Review

Clin Ter 2014; 165 (4):e323-329. doi: 10.7417/CT.2014.1750

Drug cutaneous side effect: focus on skin ulceration

S. D'Epiro, M. Salvi, A. Luzi, C. Mattozzi, C. Luci, L. Macaluso, F. Marzocca, V. Salvo, C. Cantisani, G. Paolino, S. Calvieri, A.G. Richetta

Department of Dermatology and Venereology, Policlinico "Umberto I", "Sapienza" University of Rome, Italy

Abstract

Skin ulcers are defined as tissue loss interesting the deeper layers of the dermis and hypodermis, with low tendency to spontaneous healing. They cause disability related to pain, risk of infection and amputation, chronic management, requiring working absence with notably economic burden. The major cause is often related to underlying vascular disease, infections, tumors, autoimmunity, trauma, even if literature occasionally reported several cases of drug inducing skin ulceration. Most of drugs involved are chemotherapy agents and more recently molecular target therapies.

Evidences supporting these drugs as the major cause of skin ulcers include delay of onset after therapy initiation, improvement after withdrawal of the drug, recurrence after its reintroduction and, sometimes, simultaneous occurrence of other skin lesions that have previously been reported to be associated with these agents.

Attention should be reserved to patients undergoing antineoplastic agents, especially if previously affected by predisposing comorbidities, considering such side effect as possible differential diagnosis for skin ulceration in neoplastic patients. ***Clin Ter 2014; 165(4):e323-329. doi: 10.7417/CT.2014.1750***

Key words: *drug, skin, side effects, ulceration*

Introduction

Skin ulcers are defined as tissue loss interesting the deeper layers of the dermis and hypodermis, with low tendency to spontaneous healing (1).

Chronic ulcers affect over 6 million people in the United States, with an incidence that is expected to grow as the increasing rate of general population mean age and the number of individuals with diabetes. Chronic ulcers strongly affect the quality of life and productivity of the patients, representing a financial burden to the health care system (1).

Several mechanisms may be implicated in the pathogenesis, then wounds can be classified as: venous, arterial (large and small vessels), neurotrophic, hypertensive, infectious, hematologic, neoplastic, related to physical and chemical agents and pyoderma gangrenosum. Among these, venous insufficiency is the main cause of ulceration (70%), mostly localized to lower legs. Other frequent mechanisms involved are vascular diseases related to diabetes and chronic lymphoedema, malignancy and trauma (1, 2).

Moreover, skin ulceration have occasionally been reported in literature as drugs side effects, especially related to the administration of traditional chemotherapy agents and new molecular target therapies such as: Epidermal Growth Factor Receptor (EGFR) inhibitors (Gefitinib, Cetuximab) (3, 4); Angiogenesis inhibitors (Sorafenib, Sunitinib, Bevacizumab) (5-7); BCR-ABL, c-KIT, Platelet-Derived Growth Factor (PDGFR) inhibitors (Imatinib) (8); Mammalian Target Of Rapamycin (M-Tor) inhibitor (Sirolimus) (9); Antimetabolites (Methotrexate, Gemcitabine) (10,11); Antiproliferative (Hydroxyurea) (12) (Table 1).

Authors aim to investigate literature data concerning skin ulceration related to drugs administration, focusing on particular drug categories, the possible implied mechanism of action, the evolution related to the underlying neoplastic disease, and suggesting an emerging new class of wounds which physicians should be aware in clinical practice.

EGFR Inhibitors

Gefitinib

Gefitinib is an antineoplastic agent that inhibits epidermal growth factor receptors (EGFR) signal transduction, effective in patients with advanced non-small cell lung cancer (NSCLC). It has been associated with multiple cutaneous effects, most of which of mild entity and well tolerated. Acneiform eruption, seborrheic dermatitis, and paronychia are common dose-dependent adverse cutaneous reactions (3).

Two cases of skin ulceration induced by Gefitinib are reported in literature (13, 14).

