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ARTICLE

Curcuma longa (Turmeric) for Prevention of Capecitabine-Induced Hand-Foot Syndrome: A Pilot Study

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ABSTRACT

Hand-foot syndrome (HFS) is common and frequently occurs in the first cycle of treatment in approximately 40% to 50% of patients who receive capecitabine. Turmeric (*Curcuma longa*) is a plant used in Ayurvedic medicine with clinical activity in various inflammatory conditions. Our objective was to evaluate whether turmeric was active for the prevention of capecitabine-induced HFS. We included patients older than 18 years of age without previous exposure to capecitabine who were scheduled to receive this medication. Before starting treatment, after three weeks and at the end of six weeks, we evaluated dermatologic toxicity, conducted quality-of-life questionnaires (EORTC-QLQC30 and DLQI) and collected serum inflammatory biomarkers (inerleukin-6 (IL-6), tumor necrosis factor-a (TNF-a), C-reactive protein (CRP), and albumin). We administered turmeric at a dose of 4 g/day (2 pills 12 hours apart) starting at the beginning of capecitabine treatment and lasting six weeks. We included 40 patients whose mean age was 62 years. Most were female (80%), 52% had breast cancer, and 47.5% had GI tumors. After the first cycle of capecitabine treatment, we observed that 11 of 40 patients developed HFS (27.5%; 95% CI [15, 42]), whereas four patients developed HFS equal or superior to grade 2 (10%; 95% CI [3.3, 23]). We did not find any correlations between the inflammatory markers tested and HFS. We show that turmeric combined with capecitabine seems to produce a lower rate of HFS, especially grade 2 or higher. These findings need to be reproduced in larger controlled studies.

KEYWORDS

capecitabine; *Curcuma*; hand-foot syndrome

Introduction

Hand-foot syndrome (HFS) is a dermatologic toxicity most frequently linked to cytotoxic drugs such as 5-fluorouracil and capecitabine and multikinase inhibitors such as sorafenib and sunitinib (Janusch et al., 2006; Degen et al., 2010). HFS is common and frequently occurs in the first cycle of treatment in approximately 40% to 50% of patients who receive capecitabine (Wolf et al., 2010; Blum et al., 2001). The diagnosis of HFS is clinical. Patients usually complain of palmoplantar dysesthesia, which can evolve within a few days to symmetric erythema and edema and, in severe cases, blistering, desquamation, and subsequent ulceration. HFS usually

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resolves within a few weeks after the discontinuation of treatment (Janusch et al., 2006; Degen et al., 2010).

The mechanisms underlying HFS are still unknown. Milano et al. (2008) evaluated 12 normal volunteers comparing skin biopsies from their palms and dorsum and found that the epidermal basal cell proliferation rate (Ki67 staining) was significantly higher in the palms compared to the dorsum. These authors also showed that the levels of expression of 5FU-metabolizing enzymes thymidine phosphorylase (TP) and dihydropyridine dehydrogenase (DPD) were significantly higher in the palms. Since TP metabolizes capecitabine to 5-FU, higher concentrations of this active cytotoxic drug may occur in the palms. Furthermore, a higher proliferation rate may render palm basal epidermal cells more sensitive to chemotherapy. The toxic effects of 5-FU in the skin may turn on an inflammatory response that may, in turn, activate COX-2 pathways (Saif, 2011). In fact, a previous trial for the prevention of capecitabine-induced HFS comparing the COX-2 inhibitor celecoxib with placebo reduced in about 50% the rate of grade 2 HFS.

Turmeric (*Curcuma longa*) is a plant used in Ayurvedic medicine (Jurenka, 2009) with clinical activity in various inflammatory diseases, most likely secondary to curcumin, which is a polyphenol derived from *Curcuma longa*. Interestingly, in an experimental rat inflammatory colitis model, curcumin significantly induced the down-regulation of COX-2, which is probably mediated by a reduction in the activation of the p38 MAPK pathway (Camacho-Barquero et al., 2007).

