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REVIEW

Capecitabine Associated Hand-Foot Syndrome: A Review

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Abstract: Hand-foot syndrome (HFS), also known as palmar-plantar erythrodysesthesia, is a relatively frequent dermatologic toxic reaction associated with several chemotherapeutic drugs used in cancer treatment. The lesions are typically localised in the palmar and plantar surfaces of the hands and feet in patients who are taking oral capecitabine or other drugs as a cancer treatment. Usually, the hands are more commonly affected than the feet and might even be the only area affected in several patients.

The syndrome is characterized by a tingling sensation and dysesthesia as the two first symptoms, which can progress to a burning pain, swelling and erythema with increased palmar and plantar temperature. Although it typically resolves in 1–2 weeks after stopping capecitabine, delay in its management progresses to blistering desquamation, ulceration, crusting and epidermal necrosis. In these cases, HFS would become an extremely painful and debilitating condition with secondary discomfort and significant impairment of function, leading to a deterioration in quality of life in these patients receiving capecitabine, which otherwise is very well-tolerated.

Keywords: capecitabine, fluoropyrimidines, hand-foot syndrome, xeloda

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Introduction

Hand-foot syndrome (HFS), also known as palmar-plantar erythrodysesthesia, is a relatively frequent dermatologic toxic reaction associated with several chemotherapeutic drugs used in cancer treatment.[1]

Since it was first described in 1984, as a side-effect of a continuous 5-fluorouracil (5-FU) infusion,[2] several new agents have been associated with this toxicity, such as docetaxel, gemcitabine, vinorelbine, pegylated liposomal doxorubicin and oral fluoropyrimidines such as capecitabine.[3–5]

In the last few years, the use of capecitabine in daily clinical practice has been increasing progressively in several fields of oncology,[1] but mainly in colorectal cancer due to its favourable toxicity profile. Capecitabie is therapeutically equivalent when it has been compared to an infusion or bolus of 5-FU, as has been confirmed in numerous phase III studies. Therefore, capecitabine has become an acceptable alternative to 5-FU in several indications.[6–9]

These comparative trials have shown that HFS was the only clinical adverse event and it occurred more frequently in the capecitabine arm.[10]

This is the reason why the HFS is emerging as an increasingly common and dose-dependent toxicity which requires an extensive knowledge of its incidence and diagnosis to enable early management of the symptoms.

The aim of this paper is to offer a complete description of this syndrome in capecitabine-treated patients, and to offer a review about its etiology, clinical and histological features and its optimal prevention or management.

Capecitabine (Xeloda®)

Capecitabine is a prodrug of 5-FU which is rapidly converted to 5-FU in neoplastic tissues.[11,12] After oral administration, capecitabine is rapidly absorbed by the gut and converted into its metabolites 5-deoxy-5-fluorocytidine and 5-deoxy-5-fluorouridine. First it is metabolized to 5-deoxy-5-fluorocytidine in the liver by a carboxylesterase. This metabolite is converted to 5-deoxy-5-fluorouridine by a cytidine deaminase in the liver and also in tumour tissues, and finally transformed into 5-FU intracellularly by thymidine phosphorylase. The inactivation of 5-FU is achieved by dihydropyrimidine dehydrogenase (DPD).[12,13]

Systemic levels of 5-FU after taking capecitabine are low. The absolute bioavailability is estimated to be 40%–45%.[13] Capecitabine binds to albumin by 54% and its metabolites 5-deoxy-5-fluorocytidine/5-deoxy-5-fluorouridine and also 5-FU by 10%, 62% and 10% respectively.[14] Due to its relatively low rate of binding to albumin, no relevant interactions at this level are to be expected.

Capecitabine is eliminated mainly as metabolites (95% of the dose) via the urine. No clinically relevant demographic or ethnic factors affecting its pharmacokinetics have been found.[12]

Although, clinically, the most important interaction between capecitabine and other drugs is with coumarins, the combination with inhibitors of DPD could induce severe toxicity, as seen when it is combined with antivirals such as sorivudine.[15–16] There is no controlled study available about alternative medicine use with capecitabine.[17]

Due to known toxicity, it is necessary to be cautious when administering capecitabine in patients with liver or renal function impairment. In mild-to-moderate liver disease, the absolute bioavailability of capecitabine is higher than in patients without liver dysfunction, so it would be safe to reduce the dose. In cases of renal dysfunction, dose reductions may also be necessary. Creatinine clearance of 30–50 ml/minute is associated with increased exposure and higher incidence of serious adverse events, and in the case of creatinine clearance that is lower than 30 ml/minute, capecitabine therapy is not recommended.[12,13,18]

On the other hand, no relevant effect of age was found in patients undergoing capecitabine therapy.[12]

The recommended dose of capecitabine as a single agent is 1,250 mg/m^2 b.i.d. for 14 days repeated on day 22; although there are other schedules, this is the most usual.