Sagara et al. described the case of a 55-year-old man suffering from non-small cell lung cancer who developed an ulcerated erythematous plaque on the hypogastrium,

Correspondence: A.G. Richetta, Department of Dermatology and Venereology, Policlinico "Umberto I", "Sapienza" University of Rome, Italy. Tel.: +39.06.49976966. E-mail: antoniorichetta@hotmail.com

ISSN 1972-6007

Table 1. Classification of traditional chemotherapy agents and new molecular target therapies inducing skin ulcers.

TYPE	FUNCTION	DRUG	MOLECULAR TARGET
EGFR inhibitors	Tyrosine kinase inhibitors Monoclonal antibodies	Gefitinib Cetuximab	EGFR
Angiogenesis Inhibitors	Multikinase multitarget inhibitors Recombinant human monoclonal antibody	Sorafenib Sunitinib Bevacizumab	VEGFR1, 2 , 3; Flt3; c-KIT; PDGFR; RAF VEGF
BCR-ABL, c-KIT, PDGFR inhibitors	Tyrosine kinase inhibitors	Imatinib	BCR-ABL;c-KIT;PDGFR
m-TOR inhibitors	Serine-threoninne kinases	Sirolimus	VEGF; HIF
Antimetabolites	Folic acid antagonists Pyrimidines antagonists	Methotrexate Gemcitabine	DHFR Ribonucleotide Reductase
Antiproliferative	DNA synthesis inhibitor	Hydroxyurea	Ribonucleotide reductase

with central necrosis and hypertrophic border, clinically and histologically compatible with the diagnosis of pyoderma gangrenosum-like lesion (13).

Fernández-Guarino et al. reported the case of a perforating dermatosis after treatment with Gefitinib (14).

These adverse skin reactions disappeared with dose reduction.

Cetuximab

Cetuximab is a chimeric monoclonal antibody binding to the epidermal growth factor receptor (EGFR), inhibiting tumour growth, invasion, angiogenesis and metastasis. It is used for treatment of metastatic colorectal and squamous cell carcinoma of head and neck (15). Among side effects, in literature are described only few cases of Cetuximab inducing skin ulcerations.

Tsuboi et al. described a particular case of Cetuximab-associated cutaneous ulcers in a 82-years old female with metastatic colorectal cancer. The patient, after 18 weeks of adjuvant chemotherapy following a curative surgical resection, developed two skin ulcerations around her stoma, healed only after Cetuximab withdrawal (4).

Busam et al. examined 10 patients with renal cell carcinoma treated with C225, who developed several cutaneous side-effects such as painfull fissurations of the distal fingers tufts. Another frequent side effect was a follicular rash with acneiform distribution appearing approximately 1 week after the beginning of therapy. Other patients developed intraoral aphtous ulcers. The clinical features and timing of the findings in 10 different patients following monotherapy with C225 strongly suggested a direct biological effect of the drug.

The authors showed that treatment with C225 results in upregulation of p27Kip1 in epidermal keratinocytes, which can affect follicular and epidermal homeostasis. Further investigations concerning the role of EGFR pathway in keratinocytes regulation may be significant to explain ulceration and acneiform skin eruptions (16).

Angiogenesis inhibitors

Sorafenib

Sorafenib is an oral multitargeted kinase inhibitor (MKI) that shows anti-mytotic and anti-angiogenetic properties. It targets both c-Raf and b-Raf, MAP kinase (MEK) and extracellular regulated kinase (ERK) phosphorylation, preventing cancer growth (17).

It also reduces angiogenesis, demonstrating a significant activity against several tyrosine kinase receptors involved in neo-vascularization and tumour progression, such as vascular endothelial growth factor 2 and 3 (VEGFR), platelet-derived growth factor receptor-β (PDGFR), FMS-like tyrosine kinase-3 (FLT), c-KIT and RET receptor tyrosine kinase (18).

Therefore, Sorafenib may inhibit cancer growth by a dual mechanism, acting either directly on the neoplasia or on endothelial cells, implicated in the tumoral neoangiogenesis (17).

It has recently been approved by the Food and Drug Administration (FDA) for advanced renal cell carcinoma and hepatocellular carcinoma (17).

