oncol. 2007;14:759–65.
46. Kesmodel SB, Ellis LM, Lin E, et al. Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. J Clin Oncol. 2008;26:5254–60.
47. Mahfud M, Breitenstein S, El-Badry AM, et al. Impact of preoperative bevacizumab on complications after resection of colorectal liver metastases: case-matched control study. World J Surg. 2010;34:92–100.
48. Tamandl D, Gruenberger B, Klinger M, et al. Liver resection remains a safe procedure after neoadjuvant chemotherapy including bevacizumab: a case-controlled study. Ann Surg. 2010;252:124–30.
49. Constantinidou A, Cunningham D, Shurmahi F, et al. Perioperative chemotherapy with or without bevacizumab in patients

with metastatic colorectal cancer undergoing liver resection. Clin Colorectal Cancer. 2013;12:15–22.
50. Dede K, Mersich T, Besznyák I, et al. Bevacizumab treatment before resection of colorectal liver metastases: safety, recovery of liver function, pathologic assessment. Pathol Oncol Res. 2013;19:501–8.
51. Lubezky N, Winograd E, Papoulas M, et al. Perioperative complications after neoadjuvant chemotherapy with and without bevacizumab for colorectal liver metastases. J Gastrointest Surg. 2013;17:527–32.
52. Li DB, Ye F, Wu XR, et al. Preoperative administration of bevacizumab is safe for patients with colorectal liver metastases. World J Gastroenterol. 2013;19:761–8.
53. Reddy SK, Morse MA, Hurwitz HI, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. J Am Coll Surg. 2008;206:96–106.
54. Clark AJ, Butowski NA, Chang SM, et al. Impact of bevacizumab chemotherapy on craniotomy wound healing. J Neurosurg. 2011;114:1609–16.
55. Roman CD, Choy H, Nanney L, et al. Vascular endothelial growth factor-mediated angiogenesis inhibition and postoperative wound healing in rats. J Surg Res. 2002;105:43–7.
56. Kaftan H, Reuther L, Miehe B, et al. Delay of tympanic membrane wound healing in rats with topical application of a tyrosine kinase inhibitor. Wound Repair Regen. 2008;16:364–9.
57. Kaftan H, Reuther L, Miehe B, et al. The influence of inhibition of the epidermal growth factor receptor on tympanic membrane wound healing in rats. Growth Factors. 2010;28:286–92.
58. Lee SM, Buchler T, Joseph T, et al. Bilateral eardrum perforation after long-term treatment with erlotinib. J Clin Oncol. 2008;26:2582–4.
59. Kaftan H, Reuther L, Miehe B, et al. Inhibition of fibroblast growth factor receptor 1: influence on tympanic membrane wound healing in rats. Eur Arch Otorhinolaryngol. 2012;269:87–92.
60. Food and Drug Administration. Product reviews and labels. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed 10 Sep 2013.
61. European Medicines Agency. European public assessment reports: assessment history and product information. http://www.emea.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. Accessed 10 Sep 2013.
62. European Medicines Agency. European public assessment report for Sutent (sunitinib) (10 January 2007). http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000687/WC500057733.pdf. Accessed 10 Sep 2013.
63. Ko J, Ross J, Awad H, et al. The effects of ZD6474, an inhibitor of VEGF signaling, on cutaneous wound healing in mice. J Surg Res. 2005;129:251–9.
64. Johannsen M, Florcken A, Bex A, et al. Can tyrosine kinase inhibitors be discontinued in patients with metastatic renal cell carcinoma and a complete response to treatment? A multicentre, retrospective analysis. Eur Urol. 2009;55:1430–9.
65. Johannsen M, Staehler M, Ohlmann CH, et al. Outcome of treatment discontinuation in patients with metastatic renal cell carcinoma and no evidence of disease following targeted therapy with or without metastasectomy. Ann Oncol. 2011;22:657–63.
66. Harshman LC, Yu RJ, Allen GI, et al. Surgical outcomes and complications associated with presurgical tyrosine kinase inhibition for advanced renal cell carcinoma (RCC). Urol Oncol. 2013;31:379–85.
67. Govindan R, Behnken D, Read W, et al. Wound healing is not impaired by the epidermal growth factor receptor-tyrosine kinase inhibitor gefitinib. Ann Oncol. 2003;14:1330–1.
68. Johnson KS, Levin F, Chu DS. Persistent corneal epithelial defect associated with erlotinib treatment. Cornea. 2009;28:706–7.
69. Ibrahim E, Dean WH, Price N, et al. Perforating corneal ulceration in a patient with lung metastatic adenocarcinoma treated with gefitinib: a case report. Case Rep Ophthalmol Med. 2012;2012:379132.
70. Yano S, Kondo K, Yamaguchi M, et al. Distribution and function of EGFR in human tissue and the effect of EGFR tyrosine kinase inhibition. Anticancer Res. 2003;23(5A):3639–50.
71. Saint-Jean A, Sainz de la Maza M, Morral M, et al. Ocular adverse events of systemic inhibitors of the epidermal growth factor receptor: report of 5 cases. Ophthalmology. 2012;119:1798–802.
72. Food and Drug Administration. Regranex (becaplermin) label approved on 11 March 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103691s5095lbl.pdf. Accessed 10 Sep 2013.
73. Yu CQ, Zhang M, Matis KI, et al. Vascular endothelial growth factor mediates corneal nerve repair. Invest Ophthalmol Vis Sci. 2008;49:3870–8.
