Randomized trial of vitamin B_6 for preventing hand-foot syndrome from capecitabine chemotherapy

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Background Capecitabine is an oral fluoropyrimidine that is used to treat various malignancies. Hand-foot syndrome (HFS) is a dose-limiting toxicity of capecitabine that can limit the use of this agent in some patients. Some investigators have observed that pyridoxine (vitamin B_6) can ameliorate HFS that is caused by capecitabine. We designed a prospective trial to determine if pyridoxine can prevent HFS in patients who receive capecitabine.

Methods In our double-blind, placebo-controlled trial, we randomly assigned eligible patients who were treated with capecitabine to receive either daily pyridoxine 100 mg or placebo along with their capecitabine-containing chemotherapy regimen. Patients were observed during the first 4 cycles of capecitabine treatment. The primary endpoint was the incidence and grade of HFS that occurred in both study arms.

Results Between 2008 and 2011, 77 patients were randomly assigned to receive either pyridoxine (n = 38) or placebo (n = 39). Dosages of capecitabine were equally matched between both arms of the study. HFS occurred after a median of 2 chemotherapy cycles in both groups. HFS developed in 10 of 38 (26%) patients in the pyridoxine group and in 8 of 39 (21%) patients in the placebo group (P = .547). Therefore, the risk of HFS was 5 percentage points higher in pyridoxine group (95% confidence interval [CI] for difference, –13 percentage points to +25 percentage points). Given our study results, a true benefit from pyridoxine can be excluded. No difference in HFS grades was observed.

Limitations Single-institution study.

Conclusion Prophylactic pyridoxine (vitamin B_6), given concomitantly with capecitabine-containing chemotherapy, was not effective for the prevention of HFS.

Capecitabine is a rationally designed oral fluoropyrimidine carbonate that is metabolized by the liver and converted into 5-fluorouracil (5-FU) by the enzyme thymidine phosphorylase (TP), which is found at higher levels within tumor cells, compared with normal cells.1 5-FU works by several different pathways to induce tumor cell death. 5-FU inhibits thymidilate synthase (TS) and is also incorporated into deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), interfering with cell replication. Capecitabine is currently registered for the following 4 indications:

- Monotherapy in the first-line treatment of advanced colorectal cancer.
- Adjuvant treatment in patients with stage III colon cancer.
- In combination with docetaxel in the treatment of locally advanced or metastatic breast cancer.
- As monotherapy in advanced breast cancer after failure of taxane- and anthracycline-containing chemotherapy for patients for whom an anthracycline is contraindicated.

The recommended dosage of capecitabine is usually 1,000 to 1,250 mg/m^2 twice daily for 14 days, repeated every 21 days. The dose-limiting toxicities of this agent are mucositis, diarrhea, and hand-foot syndrome (HFS).[2]

Hand-foot syndrome, also known as palmar-plantar erythrodysesthesia, is a widely recognized dose-limiting toxicity of certain agents, specifically capecitabine, infusional 5-FU, cytarabine, and liposomal doxorubicin; capecitabine is the drug most frequently associated with chemotherapy-induced HFS.[3-7] HFS is reported in 45%-56% of patients who are treated with capecitabine, and can be severe in 15%-20% of patients, making dose reductions or

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treatment delays a common problem during capecitabine therapy.

Hand-foot syndrome is a skin reaction that appears on the palms of the hands or the soles of the feet.[8] It was first described in 1974 in association with mitotane therapy for renal cell carcinoma.[9] The disease presents initially with prodrome of dysesthesia and numbness on the palms and soles, followed in a few days by painful, well-defined erythema and edema. In one study, 92% of patients who were treated with capecitabine and had HFS developed it in the first 2 cycles of treatment.[3] It has been suggested that 5-FU metabolites, not 5-FU itself, are responsible for the HFS. The following 3 theories offer possible causes of the HFS:

- The TP enzyme that is responsible for 5-FU metabolism is present in abundance in the skin, leading to a high level of 5-FU metabolites in the skin.
- Capecitabine is excreted in eccrine glands, which are found in high concentration in the skin, and particularly in the dermis of the hands and feet, hence the predominant palm and sole involvement.
- 5-FU metabolites are extravasated from small capillaries in areas of constant pressure (like palms and soles) into the dermis, causing direct toxic effect.

