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ORIGINAL ARTICLE

Hand-foot syndrome due to sorafenib in hepatocellular carcinoma treated with vitamin E without dose modification; A preliminary clinical study

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Summary

Purpose: *Sorafenib has been found to have significant clinical activity against hepatocellular carcinoma (HCC). Hand-foot skin syndrome (HFS) has been described with the usage of sorafenib. It is a dose-limiting toxicity and may lead to compromised efficacy because of dose reduction.*

Methods: *From 14 patients diagnosed with HCC 10 who developed HFS while on treatment with sorafenib were included in this study. Sorafenib was administered orally at a dose of 400 mg twice daily vitamin E usage can be effective in HFS due to sorafenib, therefore vitamin E 300 mg/day was started when HFS occurred. HFS was graded according to the National Cancer Institute (NCI) criteria.*

Results: *Grade 2-3 HFS was found in 10 of 14 patients. Vitamin E was started to all patients without using topical agents. Mean time to the appearance of HFS was 15±3 days (range 10-22) after starting sorafenib. Grade was 3 in 4 patients, 2 in 4 patients and 1 in 2 patients. Vitamin E administration had a marked effect after 10-12 days of its initiation. Skin lesions disappeared without any dose modification.*

Conclusion: *Sorafenib is the gold standard for HCC treatment. Dose modification due to HFS decreases the effectiveness of this agent. Adding vitamin E to sorafenib is effective in HFS without dose reduction or treatment interruption. This is the first clinical study to report resolution of HFS with vitamin E due to sorafenib therapy.*

Key words: hand-foot syndrome, hepatocellular carcinoma, sorafenib, vitamin E

Introduction

Sorafenib is a multi-targeted orally active small molecule tyrosine kinase inhibitor (TKI) that inhibits Raf kinase and also blocks the intracellular portion of the vascular endothelial growth factor receptor (VEGFR) [1]. Results from the phase III SHARP trial suggest a survival benefit in patients with HCC compared to best supportive care alone [2]. As with other antineoplastic agents, sorafenib is associated with a number of side effects including diarrhea, nausea, fatigue, hypertension and dermatological toxicity. In a phase II placebo-controlled randomized discontinuation trial using sorafenib in patients with metastatic renal cell cancer, dermatologic changes including HFS, alopecia, stomatitis, facial and scalp erythema and subungual splinter hemorrhages were reported in > 90% of the patients, with HFS among the more frequent adverse manifestations [3].

Although sorafenib-associated HFS (also called hand-foot skin reaction, palmar-plantar erythrodysesthesia, acral erythema, and Burgdorf reaction) is similar to conventional HFS, some features are different [4,5]. HFS is a distinct localized cutaneous reaction characterized by erythema, numbness, tingling, and either dysesthesia or paresthesia, particularly on the palms and/or soles. It rarely affects the trunk, neck, chest, scalp and extremities. Swelling of the skin, desquamation, ulceration or blistering may occur in advanced cases [5]. It was first described in patients receiving mitotane therapy for hypernephroma in 1974 [6]. In 1984, Lokich and Moore reported the HFS associated with continuous infusion of various chemotherapeutic agents [7].

HFS has been associated with several systemic

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chemotherapeutic agents including 5fluorouracil (5FU), capecitabine, doxorubicin, cyclophosphamide, vinorelbine and docetaxel. The frequency and severity of HFS is dose-related and affected by accumulation of chemotherapeutic agents and duration of treatment [8].

HFS is usually not a life-threatening side effect but it is a dose-limiting toxicity. These cutaneous toxicities affect patient's function and quality of life, which may lead to dose modification or discontinuation of critical antineoplastic therapy [9,10]. We have previously described the effectiveness of vitamin E on HFS that occurred during capecitabine treatment without dose modification [4]. With the experience of this study [4] we planned to give vitamin E to HFS due to sorafenib in HCC patients.

Methods

Patients

Ten patients diagnosed with HCC who were treated with sorafenib and developed HFS after sorafenib therapy were enrolled in the study. Sorafenib was administered orally at a dose of 400 mg twice daily. Treatment was continued until disease progression, unacceptable toxicity, or patient refusal. Clinical data were collected when the occurrence of cutaneous lesions began during therapy. HFS was classified according to the NCI common toxicity criteria, version 3.0 (Table 1) [11]: Grade 1 HFS: minimal skin changes or dermatitis (e.g. erythema) without pain; grade 2: skin changes (e.g. peeling, blisters, bleeding, edema) or pain, not interfering with function; grade 3: ulcerative dermatitis or skin changes with pain interfering with function [11,12]. The different HFS classification systems are shown in Table 1. Patients were staged according to AJCC TNM staging system [13]. Child-Pugh scoring system was used for assessment of liver function [14].