Hand-Foot Syndrome (HFS)

HFS is typically described as localised and non-specific dermatologic toxicity affecting the palmar and plantar surfaces of the hands and feet in patients who are taking oral capecitabine or other drugs as a cancer treatment.[5,10,19–22] It has been reported a variable incidence depending on the drug used. There are clear differences between a continuous infusion of 5-FU with an incidence of 34% and a bolus of

5-FU with 13%.[3,23] With capecitabine, the incidence of grade 3 HFS is approximately of 5%–20%. Differences related to race, gender and age have not been described.[24–28]

Little is known about the predisposing factors that influence its emergence or its intensity. In the study by Heo et al[27] evaluating three combination schedules with capecitabine (capecitabine/cisplatin/docetaxel, capecitabine/vinorelbine and capecitabine/cisplatin), they suggest that the combined treatment agent and the patient's susceptibility to chemotherapy-related toxicity may increase the risk of capecitabine-induced HFS. In this way, they observed that combined use of docetaxel and preceding chemotherapy-related stomatitis were significant risk factors for the development of HFS.

Long-term alcohol intake, increased pressure or temperature in the hands and feet, or strenuous physical activity could increase the chance of HFS. Pre-existing inflammatory skin disease might contribute to the involvement of skin areas other than the hands and feet, e.g. the trunk, neck, chest, scalp or extremities, but more studies are needed to confirm all these data.[1,5]

HFS is characterized by a tingling sensation and dysesthesia as the two first symptoms, which can progress in 3–4 days to a burning pain and symmetric swelling and erythema with increased palmar and plantar temperature.[8,28] Usually, the hands are more commonly affected than the feet, and might even be the only area affected in several cases.[1] HFS is uncomfortable and can interfere with daily activity, mainly when blistering, desquamation or ulceration have appeared.[1,20]

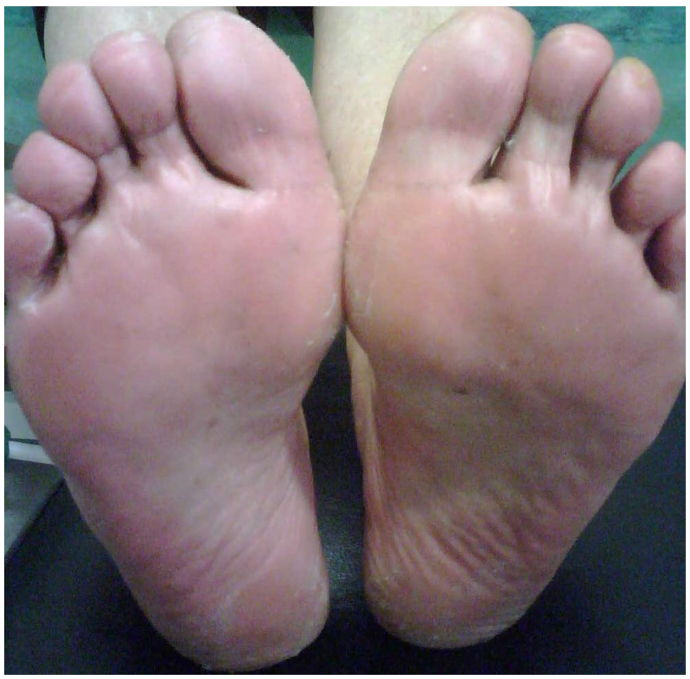

Figure 1. Capecitabine-induced grade 1 HFS on the soles.

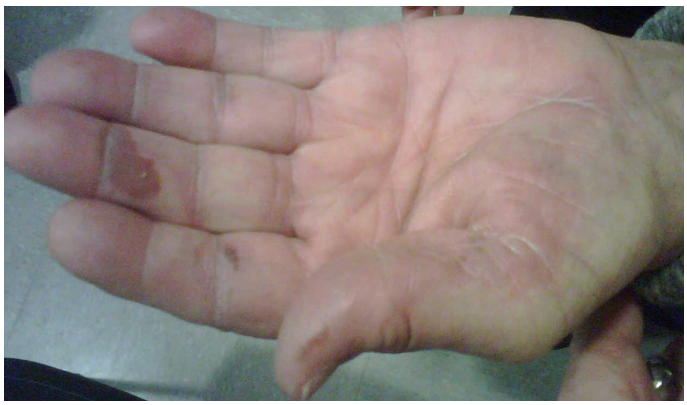

Figure 2. Capecitabine-induced grade 2 HFS on the palms.