Currently, the mainstay of the management of HFS that is caused by capecitabine is dose reduction, and – if the HFS is severe – withdrawal of treatment. If the HFS could be prevented or decreased in severity or duration, there might be less need for dose reductions of capecitabine, and therefore improved efficacy of the drug and better outcomes for these patients.

Currently, no prevention or therapy for HFS has been proved in large-scale clinical trials. Interestingly, some investigators observed that HFS resembles a disease seen in rats called acrodynia, which is caused by vitamin B_6 deficiency.[10] This observation led to the first use of vitamin B_6 in 1 patient whose 5-FU–induced HFS was successfully treated without interruption of 5-FU.[11] Subsequently, 4 of 5 patients were treated with pyridoxine supplement for 5-FU treatment–related HFS.[12] In another study of 26 patients, a significant proportion of those treated with pyridoxine experienced amelioration of their HFS.[13]

Despite the limited evidence for its effectiveness, some physicians use pyridoxine for prevention or treatment of HFS because it is inexpensive and relatively safe. Others have tried alternative therapies, including emollients, both topical and systemic steroids, or topical dimethyl sulfoxide (DMSO), but none has been proved effective in any randomized, controlled trial. We therefore performed a prospective, randomized, double-blind, placebo-controlled trial to determine if pyridoxine can prevent HFS in cancer patients who are treated with capecitabine.

Materials and methods

Eligibility

Patients older than 18 years of age were eligible for the study if they had cancer requiring capecitabine therapy and had never received capecitabine before. After they were adequately randomized, patients started capecitabine chemotherapy at the same time they started pyridoxine or placebo. Other patient inclusion criteria were the following:

- A performance status of 0 to 2, according to the Eastern Cooperative Oncology Group (ECOG) classification.
- Life expectancy was longer than 6 months.
- Not being on vitamin B supplements.
  No prior HFS.
- No contraindication to chemotherapy (ie, patient had adequate bone marrow function, including an absolute neutrophil count > 1,500 cells/L and a platelet count > 100,000/L).
- Adequate renal function (as indicated by a serum creatinine concentration < 1.5 mg/dL).
- Adequate liver function (as indicated by a serum bilirubin concentration < 1.5 mg/dL, a transaminase level < 3 times the upper normal limit, and a serum albumin level > 2.5 mg/dL).

Exclusion criteria included previous treatment for HFS; hypersensitivity to pyridoxine; immunosuppression or positive human immunodeficiency virus (HIV) serology; and pregnancy or lactation. During the study, no other vitamin or pharmacologic intervention that was specifically intended for the prevention or treatment of HFS (other than analgesics) was allowed. The following topical agents were specifically not permitted to be used during the study because they contain urea or lactic acid:

- Aqua Care medicated calamine lotion (0.3%).
- Dr. Scholl's Smooth Touch deep moisturizing cream.
- Dove moisturizing cream wash.