Sorafenib is associated with several side effects, such as diarrhoea, nausea, fatigue and hypertension (19).

Cutaneous adverse events include mucositis, stomatitis, rash, facial and acral erythema, splinter hemorrhages, alopecia, xerosis, and hand-and-foot skin reaction (HFSR) (5).

Moreover, squamous cell carcinoma, keratoacanthoma and eruptive melanocytic lesions have been associated with MKI therapy (20).

Literature reports a case of skin ulceration described in a 79-years-old man with metastatic renal cell carcinoma. The patient developed painful erythematous plaques and bullae that evolved in skin erosions and ulcerations on lower limbs and elbows about 20 days after starting Sorafenib therapy (21).

The reasons for ulcerations are probably linked to the anti-mytotic and anti-angiogenetic properties of Sorafenib, which mechanism of action may affect and compromise skin homeostasis (22).

The complete resolution of skin erosions and ulcerations was obtained only after treatment withdrawal, meanwhile the patient developed new lesions after reintroducing Sorafenib at half doses, indicating a not dose-dependent pathogenesis for cutaneous side effect (21).

Literature also reports a case of skin ulceration due to a leukocytoclastic vasculitis, where authors could reintroduce Sorafenib at a lower dose without recurrence of the vasculitic lesions (23).

The development of cutaneous side effects during therapy with Sorafenib has been associated with a better treatment response: a recent study reported a lower tumour progression in a patient with skin lesions and diarrhea (24).

Sunitinib

Sunitinib is a multi-targeted kinase inhibitor (MKI) affecting tumor cell angiogenesis and proliferation through inhibition of several receptor tyrosine kinases, including the vascular endothelial growth factor receptor 2 and 3 (VEGF), platelet-derived growth factor receptor (PDGF α and β), Tyrosine-Protein Kinase (KIT), FMS-like tyrosine kinase 3 (FLT3) , colony-stimulating factor-1 (CSF1) and rearranged during transfection (RET) (25).

Currently, Sunitinib has gained US Food and Drug Administration approval for treatment of advanced renal cell carcinoma and provided an increase of progression-free survival among patients with metastatic disease compared with the previous standard of therapy, Interferon α. Sunitinib has also demonstrated efficacy in Imatinib-resistant gastrointestinal stromal tumor (GIST) and Hepatocarcinoma (26).

80% of treated patients developed cutaneous manifestations, such as hand-and-foot skin reaction (36%), stomatitis (36%), skin/hair depigmentation (30%), facial swelling (24%), subungual haemorrhages (10%) (6).

Among side effects, in literature are described few cases of Sunitinib inducing skin ulceration.

Durant et al described the case of a 50-year-old woman with sensory neuropathy who developed necrotic ulcers of the extremities (hands and feet) one month after starting Sunitinib therapy (27).

Feyerabend S, Schilling D, Wicke C et al. reported the case of necrotic lesion of the foot developed 8 days later Sunitinib treatment in a patient with type II diabetes, then forced to amputation (28).

Guyot-Caquelin et al. reported the case of a 73-year-old woman with a history of deep venous thrombosis of the right leg who developed chronic ulcers in the same leg 6 weeks after starting Sunitinib (29).

Kluger et al. described the case of a 55-year-old man with advanced renal cell cancer with bone, lung and lymph node metastases that one week later Sunitinib treatment developed lower limbs erosion with painful fibrous and inflammatory borders.

Moreover, an examination revealed bilateral erythema of the palms and soles, bullous swelling of the soles, keratotic paronychia and subungual splinter haemorrhages. The simultaneous occurrence of erosive leg lesions and hand-foot skin reactions with subungual haemorrhages suggested the presence of multiple cutaneous side effects related to Sunitinib (30).

Ulcerations may be the consequence of the antiangiogenic effect with ischemia related to an impairment in skin microcirculation (30). Sunitinib may also interfere with contractile interactions between fibroblasts and the surrounding extracellular matrix, by modifying the differentiation of fibroblasts into myofibroblasts (31). Furthermore, in literature have been reported two cases of Sunitinib-associated pyoderma gangrenosum (PG) developed during the treatment of metastatic renal cell carcinoma and hepatocellular carcinoma (32).