Although it typically resolves in 1–2 weeks after stopping capecitabine treatment, without significant sequelae, it may, however, progress to blistering desquamation, ulceration, crusting and epidermal necrosis if the treatment is not promptly stopped or its dose reduced.[1,20] In these cases, HFS would progress to an extremely painful and debilitating condition, and although usually it is not life-threatening, the secondary discomfort and relevant impairment of function,[1] lead to a deterioration in quality of life in patients receiving capecitabine, which otherwise is very well-tolerated.

The lesions of this syndrome have been classified according to its severity in several grades which are illustrated in Table 1.

Mechanism of Hand-Foot Syndrome (Hfs)

5-FU was the first agent to be consistently identified as a causative drug for HFS and the agent most frequently associated with HFS, particularly when administered by continuous infusion.[2] More recently capecitabine has substituted for 5-FU in colorectal cancer treatment and HFS has became a recognized secondary event and one of the most common adverse effects with this relatively new agent.[1,28]

Table 1. Common terminology criteria for adverse events v3.0 (CTCAE).[55,64]

Hfs grading adapted to the five-grade common toxicity criteria (CTC) of the world health organisation (WHO)	
Grade 1	Minimal skin changes or dermatitis (e.g. erythema) without pain, dysesthesia/paresthesia, tingling, painless swelling or erythema of hands and/or feet, and/or discomfort that does not impair the patient's normal activities.
Grade 2	Skin changes (e.g. peeling, blisters, bleeding, oedema) or pain that does not interfere with function, painless erythema and swelling of hands and/or feet causing discomfort that affects daily activity of the patient.
Grade 3	Ulcerative dermatitis or skin changes with pain interfering with function, painful erythema and swelling of palms and soles.
Grade 4–5	Life-threatening side-effects or death have not been reported so far in the literature.

The exact mechanism of HFS is not known, and the symptoms and signs of this syndrome may vary according to the type of cytotoxic agent used.[10]

With 5-FU and also with capecitabine, HFS is dose-dependent and probably related to drug accumulation in the skin but whereas HFS induced by 5-FU is more common in elderly women, this relationship has not been encountered in capecitabine treatment.[1,10,12]

The frequency or severity of HFS appears to correlate with plasma concentrations of various fluoropyrimidines metabolites.[29,30] Several hypotheses have been proposed. Asgari et al[31] have hypothesized that keratinocytes may increase the levels of the enzyme thymidine phosphorylase, which could cause the accumulation of capecitabine metabolites. This might result in an increased likelihood of developing HFS. Mrozek-Orlowski et al[32] have suggested that capecitabine might be eliminated by the eccrine system throught sweat secretion. This might be the cause of HFS and its severity would be related to the number of eccrine glands present on the hands and feet. Others have argued that cyclooxigenase 2 (COX-2) overexpression might be a potential mediator for the development of this syndrome.[33]

Globally, although several mechanisms have been suggested, the precise mechanism which leads to the onset of HFS is largely not known to date.[1]

Histology

Although the diagnosis of HFS in general can be established by the clinical picture and its course after stopping treatment, in some cases, it has been necessary to take biopsies to exclude other causes.[28] It is in these cases where histological findings have been described. They are nonspecific and consistent with a basal keratinocyte toxicity as has been demonstrated in cases secondary to other chemotherapeutic drugs.[34,35] In cases where HFS appears after pegylated liposomal doxorubicin, the epidermis shows a marked tendency to premature keratinization (dyskeratosis) and keratinocyte proliferation rate is usually high.[36] In a general way, not specifically related to capecitabine, it has been shown that basal dyskeratosis and hyperproliferation are not equally distributed. Broadly dilated capillaries with pericyte proliferation are found in the papillary dermis. Activation (swelling) of endothelial cells and multinuclear pericytes can be recognized in the microvessels of the upper dermis. The basal lamina seems to be intact and eccrine sweat glands are absent.[28]

Prevention and Management of Hfs

If treatment combinations or schedules are likely to induce HFS, patient education is necessary, with the aim of helping patiens to recognize early symptoms in order to start therapy or dose modifications without any delay.[1]

Several reports have been published on successful alleviation of HFS with use of different agents such as vitamin products, antiinflammatory agents, peripheral vasoconstricting drugs, steroids or topical treatments.[10,28,37,38]

