BJO
Brazilian Journal of Oncology
ORIGINAL ARTICLES CLINICAL ONCOLOGY

Lanolin-based dexpanthenol cream, topical hydrocortisone or observation in the prevention of capecitabine-induced hand-foot syndrome: a phase III trial

Creme de dexpantenol à base de lanolina, hidrocortisona tópica ou observação na prevenção da síndrome mão-pé induzida por capecitabina: um estudo de fase III

Cintia Sayuri Kurokawa La-Scala[1], Artur Malzyner[2,3], Carmen Silvia Passos Lima[4], Daniela Dornelles Rosa[5,6], Fabio André Franke[7], Fernanda Maris Peria[8], Giuliano Santos Borges[9], Gustavo Colagiovanni Girotto[10,11], Leandro Brust[12], Magda Conceição Barbosa Gomes[13], Nilciza Maria de Carvalho Tavares Calux[14], Roberto Magnus Duarte Sales[15], Ruffo Freitas-Junior[16], Sergio Vicente Serrano[17]

ABSTRACT

Introduction: The use of capecitabine is associated with hand-foot syndrome (HFS). Since there is anecdotal evidence that lanolin-based creams and topical steroids are useful for the treatment of HFS, we conducted a three- arm phase III trial to compare observation, lanolin-based cream with dexpanthenol (L-D), and topical hydrocortisone in the prevention of HFS. **Material and Methods:** Patients with breast or colorectal cancer with indication to use capecitabine as a single agent or in combination were randomized in an open-label fashion to one of the three arms. The initial capecitabine dose was 1,000 or 1,250mg/m^2, according to the physicians discretion and clinical practice, and dose adjustments followed the local label. The primary endpoint was the frequency of HFS of any grade in the intent-to-treat population, whereas quality of life (QoL), change from baseline in performance status and adverse events were secondary endpoints. **Results:** Mean age among the 595 patients randomized was 58 years, and 69% were women. 37% of patients had advanced breast cancer and 63% of patients had colorectal cancer. Capecitabine was used as a single agent in 67% of patients; among the remaining 33% of patients, 82% were treated with oxaliplatin-based combinations. HFS of any grade was seen in 35.6% of patients in the observation group, 24.9% with L-D, and 34.3% with hydrocortisone (p=0.039). The unadjusted odds ratio for the frequency of HFS in the arm treated with L-D was 0.60 (95%CI, 0.39 to 0.92).

1. Produtos Roche Químicos e Farmacêuticos S.A., Departamento Médico - São Paulo - São Paulo - Brazil.
2. Clinonco - Clinica de Oncologia Médica, Oncologia - São Paulo - São Paulo - Brazil.
3. Hospital Albert Einstein, Serviço de Oncologia e Hematologia - São Paulo - São Paulo - Brazil.
4. Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Departamento de Clínica Médica - Campinas - São Paulo - Brazil.
5. Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Patologia - Porto Alegre - Rio Grande do Sul - Brazil.
6. Hospital Moinhos de Vento, Centro de Oncologia - Porto Alegre - Rio Grande do Sul - Brazil.
7. Hospital de Caridade de Ijuí, Centro de Alta Complexidade em Oncologia Clínica (CACON) - Ijuí - Rio Grande do Sul - Brazil.
8. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Divisão de Oncologia Clínica do Departamento de Imagens Médicas, Hematologia e Oncologia Clínica – Ribeirão Preto – São Paulo - Brazil.
9. Clínica de Neoplasias Litoral, Centro de Novos Tratamentos Itajaí - Itajaí - Santa Catarina - Brazil.
10. Hospital de Base de São José do Rio Preto, Centro Integrado de Pesquisa e Serviço de Oncologia Clínica - São José do Rio Preto - São Paulo - Brazil.
11. Santa Casa de São José do Rio Preto, Serviço de Oncologia Clínica - São José do Rio Preto - São Paulo - Brazil.
12. Hospital Bruno Born, Disciplina de Oncologia, Curso de Medicina da UNIVATES - Lajeado - Rio Grande do Sul - Brazil.
13. Universidade Federal Fluminense, Hospital Universitário Antônio Pedro - Rio de Janeiro - Rio de Janeiro - Brazil.
14. Escola Paulista de Medicina, Universidade Federal de São Paulo, Departamento de Ginecologia - São Paulo - São Paulo - Brazil.
15. Liga Norte Riograndense contra o Câncer - Natal - Rio Grande do Norte - Brazil.
16. Universidade Federal de Goiás, Programa de Mastologia - Goiânia - Goiás - Brazil.
17. Hospital de Câncer de Barretos, Departamento de Oncologia Clínica - Barretos - São Paulo - Brazil.

Financial support: The study was funded by Roche Brazil, that also funded medical writing assistance provided by DENDRIX.

Conflicts of interest: CSKLS is an employee of Produtos Roche Químicos e Farmacêuticos S.A. AM has declared no conflicts of interest. CSPL has received fellowships and financial support from Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Tecnológico (CNPq), and has declared not receiving drugs, reagents nor equipaments from any pharmaceutical company or other institution. DDR has received financial support from Conselho Nacional de Desenvolvimento Tecnológico (CNPq) and L'Òreal and has participated in advisory boards from Novartis, Lilly and Zodiac. FAF has declared no financial conflicts of interest. FMP has participated as principal investigator/investigator in clinical studies sponsored by Roche and is participating as principal investigator/investigator in clinical trials sponsored by Astra-Zeneca and MSD-Brazil. GSB has declared no conflicts of interest. GCG has only received fees for study procedures. LB has declared no conflicts of interest. MCBG has declared no conflicts of interest. NMCTC has declared no conflicts of interest. RMDS has declared no conflicts of interest. RFJ has received fees for talks and consulting from Produtos Roche Químicos e Farmacêuticos. SVS has declared no conflicts of interest.

Correspondence author: Cintia Sayuri Kurokawa La-Scala.
E-mail: cintia.scala@roche.com

Received on: June 14, 2022 | **Accepted on:** August 19, 2022 | **Published on:** December 13, 2022
DOI: https://doi.org/10.5935/2526-8732.20220355

Only between 2.6% and 9.4% of patients had grade 3 HFS. There were no statistically significant differences in mean change from baseline in any of the QoL scores, the distribution of performance status, or the frequency of adverse events among the three arms. **Conclusion:** L-D could be considered a standard strategy in the attempt to prevent capecitabine-induced HFS.

Keywords: Breast neoplasms; Capecitabine; Colorectal neoplasms; Glucocorticoids; Hand-foot syndrome; Dexpanthenol.