The mechanism of Sunitinib inducing Pyoderma gangrenosum is still unclear; the concomitant inhibition of c-KIT and VEGFR in predisposed patient may conduce to the development of necrotic lesions with neutrophilic infiltration eliciting Pyoderma gangrenosum (32).

Evidences supporting Sunitinib as the major cause of skin ulcers in the cases reported are: delay of onset at least one week after Sunitinib intake; improvement after withdrawal of the drug; recurrence after its reintroduction and concurrency of other skin lesions that have previously been reported to be associated with Sunitinib (hand-foot syndrome, splinter haemorrhages) (30).

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), approved by the US Food and Drug Administration for metastatic colon cancer, non –small cell lung cancer, renal cell carcinoma, and recurrent glioblastoma multiforme (33). Adverse events related to Bevacizumab include hypertension, proteinuria, deep vein thrombosis, gastrointestinal perforation and hemorrhages (34).

Among side effects, in literature are described some cases of impairing or delay in wound healing.

Scappaticci et al. reported an increase of postoperative wound healing complications in patients who had major surgery during Bevacizumab therapy for metastatic colorectal cancer (CRC) (7).

Moreover, the results of their analysis suggested that the use of Bevacizumab in combination with 5-fluorouracil/leucovorin-based chemotherapy, 28–60 days after primary cancer surgery, caused no increased risk of wound healing complications compared with chemotherapy alone (7).

Peters et al. presented four cases of ulcerated striae distensae in primary brain tumor patients on concurrency of corticosteroid and Bevacizumab therapy (35).

Authors hypothesized that ulceration in striae distensae is a two-step process: at first, corticosteroids modify collagen synthesis, impair tensile strength and lead to striae development; then, Bevacizumab delay healing of these areas owing to inhibition of VEGF predisponing the weakened striae to ulceration (35).

BCR-ABL, c-KIT, PDGFR Inhibitors

Imatinib

Imatinib is a specific tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia Ph+ which acts by blockingthe Bcr-Abl oncogene protein on the cell surface (36).

It is generally well tolerated and the most frequent side effect is generalized skin rash.

Oral painful erosions and lichenoid reactions have also been related to Imatinib , requiring treatment with oral steroids or even withdrawal (37).

Basso at al. reported two cases of painful oral ulcerative lesion in patients with CML Ph+, after the beginning of Imatinib therapy. In both cases lesions underwent complete remission after withdrawal of the drug. It can be hypothesized that the phenomenon is dose-dependent. However, patients using Imatinib are frequently on multiple drugs, which could make the determination of the causative agent difficult. Allopurinol and drugs with CYP3A4 interactions (omeprazol and derivates) are the most important agents. Anyway, these patients were not assuming these drugs during the onset of the described side effects (8).

m-TOR Inhibitors

Sirolimus

Sirolimus inhibits the kinase activity of mTOR, blocking the cell cycle progression in the mid- to late-G1 phase. It also has inhibitory effects on interleukin-2-dependent and -independent proliferation of B lymphocytes and production of immunoglobulins A, M, and G (38).

Among side effects, in literature are described cases of skin manifestations, mainly consisting of aphthous mouth ulcerations, rash or acne (9).

Tracey et al. reported the case of a debilitating ulcerating maculopapular rash in a liver transplantation woman affected by cryptogenic cirrhosis, 3 months later immunosuppressive treatment with Sirolimus requiring the withdrawal of therapy (9).

Schaffellner et al. analyzed several cases of mouth ulcers induced by Sirolimus that appeared after 2-6 weeks of therapy and regressing with dose reduction (39).

Antimetabolites

Methotrexate

Methotrexate (MTX) is a folate analogue drug that inhibits the DNA synthesis by competition with dihydrofolate reductase, lymphocyte proliferation and polymorphonuclear chemotaxis (40).