74. Muller AK, Meyer M, Werner S. The roles of receptor tyrosine kinases and their ligands in the wound repair process. Semin Cell Dev Biol. 2012;23:963–70.
75. Bao P, Kodra A, Tomic-Canic M, et al. The role of vascular endothelial growth factor in wound healing. J Surg Res. 2009;153:347–58.
76. Somanath PR, Chen J, Byzova TV. Akt1 is necessary for the vascular maturation and angiogenesis during cutaneous wound healing. Angiogenesis. 2008;11:277–88.
77. Perrotte P, Matsumoto T, Inoue K, et al. Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. Clin Cancer Res. 1999;5:257–65.
78. Pastor JC, Calonge M. Epidermal growth factor and corneal wound healing: a multicenter study. Cornea. 1992;11:311–4.
79. Lou-Bonafonte JM, Bonafonte-Marquez E, Bonafonte-Royo S, et al. Posology, efficacy, and safety of epidermal growth factor eye drops in 305 patients: logistic regression and group-wise odds of published data. J Ocul Pharmacol Ther. 2012;28:467–72.
80. Schneider MR, Werner S, Paus R, et al. Beyond wavy hairs: the epidermal growth factor receptor and its ligands in skin biology and pathology. Am J Pathol. 2008;173:14–24.
81. Yu FX, Yin J, Xu K, et al. Growth factors and corneal epithelial wound healing. Brain Res Bull. 2010;81:229–35.
82. Márquez EB, De Ortueta D, Royo SB, et al. Epidermal growth factor receptor in corneal damage: update and new insights from recent reports. Cutan Ocul Toxicol. 2011;30:7–14.
83. Majumdar AP, Edgerton EA, Arlow FL. Gastric mucosal tyrosine kinase activity during aging and its relationship to cell proliferation in rats. Biochim Biophys Acta. 1988;965:97–105.
84. Lin W, Kao HW, Robinson D, et al. Tyrosine kinases and gastric cancer. Oncogene. 2000;19:5680–9.
85. Tarnawski AS. Cellular and molecular mechanisms of gastrointestinal ulcer healing. Dig Dis Sci. 2005;50(Suppl 1):S24–33.
86. Tarnawski AS, Ahluwalia A. Molecular mechanisms of epithelial regeneration and neovascularization during healing of gastric and esophageal ulcers. Curr Med Chem. 2012;19:16–27.
87. Pai R, Szabo IL, Giap AQ, et al. Nonsteroidal anti-inflammatory drugs inhibit re-epithelialization of wounded gastric monolayers by interfering with actin, Src, FAK and tensin signaling. Life Sci. 2001;69:3055–71.
88. Choi GH, Park HS, Kim KR, et al. Increased expression of epidermal growth factor receptor and betacellulin during the early stage of gastric ulcer healing. Mol Med Rep. 2008;1:505–10.

89. Elitsur Y, Majumdar AP, Tureaud J, et al. Tryosine kinase and ornithine decarboxylase activation in children with *Helicobacter pylori* gastritis. Life Sci. 1999;65:1373–80.
90. Meyer-ter-Vehn T, Covacci A, Kist M, et al. *Helicobacter pylori* activates mitogen-activated protein kinase cascades and induces expression of the proto-oncogenes c-fos and c-jun. J Biol Chem. 2000;275:16064–72.
91. Wong BC, Wang WP, So WH, et al. Epidermal growth factor and its receptor in chronic active gastritis and gastroduodenal ulcer before and after *Helicobacter pylori* eradication. Aliment Pharmacol Ther. 2001;15:1459–65.
92. Coyle WJ, Sedlack RE, Nemec R, et al. Eradication of *Helicobacter pylori* normalizes elevated mucosal levels of epidermal growth factor and its receptor. Am J Gastroenterol. 1999;94: 2885–9.
93. Duan WR, Patyna S, Kuhlmann MA, et al. A multitargeted receptor tyrosine kinase inhibitor, SU6668, does not affect the healing of cutaneous full-thickness incisional wounds in SKH-1 mice. J Invest Surg. 2006;19:245–54.
94. Schäfer M, Werner S. Cancer as an overhealing wound: an old hypothesis revisited. Nat Rev Mol Cell Biol. 2008;9:628–38.
95. Ceelen W, Pattyn P, Mareel M. Surgery, wound healing, and metastasis: recent insights and clinical implications. Crit Rev Oncol Haematol. 2014;89:16–26.
96. Chmielowiec J, Borowiak M, Morkel M, et al. c-Met is essential for wound healing in the skin. J Cell Biol. 2007;177:151–62.
97. Luo JC, Lin HY, Lu CL, et al. Growth factors expression in patients with erosive esophagitis. Transl Res. 2008;152:81–7.
98. Meyer M, Muller AK, Yang J, et al. FGF receptors 1 and 2 are key regulators of keratinocyte migration in vitro and in wounded skin. J Cell Sci. 2012;125(Pt 23):5690–701.
99. Demidova-Rice TN, Wolf L, Deckenback J, et al. Human platelet-rich plasma- and extracellular matrix-derived peptides promote impaired cutaneous wound healing in vivo. PLoS ONE. 2012;7(2):e32146.
100. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003;83:835–70.
101. Cazander G, Jukema GN, Nibbering PH. Complement activation and inhibition in wound healing. Clin Dev Immunol. 2012;2012:Article ID 534291.
102. Miyamoto K, Kobayashi T, Hayashi Y, et al. Involvement of stem cell factor and c-kit in corneal wound healing in mice. Mol Vision. 2012;18:1505–15.