RESUMO

Introdução: O uso de capecitabina está associado à síndrome mão-pé (SMP). Como há poucas evidências sobre a eficácia de cremes à base de lanolina e esteroides tópicos no tratamento da SMP, realizamos um estudo de fase III de três braços para comparar observação, creme à base de lanolina com dexpantenol (L-D) e hidrocortisona tópica na prevenção de SMP. **Material e Métodos:** Pacientes com câncer de mama ou colorretal com indicação de uso de capecitabina como agente único ou em combinação foram randomizados de forma aberta para um dos três braços. A dose inicial de capecitabina foi de 1.000 ou 1.250mg/m^2, conforme critério médico e prática clínica, e os ajustes de dose seguiram a bula local. O *endpoint* primário foi a frequência de SMP de qualquer grau na população com intenção de tratamento, enquanto a qualidade de vida (QoL), mudanças em *performance status* em relação ao início do estudo e eventos adversos foram *endpoints* secundários. **Resultados:** A média de idade entre os 595 pacientes randomizados foi de 58 anos, e 69% eram mulheres. 37% dos pacientes tinham câncer de mama avançado, e 63% dos pacientes tinham câncer colorretal. A capecitabina foi usada como agente único em 67% dos pacientes; entre os 33% restantes, 82% foram tratados com combinações à base de oxaliplatina. SMP de qualquer grau foi observada em 35,6% dos pacientes do grupo de observação, 24,9% com L-D e 34,3% com hidrocortisona (p=0,039). A razão de chances (não ajustada) para a frequência de SMP no braço tratado com L-D foi de 0,60 (IC95%, 0,39 a 0,92). Apenas entre 2,6% e 9,4% dos pacientes tiveram SMP de grau 3. Não foram encontradas diferenças estatisticamente significativas na mudança média de nenhum dos escores de QoL em relação ao início do estudo, na distribuição do *performance status* ou na frequência de eventos adversos entre os três braços. **Conclusão:** A L-D pode ser considerada uma estratégia padrão na tentativa de prevenir a SMP induzida pela capecitabina.

Descritores: Neoplasias mamárias; Capecitabina; Neoplasias colorretais; Glicocorticóides; Síndrome mão-pé; Dexpantenol.

INTRODUCTION

Capecitabine is an important component of various regimens that are currently used to treat advanced breast cancer, as well as of the adjuvant and palliative treatment of colorectal cancer.[1-8] Although generally safe, the use of capecitabine is associated with hand-foot syndrome (HFS), a distinct adverse event that is often managed clinically by dose-reductions and delays and through the use of topical measures, such as emollient creams and corticosteroids.[9,10] Lanolin is a natural yellow fat obtained from the wool of sheep that has been used for skin care purposes.[11] There is anecdotal evidence that lanolin-based creams are useful for the treatment of established HFS.[12] However, no definitive data are available in the literature to suggest that either lanolin-based creams or topical corticosteroids are useful for the prevention of HFS.

Moreover, various interventions have been used in the past to prevent or ameliorate HFS, including corticosteroids, pyridoxine (vitamin B_6), cycloxygenase-2 inhibitors, and vitamin E.[13,14] However, the efficacy of these strategies remains controversial, as most randomized clinical trials assessing these interventions to date have either been negative[15-17] or relatively small,[18-21] with a few exceptions showing a positive impact in HFS prevention or/and treatment.[14,22,23] Despite the accumulated clinical experience with such topical and systemic measures, there are not enough data in the literature to guide the use of any of these interventions for the prevention of HFS. Given the prevailing uncertainties about preventive measures for HFS and the current role played by capecitabine as a chemotherapeutic agent, we conducted a phase III trial to assess the worth of a lanolin-based cream with dexpanthenol (the D enantiomer of panthenol, the alcohol analog of pantothenic acid or vitamin B_5), and a topical corticosteroid, hydrocortisone, in the prevention of HFS.

MATERIAL AND METHODS

Eligibility criteria

The protocol for the current study (ClinicalTrials.gov, NCT00661102) was approved by the research ethics committees of all participating institutions, and all patients enrolled provided their written informed consent before randomization. Eligible patients had at least 18 years of age; confirmed diagnosis of breast cancer or colorectal cancer, with indication by their primary physician of treatment with capecitabine as a single agent or in combination for any treatment line; inclusion and randomization at a maximum of 5 days since day 1 of the first cycle of capecitabine-based chemotherapy; no evidence

of HFS upon randomization; no current or previous (≤3 months) use of any pharmaceutical formulation of doxorubicin (including liposomal), or cytarabine; no history of diabetes mellitus; no current pregnancy or intention to get pregnant during the study, no known history of hypersensitivity to any of the study medications; and no use of other investigational agents within the previous 30 days.

Study design and treatment plan

Patients were randomized in an open-label fashion to one of three arms: observation, topical lanolin-based cream with dexpanthenol, and topical hydrocortisone cream. Before enrollment, all patients were carefully instructed about HFS and its recognition. Randomization was done through an electronic case report form and took place on the first study visit. Both creams were provided by Roche Brazil in their commercially available formulations (Bepantol® and Berlison®). In active-treatment arms, patients were instructed to apply a thin and uniform layer of topical medications in the palms of hands and soles of feet according to the prescribing information for each cream: lanolin-based cream with dexpanthenol was to be used three times a day, and hydrocortisone cream was to be used twice a day (approximately every 8 and 12 hours, respectively). These patients were instructed to use topical treatments continuously, even when there were chemotherapy delays between cycles. Patients in the observation arm received identical information, except that regarding the use of topical creams.

The starting dose of capecitabine in breast and colorectal cancer patients was 1,000 or 1,250mg/m^2, based on the investigator's discretion and clinical practice, administered every 12 hours, for 14 consecutive days followed by a 7-day resting period. Dose reduction was done according to the prescribing information for this agent in Brazil. Following the available literature, on the palliative therapy for breast cancer, patients could receive capecitabine until progression or serious adverse events. Treatment with study creams was continued until the development of HFS, discontinuation of on-study capecitabine-based chemotherapy, or consent withdrawal. For all patients discontinued prematurely from the study, further anticancer treatment was left to physician's discretion.

Patient evaluation

Patients were assessed at baseline and during follow-up using structured instruments. After the baseline visit and one planned visit before the third chemotherapy cycle, follow-up was slightly different between patients on palliative therapy for breast or colorectal cancer (a third visit before the fifth cycle and the final visit after the sixth cycle) and those on adjuvant therapy for colon cancer (a third visit before the sixth cycle and the final visit after the eight cycle), but did not vary according to the three randomization arms. HFS was assessed at each visit and classified, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, as grade 0 when absent, grade 1 when skin changes or erythema were minimal and caused no pain, grade 2 when there was pain or more pronounced skin changes (e.g., peeling, blisters, bleeding, or edema) but no interference with function, and grade 3 when skin changes led to pain and interfered with function.[24] Health-related quality of life (HRQoL) was assessed at each visit using the validated Brazilian version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30), version 3.0.[25-27] This HRQoL instrument assesses five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea/vomiting); individual symptoms (dyspnea, insomnia, appetite loss, constipation, and diarrhea); the financial impact of treatment; and a global health and quality-of-life scale. Only a summary of results for the analysis of quality of life is presented herein. Adverse events other than HFS were also assessed using CTCAE, version 3.0.[24]

Statistical analysis

The primary endpoint was the frequency of HFS of any grade. Secondary endpoints were various HRQoL scores (for global health status, functional scales, symptom scales, individual symptoms, and financial impact of therapy), change from baseline in performance status (according to the Eastern Cooperative Oncology Group scale), and the incidence of adverse events. No assessment was made of chemotherapy efficacy, given the expected absence of systemic effect from topical creams. The required sample size for this study was estimated under the assumption that the incidence of HFS of any grade in the observation arm would be 53%. Using a one-sided type I error of 5%, the enrollment of 489 patients (163 per arm) would give the study 80% power to detect a difference of at least 15% in the frequency of HFS of any grade between any of the active-treatment arms and the observation arm, allowing for a dropout rate of 20%. Although analyses were conducted in intention-to-treat (ITT) and per-protocol (PP) populations, the primary analysis was the frequency of HFS of any grade in the ITT population, which comprised all randomized patients that received any amount of study treatment. The PP population included only patients in the ITT population that either completed the whole planned capecitabine treatment or were discontinued before completion because of the development of HFS, disease progression, adverse event or death (other reasons for discontinuation led to the removal of patients from the PP population). The frequency (and 95% confidence interval [CI]) of HFS of any grade was compared between arms using the chi-square test, and logistic regression models were used to explore the association between baseline characteristics and this outcome.