MTX was initially employed as an antineoplastic agent in the treatment of carcinomas, leukemias and lymphomas (high-dose treatment). It is widely FDA approved as a disease modifying agent (DMARD) in the treatment for autoimmune conditions such as rheumatoid arthritis (RA) and psoriatic arthritis (61).

Common side events, even with low-dose MTX therapy, include liver toxicity, impaired renal function, gastrointestinal effects and bone marrow suppression.

Less commonly, MTX toxicity has been associated with adverse cutaneous reactions that are usually dose-related and may occur in patients receiving high doses of drug.

Skin ulceration has often been reported as an adverse effect of MTX in psoriatic patients (42).

Pearce and Wilson revised 47 patients, who developed ulceration or erosion of psoriatic plaques meanwhile treated with MTX. The most common risk factors were high dosage, concomitant non-steroidal anti-inflammatory drugs (NSAIDS), renal failure, infection, older age and pustular psoriasis (43).

Ulceration localized into psoriatic plaques may be related to higher uptake of MTX by the hyperproliferative keratinocytes compared to normal skin (Fig. 1) (10).

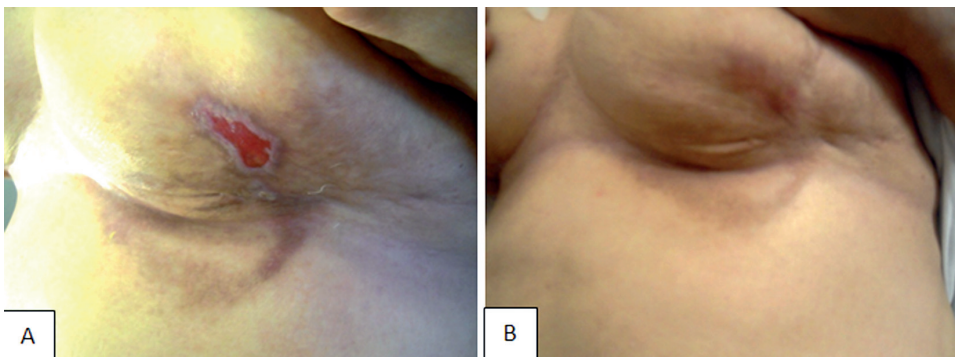

Fig.1 Cutaneous ulceration of psoriatic plaque as a sign of MTX toxicity in patients with psoriasis (A), healed after drug decreasing dosage (A).

Gemcitabine

Gemcitabine is an antimetabolite nucleoside employed in the treatment of carcinoma of the lung, pancreas and urothelium. It is usually well tolerated, with cutaneous toxicity reported in approximately 25% of patients, including alopecia, maculo-papular eruption, urticaria, palmar-plantar erythrodysesthesia and acute lipodermatoslerosis-like reactions (44).

Recently, Gemcitabine has been associated with notable vascular side effects such as acute arterial events, venous thromboembolism, digital ischemia, vasculitis and thrombotic microangiopathy (11).

Literature reports the case of a 82-year-old woman with extensive necrotic ulcerative lesions on the back side of her lower limbs, arised after the second cycle of chemotherapy with Gemcitabine for metastatic pancreatic cancer. A temporal relationship was observed between gemcitabine administration and skin ulcerations, with a progressive shrinkage of the lesions observed with chemotherapy withdrawal (45). The mechanisms implied in the pathogenesis of vascular toxicity may be endothelial damage, increased adherence of platelets, deposition of immune complexes and a hypercoagulable state (44).

Antiproliferative

Hydroxyurea

Hydroxyurea (Hydroxycarbamide; HU), an antitumor agent belonging to the family of antimetabolites, is commonly used for the long-term treatment of patients with Philadelphia-chromosome negative chronic myeloproliferative disorders (MPNs) (46).

Although this agent is usually well-tolerated, several cutaneous adverse events are described in literature; among them leg ulcers have been noted in association with long-term administration (12).

A retrospective study on a large multicenter series of 3,411 patients affected by MPNs and treated with Hydroxyurea, revealed significant drug-related toxicities.

Twenty-eight patients (24 females and 4 males) developed painful oral mucosal lesions obtaining complete healing only after HU dose reduction or suspension.

