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Efficacy of Vitamin E Treatment for Hand-Foot Syndrome in Patients Receiving Capecitabine

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Capecitabine is a novel oral fluoropyrimidine that is converted within tumor cells to fluorouracil by thymidine phosphorylase [1]. Hand-foot syndrome (HFS) is the most frequent side effect of capecitabine and has been reported in up to 71% of patients receiving a starting dose of 1,250 mg/m^2 twice daily [2–7]. Grade 3 HFS was reported in up to 10–24% of patients. Treatment interruption and, if required, dose reduction usually ameliorate symptoms without compromising efficacy [8, 9]. Supportive treatments such as topical wound care, elevation, and cold compresses may help to relieve pain [10, 11]. Use of systemic corticosteroids, pyridoxine (vitamin B6), and cox-2 inhibitors have been used in patients developing HFS with cytotoxic agents including capecitabine and pegylated liposomal doxorubicin with varying success [11–13]. Kara et al. [13] from Turkey reported apparent benefit of vitamin E in managing HFS. Therefore we conducted this study to examine the efficacy of vitamin E in managing capecitabine-induced HFS.

This retrospective, multicenter study was undertaken between 2005 and 2009 in HER2-negative patients with breast cancer treated with oral capecitabine 828 mg/m^2 twice daily on days 1–21 every 4 weeks. Patients with symptoms of grade 2 HFS received oral vitamin E (Tocopherol Acetate, Eisai Pharmaceuticals, Tokyo, Japan) 100 mg/day without chemotherapy dose modification. Patient and treatment-related data, e.g. chemotherapy-related toxicities, dose of vitamin E, severity of symptoms, and tumor response to therapy, were recorded every 4 weeks. Patients underwent a complete dermatological examination at every visit. HFS including pain was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE v3.0). Wilcoxon signed rank test was used to examine patient demographics and treatment information. Median time to onset of grade 2 HFS was estimated. Severity of HFS was compared before and after vitamin E administration. We identified 32 patients developing grade 2 HFS during capecitabine therapy between January 2005 and February 2009, who subsequently received vitamin E with or without capecitabine treatment modification. The median time to first onset of HFS was 7.3 months (range 4.1–9.6). The initial starting dose of vitamin E for treatment of HFS was 100 mg/day, and the median dose of vitamin E was 200 mg (range 100–400 mg/day). Vitamin E application had a marked effect on dermatological complications within 7 days of initiation. The effect lasted throughout administration. Desquamation and pain reduced gradually (figs. 1 and 2), and the comfort level of the patients improved. Fifteen of 32 patients (46.9%) with HFS experienced symptom improvement with vitamin E (100 mg/day) ($p < 0.05$; before vs. after 2 months vitamin E administration). Neurological symptoms improved. Thirteen patients still had pain, but this decreased after vitamin E dose escalation to 400 mg/day. The remaining 4 patients had considerable pain interfering with function after vitamin E 100 mg/day, but this reduced after vitamin E dose escalation to 400 mg/day and dose reduction of capecitabine as described previously [14]. Among all 32 patients included, the overall response rate to capecitabine was 37.5%, comprising 2 complete and 10 partial responses. Patients receiving capecitabine and vitamin E (100–400 mg) had longer time to progression than did patients receiving dose reduction of capecitabine (median 10.2 months vs. 6.1 months).

In this retrospective study, 15 of 32 patients with HFS improved with vitamin E 100 mg/day, suggesting a beneficial effect of vitamin E therapy. Vitamin E is a widely used skin care product and functions as 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 lysomal membrane, a function shared with glucocorticoids [13]. Systemic vitamin E and glucocorticoids inhibit the inflammatory response and collagen synthesis, thereby possibly impeding the

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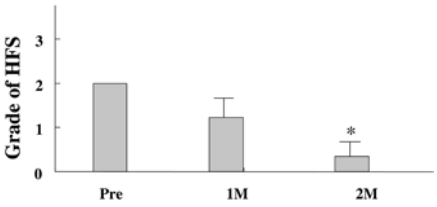

Fig. 1. Hand-foot syndrome (HFS) began to disappear after 1 month of vitamin E treatment; 15 of 32 patients (47%) with HFS experienced symptom improvement with vitamin E (100 mg/day) ($p < 0.05$).

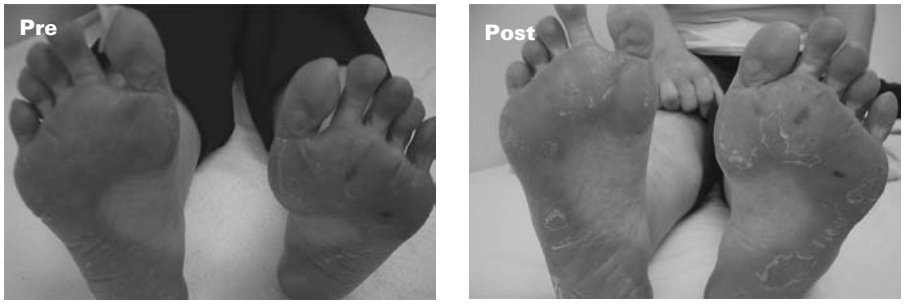

Fig. 2. Clinical presentation of hand-foot syndrome. After vitamin E without dose reduction of capecitabine, the skin lesions had disappeared.

healing process. Therefore the use of vitamin E may be useful for patients with HFS. The mechanism of HFS is unclear and may vary among the different agents associated with this effect [15–17]. In patients receiving capecitabine, HFS is dose-dependent and probably related to accumulation of drug and/or metabolites in the skin. It has been suggested that capecitabine-induced HFS may result from increased concentrations of the enzyme thymidine phosphorylase (TP) in specialized skin cells [18]. TP plays a crucial role in the activation of capecitabine and thus this localization in the skin cells may explain capecitabine metabolite accumulation, resulting in HFS. Alternatively, a recent study showed that the high proliferation rate of epidermal basal cells in the palm could make them more sensitive to local action of 5-fluorouracil, thus contributing to the occurrence of HFS [19]. While our observations and the potential role of vitamin E deserve further investigation, patient education and good follow-up during capecitabine therapy remain the cornerstones of management. Early recognition is critical to the effective management of HFS. When patients are appropriately managed, they will receive maximum benefit from this agent. Vitamin E-containing preparations appear to offer some benefit as an adjunctive approach for the treatment of capecitabine-induced HFS.

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Conflict of Interest

The authors declare no conflict of interests.

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