Our objective in this pilot noncontrolled study was to evaluate whether turmeric had any activity in the prevention of capecitabine-induced HFS. We also assessed inflammatory parameters, such as Glasgow Prognostic Score (GPS), interterleukin-6 (IL-6), and tumor necrosis factor (TNF) levels, and the quality of life (QOL) of the patients included in this trial.

Patients and methods

Study design

Patients

This study was approved by the institutional review boards from both the ABC Foundation School of Medicine (FMABC, Brazil) and the Instituto Brasileiro para Controle do Câncer (IBCC, Brazil). All patients signed informed consent forms. We included patients older than 18 years of age without previous exposure to capecitabine and with a diagnosis of gastrointestinal malignancy or breast cancer who were scheduled to receive this medication. We excluded patients with cognitive deficits that could impair their participation and those who spoke no Portuguese or were illiterate. We also excluded patients with poor performance status, electrocorticography (ECOG) ≥ 3, and Karnofsky Performance Status (KPS) $\leq 70\%$ or with other comorbidities that could interfere with laboratory findings, such as patients with chronic use of anti-inflammatory steroidal drugs or NSAIDs.

Treatments

Patients received capecitabine at doses above or equal to 1 gram/m^2 orally twice a day for 14 of 21 days in each cycle or continuously at a dose of 1.650 gram/m^2 if combined with radiation therapy.

We gave turmeric at a dose of 4 g/day (2 pills 12 hours apart) started at the beginning of capecitabine treatment for six weeks. We used GNC Herbal Plus Turmeric Curcumin (1,050 mg) Extra Strength from General Nutrition Centers (GNC; www.gnc.com) containing 95% turmeric root extract (1,000 mg per pill).

Evaluations

Before starting treatment, after three weeks, and at the end of six weeks, we evaluated the dermatologic toxicities, conducted quality-of-life questionnaires, and collected serum inflammatory biomarkers (IL-6, tumor necrosis factor-α [TNF-α], C-reactive protein [CRP], and albumin). We evaluated dermatologic toxicities with the help of photographs of feet and hands at these same timepoints.

We employed the Common Terminology Criteria for Adverse Events (CTCAE; version 3) to assess the intensity of HFS as follows: Grade 1 = minimal skin changes of dermatitis (e.g., erythema) without pain; Grade 2 = skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function; and Grade 3 = skin changes with pain, interfering with function (Protocol Development | CTEP [Internet] (2017)).

Primary and secondary objectives

The primary endpoint was to evaluate whether there was a reduction in the incidence of HFS of any degree within six weeks of treatment. Secondary objectives included the relationship of HFS and its treatment with inflammatory markers and its effect on the quality of life of patients.

We employed the quality-of-life questionnaires from the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) and the Dermatological Quality of Life Questionnaire (DLQI), both already validated in Portuguese (Franceschini et al., 2010; Paula et al., 2014).

For the evaluation of IL-6, TNF-α, albumin, and ultrasensitive C-reactive protein (usCRP) levels, we drew 10.0 mL of peripheral blood by venipuncture. The samples were centrifuged at 2,000 rpm at room temperature to obtain the serum. We used a colorimetric enzymatic method. We evaluated usCRP, IL-6, and TNF-α by a chemiluminescent immunoassay method using the Siemens IMMULITE 1000 Immunoassay System (https://www.healthcare.siemens.com/immunoassay/systems/immulite-1000-immunoassay-system/assays). We calculated Glasgow Prognostic Score (GPS) according to McMillan (2013).

Statistics

For this pilot feasibility study, we assumed from the literature that the incidence of any degree of HFS was 50% (Wolf et al., 2010; Blum et al., 2001). We then estimated the required number of patients to evaluate a decrease in the rate of HFS by 30% to 20% with a type I error of 0.05 and 80% power. We assumed a loss of 10% to 15% of the population of the study, yielding a sample size of 40 patients. We conducted all statistical calculations with NCCS (www.ncss.com) and Graphpad (https://www.graphpad.com) software.