Variables showing an association with HFS at *p*-value ≤0.20 in the univariate analysis were included in a multivariate logistic regression analysis performed using a stepwise selection process and a maintenance level of 0.25. Numerical variables were compared between arms using t-tests and analysis of variance (ANOVA) for two and three-way comparisons, respectively, of normally distributed variables, or the Mann-Whitney and the Kruskal-Wallis tests for corresponding comparisons of variables with non-normal distribution. Moreover, repeated-measures ANOVA was used to explore time trends in HRQoL scores. Statistical analysis was conducted using SAS (version 9.1.3), and significance was considered for two- tailed *p*-values <0.05.

RESULTS

Patient characteristics

Between January 2009 and October 2010, 598 patients were randomized in 31 centers in Brazil. Of these patients, three patients were removed from the study because they did not sign the consent form (two in the control arm and one in the hydrocortisone arm). Of the remaining 595 patients, 393 were prematurely discontinued from the study, more often due to development of HFS (n=182) and disease progression (n=51). Figure 1 depicts patients' flow in the study, including the reasons for treatment discontinuation across the three study arms. Among patients withdrawn from the study, premature discontinuation due to HFS was reported for 72/146 (49.3%), 53/129 (41.1%) and 57/118 (48.3%) in the observation, lanolin-based cream with dexpanthenol, and hydrocortisone cream study arms, respectively. Selected baseline patient characteristics are shown in Table 1 and were evenly distributed among arms. Overall, the mean age was 58 years, and 69% of patients were women. The vast majority of patients had performance status of 0 or 1. Advanced breast cancer was the underlying diagnosis in 37% of patients, and 63% of individuals had colorectal cancer (22% in adjuvant therapy and 41% in palliative therapy for advanced disease). Capecitabine was used as single agent in 67% of patients; for the vast majority (82%) of the remaining 33% of patients treated with combinations, oxaliplatin was the chemotherapy partner. There were no significant differences in the mean daily dose of capecitabine prescribed in the first chemotherapy cycle among arms. Chemotherapy lines were also evenly distributed among the three arms (data not shown).

Frequency and severity of HFS

Overall, the frequency of HFS of any grade during the study was 35.6% (95%CI, 29.4% to 42.4%) with observation, 24.9% (95%CI, 19.5% to 31.2%) with lanolin-based cream with dexpanthenol, and 34.3% (95%CI, 27.7% to 41.4%) for hydrocortisone cream (*p*=0.039). When compared with observation, the unadjusted odds ratio for the frequency of HFS in the arm treated with the lanolin-based cream with dexpanthenol was 0.60 (95%CI, 0.39 to 0.92), indicating a 40% relative reduction in the frequency of this adverse event. Adjusting for other covariates that showed an association with HFS development at *p*-values ≤0.20 in the univariate analyses (i.e., cancer site, metastatic disease, treatment line, heart disease, hypertension, smoking, systolic blood pressure, and prescribed dose of capecitabine at visit 1), this odds ratio was 0.61 (*p*=0.047); the only other covariate significantly associated with the occurrence of HFS was the dose of capecitabine (data not shown). As shown in Table 2, differences across groups were more pronounced during the first two cycles (between the first and second visits). Such findings do not seem to be explained by dose adjustments, as the mean dose of capecitabine during the study did not vary significantly across arms (Table 3).

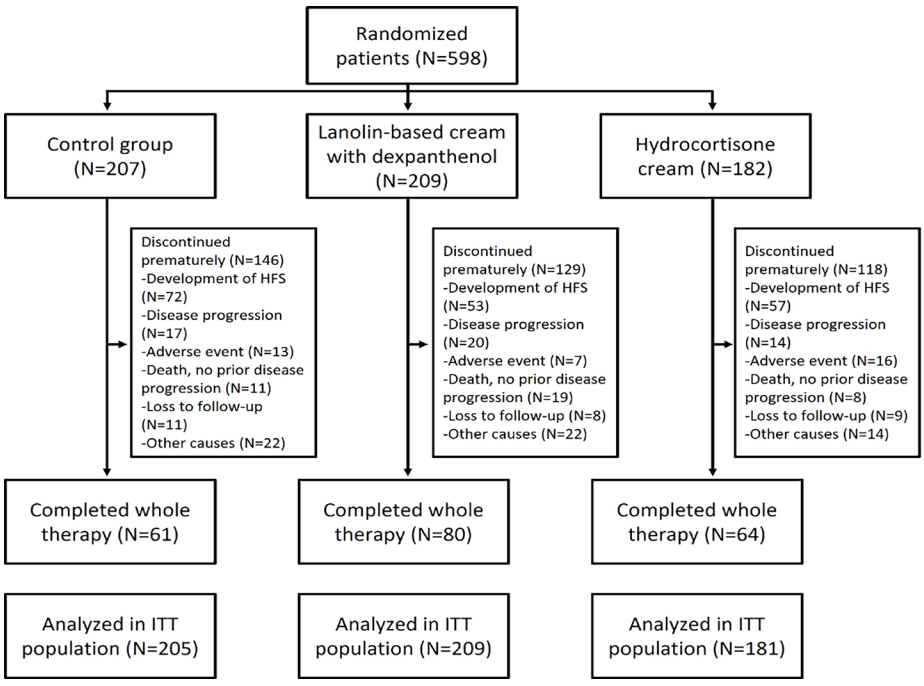

Figure 1. Patient flow during the study. Abbreviations: HFS = Hand-foot syndrome; ITT = Intention-to-treat.

Likewise, there were no significant differences in the distribution of the severity of HFS across the three arms, when the overall study duration was considered (p=0.694). Grade 1 HFS was noted in 53.1% of patients with this adverse event along the study in the observation arm, 61.5% of patients treated with the lanolin-based cream with dexpanthenol, and 59.0% of patients in the hydrocortisone cream arm. Corresponding figures for grade 2 HFS were 37.5%, 34.6%, and 38.5%, respectively. Only between 2.6% and 9.4% of patients in three study arms had grade 3 HFS.

Exploratory analyses conducted in the PP population corroborated the analyses conducted in the ITT population. The frequency of HFS of any grade during the study in the PP population was 47.2% (95%CI, 51.6% to 69.5%) with observation (n=142), 31.1% (95%CI, 29.1% to 45.7%) with lanolin-based cream with dexpanthenol (n=151), and 44.4% (95%CI, 41.6% to 60.2%) for hydrocortisone cream (n=124; p=0.012 for the comparison of the three arms). Once again, there were no significant differences in the distribution of the severity of HFS among the three arms in the PP population, when the overall study duration was considered; moreover, such distribution in the PP population closely mirrored the one found for the ITT population (data not shown). No exploratory analyses were conducted with regard to potential differences in treatment efficacy among subgroups of patients defined by baseline characteristics, including tumor type and treatment intent.

HRQoL and performance status results

Table 4 shows HRQoL scores at baseline and at all follow-up visits, while Table 5 shows the mean change in HRQoL scores from baseline. Apart from a slight imbalance in cognitive function with a statistically significantly higher score in the hydrocortisone arm (p=0.038), there were no significant differences in other scores among the three study arms at baseline (all p>0.05).