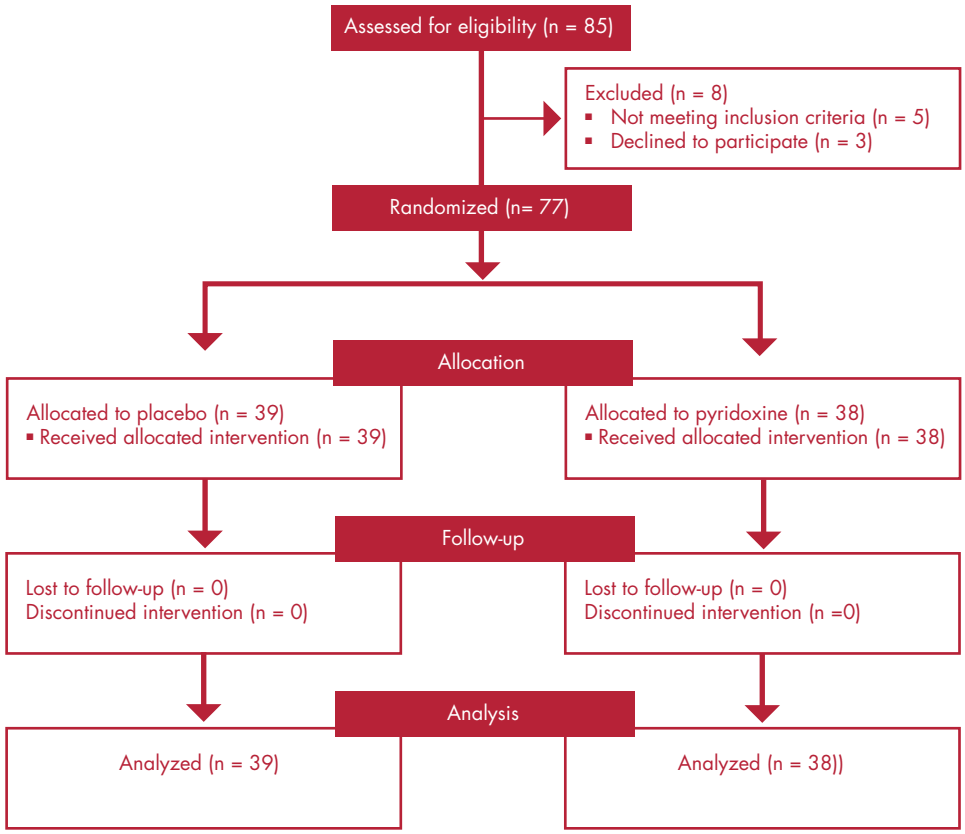
Hand-foot syndrome toxicity was graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Effects (NCI-CTCAE; v3.0) toxicity grading criteria.[14] All patients provided written informed consent before enrollment (Figure 1).

Study design and outcome

Our study was a randomized, placebo-controlled, double-blind trial that compared the incidence of HFS among cancer patients receiving capecitabine-containing chemotherapy with either vitamin B_6 or placebo. In this study, eligible patients were randomized to receive either pyridoxine at a dose of 100 mg/day plus capecitabine-containing chemotherapy, or placebo plus capecitabine-containing chemotherapy. Prior to initiation of the study, placebo tablets were

purchased from the hospital wholesaler and were evaluated for the similarity to pyridoxine 50-mg tablets. The decision to purchase commercially available tablets instead of overencapsulating pyridoxine to match the placebo was based on limited resources. During the study period, the manufacturer available in the pharmacy for dispense was Rugby and pyridoxine 50-mg tablets were on the hospital's formulary. The investigators deemed the size, smell, and color of the placebo tablets to be similar to that of the pyridoxine 50 mg tablets. However, the potency of pyridoxine 50 mg was not evaluated, and the lot numbers were not the same because of the duration of the study and the availability of pyridoxine tablets provided by the hospital pharmacy. Pyridoxine 100 mg or placebo was initiated on the first day of capecitabine treatment. After each cycle, the oncologist completed an on-study sheet to provide all the required data for study patients and a follow-up sheet to monitor their responses to intervention. Because most patients who develop HFS on capecitabine do so within the first 2 cycles,[3] the study followed patients for up to 4 cycles of chemotherapy. Patients were off study after completing their 4, 21-day cycles of capecitabine. The study was conducted from 2008 to 2011.

FIGURE 1 Patient eligibility and enrollment



To ensure compliance with capecitabine as well as vitamin B_6 versus placebo, study investigators called patients by phone during the third week of each chemotherapy cycle to inquire about symptoms as well as compliance with medications. In addition, compliance was measured by counting the pyridoxine/placebo tablets during each oncology visit. Patients, primary investigators, and treating oncologists were blinded to which drug B_6 versus placebo) the patient was receiving. Patients were followed every 3 weeks by their primary oncologists during the treatment period, for a total duration of 4-6 months, depending on when the fourth cycle of chemotherapy was completed.

The study protocol was approved by the institutional review board at John H. Stroger Jr. Hospital of Cook County, Illinois. The protocol and the statistical analysis plan are available at Clinicaltrial.gov (ClinicalTrials.gov Identifier: NCT00767689).