Pyridoxine

Pyridoxine, also known as vitamin B6, is the most popular treatment in clinical practice. Although its mechanism of action is not known, the use of pyridoxine at variable doses has been reported as being useful for prophylaxis and treatment of HFS induced by several cytotoxic drugs.[10] A study carried out in

a non-Hodgkin's lymphoma canine model involving liposomal doxorubicin treatment showed that oral pyridoxine delayed the onset and severity of HFS but did not prevent it.[38] Similar results were obtained by Fabian et al in a small study of 25 patients. They found that 5 of the 16 patients with metastatic colon cancer who developed HFS from 5-FU continuous infusion were treated with 50 mg or 150 mg of pyridoxine each day. When severe HFS developed, concurrent oral pyridoxine enabled patients to continue chemotherapy infusions for an average of 3.5 months longer than those who did not receive the pyridoxine without influence on clinical response rates.[38] But unfortunately, although these results are promising, the number of patients who received pyridoxine was very small, so this treatment needs further research.

The useful doses are not clear but it has been suggested that higher doses of pyridoxine might be better for alleviating the symptoms. Lauman et al[39] carried out a retrospective study comparing three groups with capecitabine and pyridoxine for HFS. The groups were:

- capecitabine alone
- pyridoxine prophylactically along with capecitabine
- pyridoxine to alleviate symptoms of HFS.

Patients who took ≥200 mg pyridoxine per day had better symptom control of their HFS than patients who took <200 mg per day.

Another study carried out by Yoshimoto et al tried to assess the impact of prophylactic pyridoxine on HFS in patients taking capecitabine for metastatic breast cancer.[40] They administered prophylactic pyridoxine to 38 patients receiving capecitabine (alone or in combination with cyclophosphamide) and compared their clinical outcomes against historical data from a control group 40 patients receiving capecitabine without pyridoxine in their institution. At the same time, they assessed the impact of urea ointment. They found that 52.6% patients developed HFS in spite of receiving pyridoxine treatment compared to the control group, which showed an 82.5% rate of HFS ($P < 0.01$). They also detected a nonsignificant trend towards less severe HFS among patients who received urea ointment at the first appearance of symptoms. In addition, nonsignificant trends towards higher rates of HFS were seen among those who were older than 60 years and those who derived clinical benefit (clinical response or stable disease) from capecitabine. They concluded that prophylactic pyridoxine and urea ointment at first appearance of symptoms appears to reduce the risk of severe capecitabine-induced HFS.

However, the true benefit should be determined after randomized, placebo-controlled studies evaluating the role of pyridoxine in the prevention of HFS. Such studies need to confirm whether pyridoxine has no effect on capecitabine efficacy and whether effective prophylaxis might permit administration of a higher cumulative dose of capecitabine.

Corticosteroids

Topical steroids have been reported to be useful for prophylaxis and treatment of HFS induced by several cytotoxic drugs, although their use in capecitabine-associated HFS is unproven.[28,41,42] In the cases with blistering and erosions, the use of high-potency steroids has been found to be as effective as topical therapy.[28] While steroids are anti-inflammatory agents that are capable of reducing inflammation, their long-term use can lead to thinning of the skin, which can cause more symptoms.[43–45] Two case studies of oral steroids used to treat cytarabine-induced HFS showed that they appeared to be beneficial for these two patients; however, no larger studies have been done to determine the risks and efficacy of oral steroids.[46,47]

Anti-inflammatory drugs

Cyclooxigenase (COX-2) inhibition has also been shown to be effective as a systemic approach for prophylaxis of chemotherapy-associated HFS. Celecoxib is a COX-2 antagonist used for control of pain and arthritis.[48]

In a retrospective series of more than 60 patients receiving capecitabine, the addition of celecoxib showed a reduction of the rate of severe HFS (more than grade 1) from 34% with capecitabine alone to 13% with capecitabine plus celecoxib. However, in this series, most patients required dose reductions.[48] Although this study has served to hypothesize that celecoxib might help in treating HFS, it needs to be tested in a prospective randomised setting. Until then, there is insufficient evidence to recommend the use of celecoxib in the prophylaxis of HFS.