Table 1. Baseline characteristics of patients.

Characteristic	Observation n=205	Lanolin-based dexpanthenol cream n=209	Hydrocortisone cream n=181	*p*-value
Age, years (mean ± SD)	57.4 ± 13.9	58.5 ± 13.4	58.5 ± 14.0	0.65
Gender (%)				0.39
Female	69.8	66.0	72.4	
Male	30.2	34.0	27.6	
Performance status (%)				0.89
0	46.3	47.6	49.2	
1	39.5	38.0	37.6	
2	12.2	11.1	8.8	
3	2.0	3.4	4.5*	
Primary diagnosis (%)				0.91
Advanced breast cancer	36.3	35.1	39.2	
Colorectal cancer, adjuvant therapy	21.5	24.0	21.5	
Advanced colorectal cancer	42.0	40.9	39.2	
Capecitabine use (%)				0.65
Single agent	64.4	68.3	68.0	
Combination	35.6	31.7	32.0	
Capecitabine dose at cycle 1, mg/m^2/day (mean ± SD)	2060 ± 556	2051 ± 548	2030 ± 536	0.86
Treatment line (%**)				0.96
First	44.9	43.1	46.4	
Second	33.7	32.5	32.0	

*One patient in this group was coded as having performance status of 4. **Only applies to metastatic disease, but percentages refer to total number of patients in each arm.
Abbreviations: HRQoL = Health-related quality of life; SD = Standard deviation.

Table 2. Frequency of hand-foot syndrome along the study (see text for timing of visits).

Assessment visit	Observation n=205	Lanolin-based dexpanthenol cream n=209	Hydrocortisone cream n=181	p-value
First	20.5%	12.4%	13.8%	0.057
Second	8.8%	9.2%	11.4%	0.721
Third	19.1%	9.9%	17.4%	0.142
Final	1.7%	0	7.9%	0.011
Overall	35.6%	24.9%	34.3%	0.039

Table 3. Mean doses of capecitabine along the study (mg/m^2/day).

Study period	Observation n=205	Lanolin-based dexpanthenol cream n=209	Hydrocortisone cream n=181	p-value
At second visit	2005 ± 557	2000 ± 517	1967 ± 515	0.813
At third visit	1978 ± 568	1929 ± 451	2003 ± 536	0.577
At final visit	1976 ± 496	1832 ± 342	1838 ± 355	0.808
Overall*	2064 ± 558	2040 ± 535	2018 ± 522	0.704

*Computation of overall dose includes data on dose at cycle 1 shown in Table 1.

Table 4. Health-related quality of life scores at baseline and follow-up visits assessed using the validated Brazilian version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

EORTC QLQ-C30 scores	Observation				Lanolin-based dexpanthenol cream				Hydrocortisone cream			
	Visit 1 Mean ± SD	Visit 2 Mean ± SD	Visit 3 Mean ± SD	Visit 4 Mean ± SD	Visit 1 Mean ± SD	Visit 2 Mean ± SD	Visit 3 Mean ± SD	Visit 4 Mean ± SD	Visit 1 Mean ± SD	Visit 2 Mean ± SD	Visit 3 Mean ± SD	Visit 4 Mean ± SD
Global health and QoL scale	64.4 ± 25.5	65.3 ± 24.7	66 ± 24.9	68.2 ± 23.4	63.1 ± 27.4	65.7 ± 26.3	66.5 ± 27.5	73.8 ± 24	67.3 ± 22.5	67.1 ± 23.7	68.9 ± 25.6	73 ± 22.8
Physical function	69.5 ± 26.3	69.4 ± 25.7	65.6 ± 30.4	69.6 ± 27.5	67.3 ± 28	67.5 ± 28.2	68.9 ± 29.4	76 ± 26.6	71.4 ± 26.2	67.1 ± 27.8	71.7 ± 25.5	73 ± 26.1
Role function	64.6 ± 34.5	68.7 ± 34	62.9 ± 36.6	67.5 ± 35.5	60.3 ± 38	66.4 ± 35	68.2 ± 35.1	73.1 ± 31.9	67 ± 35.3	66.7 ± 36.3	69.7 ± 35.9	71.1 ± 34.5
Emotional function	63 ± 29.7	66.2 ± 29	62.9 ± 31.6	71.6 ± 28.9	59.7 ± 30.8	62.8 ± 30.7	68.2 ± 29.6	67.1 ± 33.3	63.3 ± 31.7	64.9 ± 29.9	64.1 ± 31	68 ± 29.4
Cognitive function	70.7 ± 30.6	73.5 ± 28.8	68.1 ± 32.2	73.7 ± 28.6	73.9 ± 27.1	74.6 ± 29.6	72.7 ± 31.1	74.6 ± 31.6	78.1 ± 26.5	75 ± 27	69.9 ± 30.5	70.6 ± 28.9
Social function	71.3 ± 32.2	77.2 ± 28.1	73.8 ± 34.3	74.3 ± 31.5	68.5 ± 33.9	72.7 ± 34.1	74.9 ± 32.6	79.4 ± 32.3	76.1 ± 30	76.4 ± 29.5	80.5 ± 28.6	77.9 ± 29.4
Fatigue	35.5 ± 30.1	29.7 ± 28	28.5 ± 29.2	29.2 ± 28.1	36.4 ± 30.6	30.4 ± 29.1	27.1 ± 29.4	24.9 ± 25.9	33.9 ± 30.1	31.4 ± 29.6	26.8 ± 25.9	25 ± 26.9
Nausea/vomiting	13.3 ± 22.8	13.5 ± 21.8	12.6 ± 17.7	14.1 ± 21.8	12.4 ± 20.6	15.1 ± 21	11.4 ± 17.8	9.8 ± 17.3	13.1 ± 21.8	15.2 ± 23.2	14 ± 18.4	10.4 ± 19.8
Pain	36.5 ± 35.2	30.1 ± 33.6	31 ± 33.1	31.1 ± 31	38.9 ± 37.6	31.8 ± 31.1	26.9 ± 32.7	26.5 ± 32.4	34.3 ± 35.2	27.6 ± 31.8	24.9 ± 30.9	25.3 ± 30.4
Dyspnea	15 ± 27.1	14.4 ± 28.5	11.6 ± 24.2	14.9 ± 28	16.3 ± 28.6	14.8 ± 27.3	13.5 ± 23.8	11.5 ± 22	12.3 ± 26.1	10 ± 20.8	8.4 ± 18.3	6.9 ± 16
Insomnia	33.3 ± 36.8	23.6 ± 31.9	28.5 ± 35	28.7 ± 34.5	35.7 ± 38	28.7 ± 35.4	27.7 ± 35.2	26.9 ± 37.2	33.1 ± 36.1	32.1 ± 35.8	28.2 ± 35.8	20.6 ± 30.8
Appetite loss	26.2 ± 35.7	22.4 ± 31.6	21 ± 30.3	27 ± 34.5	26.9 ± 37.4	28 ± 35.8	23.6 ± 33.5	15.4 ± 27.2	24.7 ± 35.2	26.3 ± 37.6	20.1 ± 31.4	20.1 ± 35.7
Constipation	15.4 ± 29.5	8.2 ± 19.4	13.5 ± 26	15.5 ± 28.8	18.2 ± 31.6	12.7 ± 24.6	11.3 ± 21.5	10.8 ± 22.6	17.1 ± 30.9	16.3 ± 27.7	13.2 ± 25.8	13.8 ± 30.3
Diarrhea	8.6 ± 20.5	12.2 ± 24.7	11.6 ± 19.5	7.5 ± 15.3	9.5 ± 23.2	15.2 ± 25.7	13.2 ± 23.3	13.7 ± 24.3	8.1 ± 20.1	13.1 ± 26.3	11.4 ± 22.9	11.6 ± 20.9
Financial difficulties	33 ± 37.2	27.4 ± 33.7	31.5 ± 37.7	31 ± 35.6	34.3 ± 37.9	30.6 ± 37.1	25.5 ± 36.4	23.1 ± 32.4	31.3 ± 38	30.7 ± 39.2	26.7 ± 35.6	26.4 ± 35

Abbreviations: EORTC-QLQ C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; QoL = Quality of Life; SD = Standard deviation.