Cutaneous ulcers were recorded in 118 patients (72 females and 46 males), frequently on the perimalleolar region and on the pretibial area. In 62 patients at least one concurrent risk factor was identified: arterial hypertension (16), peripheral vascular disease (13), diabetes (4).

A complete wound healing was obtained in 53 patients in a median of 5 months, following withdrawal of HU and concurrent use of therapeutic strategies such as decompression chamber, wounds surgical toilettes, local therapy with antibiotics and heparin. Thirty-one patients continued to assume HU at a reduced dosage; in 8 some improvement of ulcer without healing was reported over several months (Fig. 2) (12).

The exact mechanisms of skin ulceration are controversial. Hydroxyurea selectively kills cells during the synthesis phase of the cell cycle, therefore damaging basal keratinocytes and collagen synthesis. Moreover, inhibition of DNA synthesis can cause red blood cells to become megaloblastic, impairing blood flow in the microcirculation (47, 48).

Altered microcirculation occur in patients affected by essential thrombocythemia, then careful evaluation of peripheral circulation should be reserved in patients before the administration of HU.

Conclusions

Cutaneous ulcers represent a major public health, concerning disability related to pain, risk of infection and amputation, chronic management, requiring working absence with notably economic burden. The major cause is often related to underlying vascular disease, infections, tumors, autoimmunity, trauma, even if literature occasionally reported several cases of drug inducing skin ulceration. Most of drugs involved are chemotherapy agents and more recently molecular target therapies.

Individual predisposition, sex, age, co-morbidities, concomitant therapies and dose administered may contribute to ulceration.

Drugs inhibiting target molecules such as VEGFR, PDGFR and EGFR, imply an impairment

in vessels repair which results in the onset of dermo-epidermal injury. Endothelial damage also leads to a local drug release with consequent onset of inflammation. Antiproliferative and antimetabolities agents are also implicated in dermo-epidermal integrity loss.

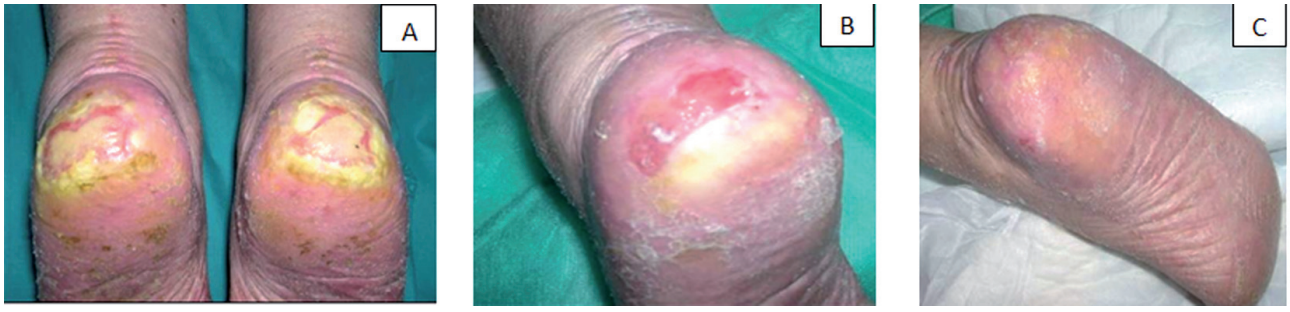

Fig. 2 (A, B, C). Ulcerative lesions in progressive healing in patients treated with hydroxyurea.

Evidences supporting these drugs as the major cause of skin ulcers include: delay of onset after therapy initiation, improvement after withdrawal of the drug, recurrence after its reintroduction and, sometimes, simultaneous occurrence of other skin lesions that have previously been reported to be associated with these agents (hand-foot syndrome, splinter haemorrhages).

Most of cases tend to spontaneously healing with dose reduction or drug withdrawal.

Moreover, physician should consider the entity of neoplastic disease together with the severity of skin ulceration, avoiding drug interruption if risk related to ulcerative lesions appears acceptable considering the significant survival benefit of the drug.