Topical treatments

Several topical pharmacologic and nonpharmacologic treatments have been used as prevention strategies for HFS. Nonpharmacologic therapy include avoiding of extremes of temperature, undue pressure, friction on the skin and vigorous exercise.[1,49]

Several retrospective studies have been published on HFS that is secondary to pegylated liposomal doxorubicin. In these studies, regional cooling with ice packs around the wrists and ankles was combined with taking iced liquids during pegylated liposomal doxorubicin infusion. A reduced frequency and severity of HFS was reported compared with cases where these measures were not used.[50,51]

In addition, these type of measures have been demonstrated to be useful as a palliative treatment through cooling the affected areas without intensive friction or washing.[1]

Although regional cooling appears promising for the prevention of HFS and also treatment, the data are not sufficient to support its routine use in clinical practice. In addition, no data are available for patients receiving capecitabine.

On the other hand, the use of topical emollients and moisturizing creams[52,53] such as Bag Balm® or aloe vera lotions would appear to be helpful as a prophylactic and symptomatic treatment at the first signs of grade 1 HFS, although there have been no controlled trials.

Bag Balm® has been evaluated in the study by Chin et al.[54] They studied 39 patients receiving several agents of chemotherapy. Thirteen patients developed HFS: four with grade 1, eight with grade 2 and one with grade 3. All of them received Bag Balm® three times daily to the affected areas. Twelve patients showed clear improvement when their HFS symptoms were evaluated by the objective grading of severity according to the National Cancer Institute Common Toxicity Criteria.[55] Despite these results and because this study was not blinded, it has been suggested that some patients may have experienced a placebo effect. This is the reason why larger and placebo-controlled studies are needed to determine the effectiveness of this measure.

Topical petroleum-lanolin-based ointment with antiseptic hydroxyquinoline sulphate applied three times a day has been reported to alleviate the symptoms of HFS induced by several chemotherapeutic agents, including capecitabine. Its mechanism of action appears to be related to maintaining skin integrity.[1]

Topical administration of 99% dimethyl sulfoxide (DMSO) has also been reported to alleviate HFS.[51] Historically, DMSO was used to treat chemotherapy drug extravasation because it rapidly penetrates tissues following topical application. DMSO has been used successfully to treat extravasation of conventional doxorubicin.[56,57]

It is a known potent free radical scavenger with anti-inflammatory properties. Lopez et al used topical DMSO in two patients who were taking pyridoxine for mild HFS.[58] Despite the pyridoxine use, both patients experienced worsening of their HFS, and in both cases, the condition progressed to grade 3 toxicity. Topical DMSO enabled these patients to continue therapy while simultaneously resolving all the signs and symptoms of HFS.

A recent study suggests that the application of henna (dye derived from *Lawsonia inermis*) reduces the symptoms of this syndrome.[59]

Unfortunately, all these studies have concluded that treatment interruption or dose reduction remains the only method to manage HFS effectively, but supportive measures to reduce pain and discomfort and prevent secondary infection are very important. Therefore, prospective randomized controlled trials are needed to prove the efficacy of the various methods used to treat HFS. The study by Gressett et al[60] confirmd this statement after evaluating the effectiveness of topical emollients and creams, topical corticosteroids, nicotine patches, vitamin E, pyridoxine and COX-2 inhibitors as measures to manage HFS induced by capecitabine.

Nicotine patches

An interesting approach is the prophylactic use or treatment of HFS with local vaso-constrictive nicotine patches. Several ongoing clinical trials are being conducted but have not yet obtained conclusive results. Many clinicians have used this measure to achieve a reduction in the symptoms associated with HFS on the basis of a case report in which symptoms were alleviated in a patient receiving a continuous infusion of 5-FU.[61]

The investigators hypothesize that because nicotine is a peripheral vasoconstrictor, it could be able to

reduce the signs and symptoms of HFS by decreasing the amount of blood, and therefore the amount of drug, that reaches the hands and feet. This could reduce the accumulation of drugs in the eccrine glands.[10,62]

Dose modification or drug Interruption

While HFS is almost always manageable, if left untreated it can progress rapidly to a more severe toxicity.[1] Reacting quickly to the first signs and symptoms should prevent development of grade 2 or 3 toxicity and therefore reduce the impact on dose intensity.[1]

Despite all measures described previously, capecitabine dose interruption or dose reduction is often necessary.[61,63] Reducing the capecitabine dose without stopping the treatment at the first signs of HFS is likely to result in progression of the syndrome to a more severe toxicity.[1] Dose interruption followed, if necessary, by dose reduction has become the mainstay of HFS management. The discontinuation of capecitabine usually leads to healing after several days or weeks, depending on the syndrome severity.[64]

After the first episode of HFS, and once symptoms and signs have been reduced, therapy can usually be restarted according to the initial doses and schedule. But when the episode recurs or appears even more severely, dose reduction becomes mandatory.[10]

Following discontinuation of capecitabine treatment, the guidelines for dose reduction should be the same as guidelines used for the management of any adverse events occurring during capecitabine therapy as specified in the summary of the product.[1]

To establish general recommendations, it is relevant to distinguish between the first appearance of HFS and recurrence of the syndrome, and to evaluate the severity of this toxicity. When these guidelines are followed, the rate of more significant HFS is extremely low.