Table 5. Changes in health related quality of life scores at visits 2, 3 and 4 as compared with baseline, using the validated Brazilian version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

	Observation			Lanolin-based dexpanthenol cream			Hydrocortisone cream		
Change in EORTC QLQ-C30 from visit 1	**Visit 2 Mean ± SE [95%CI]**	**Visit 3 Mean ± SE [95%CI]**	**Visit 4 Mean ± SE [95%CI]**	**Visit 2 Mean ± SE 95%CI]**	**Visit 3 Mean ± SE [95%CI]**	**Visit 4 Mean ± SE [95%CI]**	**Visit 2 Mean ± SE [95%CI]**	**Visit 3 Mean ± SE [95%CI]**	**Visit 4 Mean ± SE [95%CI]**
Global health and QoL scale	-1.5 ± 2 [-5.4 ; 2.5]	0.8 ± 3.2 [-5.5 ; 7.1]	2 ± 3.7 [-5.4 ; 9.4]	-1.2 ± 2.2 [-5.5 ; 3.1]	-0.6 ± 2.6 [-5.8 ; 4.6]	5 ± 3.1 [-1.2 ; 11.1]	-0.4 ± 2.2 [-4.8 ; 3.9]	1.4 ± 2.6 [-3.8 ; 6.7]	5.6 ± 3.3 [-1 ; 12.2]
Physical function	-2.5 + 1.7 [-5.8 ; 0.9]	-4.8 + 2.8 [-10.3 ; 0.7]	-1.6 + 3.1 [-7.8 ; 4.7]	-2.4 ± 1.5 [-5.4 ; 0.6]	-3 ± 2.4 [-7.7 ; 1.6]	1.6 ± 2.4 [-3.2 ; 6.4]	-4.2 ± 1.9 [-8.1 ; -0.4]	-2.7 ± 2.5 [-7.7 ; 2.3]	-4.1 ± 3.4 [-10.8 ; 2.7]
Role function	1.8 ± 2.9 [-4 ; 7.6]	-1.2 ± 4.1 [-9.4 ; 6.9]	2.8 ± 4.7 [-6.6 ; 12.2]	2.5 ± 2.3 [-2.1 ; 7]	3.6 ± 3.5 [-3.2 ; 10.5]	5 ± 3.3 [-1.5 ; 11.5]	0.7 ± 2.5 [-4.2 ; 5.7]	2.7 ± 3.5 [-4.3 ; 9.6]	5.2 ± 5.1 [-5 ; 15.4]
Emotional function	1.2 ± 2.3 [-3.5 ; 5.8]	-1.8 ± 3.3 [-8.3 ; 4.8]	7.8 ± 3.9 [-0.1 ; 15.6]	1.8 ± 2 [-2.2 ; 5.8]	3.6 ± 2.5 [-1.4 ; 8.6]	3 ± 3.2 [-3.4 ; 9.5]	1.5 ± 2.4 [-3.2 ; 6.2]	-0.9 ± 2.9 [-6.7 ; 4.9]	4.8 ± 2.8 [-0.8 ; 10.5]
Cognitive function	1.5 ± 2.3 [-3 ; 5.9]	-5 ± 2.9 [-10.7 ; 0.8]	1.7 ± 3.7 [-5.6 ; 9]	-2.6 ± 1.8 [-6.1; 1]	-6.5 ± 2.2 [-10.8 ; -2.1]	-6 ± 3 [-12 ; -0.1]	-2.6 ± 2.2 [-7 ; 1.7]	-7.9 ± 2.7 [-13.2 ; -2.5]	-5.5 ± 4 [-13.5 ; 2.5]
Social function	2.4 ± 2.6 [-2.7 ; 7.6]	-0.9 ± 3.7 [-8.3 ; 6.5]	-2.5 ± 4.8 [-12.2 ; 7.1]	1.3 ± 2.1 [-2.9 ; 5.5]	-2 ± 3.2 [-8.3 ; 4.3]	-0.2 ± 3.2 [-6.6 ; 6.2]	-0.6 ± 2.2 [-4.9 ; 3.7]	1.1 ± 2.8 [-4.5 ; 6.6]	-1.3 ± 3.5 [-8.3 ; 5.8]
Fatigue	-2.3 ± 2.4 [-6.9 ; 2.4]	-5.8 ± 3.1 [-11.9 ; 0.2]	-4.9 ± 3.9 [-12.7 ; 3]	-2.1 ± 1.6 [-5.3 ; 1.1]	-1.8 ± 2.4 [-6.4 ; 2.9]	-3.7 ± 2.6 [-8.9 ; 1.4]	-1.3 ± 2.5 [-6.1 ; 3.6]	-2 ± 2.8 [-7.6 ; 3.6]	-4.9 ± 3.9 [-12.7 ; 3]
Nausea/vomiting	1.1 ± 2.2 [-3.3 ; 5.5]	-0.5 ± 2.8 [-6.1 ; 5.1]	1.7 ± 3.5 [-5.3 ; 8.7]	5.5 ± 1.6 [2.4 ; 8.7]	4.1 ± 1.5 [1.1 ; 7]	2.9 ± 1.7 [-0.5 ; 6.4]	2.3 ± 2 [-1.7 ; 6.2]	3 ± 2.1 [-1 ; 7.1]	-0.8 ± 3.2 [-7.3 ; 5.7]
Pain	-2.7 ± 2.8 [-8.2 ; 2.8]	-4.4 ± 3.2 [-10.8 ; 1.9]	-3.7 ± 4.5 [-12.7 ; 5.3]	-4 ± 2.4 [-8.7 ; 0.6]	-4.4 ± 2.9 [-10 ; 1.3]	-1.1 ± 3.3 [-7.7 ; 5.6]	-6.2 ± 2.6 [-11.4 ; -1]	-9.1 ± 3.5 [-16.1 ; -2.2]	-8.6 ± 4.8 [18.2 ; 1]
Dyspnea	-1 ± 2.2 [-5.3 ; 3.3]	-3.7 ± 2.8 [-9.3 ; 1.8]	0.6 ± 4.2 [-7.9 ; 9]	1.3 ± 2 [-2.6 ; 5.1]	1.3 ± 2.4 [-3.4 ; 5.9]	-0.9 ± 2.9 [-6.7 ; 4.9]	-0.2 ± 1.8 [-3.8 ; 3.3]	-1.1 ± 2 [-5.2 ; 3]	-1.6 ± 3 [-7.5 ; 4.3]
Insomnia	-5.3 ± 2.6 [-10.5 ; -0.1]	0.8 ± 3.7 [-6.6 ; 8.1]	2.3 ± 5.6 [-8.9 ; 13.5]	-3.8 ± 2.2 [-8.2 ; 0.6]	-0.3 ± 2.8 [-5.9 ; 5.3]	-1.3 ± 4.4 [-10 ; 7.4]	-0.7 ± 2.5 [-5.7 ; 4.2]	-5.9 ± 3.5 [-12.8 ; 1.1]	-12.2 ± 4.5 [-21.3 ; -3.1]
Appetite loss	1.7 ± 2.6 [-3.4 ; 6.9]	0.4 ± 3.6 [-6.8 ; 7.5]	8 ± 5.5 [-2.9 ; 19]	6.4 ± 2.8 [0.9 ; 11.9]	4.7 ± 3.2 [-1.7 ; 11.1]	-0.4 ± 3.4 [-7.2 ; 6.4]	3.9 ± 3.1 [-2.3 ; 10.1]	-3.7 ± 3.5 [-10.6 ; 3.3]	-4.8 ± 5.1 [-15 ; 5.4]
Constipation	-4.5 ± 2.4 [-9.2 ; 0.1]	-1.1 ± 3.3 [-7.7 ; 5.4]	3.4 ± 4.4 [-5.3 ; 12.2]	-3.4 ± 2.1 [-7.5 ; 0.7]	-3.1 ± 2.7 [-8.6 ; 2.3]	-0.9 ± 3.3 (-7.4 ; 5.6]	-2 ± 2.3 [-6.6 ; 2.6]	-5.6 ± 3.3 [-12.1 ; 1]	-3.8 ± 4.5 [-12.8 ; 5.3]
Diarrhea	2.5 ± 2.5 [-2.4 ; 7.4]	0.7 ± 2.5 [-4.2 ; 5.7]	-2.3 ± 3.1 [-8.4 ; 3.8]	5.3 ± 2.1 [1.1; 9.5]	2.5 ± 2.2 [-1.8 ; 6.8]	1.3 ± 3.2 [-5.2 ; 7.7]	5.4 ± 2.5 [0.4 ; 10.3]	2.9 ± 3 [-3 ; 8.8]	4.8 ± 3.3 [-1.8 ; 11.3]
Financial difficulties	-5.7 ± 2.4 [-10.5 ; -1]	-6.4 ± 4.1 [-14.6 ; 1.8]	-7 ± 5.7 [-18.4 ; 4.4]	-3.8 ± 2.5 [-8.8 ; 1.2]	-3.5 ± 2.9 [-9.1 ; 2.2]	-3 ± 3 [-9.1 ; 3]	-3.4 ± 2.4 [-8.2 ; 1.4]	-4.4 ± 3 [-10.4 ; 1.7]	-2.1 ± 4.3 [-10.8 ; 6.5]