Statistical analysis

The study explored the ability of pyridoxine in preventing HFS in patients receiving capecitabine, by comparing all grades of HFS in patients receiving pyridoxine and in patients receiving placebo with capecitabine chemotherapy. Study patients were evaluated every 3 weeks by their oncologists. The treating oncologist assessed toxicity, and, in case of documented hand-foot syndrome, the HFS grade was assessed by a nurse clinician according to the NCI-CTCAE (v3.0; Table 1).[14] The nurse clinician was blinded to the treatment assignments. The reason for dedicating the nurse to grade the HFS toxicity was to reduce interobserver variability and to standardize HFS grading among all study patients. A sample size of 47 subjects was planned in each group to provide 80% power to detect a difference of 30 percentage points between groups in the incidence of HFS (eg, 25% vs 55%), assuming an alpha error of 5%. However, because of slow accrual, 38 patients were enrolled in the vitamin B6 arm and 39 patients were enrolled in the placebo arm. The reason for the slow accrual was the tendency for most oncologists in our hospital group to prefer 5-FU infusion over capecitabine The number of patients developing any grade of HFS in both study arms was obtained. The

TABLE 1 NCI-CTCAE grading of hand-foot syndrome (v3.0)

Grade	Symptoms
1	Painless skin changes or dermatitis.
2	Painful skin changes (erythema or peeling) that do not interfere with daily activities and function.
3	Painful skin changes (erythema or peeling) causing discomfort that interferes with daily activities and function.

NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Effects

percentage of HFS in both arms was compared. In order to determine whether the difference between groups was significant, the number of patients receiving capecitabine, with and without HFS, was obtained, and the *P* value was determined through chi-square and Fisher exact calculation.

Results

In all, 77 patients were enrolled in the study, including 38 patients who were randomized to pyridoxine and 39 patients randomized to placebo. The mean patient age (+/- standard deviation) was 54.1 +/- 10.41 years (range, 25-78 years), and 10 patients of 77 (13%) were aged ≥ 65 years. Of the 77 enrollees, 48 patients (62%) were women and 29 (38%) were men. Both sexes were equally distributed in both arms of the study. The majority of patients (53%) were African American, 21% were white, 18% were Hispanic, and 7% were of Asian ethnicity (Table 2).

The dosage of capecitabine that was used in the majority of the patients was 1,000 mg/m^2 twice daily on days 1 through 14 in every 21-day cycle. Capecitabine was given as a single agent in 43 of 77 patients) or in combination with other agents (such as capecitabine plus oxaliplatin or lapatinib) in 34 of 77 patients (Table 2). In all, 10 patients were on a monoclonal antibody (trastuzumab) or cetuximab in combination with capecitabine). Also, 16 patients received capecitabine concurrently with radiotherapy.

Of the 38 patients who received pyridoxine, 21 patients were on single-agent capecitabine and 17 patients were on a capecitabine-containing chemotherapy combination. Of the patients who were on placebo, 22 patients were on single-agent capecitabine and 17 were on a capecitabine-containing chemotherapy combination.

The mean number of capecitabine chemotherapy cycles did not differ between groups. Mean compliance for taking the assigned intervention (pyridoxine versus placebo) was measured by using the percentage of the patients on the study who used all the intervention tablets in the bottles (96% versus 98%, respectively). The majority of patients (69 patients) received a capecitabine dosage of 1,000 mg/m^2 twice daily. A total of 5 patients received capecitabine 825 mg/m^2 twice daily, 2 patients received capecitabine 700 mg/m^2 twice daily, and 1 patient received capecitabine 500 mg/m^2 twice daily.

HFS occurred after a median of 2 chemotherapy cycles in both groups. Overall, 23% of patients developed HFS (all grades), of whom 16% developed grade 2 or 3 events. HFS developed in 10 of 38 (26%) patients in the pyridoxine group and in 8 of 39 (21%) patients in the placebo group (P = .547). Therefore, the risk of HFS was 5 percentage points higher in pyridoxine group (95% confidence interval for difference, -13 percentage points to +25 percentage points). Given our study results, a true benefit from pyridoxine can be excluded. No difference in HFS grades was observed. No difference was seen between groups in grade 2/3 events; 6 of 12 events (50%) occurred in both the pyridoxine group and the placebo group (Figure 2). Capecitabine dose reductions occurred in 9 patients in the pyridoxine group, including 2 patients who had grade 3 diarrhea that required hospitalization, 1 patient with grade 3 stomatitis, 4 patients with grade 3 HFS, and 2 patients with grade 3 neutropenia. In patients who received placebo, the capecitabine dose was reduced in 8 patients, including 3 patients with grade 3 HFS, 3 patients with grade 3 diarrhea, and 2 patients with grade 3 stomatitis.