When the first evidence of HFS appears. the therapeutic approach should be different according to the grade of severity[28] (see Table 2).

In cases of grade 2 or 3 HFS, after initial interruption of therapy until reaching grade 0–1, the drug should be reinitiated with the same dosage as at the beginning, or dosage should be reduced, re-starting with 75% of the initial dose.[28] When two or more recurrences of grade 2 or 3 HFS occur, it is necessary to reduce doseage in all cases or to withdraw the therapy completelyt.[28] But in cases with grade 1 toxicity, no dose adjustment seems to be necessary.

Conclusions

HFS is a common and uncomfortable side-effect of capecitabine therapy. Although the condition is easily managed with dose interruption or, if necessary, dose reduction, prompt intervention helps to the patients to maintain dose intensity for long periods of time and continue to benefit from capecitabine therapy.

Patients should be given appropriate education with the aim of enabling them to recognize early symptoms in order to start therapy or dose modifications without any delay, requiring patients to become active in their own treatment. In this way, the side-effects might be prevented, recognised early and managed adequately.

Disclosures

This manuscript has been read and approved by the author. This paper is unique and is not under

Table 2. Managing a patient with HFS and capecitabine dose-modification.[1,28]

CTCAE toxicity grade	Toxicity	During therapy	Next cycle (related with initial dose)
1	–	No modification	No modification
2	First time	Stop until recovery to grade 0–1	100%
	Second time	Stop until recovery to grade 0–1	75%
	Third time	Stop until recovery to grade 0–1	50%
	More times	Stop definitively	–
3	First time	Stop until recovery to grade 0–1	75%
	Second time	Stop until recovery to grade 0–1	50%
	Third time	Stop definitively	–
4–5	First time	Stop definitively	–

consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

References

1. Lassere Y, Hoff P. Management of hand-foot syndrome in patients treated with capecitabine (Xeloda®). *Eur J Oncol Nursing*. 2004;8:31–40.
2. Lokich JJ, Moore C. Chemotherapy associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med*. 1984;101:798–9.
3. Comandone A, Bretti S, La Grotta G, et al. Palmar-plantar erythrodysestesia syndrome associated with 5-fluorouracil treatment. *Anticancer Res*. 1993;13:1781–3.
4. Ellis GK, Livingstone RB, Gralow JR, et al. Dose-dense anthracycline-bases chemotherapy for node-positive breast cancer. *J Clin Oncol*. 2002;20:3637–43.
5. Lorusso D, Di Stefano A, Carone V, et al. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ("hand-foot syndrome"). *Ann Oncol*. 2007;18:1159–64.
6. Cassidy J, Twelves C,Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favourable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol*. 2002;13:566–75.
7. Twelves C, Wong A, Nowacki M, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med*. 2005;352:2696–704.
8. Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol*. 2008;26:2006–12.
9. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26:2013–9.
10. Clark AS, Vahdat LT. Chemotherapy induced palmar-plantar erythrodysesthesia syndrome: etiology and emerging therapies. *Support Cancer Ther*. 2004;1(4):213–8.
11. Malet-Martino M, Jolimaitre P, Martino R. The prodrugs of 5-fluorouracil. *Curr Med Chem Anticancer Agents*. 2002;22:439–43.
12. Schellens J. Capecitabine. *The Oncologist*. 2007;12:152–5.
13. Twelves C, Glynne-Jones R, Cassidy J, et al. Effect of hepatic dysfunction due to liver metastasis on the pharmacokinetics of capecitabine and its metabolites. *Clin Cancer Res*. 1998;4:941–8.
14. Xu Y, Grem JL. Liquid chromatography-mass spectrometry method for the analysis of the anti-cancer agent capecitabine and its nucleoside metabolites in human plasma. *J Chromatogr B Biomed Appl*. 2003;783:273–85.
15. Okuda H, Ogura K, Kato A, et al. A possible mechanism of eighteen patient deaths caused by interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. *J Pharmacol Exp Ther*. 1998;287:791–9.
16. Rätz AE, Hofer S, Krähenbühl S, et al. Fatal drug-drug interaction of brivudine and capecitabine. *Acta Oncologica*. 2009;48(4):631–3.
17. Beijnen JH, Schellens J. Drug interactions in oncology. *Lancet Oncol*. 2004;5:689–96.
18. Giescke R, Burger HU, Reigner B, et al. Population pharmacokinetics and concentration-effect relationships of capecitabine metabolites in colorectal cancer patients. *Br J Clin Pharmacol*. 2003;55:252–63.
19. Baack BR, Burgdorf WHC. Chemotherapy induced acral erythema. *J Am Academy Dermatol*. 1991;24(3):457–61.
20. Jucgla A, Sais G. Diagnosis in oncology: HFS. *J Clin Oncol*. 1997;15(9):3164.
21. Kroll SS, Koller CA, Kaled S, et al. Chemotherapy induced acral erythema: desquamating lesions involving the hands and feet. *Ann Plast Surg*. 1989;23(3):263–5.
22. Nagore E, Insa A, Sanmartín O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia (hand-foot) syndrome: incidence, recognition and management. *Am J Clin Dermatol*. 2000;1(4):225–34.
23. Meta-analysis Group in Cancer. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol*. 1998;16:3537–41.
24. Blum J, Jones S, Buzdar A, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol*. 1999;17:485–93.
25. Abushullaih S, Saad E, Munsell M, et al. Incidence and severity of hand-foot syndrome in colorectal cancer patients treated with capecitabine: a single-institution experience. *Cancer Invest*. 2002;20:3–10.
26. Van Cutsem E, Findlay M, Osterwalder B, et al. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. *J Clin Oncol*. 2000;18:1337–45.
27. Heo YS, Chang HM, Kim TW, et al. Hand foot syndrome in patients treated with capecitabine-containing combination chemotherapy. *J Clin Pharmacol*. 2004;44(10):1–66–1172.
28. Janush M, Fischer M, Marsch WCH, et al. The hand-foot syndrome—a frequent secondary manifestation in antineoplastic chemotherapy. *Eur J Dermatol*. 2006;16(5):494–9.
29. Leo S, Tatulli C, Taveri R, et al. Dermatological toxicity from chemotherapy containing 5-fluorouracil. *J Chemother*. 1994;6(6):423–6.
30. Bellmunt J, Navarro M, Hidalgo R, et al. Palmar-plantar erythrodysesthesia síndrome associated with short-term continuous infusion (5 days) of 5-fluorouracil. *Tumori*. 1988;74(3):329–31.
31. Asgari MM, Haggerty JG, McNiff JM, et al. Expression and localization of thymidine phosphorylase/platelet-derived endothelial cell growth factor in skin and cutaneous tumors. *J Cutaneous Pathol*. 1999;26(6):287–94.
32. Mrozek-Orlowski ME, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia (hand-foot) syndrome: incidence, recognition and management. *Am J Clin Dermatol*. 2000;1(4):225–34.
33. Lin E, Morris JS, Ayers GD. Effect of celecoxib on capecitabine-induced hand foot syndrome and antitumor activity. *Oncology (Williston Park)*. 2002;16:31–37.
34. Lotem M, Hubert A, Lyass O, et al. Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. *Arch Dermatol*. 2000;136:1475–80.
35. Baack BR, Burgdorf WH. Chemotherapy-induced acral erythema. *J Am Acad Dermatol*. 1991;24:457–61.
36. Gordon KB, Tajuddin A, Guitart J, et al. Hand-foot syndrome associated with liposome-encapsulated doxorubicin therapy. *Cancer*. 1995;75:2169–73.
37. Von Moos R, Thuerlimann BJK, Aapro M, et al. Pegylated liposomal doxorubicin associated hand-foot syndrome: Recommendations of an international panel of experts. *Eur J Cancer*. 2008;44:781–90.
38. Vail D, Chun R, Thamm D, et al. Efficacy of pyridoxine to ameliorate the cutaneous toxicity associated with doxorubicin containing pegylated (stealth) liposomes : a randomized, double-blind clinical trial using a canine model. *Clin Cancer Res*. 1998;4:1567–71.
39. Lauman MK, Mortimer J. Effect of pyridoxine on the incidence of palmar plantar erythrodysesthesia (PPE) in patients receiving capecitabine. *Proc Am Soc Clin Oncol*. 2001;20:392a (Abstract 1565).
40. Yoshimoto N, Yamashita T, Fujita T, et al. Impact of prophylactic pyridoxine on occurrence of hand-foot syndrome in patients receiving capecitabine for advanced or metastatic breast cancer. *Breast Cancer*. 2009;Sep 30 (epub ahead of print).
41. Esteve E, Schillio Y, Vaillant L, et al. Efficacité de la corticothérapie séquentielle dans un cas d´érythème acral douloureux secondaire au 5-fluorouracile à fortes doses. *Ann Med Interne (Paris)*. 1995;146(3):192–3.
42. Komamura H, Higashiyama M, Hashimoto K, et al. Three cases of chemotherapy induced acral erythema. *J Dermatol*. 1995;22(2):116–21.
43. Hoff PM, Valero V, Ibrahim M, et al. HFS following prolonged infusion of high doses of vinorelbine. *Cancer*. 1998;83(5):965–9.
44. Titgan MS. Prevention of palmar-plantar erythrodysesthesia associated with liposome-encapsulated doxorubicin by oral dexamethasone. *Proc Am S Clin Oncol*. 1997;16:82A (abstract).
45. Hellier I, Bessis D, Sotto A, et al. High-dose methotrexate-induced bullous variant of acral erythema. *Arch Dermatol*. 1996;132(5):590–1.
46. Brown J, Burck K, Black D, et al. Treatment of cytarabine acral erythema with corticosteroids. *J Am Acad Dermatol*. 1991;24:1023–4.