Abbreviations: EORTC-QLQ C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; QoL = Quality of Life; SE = Standard error.

There were no statistically significant differences in mean change from baseline in any of the HRQoL scores among the three study arms (Table 5). However, there were statistically significant improvements across the three arms, in comparison with baseline scores, in the global health and quality-of-life scale in the last visit (p=0.033); in emotional function in the final visit (p=0.008); nausea/vomiting in the second (p=0.008) and third (p=0.076) visits; in appetite loss in the second visit (p=0.016); and in diarrhea in the second visit (p=0.002). On the other hand, in the three study arms there was statistically significant worsening of physical function in the second (p=0.002) and third (p=0.017) visits; of cognitive function in the third visit (p<0.001); of fatigue in the third (p=0.043) and final (p=0.025) visits; of pain in the second (p=0.004) and third (p=0.001) visits; of insomnia in the second visit (p=0.021); of constipation in the second visit (p=0.011); and of the financial impact of treatment in the second (p=0.003) and third (p=0.014) visits, always in comparison with baseline. There were no statistically significant differences in the distribution of performance status among the three arms during the study.

Safety

Overall, the frequency of adverse events along the study did not vary significantly among study arms (Table 6). Nearly 60% of patients in the three arms had at least one adverse event. As shown in Table 6, the frequency of serious adverse events and the severity of adverse events, as indicated by CTCAE grading, also did not vary significantly among study arms. The most frequent adverse events reported by at least five patients in any arm were nausea, diarrhea, vomiting, fatigue, and pain, with no notable differences in their distribution among study arms. Thirty-seven deaths were reported during the study; in 34 of these cases, death was attributed to disease progression (in nine patients in the observation arm, 20 in the lanolin-based cream with dexpanthenol arm, and five in the hydrocortisone cream arm).

DISCUSSION

HFS is the most common reason for dose reductions and delays among patients treated with capecitabine.[28-30] The current phase III trial has shown that a lanolin-based cream with dexpanthenol is effective in the prevention of capecitabine-induced HFS, when compared with observation and a hydrocortisone cream. Interestingly, we found no beneficial effect from the topical corticosteroid analyzed in the study. In relative terms, the frequency of HFS was reduced by 40% with the use of lanolin-based cream with dexpanthenol, in comparison with observation. No notable adverse events were recorded from either this topical therapy or from the use of hydrocortisone cream, and no significant differences were found among treatment arms in secondary efficacy endpoints, including HRQoL parameters. Therefore, a lanolin-based cream with dexpanthenol could be considered a standard measure in the attempt to prevent capecitabine-induced HFS.

Previous phase III trials have failed to demonstrate the efficacy of preventive measures for HFS. On behalf of the North Central Cancer Treatment Group Study, Wolf et al. (2010)[16] reported negative results for a urea/lactic acid-based topical keratolytic agent that was compared with placebo in 137 patients. As a matter of fact, the active-treatment arm of that study had a higher frequency of HFS than the placebo arm, thus leading the authors to suggest possible skin toxicity from the urea/lactic acid-based topical keratolytic agent. Likewise, Kang et al. (2011)[15] reported negative results for oral pyridoxine (200mg/day), in comparison with placebo, in the prevention of grade 2 or higher HFS among 389 patients from South Korea. In a randomized trial of smaller size (n=106), Corrie et al. (2012)[20] could not find statistically significant reductions in the frequency of HFS or of capecitabine dose adjustments, when pyridoxine (50mg/day) was compared with placebo, despite nominal improvements in both endpoints. In a second randomized trial of small size (n=56), Chalermchai et al. (2010)[18] found a possible dose-response relationship for this agent, as patients treated with a daily dose of 400mg had a lower frequency of grade 3 HFS than those treated with 200mg/day.

Table 6. Frequency of adverse events along the study.

Category	Observation n=205	Lanolin-based dexpanthenol cream n=209	Hydrocortisone cream n=181	p-value
Any adverse event	59%	56.5%	63.0%	0.42
Treatment-related adverse event	1.0%	1.0%	2.8%	0.29
Serious adverse event	15.1%	16.7%	17.1%	0.85
Severity of adverse event*				
Grade 1	40.0%	40.7%	46.4%	0.38
Grade 2	33.7%	28.7%	32.6%	0.52
Grade 3	17.1%	12.0%	17.7%	0.22
Grade 4	3.4%	1.4%	2.8%	0.43
Grade 5	8.3%	12.0%	7.7%	0.29
Unknown	0.5%	0.5%	1.7%	0.39

*Considering the worst grade recorded in each patient.