Discussion

The advent of new therapeutic agents in the battle with cancer has offered an increase in the survivorship of these patients. Nevertheless, the treatment objective in most advanced-stage cancers is still palliation. Because cancer patients are living longer, the idea of converting cancer into a chronic illness requires particular attention to the patient's quality of life. Physicians and health care professionals who take care of cancer patients are now focusing on methods to improve tolerability of these chemotherapeutic agents and achieve a balance between good tumor control and minimized toxicity. In this randomized, double-blind, placebo-controlled clinical trial involving patients with different types of cancer that were treated with capecitabine, prophylactic vitamin B_6 was not found to lower the incidence of HFS, compared with placebo. Furthermore, there was no difference in the grades of HFS in both arms of the study.

Several reports and anecdotal evidence have suggested the use of different strategies to lower the incidence of HFS, such as the use of vitamin B_6. Several studies have examined the use of prophylactic vitamin B_6 to prevent HFS.[11-16] The results of a study of vitamin B_6 in the prophylactic setting indicated that the incidence of HFS was lower in the study group, compared with historic control.[14] We have examined prospectively the role of vitamin B_6 in the prophylactic setting, compared with placebo, and our results were similar to a recently published study that showed no difference in the incidence of HFS with the use of vitamin B_6.[16]

HFS has been reported to be the most common adverse effect of capecitabine-containing chemotherapy, with an

TABLE 2 Patient demographics and treatment

	Pyridoxine	Placebo	Total
Patients, n (median age, y)	38 (53.5)	39 (53.5)	77 (n/a)
Ethnic group, n (%)[a,b]			
African American	22 (58)	19 (49)	41 (53)
White	10 (26)	6 (15)	16 (21)
Hispanic	5 (13)	9 (23)	14 (18)
Asian	1 (2)	4 (10)	
Tumor type, n (%)			
Colon	14	15	29 (39)
Breast	14	13	27 (35)
Pancreas	7	1	8 (10)
Stomach	2	2	4 (5)
Sarcoma	0	3	4 (5)
Bile duct	0	4	4 (5)
Unknown primary	1	0	1
Chemotherapy regimen, n			
Capecitabine alone	21	22	43
Capecitabine + oxaliplatin	12	12	24
Capecitabine + lapatinib	2	3	5
Capecitabine + trastuzumab	2	1	3
Capecitabine + cetuximab	1	1	2
Dose, mg/m^2			
1,000	32	37	69
825	3	2	5
700	2	0	2
500	1	0	1

[a]The ethnicity of 1 patient was listed as 'other.' [b]Percentages do not add up because of rounding.

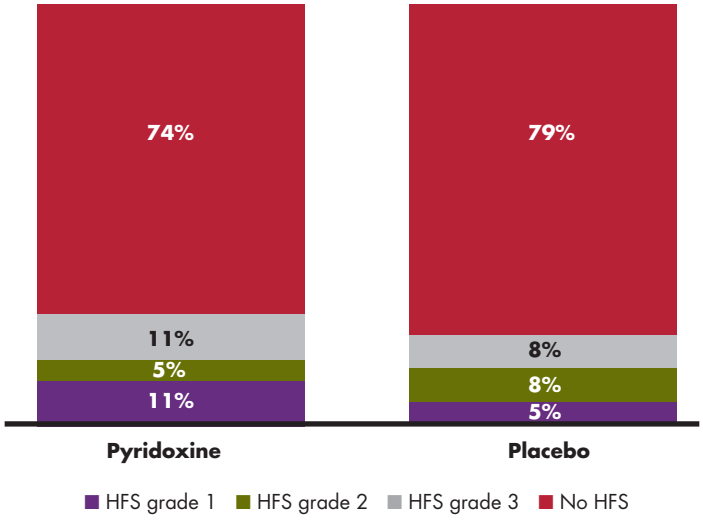
incidence of 45% to 68% in clinical trials.[16] The incidence of HFS in capecitabine-treated patients in our study was 21% and 26% in the placebo and pyridoxine arms, respectively, which is less than the reported incidence in the literature. This observation could be because the majority of the patients treated with capecitabine received a dosage of 1,000 mg/m^2 twice daily. This dosage is lower than the US Food and Drug Administration–recommended dosage of 1,250 mg/m^2 twice daily, and appears to reduce the incidence of grade 3 HFS.[17,18] In these 2 prospective studies in which capecitabine was given at a starting dosage of 1,000 mg/m^2 twice daily, only 2% of patients developed grade 3 HFS. This more tolerable dose is still highly active. In a recently reported randomized, phase III trial, the same dosage (1,000 mg/m^2 twice daily) provided a significant survival benefit, compared with the standard cyclophosphamide, methotrexate, and 5-FU (CMF).[19] The majority of study patients received 1,000 mg/m^2 of capecitabine; very few patients were allowed on the study with a lower dose due to age or liver dysfunction, and those were equally distributed in both arms of the study. The dosage of pyridoxine that we used in the study was 100 mg once daily, which is higher than the pyridoxine dosage that was used in the trial that reported an HFS-prevention benefit from pyridoxine,[14] and yet our study did not demonstrate similar benefit despite using the higher dose. High-dose pyridoxine may have a negative effect on the efficacy of chemotherapeutic agents, as pyridoxine adversely affected the response duration to hexamethylmelamine in patients treated for ovarian cancer.[16,20] However, the impact of high-dose pyridoxine has not been studied in patients treated with capecitabine.