Results

Mean age was 64±9 years (range 44-76). Eight (80%) patients were male, and 2 (20%) female. Eight of 10 patients had stage IIIB and 2 stage IV disease. Etiologic factors were assessed: 7 patients had HBV positivity, 2 had HCV positivity, and 1 patient was idiopathic. Arterial chemoembolisation was performed in 7 patients and radiofrequency ablation (RFA) was performed in 2 patients. Doxorubicin therapy was given to 3 patients for 2-3 cycles. Sorafenib was given to these patients after doxorubicin therapy due to progressive disease. Six cycles were given to 1 patient due to partial response after 3 cycles. After 6 cycles of doxorubicin therapy, sorafenib was given to this patient due to progressive

Table 1. HFS grading according to National Cancer Institute (NCI) [11], World Health Organization (WHO) criteria [11], and used in sorafenib clinical trials [12]

NCI grade	*NCI definition*
1	Skin changes or dermatitis without pain, e.g. erythema, peeling
2	Skin changes with pain, not interfering with function
3	Skin changes with pain interfering with function

WHO grade	*WHO definition*	*Clinical lesion*	*Histological findings*
1	Dysesthesia/paraesthesia, tingling in the hands and feet	Erythema	Dilated blood vessels of the superficial dermal plexus
2	Discomfort in holding objects and upon walking, painless swelling or erythema	1+edema	
3	Painful erythema and swelling of epidermis	2+fissuration	Isolated necrotic keratinocytes in higher layer of the epidermis
4	Periungual erythema and swelling Desquamation, ulceration, blistering, severe pain	3+blister	Complete epidermal necrosis

Clinical trial' grade	*Symptoms*
1	Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort in the hands and feet, not affecting the patient's activities of daily living
2	Painful erythema, swelling of the hands or feet, and/or discomfort affecting the patient's activities of daily living
3	Moist desquamation, ulceration, blistering, or severe pain of the hands and feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living

disease. Sorafenib was given to all patients in a dosage of 400 mg twice daily. Patient characteristics and treatment are shown in Table 2. Patients were assessed on days 15, 20-25, and 30-35 and monthly thereafter (Table 3). Mean time to appearance of HFS was 15±3 days (range 10-22). Toxicity grade was 3 in 4 patients, 2 in 4 patients and 1 in 2 patients. Vitamin E was started at dosage of 300 mg/day and its administration had a marked effect after 10-12 days from initiation. Pain was reduced and improved comfort level of patients was observed. Grading of HFS decreased to grade 1 in 4 patients and HFS was totally resolved in 6 patients. HFS grade increased from grade 1 to grade 2 due to no proper usage of vitamin E in 1 patient (patient number 5 in Table 3). Nevertheless, skin lesions disappeared after regular vitamin E usage in this patient. Vitamin E was given to the patients when HFS appeared with no dose reduction or interruption of sorafenib therapy.

Discussion

Single-agent sorafenib therapy at standard doses of 400 mg twice daily has been shown to be well tolerated, with a total incidence of HFS in 25-30% of patients [15,16].

Sorafenib can cause a variety of different dermatologic side effects, including facial/scalp erythema and dysesthesias, alopecia, splinter hemorrhages, keratoacanthomas, leucocclastic vasculitis and epidermal inclusion cysts [3]. HFS associated with sorafenib therapy affects friction and weight-bearing acral surfaces more focally than the classic HFS, which has been reported with traditional chemotherapeutic agents such as cytarabine, 5FU, and methotrexate [17-19].

The molecular mechanism underlying the development of sorafenib-induced HFS is not well defined [9]. VEGF plays a physiological role in mucosal integrity and neuronal functioning and blocking VEGF activity may result in a combined effect which may manifest as HFS [20]. However, current studies do not support this hypothesis. Histological examination of the skin with HFS shows epidermal changes that suggest alterations in keratinocyte maturation. While sorafenib inhibits VEGFR and FLT3, these receptors are not expressed on keratinocytes [21].