However, the former patients also had a lower tumor response rate and a decreased time to tumor progression, thus raising questions as to the safety of this systemic agent. Moreover, the absence of a placebo or observation group precludes further conclusions about the efficacy of pyridoxine in that trial. More recently, pyridoxine also failed to prevent or delay the onset of grade 2 or higher HFS in a larger placebo-controlled phase III trial including 210 patients receiving capecitabine as a single-agent in a center in Singapore.[17] Serum and red-blood-cell folate levels were identified as independent predictors of HFS in a multivariate analysis.[17] In a recent meta-analysis of 14 studies involving 1,570 patients, no robust evidence that pyridoxine can prevent HFS and reduce the incidence of grade ≥2 was reported.[31]

Contrasting with the negative results reported for pyridoxine and uric-acid-based cream, celecoxib has been suggested to be effective at preventing capecitabine-induced HFS.[19,32] The first trial with a positive result for celecoxib was conducted by Chinese investigators, who reported a decreased frequency of HFS by the use of oral celecoxib, in comparison with observation in 110 patients enrolled in a randomized phase II trial.[19] The potential of celecoxib for prevention of capecitabine-induced HFS was later confirmed by the same group in a phase III trial in patients with stage II colorectal cancer.[32] However, concerns about the cardiovascular safety of celecoxib may limit the applicability of these results.

Positive-results were also reported for urea cream as Hofheinz et al. (2015)[33] found that a 10% urea cream was superior to a new ointment containing antioxidants (Mapisal) for prevention of HFS in patients with gastrointestinal tumors or breast cancer treated with capecitabine. In addition to the lower incidence of HFS, a significant longer time to any-grade HFS was observed for patients using urea cream in this study.[33] Importantly, in the study conducted by Wolf et al. (2010),[16] a mixture of urea and lactic acid was used. More recently, a randomized double-blind study reported that the prophylactic use of EVOSKIN®Palm and sole moisturizing cream (PSMC) reduced the incidence of severe HFS in patients with colorectal cancer receiving capecitabine chemotherapy.[23]

The efficacy of different strategies (pyridoxine, topical urea/lactic acid, celecoxib, and other approaches of interest) versus placebo for prevention and treatment of capecitabine-induced HFS were assessed in a meta-analysis recently published.[14] A total of 17 eligible studies published from 2012 to 2017 and involving 2081 patients were included in the analysis. Using the risk ratio with the corresponding 95% confidence interval as an effect measure, the authors found a significant association between celecoxib and a lower incidence of grade ≥2 HFS. Confirming previous findings, the meta-analysis suggested that pyridoxine and topical urea/lactic acid are not effective in preventing capecitabine-induced grade 1, 2, and 3 HFS. Regarding other potential strategies for prevention of capecitabine evaluated in this meta-analysis, moisturizing cream, neurotropin, topical silymarin and Fuzheng Jiedusan were evaluated in independent studies, with results suggesting a positive impact of the latter two.[14,21,34-36] Prophylactic administration of silymarin topical formulation was suggested to promote a significant decrease of the severity of capecitabine-induced HFS and a delay in its occurrence in patients with gastrointestinal cancer.[21] Similarly, Zhou et al. (2017)[36] reported favorable results for the use of a modified prescription of Fuzheng Jiedusan in combination with capecitabine in reducing adverse reactions such as HFS.[36] In addition to the studies included in the meta-analysis published by Huang et al. (2018),[14] a pilot study conducted in 40 patients suggested that administration of turmeric, a plant used in Ayurvedic medicine, may decrease the rate of HFS induced by capecitabine, especially grade 2 or higher.[37] Overall, these findings need confirmation in larger controlled studies to provide more conclusive data.

One limitation of the current study is the lack of use of placebo due to ethical and logistic constraints in Brazil; as a result, neither patients nor investigators were blinded during the assessment of HFS. Another limitation could be the lack of endpoints pertaining to antitumor efficacy. Due to the topical nature of the treatments for HFS prevention, in principle, this measure was considered appropriate. The use of a higher initial dose of capecitabine in monotherapy (based on the local label recommendations), but known to be higher than the most commonly used dose in clinical practice may also represent a limitation, as one could speculate what would be the study results if a lower dose of capecitabine was used. In the present study, capecitabine was administrated at doses routinely used in the clinical practice. The study results showed that the mean dose of capecitabine prescribed for all three study arms and at all visits (1, 2, 3, and 4) was 2,000mg/m^2/day, and there were no significant difference between arms at all visits.

Although it is not possible to anticipate the results in scenarios using different doses of capecitabine, we could expect that the relative effect of the treatments would not depend on the initial dose of capecitabine. In other words, a lower or higher dose of capecitabine would probably result in a lower or higher frequency of HFS onset in all study arms, respectively, but the relative difference between treatment arms would be maintained. The frequency of HFS of any grade in the observation arm of the current study (35.6%) was lower than that used for sample-size calculation (53%), probably as a result of lower mean doses of capecitabine currently used more often in clinical practice, when compared with the original starting dose of 2,500mg/m^2/day administered in the pivotal study of this agent.[1] On the other hand, the frequency of HFS noted in the observation arm is in the range of those reported by other investigators when lower starting doses of capecitabine were used.[16,38,39]

Even though this study was powered to detect a difference of at least 15% in the frequency of HFS between any of the active-treatment arms and the observation arm, an absolute difference of 10.7% between the frequencies of HFS with lanolin-based cream with dexpanthenol and observation was enough to provide statistical significance for the overall comparison among arms. Moreover, the relatively low frequency of HFS in the observation arm provided additional power to detect a 15% difference between the frequencies of HFS with hydrocortisone cream and observation. However, no significant differences were found between these two arms. Thus, we believe that the lower than expected frequency of HFS does not affect our conclusions about the efficacy of the lanolin-based cream with dexpanthenol, and the inefficacy of the hydrocortisone cream.

CONCLUSION

The reduced frequency of HFS with the use of lanolin-based cream with dexpanthenol found in the current study is noteworthy and can be considered a novel preventive option as an adjunct to therapy in patients treated with capecitabine. The impact of this preventive strategy in other capecitabine dosage context remains to be determined.

ACKNOWLEDGEMENTS

Medical writing support was provided by Dendrix Research (Sao Paulo, Brazil), and funded by Roche Brazil. We thank all the study collaborators and patients, as well as Sarah Garrido, a Roche employee, who helped the authors to consolidate this manuscript.

AUTHORS' CONTRIBUTIONS

All study investigators who agreed to participate in the writing, review, and/or revision of the manuscript were included as authors, and all authors equally contributed to the study. The authors take full responsibility for the content of the manuscript.