In conclusion, careful attention should be reserved to patients undergoing antineoplastic agents, especially if previously affected by predisposing comorbidities.

References

1. Greer N, Foman NA, MacDonald R, et al. Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review. Washington (DC): Department of Veterans Affairs, 2012; VA Evidence-based Synthesis Program Reports
2. Huljev D. Contemporary management of leg ulcer. Acta Med Croatica 2012; 66(5):387-95
3. Kobayashi I, Katsumi S. Cutaneous side-effects induced by Gefitinib. Jpn J Dermatol 2004; 114:1107-13
4. Tsuboi K, Kawase Y, Okochi O et al. Cetuximab-associated skin ulceration in patient with metastatic colorectal cancer: a case report. Gan To Kagaku Ryoho 2011; 38(9):1549-52
5. Robert C, Soria JC, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet Oncol 2005; 6(7):491-500
6. Lee WJ, Lee JL, Chang SE, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol 2009; 161:1045-51
7. 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
8. Basso FG, Boer CC, Corrêa ME, et al. Skin and oral lesions associated to imatinib mesylate therapy. Support Care Cancer 2009; 17(4):465-8
9. Tracey C, Hawley C, Griffin AD, et al. Generalized, Pruritic, Ulcerating Maculopapular Rash Necessitating Cessation of Sirolimus in a Liver Transplantation Patient. Liver Transpl 2005; 11(8):987-9
10. Del Pozo J, Martínez W, García-Silva J, et al. Cutaneous ulceration as a sign of methotrexate toxicity. Eur J Dermatol 2001; 11(5):450-2
11. Chia-Yu Chu. Gemcitabine induced acute lipodermatosclerosis-like reaction. Acta Derm Venereol 2001; 81:426-8
12. Antonioli E, Guglielmelli P, Pieri L, et al. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. Am J Hematol 2012; 87(5):552-4
13. Sagara R, Kitami A, Nakada T, et al. Adverse reactions to gefitinib (Iressa): revealing sycosis- and pyoderma gangrenosum-like lesions. Int J Dermatol 2006; 45(8):1002-3
14. Fernández-Guarino M, Aldanondo I, González-García C, et al. Gefitinib-induced perforating dermatosis. Actas Dermosifiliogr 2006; 97(3):208-11
15. Navarini AA, Kamacharova I, Kerl K, et al. Ecthymatous skin eruption during therapy with cetuximab. Eur J Dermatol 2011; 21(2):282-3
16. Busam KJ, Capodieci P, Motzer R, et al. Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. Br J Dermatol 2001; 144(6):1169-76
17. Adnane L, Trail PA, Taylor I, et al. Sorafenib (BAY 43-9006, Nexavar®), a 22 Dual-Action Inhibitor That Targets RAF/MEK/ERK Pathway in Tumor Cells and Tyrosine Kinases VEGFR/PDGFR in Tumor Vasculature. Methods Enzymol 2005; 407:597-612
18. Carlomagno F, Anaganti S, Guida T, et al. BAY 43-9006 inhibition of oncogenic RET mutants. J Natl Cancer Inst 2006; 98:326-34
19. Hahn O, Stadler W. Sorafenib. Curr Opin Oncol 2006; 18 (6):615-21
20. Hong DS, Reddy SB, Prieto VG, et al. Multiple squamous cell carcinomas of the skin after therapy with sorafenib combined with tipifarnib. Arch Dermatol 2008; 144:779-82
21. Richetta AG, Maiani E, Carlomagno V et al. Sorafenib: atypical cutaneous side effects. Eur J Dermatol 2007; 17(6):549-50. Epub 2007 Oct 19
22. Fox LP. Pathology and management of dermatologic toxicities associated with anti-EGFR therapy. Oncology (Williston Park) 2006; 20(5 Suppl 2): 26-34
23. Chung NM, Gutierrez M, Turner ML, et al. Leukocytoclastic Vasculitis Masquerading as Hand-foot Syndrome in a Patient Treated With Sorafenib. Arch Dermatol 2006; 142:1510-1
24. Strumberg D, Awada A, Hirte H, et al. Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumors: is rush associated with treatment outcome? Eur J Cancer 2006; 42:548-56
25. Mena AC, Pulido EG, Guillén-Ponce C, et al: Understanding the molecular-based mechanism of action of the tyrosine kinase inhibitor: Sunitinib. Anticancer Drugs 2010; 21:S3-11
26. Chow LQ, Eckhardt SG. Sunitinib: From rational design to clinical efficacy. J Clin Oncol 2007; 25:884-96
27. Durant C, Saint-Jean M, Connault J, et al. Necrotizing hand-foot skin reaction induced by antiangiogenic in a patient with Thevenard neuroacropathy. J Mal Vasc 2009; 34:222-5
28. Feyerabend S, Schilling D, Wicke C, et al. Toxic dermatolysis, tissue necrosis and impaired wound healing due to sunitinib treatment leading to forefoot amputation. Urol Int 2009; 82: 246-8
29. Guyot-Caquelin P, Granel-Brocard F, Cuny JF, et al. Leg ulcerations and sunitinib. Ann Dermatol Venereol 2010; 137: 626-9
30. Kluger N, Chapelle A, Jacot W, et al. Lower limbs erosions induced by sunitinib. Acta Derm Venereol 2011; 91(3):360-1
31. Pappas PJ, Lal BK, Ohara N, et al. Regulation of matrix contraction in chronic venous disease. Eur J Vasc Endovasc Surg 2009; 38:518-29
32. Akanay-Diesel S, Hoff NP, Kürle S, et al. Sunitinib induced pyoderma gangrenosum-like ulcerations. Eur J Med Res 2011; 16(11):491-4
33. Genentech Inc. Avastin (bevacizumab). www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf. Accessed 2012; January 10
34. Hurwitz H, Saini S. Bevacizumab in the treatment of metastatic colorectal cancer: safety profile and management of adverse events. Semin Oncol 2006; 33:S26-S34