However, this does not exclude the possibility that VEGF may be involved in the development of HFS by

Table 2. Patient characteristics and prior treatments

Patient number	*Gender*	*Age (years)*	*Child-Pugh stage*	*Etiology*	*TACE/times*	*RFA/times*	*Surgery*	*Chemotherapy cycles*	*Survival (months)*
1	F	69	IIIB/A	Idiopathic	0	0	0	DoxoX2	8/dead
2	F	63	IIIB/A	HBV	X3	X1	0	0	27/alive
3	M	53	IIIB/A	HBV	0	0	0	0	26/alive
4	M	64	IIIB/A	HBV	X6	0	0	DoxoX3	18/alive
5	M	44	IIIB/A	HBV	X3	0	0	DoxoX3	9/alive
6	M	71	IIIB/A	HBV	X2	0	0	0	4/alive
7	F	69	IVA/A	HCV	X2	X1	0	0	25/alive
8	M	64	IVB/A	HBV	X2	X1	0	0	60/alive
9	F	76	IIIB/A	HCV	X1	0	0	0	59/dead
10	M	60	IIIB/A	HBV	0	0	0	DoxoX6	20/dead

TACE: transarterial chemoembolisation, RFA: radiofrequency ablation, HBV: hepatitis B virus, HCV: hepatitis C virus, M: male, F: female, doxo: doxorubicin

Table 3. HFS grades and responses after vitamin E treatment

Patient number	*Gender*	*Age (years)*	*Day of HFS appearance*	*HFS grade*	*HFS grade Days 20-25*	*HFS grade Days 30-35*	*HFS grade Day 45*
1	F	69	12	3	(+)1	0	0
2	F	63	10	1	0	0	0
3	M	53	13	2	0	0	0
4	M	64	17	3	0	0	0
5	M	44	22	2	(+)/1	(+)2	0
6	M	71	11	1	0	0	0
7	F	69	18	2	(+)/1	0	0
8	M	64	15	2	0	0	0
9	F	76	17	3	(+)1	0	0
10	M	60	16	3	(+)1	0	0

HFS: hand-foot syndrome

its inhibition on vascular endothelium. Indeed, bevacizumab, a humanized antibody against VEGF, appears to enhance the incidence and severity of HFS associated with sorafenib in phase 1 trials [19].

Imatinib, sorafenib and sunitinib target the platelet derived growth factor receptor (PDGFR) and C-kit, however, the incidence of HFS associated with imatinib is quite rare but sorafenib and sunitinib have the highest association with HFS. Therefore, it is likely that inhibition of PDGFR and C-kit receptors alone would result in cutaneous manifestations of HFS. In particular, RET and Flt-3 are targeted by these two agents, indicating an important role of these targets in the development of HFS. The dual antiproliferative and antiangiogenic properties of sorafenib and sunitinib would trigger a change in sweat duct epithelium and vasculature which leads to the cutaneous manifestations seen in patients with HFS. The antiproliferative property of imatinib or the antiangiogenic effect of bevacizumab alone are not sufficient to induce significant HFS [9].

HFS is usually diagnosed from its clinical presentation, although in some patients the differential diagnosis may also include graft-versus-host disease (GVHD), erythema multiforme, other drug reactions, cellulitis, vasculitis, erythromelalgia, septic emboli, chemotherapy-induced Reynaud's syndrome and acral bleomycin toxicity [22-24].

The time of HFS onset ranges from 24 hours to 10 months after starting the causative medication [23] with median times varying widely between case series, from 6 to 126 days [7,25,26]. But in our recent study the mean time of HFS appearance was 15±3 days (range 8-20).

In sorafenib trials, HFS has generally appeared within the first 6 weeks of therapy [29].

In our study appearance of HFS was observed after 10-15 days from the beginning of the sorafenib therapy. Some risk factors were identified for HFS in the English language literature, and included specific pharmacologic properties like dose, peak plasma level, total cumulative dose and schedule of administration [23]. More severe reactions were observed in phase I trials with sorafenib administration higher than 400 mg/day [27-29]. All of our patients were treated with sorafenib 400 mg twice daily. There is clear association between dose and both frequency and severity of HFS [5]. Additionally, a phase I trial measuring plasma levels of sorafenib indicated that skin toxicity associated with sorafenib was significantly correlated with both the maximum plasma concentration and the area under the curve [29] and HFS appearance was observed on days 10-15. This could be accompanied by sorafenib dose higher than 400 mg/day and older patients with their slow metabolism and high plasma levels.