47. Takeuchi M, Tanizawa A, Fukumoto Y, et al. Skin toxicity associated with bolus infusión of low-dose cytarabine. *Rinsho Ketsucki*. 2001;42:216–7.
48. Lin E, Morris JS, Ayers GD. Effect of celecoxib on capecitabine-indiced hand foot syndrome and antitumor activity. *Oncology (Williston Park)*. 2002;16:31–7.
49. Edwards SJ. Prevention and treatment of adverse effects related to chemotherapy for recurrent ovarian cancer. *Semin Oncol Nurs*. 2003;19:19–39.
50. Molpus KL, Anderson LB, Craig CL, et al. The effect of regional cooling on toxicity associated with intravenous infusion of pegylated liposomal doxorubicin in recurrent ovarian carcinoma. *Gynecol Oncol*. 2004;93:513–6.
51. Sayer RA, Apte S, Tedjarati SS. Regional cooling significantly reduces liposomal doxorubicin-induced palmar-plantar erythrodysesthesias (PPE) in patients with recurrent ovarian cancer. *Proc Am Soc Clin Oncol*. 2006;24(18S):18507 (abstract).
52. Gerbrecht BM. Current Canadian experience with capecitabine. *Cancer Nursing*. 2003;26(2):161–7.
53. Gilbar P. Palmar-plantar erythrodysesthesia. *J Clin Pharm Pract*. 2003;9:137–50.
54. Chin SF, Chen NT, Oza AM, et al. Use of Bag Balm as topical treatment of palmar-plantar erythrodysesthesia syndrome (PPES) in patients receiving selected chemotherapeutic agents. *Proc Am Soc Clin Oncol*. 2001;20:1632a (Abstract).
55. Cancer therapy evaluation program: common terminology criteria for adverse events, Version 3.0, DCTD, NCI, NIH, DHHS. (http://ctep.cancer.gov). Accessed March 31, 2003.
56. Berrelli G, Gozzo A, Forno G, et al. Topical dimethyl sulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. *J Clin Oncol*. 1995;13:2851–5.
57. Olver I, Aisner J, Hament A, et al. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. *J Clin Oncol*. 1998;6:1732–5.
58. Lopez A, Wallace L, Dorr R, et al. Topical DMSO treatment for pegylated liposomal doxorubicin-induced palmar-plantar erythrodysesthesia. *Cancer Chemother Pharmacol*. 1999;44:303–6.
59. Yucel I, Guzin G. Topical henna for capecitabine induced hand-foot syndrome. *Invest New Drugs*. 2008 Apr;26(2):189–92.
60. Gressett SM, Stanford BL, Hardwicke F. Management of hand-foot syndrome induced by capecitabine. *J Oncol Pharm Pract*. 2006;12(3): 131–41.
61. Kingsley E. 5-fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med*. 1994;120:813.
62. Kingsley E. 5-fluorouracil dermatitis prophylaxis with a nicotine patch. *Ann Intern Med*. 1994;120:813.
63. Abushullaih S, Saad ED, Munsell M, Hoff PM. Incidence and severity of HFS in colorectal cancer patients treated with capecitabine: a single institution experience. *Cancer Invest*. 2002;20(1):3–10.
64. Scheithauer W, Blum J. Coming to grips with hand-foot syndrome. Insights from clinical trials evaluating capecitabine. *Oncology (Williston Park)*. 2004;18:1161–1168.