Results

We included 40 patients whose clinical characteristics are shown in Table 1. The mean age was 62 years, most were female (80%), 52% had breast cancer, and 47.5% had GI tumors. Forty percent of patients underwent concomitant radiation therapy, and dose reduction occurred in only 10% of patients.

After the first cycle of capecitabine treatment, we observed that 11 of 40 patients developed HFS (27.5%; 95% CI [15, 42]), whereas four patients developed HFS equal or superior to grade 2 (10%; 95% CI [3.3, 23]). After the second cycle, we observed that 10 of 29 patients developed

Table 1. Clinical and pathological characteristics of patients.

Clinical characteristics	*N*	%
Age (mean)	62 (30 – 89)	
Sex		
Female	32	80
Male	8	20
ECOG		
0	22	55
1	17	42
2	1	3
Tumor type		
Breast	21	52.5
Rectal	15	37.5
Stomach	2	5
Colon	1	2.50
Tumor stage		
1	0	0
2	3	7.5
3	13	32.5
4	24	60
Capecitabine dose		
2,000 mg/m2/day D1–D14	16	40
1,650 mg/m2/day + RxT	24	60
Dose reduction		
0%	36.0	90
15%	1	2.5
20%	1	2.5

ECOG = electrocorticography.

HFS of any grade (34%; 95% CI [19; 52]) and 3 developed grade ≥ 2 (10.3%; 95% CI [2.7, 27]) (Table 2).

We did not find any correlations of inflammatory parameters such as IL-6, TNF, neutrophil/lymphocyte index, and GPS with HFS severity (data not shown) at the end of the first or second cycles of capecitabine or during the six weeks of observation (Figure 1).

We could not identify any predictive factors for HFS development such as age, sex, tumor type, pretreatment GPS, IL-6, TNF, or lymphocyte/neutrophil index. Even though we found a positive expected correlation between HFS severity and DLQI scores, we found no significant associations between any of the dimensions of the EORTC QOL scores and the occurrence of HFS or any significant variations during the six weeks of observation (Figure 1).

Table 3 shows the toxicities observed during the six weeks of the protocol.

Discussion

This pilot study evaluated the effects of turmeric on the incidence and severity of HFS in 40 patients undergoing treatment with capecitabine. We designed our study to be able to show a reduction in the incidence of all grades of HFS from 50% to 20% with a power of 80% and a

Table 2. HFS incidence in cycles 1 and 2.

	Cycle 1 All grades (*N* = 40)	Cycle 1 Grades ≥ 2 (*N* = 29)	Cycle 1 All grades (*N* = 40)	Cycle 2 Grades ≥ 2 (*N* = 29)
HFS	11.0	4	10	3
%	27.5	10	34	10.3
95% CI	[15, 42]	[3.3, 23]	[19, 52]	[2, 27]

HFS = hand-foot syndrome; CI = confidence interval.