Most studies analysing risk factors of HFS have recorded any risks that are independent from the chemotherapeutic agents or their methods of administration [11,30,31]. It is worth emphasizing that there is no study to date showing an association between the type of underlying malignancy and HFS incidence. This simplifies the analysis of available data by allowing data pool across malignancies. However, a recent systematic review of 4883 patients enrolled in 11 trials of single-agent sorafenib found a higher rate of HFS among renal cell carcinoma (RCC) patients than among patients with other malignancies (relative risk/PR 1.52; 95% confidence interval/CI: 1.32-1.75) [5], although these data have yet to be confirmed in further studies [3,30]. Chu et al. reported that the overall incidence of all grades of HFS was 33.8% (95% CI: 24.5-44.7) with the majority of doses affected by HFS being grades I and II with a significant proportion of those being grade III (8.9%) in their analysis of 5005 patients of RCC and other malignancies. Patients with RCC had significantly decreased risk of HFS compared with patients with non-RCC malignancy (RR 0.56; 95% CI: 0.50-0.64, $p<0.001$) in their study [9].

Other identified independent risk factors for HFS include advanced age, female sex [6, 33] performance status [32] and exposure to total body irradiation [33]. Advanced age could be the risk factor for HFS in this study.

Various treatment strategies have been employed since the discovery of HFS in the mid-1970's [5,9]. Because of the high incidence of HFS associated with sorafenib usage, early detection and timely treatment will be a vital component of managing patients during their treatment to allow for continued treatment. Initial consideration is the decision to dose reduction, treatment interruption or - if severe enough toxicity is found - to ultimately discontinue the treatment. It is suggested by the manufacturer's package insert that for those experiencing grade I toxicity to consider topical therapy. Grade II lesions are suggested to be treated with treatment interruption with or without subsequent dose reduction if not improved with topical treatment or for multiple recurrences. Grade III toxicity is managed by treatment interruption with or without subsequent dose reduction unless it recurs more than twice, for which discontinuation is recommended (Table 4) [9,34,36].

Vitamin E is popular in consumers for skin care and to prevent scar formation. It is the major lipophilic antioxidant, preventing peroxidation of lipids and resulting in more stable cell membranes. The antioxidant-membrane stabilizing effect of vitamin E also includes stabilization of the lysosomal membrane, a function shared with glucocorticoids [37].

Systemic vitamin E and glucocorticoids inhibit the

Table 4. Management options for HFS [5]

Dose reduction/treatment interruption
Pyridoxine (50-150 mg daily up to 3 times daily)
COX-2 inhibitors
Vasoconstrictive therapies
Regional cooling
Nicotine patch
Topical therapies
Corticosteroids
Dimethyl sulfoxide
Henna
Keratolytics (e.g. urea 12.5%)
Emollients
Systemic therapies
Corticosteroids
Amifostine (intravenous)
Vitamin E (oral)
Life style modification
Avoiding excessive temperatures
Avoiding excessive exercise
Avoiding ill-fitting clothes, shoes

HFS: hand-foot syndrome

inflammatory response and collagen synthesis, thereby possibly impeding the healing process. The effect of vitamin E on wound healing is complex; it may have alternative effects in different types of wounds and in the presence of other nutrients, as well as different functions for water-soluble vs. lipid-soluble preparations of vitamin E. Animal studies about vitamin E supplementation on surgical wounds show conflicting results. Greenwald et al. showed that flexor tendon repair thickness treated with vitamin E had breaking strength less than half that of controls measured on days 7 and 45 after surgical repair [38]. Another animal study showed impaired collagen synthesis in rats treated with vitamin E after wounding [39]. The researchers cite the glucocorticoid-like effect of vitamin E as the cause of the negative results.

Paradoxical results found by Galeano et al. showed that a hydrophilic vitamin E preparation positively impacted delayed wound healing in diabetic mice. Increased breaking strength and collagen content of the wound was found in treated animals. These authors speculated that inhibition of lipid peroxidation accounted for the positive results [40]. In addition, prophylactic administration of vitamin E has been shown to increase breaking strength and normalize the healing of wounds exposed to preoperative irradiation [41] and to decrease the development of intraperitoneal adhesions in animals [42]. In terms of HFS we do not know how vitamin E functions in resolving skin lesions. Its effect on wound healing or its glucocorticoid-like effect may play a role in resolving skin lesions due to capecitabine usage [4].