In our study, there was a trend towards higher incidence of HFS in the pyridoxine group. To our knowledge, there has never been a description of HFS associated with pyridoxine use. In addition, this higher incidence of HFS in the pyridoxine group did not reach statistical significance and should be interpreted carefully, in light of the small number of study patients. Our study included higher proportions of African Americans, because the patients we see at John H Stroger Jr Hospital of Cook County in Chicago are predominantly of African American ethnicity. To our knowledge, no data in the literature confirm ethnic disparity in the incidence of HFS in patients receiving capecitabine.

The limitations of our study include the low percentage of Asian patients. As a result, our conclusion applies only to the other ethnicities that constituted the majority of the study population. In addition, the number of patients in both arms did not reach the preplanned accrual number to achieve the power to detect 30% difference. Nevertheless, given our study results, a true benefit from pyridoxine can be excluded. Finally, we did not include the dose of capecitabine in the eligibility criteria, and we did include patients who received doses of capecitabine that were lower than the standard dose, which might explain the lower incidence of HFS in the studied population.

Several strategies have been suggested to prevent HFS secondary to capecitabine chemotherapy. Although topical or systemic corticosteroids have been reported useful in the prophylaxis and treatment of HFS induced by oth-

FIGURE 2 Incidence and grades of hand-foot syndrome in pyridoxine and placebo groups



er agents, including liposomal doxorubicin, cytarabine, and docetaxel, efficacy in patients with capecitabine-associated HFS has, to the best of our knowledge, never been determined.[16] In addition, urea or lactic acid–based cream (12% or 6%, respectively) is extensively used in dermatology for a wide variety of conditions, including eczema and xerosis, because of its keratolytic and hydration properties. This cream was studied in HFS secondary to capecitabine by the North Central Cancer Treatment Group (N05C5 study) in a phase III randomized, double-blind trial. The data from that study did not support the efficacy of urea/lactic acid topical cream for preventing HFS symptoms in patients receiving capecitabine.[21] Interestingly, a cyclooxygenase-2 (COX-2) inhibitor could reduce the incidence of HFS, possibly by preventing proangiogenic tissue injuries occurring secondary to the acute inflammation of HFS.[23] However, the cited retrospective study lacked a control group. The randomized, phase III trial investigating the role of celecoxib in preventing HFS caused by capecitabine was terminated prematurely because of poor patient accrual.[22] The combination of capecitabine and lapatinib has higher HFS incidence, reaching 56%.[22]

Nevertheless, we determined to allow the participation of these patients in our study; by giving them pyridoxine, we were trying to determine whether this supplementation will even have any efficacy in preventing HFS in this group with high incidence of HFS or even lower the incidence of HFS. We did not perform any subgroup analysis to determine if there was any difference in those patients receiving a capecitabine-plus-lapatinib combination, because the number of this subgroup was too small to elucidate any conclusions.

In conclusion, our study has shown that using vitamin B_6 with capecitabine did not lower the incidence of hand-foot syndrome and other strategies should be developed to prevent capecitabine-induced HFS.

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