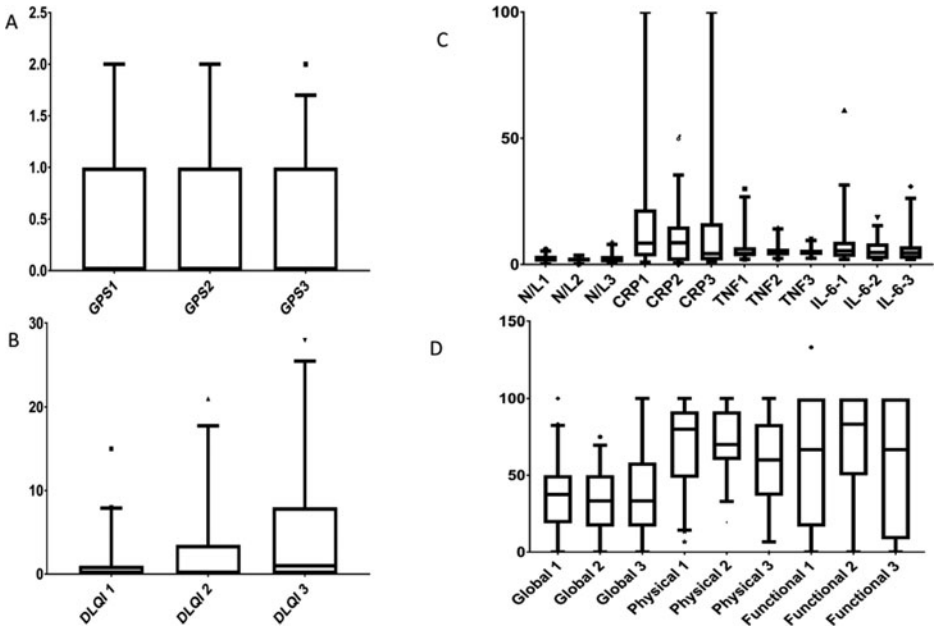

Figure 1. Correlations between inflammatory parameters and questionnaires throughout the evaluations (visits 1, 2, and 3).

type 1 error of 0.05. We observed a rate of 27% of any grade HFS after the first cycle and 34% after the second cycle of capecitabine. Interestingly, the incidence of HFS grades 2 or higher was approximately 10% after both the first and second cycles of capecitabine. Even though we did not meet our primary endpoint, the rates of HFS grades 2 or higher were very small compared to the values in the literature (Zhang et al., 2012; Kang et al., 2010; Yap et al., 2015). In fact, when we evaluated the placebo groups of three randomized trials for treatment of capecitabine-induced HFS, we observed rates of HFS grade 2 or higher of 30.5% (Kang et al., 2010), 37.8% (Yap et al., 2015), and 29.6% (Zhang et al., 2012). We believe that in this context, the 10% rate of grade 2 or higher HFS seems encouraging and warrants further confirmation in larger controlled studies.

The lack of significant changes in inflammatory parameters during the six weeks of treatment and in those who had HFS may suggest that inflammatory mechanisms may not play a decisive role in HFS genesis, as was previously suggested (Zhang et al., 2012). Since there was no control group, we cannot exclude the possibility that turmeric may have prevented an increase in inflammatory markers after capecitabine initiation.

Table 3. Toxicities observed during the first two cycles of treatment.

	Grade 0		Grade I		Grade II		Grade III	
Toxicity	*N*	%	*N*	%	*N*	%	*N*	%
Dyspnea	20	50	12	30	4	10	4	10
Insomnia	15	37.5	9	22.5	10	25	6	15
Inappetence	14	35	9	22.5	7	17.5	10	25
Constipation	16	40	11	27.5	6	15	7	17.5
Fatigue	15	37.5	12	30	9	22.5	4	10
Nausea	29	72.5	5	12.5	5	12.5	1	2.5
Pain	11	27.5	12	30	11	27.5	6	15
Diarrhea	20	50	9	22.5	3	7.5	8	20

The toxicities we observed in our study could be ascribed to capecitabine and radiation therapy since turmeric at the dosages used in this study was nontoxic and much higher doses were already safely employed in the literature (Jurenka, 2009).

An interesting finding of our study was the lack of HFS impact in any of the dimensions of the EORTC QLQ C-30 Quality of Life questionnaire (Franceschini et al., 2010). Therefore, to better evaluate HFS, specific instruments focused on dermatological toxicity such as the DLQI (Paula et al., 2014) should be employed in future HFS prevention studies.

This study has significant limitations, such as its small size and the lack of a control group. Nevertheless, we showed that turmeric can be safely combined with capecitabine and this combination may produce a lower rate of HFS, especially of grade 2 or higher HFS. These findings need to be reproduced in larger controlled studies before we can recommend the use of turmeric for HFS prevention.

Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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