Therapy interruption and dose reduction were the primary tools in HFS management in the literature. Because of this reason HFS decreases the effectiveness of sorafenib therapy. Vitamin E can be used for some pathologic conditions of the skin. In our study we showed that HFS can be managed with vitamin E therapy without dose reduction or interruption of sorafenib. Our patients were educated about HFS and in our study we did not use any local therapies or medications except vitamin E.

Vitamin E usage was first described by Kara et al. in 5 HFS cases due to capecitabine [4] and then Yamamoto et al. reported resolution of HFS, also due to capecitabine, with 100 mg/day vitamin E usage in 15 cases in their retrospective analysis [43]. Our 10 patients with HFS due to sorafenib were treated with vitamin E and skin lesions were resolved with no dose reduction or treatment interruption.

Conclusion

There are no many treatment options for HCC treatment except sorafenib therapy. Dose reduction or treatment interruption decreases the effectiveness of sorafenib therapy. Only administration of 300 mg/day vitamin E can solve the problem. It is well tolerated and feasible treatment option. This is the first preliminary report on HFS due to sorafenib therapy, but further randomized clinical studies with large series and also animal models are required to explain the positive effect of vitamin E on HFS.

References

1. Liu L, Cao Y, Chen C et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006; 66: 11851-11858.
2. Llovet JM, Ricci S, Mazzaferro V et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.
3. Ratain MJ, Eisen T, Stadler WM et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2006; 24: 2505-2512.
4. Kara IO, Sahin B, Erkisi M. Palmar-plantar erythrodysesthesia due to docetaxel-capecitabine therapy is treated with vitamin E without dose reduction. Breast 2006; 15: 414-424.
5. Lipworth AD, Robert C, Zhu AX. Hand-Foot Syndrome (Hand-Foot Skin Reaction, Palma Plantar Erythrodysesthesia): Focus on Sorafenib and Sunitinib. Oncology 2009; 77: 257-271 (Review).
6. Burgdorf WH, Gilmore WA, Ganick RG. Peculiar acral erythema secondary to high-dose chemotherapy for acute myelogenous leukemia. Ann Intern Med 1982; 97: 61-62.
7. Lokich J, Moore C. Chemotherapy associated palmar-plantar erythrodysesthesia syndrome. Ann Intern Med 1984; 101:

789-800.
8. MetaAnalysis Group in Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: Effect of administration schedule and prognostic factors. J Clin Oncol 1998; 16: 3537-3541.
9. Chu D, Lacouture ME, Weiner E, Wu S. Risk of hand-foot skin reaction with the multitargeted kinase inhibitor sunitinib in patients with renal cell and non-renal cell carcinoma: a meta-analysis. Clin Genitourin Cancer 2009; 7: 11-19.
10. 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: 1045-1051.
11. Nagore E, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome. Incidence, recognition and management. Am J Clin Dermatol 2000; 1: 225-234 (Review).
12. Lacouture ME, Wu S, Robert C et al. Evolving strategies for the management of hand-foot skin reaction associated with the multi-targeted kinase inhibitors sorafenib and sunitinib. The Oncologist 2008; 13: 1001-1011.
13. Grene F, Page D, Fleming I, Fritz A. AJJC Cancer Staging Manual (6th Edn). New York, NY: Springer-Verlag, 2002.
14. Pugh RN. Pugh's grading in the classification of liver decompensation. Gut 1992; 33: 1583.
15. Strumberg D, Awada A, Hirte H et al. Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumors: Is rash associated with treatment outcome? Eur J Cancer 2006; 42: 548-556.
16. Escudier B, Eisen T, Stadler WM et al. TARGET Study Group. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356: 125-134. Erratum in: N Engl J Med 2007; 357: 203.
17. Kong HH, Cowen EW, Azad NS, Dahut W, Gutierrez M, Turner ML. Keratoacanthomas associated with sorafenib therapy. J Am Acad Dermatol 2007; 56: 171-172.
18. Chung NM, Gutierrez M, Turner ML. Leukocytoclastic vasculitis masquerading as hand-foot syndrome in a patient treated with sorafenib. Arch Dermatol 2006; 142: 1510-1511.
19. Azad NS, Aragon-Ching JB, Dahut WL et al. Hand-foot skin reaction increases with cumulative sorafenib dose and with combination of anti-vascular endothelial growth factor therapy. Clin Cancer Res 2009; 15: 1411-1416.
20. Eskens FA, Verweij J. The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. Eur J Cancer 2006; 42: 3127-3139.
21. Autier J, Mateus C, Wechsler J, Spatz A, Robert C. Cutaneous side effects of sorafenib and sunitinib. Ann Dermatol Venereol 2008; 135: 148-53; quiz 147, 154 (Review).
22. Crider MK, Jansen J, Norins AL, McHale MS. Chemotherapy-induced acral erythema in patients receiving bone marrow transplantation. Arch Dermatol 1986; 122: 1023-1027.
23. Baack BR, Bergdorf WH. Chemotherapy-induced acral erythema. J Am Acad Dermatol 1991; 24: 457-461 (Review).
24. Horwitz LJ, Dreizen S. Acral erythemas induced by chemotherapy and graft-versus-host disease in adults with hematogeneous malignancies. Cutis 1990; 46: 397-404.
25. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C, Herzig GP. High-dose cytosine arabinoside therapy for refractory leukemia. Blood 1983; 62: 361-369.
26. Demirçay Z, Gürbüz O, Alpdoğan TB et al. Chemotherapy-induced acral erythema in leukemic patients: a report of 15 cases. Int J Dermatol 1997; 36: 593-598.
27. Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. Pharmacotherapy 2007; 27: 1125-1144 (Review).
28. Hilger RA, Kredtke S, Scheulen ME, Seeber S, Strumberg D. Correlation of ERK-phosphorylation and toxicities in patients treated with the Raf kinase inhibitor BAY 43-9006. Int J Clin Pharmacol Ther 2004; 42: 648-649.
29. Faivre S, Delbaldo C, Vera K et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 2006; 24: 25-35.
30. Heo YS, Chang HM, Kim TW et al. Hand-foot syndrome in patients treated with capecitabine-containing combination chemotherapy. J Clin Pharmacol 2004; 44: 1166-1172.
31. Comandone A, Bretti S, La Grotta G et al. Palmar-plantar erythrodysesthesia syndrome associated with 5-fluorouracil treatment. Anticancer Res 1993; 13(5C): 1781-1783.
32. Chu DT, Lacouture ME, Fillos T, Wu S. Risk of sorafenib-induced hand-foot skin reaction in patients with renal cell carcinoma and non renal cell malignancy. San Francisco, ASCO Genitourinary Cancer Symposium, 2008, abstr 3777.
33. Keohan M, D'Adamo D, Quin L et al. Analysis of toxicity in a phase II study of sorafenib in soft tissue sarcoma (STS). J Clin Oncol 2007; 25(Suppl): abstr 10061.
34. Abushullaih S, Saad ED, Munsell M, Hoff PM. Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. Cancer Invest 2002; 20: 3-10.
35. Kampmann KK, Graves T, Rogers SD. Acral erythema secondary to high-dose cytosine arabinoside with pain worsened by cyclosporine infusions. Cancer 1989; 63: 2482-2485.
36. Robert C, Soria JC, Spatz A et al. T. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet Oncol 2005; 6: 491-500 (Review).
37. Havlik RJ. Vitamin E and wound healing. Plastic Surgery Educational Foundation DATA Committee. Plast Reconstr Surg 1997; 100: 1901-1912.
38. Greenwald DP, Sharzer LA, Padawer J et al. Zone II flexor tendon repair: effects of vitamins A, E, beta-carotene. J Surg Res 1990; 49: 98-102.
39. Ehrlich HP, Tarver H, Hunt TK. Inhibitory effects of vitamin E on collagen synthesis and wound repair. Ann Surg 1972; 175: 235-240.
40. Galeano M, Torre V, Deodato B et al. Raxofelast, a hydrophilic vitamin E-like antioxidant, stimulates wound healing in genetically diabetic mice. Surgery 2001; 129: 467-477.
41. Taren DL, Chvapil M, Weber CW. Increasing the breaking strength of wounds exposed to preoperative irradiation using vitamin E supplementation. Int J Vitam Nutr Res 1987; 57: 133-137.
42. Kagoma P, Burger SN, Seifter E et al. The effect of vitamin E on experimentally induced peritoneal adhesions in mice. Arch Surg 1985; 120: 949-951.
43. Yamamoto D, Yamamoto C, Iwase S, Kuroda Y, Odagiri H, Naguma Y. Efficacy of Vitamin E Treatment for Hand-foot Syndrome in Patients Receiving Capecitabine. Breast Care 2010; 5: 415-416.