REFERENCES

1. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol. 2001 Apr;19(8):2282-92.
2. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline- pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002 Jun;20(12):2812-23.
3. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005 Jun;352(26):2696-704.
4. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006 Dec;355(26):2733- 43.
5. Thomas ES, Gomez HL, Li RK, Chung HC, Fein LE, Chan VF, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007 Nov;25(33):5210-7.
6. Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, 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(12):2006- 12.
7. Stockler MR, Harvey VJ, Francis PA, Byrne MJ, Ackland SP, Fitzharris B, et al. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. J Clin Oncol. 2011 Dec;29(34):4498-504.
8. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov;367(19):1783-91.
9. Lassere Y, Hoff P. Management of hand-foot syndrome in patients treated with capecitabine (Xeloda). Eur J Oncol Nurs. 2004;8(Suppl 1):S31-S40.
10. Kwakman JJM, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy-induced hand-foot syndrome. Oncol Rev. 2020 Feb;14(1):442.
11. Wolf R. The lanolin paradox. Dermatology. 1996;192(3):198-202.
12. Chin SF, Tchen N, Oza AM, et al. Use of "Bag Balm" as topical treatment of palmar- plantar erythrodysesthesia syndrome (PPES) in patients receiving selected chemotherapeutic agents (abstract 1632). Proc Am Soc Clin Oncol. 2001;20(Suppl 1):409a.
13. Gressett SM, Stanford BL, Hardwicke F. Management of hand-foot syndrome induced by capecitabine. J Oncol Pharm Pract. 2006 Sep;12(3):131-41.
14. Huang XZ, Chen Y, Chen WJ, Zhang X, Wu CC, Wang ZN, et al. Clinical evidence of prevention strategies for capecitabine-induced hand-foot syndrome. Int J Cancer. 2018 Jun;142(12):2567-77.
15. Kang YK, Lee SS, Yoon DH, Lee SY, Chun YJ, Kim MS, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study. J Clin Oncol. 2011 Aug;28(24):3824-9.
16. Wolf SL, Qin R, Menon SP, Rowland Junior KM, Thomas S, Delaune R, et al. Placebo- controlled trial to determine the effectiveness of a urea/lactic acid-based topical keratolytic agent for prevention of capecitabine-induced hand-foot syndrome: North Central Cancer Treatment Group Study N05C5. J Clin Oncol. 2010 Dec;28(35):5182-7.

17. Yap YS, Kwok LL, Syn N, Chay WY, Chia JWK, Tham CK, et al. Predictors of hand- foot syndrome and pyridoxine for prevention of capecitabine-induced hand-foot syndrome: a randomized clinical trial. JAMA Oncol. 2017 Nov;3(11):1538-45.

18. Chalermchai T, Tantiphlachiva K, Suwanrusme H, Voravud N, Sriuranpong V. Randomized trial of two different doses of pyridoxine in the prevention of capecitabine- associated palmar-plantar erythrodysesthesia. Asia Pac J Clin Oncol. 2010 Sep;6(3):155-60.

19. Zhang RX, Wu XJ, Lu SX, Pan ZZ, Wan DS, Chen G. The effect of COX-2 inhibitor on capecitabine-induced hand-foot syndrome in patients with stage II/III colorectal cancer: a phase II randomized prospective study. J Cancer Res Clin Oncol. 2011 Jun;137(6):953-7.

20. Corrie PG, Bulusu R, Wilson CB, Armstrong G, Bond S, Hardy R, et al. A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. Br J Cancer. 2012 Aug;107(4):585-7.

21. Elyasi S, Shojaee FSR, Allahyari A, Karimi G. Topical Silymarin administration for prevention of capecitabine-induced hand-foot syndrome: a randomized, double-blinded, placebo-controlled clinical trial. Phytother Res. 2017 Sep;31(9):1323-9.

22. Macedo LT, Lima JPN, Santos LV, Sasse AD. Prevention strategies for chemotherapy- induced hand-foot syndrome: a systematic review and meta-analysis of prospective randomised trials. Support Care Cancer. 2014 Jun;22(6):1585-93.

23. Lu W, Huang Z, Chen S, Lv H, Chen X, Lei J, et al. The effectiveness of EVOSKIN®Palm and sole moisturizing cream in treating capecitabine-associated hand-foot syndrome: a randomized double-blind clinical trial. Ann Palliat Med. 2021 Mar;10(3):3009-17.

24. U. S. Department of Health and Human Services (HHS-US). National Institutes of Health (NIH). National Cancer Institute (NCI). Cancer therapy evaluation program: common terminology criteria for adverse events, version 3.0 (CTCAE). Washington: HHS-US; 2003.

25. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar;85(5):365-76.

26. Brabo EP, Paschoal ME, Biasoli I, Nogueira FE, Gomes MC, Gomes IP, et al. Brazilian version of the QLQ-LC13 lung cancer module of the European Organization for Research and Treatment of Cancer: preliminary reliability and validity report. Qual Life Res. 2006 Nov;15(9):1519- 24.

27. Franceschini J, Jardim JR, Fernandes AL, Jamnik S, Santoro IL. Reproducibility of the Brazilian Portuguese version of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire used in conjunction with its lung cancer-specific module. J Bras Pneumol. 2010 Oct;36(5):595-602.

28. Scheithauer W, McKendrick J, Begbie S, Borner M, Burns WI, Burris HA, et al. Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. Ann Oncol. 2003 Dec;14(12):1735-43.

29. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol. 2002 Apr;13(4):566-75.

30. Blum JL, Barrios CH, Feldman N, Verma S, McKenna EF, Lee LF, et al. Pooled analysis of individual patient data from capecitabine monotherapy clinical trials in locally advanced or metastatic breast cancer. Breast Cancer Res Treat. 2012 Dec;136(3):777-88.

31. Lian S, Zhang X, Zhang Y, Zhao Q. Pyridoxine for prevention of hand-foot syndrome caused by chemotherapy agents: a meta-analysis. Clin Exp Dermatol. 2021 Jun;46(4):629-35.

32. Zhang RX, Wu XJ, Wan DS, Lu ZH, Kong LH, Pan ZZ, et al. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: result of a single-center, prospective randomized phase III trial. Ann Oncol. 2012 May;23(5):1348-53.

33. Hofheinz RD, Gencer D, Schulz H, Stahl M, Hegewisch-Becker S, Loeffler LM, et al. Mapisal versus urea cream as prophylaxis for capecitabine-associated hand-foot syndrome: a randomized phase III trial of the AIO quality of life working group. J Clin Oncol. 2015 Aug;33(22):2444-9.

34. Zhang RX, Lu ZH, Wan DS, Wu XJ, Ding PR, Kong LH, et al. Neuroprotective effect of neurotropin on chronic oxaliplatin-induced neurotoxicity in stage II and stage III colorectal cancer patients: results from a prospective, randomised, single-centre, pilot clinical trial. Int J Colorectal Dis. 2012 Dec;27(12):1645-50.

35. Naito M, Yamamoto T, Hara S, Shimamoto C, Miwa Y. Hemoglobin value is the most important factor in the development of hand-foot syndrome under the capecitabine regimen. Chemotherapy. 2017;62(1):23-9.

36. Zhou S, Zhang X, Song Z. Therapeutic effects and toxic side reactions of capecitabine combined with a modified prescription of Fuzheng Jiedusan (resistance strengthening and detoxification granules) on advanced gastric cancer. Biomed Res. 2017;28(5):1939-43.

37. Scontre VA, Martins JC, Sette CVM, Mutti H, Cubero D, Fonseca F, et al. Curcuma longa (turmeric) for prevention of capecitabine-induced hand-foot syndrome: a pilot study. J Diet Suppl. 2017;15(5):606-12.

38. Hennessy BT, Gauthier AM, Michaud LB, Hortobagyi G, Valero V. Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: retrospective analysis of patients treated at M. D. Anderson Cancer Center and a review of capecitabine toxicity in the literature. Ann Oncol. 2005 Aug;16(8):1289-96.

39. Rossi D, Alessandroni P, Catalano V, Giordani P, Fedeli SL, Fedeli A, et al. Safety profile and activity of lower capecitabine dose in patients with metastatic breast cancer. Clin Breast Cancer. 2007 Dec;7(11):857-60.