35. Peters KB, Coyle TE, Vredenburgh JJ, et al. Ulceration of striae distensae in high-grade glioma patients on concurrent systemic corticosteroid and bevacizumab therapy. J Neurooncol 2011; 101(1):155-9
36. Carella AM, Frassoni F, Melo J, et al. New insights in biology and current therapeutic options for patients with chronic myelogenous leukemia. Haematologica 1997; 82:478-95
37. O'Brien SG, Deininger MW. Imatinib in patients with newly diagnosed chronic-phase chronic myeloid leukemia. Semin Hematol 2003; 40(Suppl 2):26-30
38. Watson CJ, Friend PJ, Jamieson NV, et al. Sirolimus: a potent new immunosuppressant for liver transplantation. Transplantation 1999; 67:505-9
39. Schaffellner S, Jakoby E, Kniepeiss D, et al. Center experience in liver transplantation (LTX): management of dermal side effects caused by sirolimus. Int Immunopharmacol 2005; 5(1):137-40
40. Cronstein BN. The mechanism of action of methotrexate. Rheum Dis Clin North Am 1997; 23:739-55
41. Blits M, Jansen G, Assaraf YG, et al. Methotrexate normalizes upregulated folate pathway genes in rheumatoid arthritis. Arthritis Rheum 2013; 29
42. Lawrence CM, Dahl MG. Two patterns of skin ulceration induced by methotrexate in patients with psoriasis. J Am Acad Dermatol 1984; 11(6):1059-65
43. Pearce HP, Wilson BB. Erosion of psoriatic plaques: an early sign of methotrexate toxicity. J Am Acad Dermatol 1996; 35: 835-8
44. Dasanu CA. Gemcitabine: vascular toxicity and prothrombotic potential. Expert Opin Drug Saf 2008; 7(6):703-16
45. D'Epiro S, Salvi M, Mattozzi C, et al. Gemcitabine-induced extensive skin necrosis. Case Rep Med 2012; 2012: 831616
46. Saban N, Bujak M. Hydroxyurea and hydroxamic acid derivatives as antitumor drugs. Cancer Chemother Pharmacol 2009; 64:213-21