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Topical Diclofenac for Prevention of Capecitabine-Associated Hand-Foot Syndrome: A Double-Blind Randomized Controlled Trial

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ABSTRACT

PURPOSE Hand-foot syndrome (HFS) is a dose-limiting side effect of capecitabine. Celecoxib prevents HFS by inhibiting cyclooxygenase-2 (COX-2) that is upregulated because of the underlying associated inflammation. However, systemic side effects of celecoxib have limited routine prescription. Topical diclofenac inhibits COX-2 locally with minimal risk of systemic adverse events. Therefore, we conducted this study to assess the efficacy of topical diclofenac in the prevention of capecitabine-induced HFS.

METHODS In this single-site phase III randomized double-blind trial, we enrolled patients with breast or GI cancer who were planned to receive capecitabine-based treatment. Participants were randomly assigned in a 1:1 ratio to receive topical diclofenac or placebo gel for 12 weeks or until the development of HFS, whichever occurred earlier. The primary end point was the incidence of grade 2 or 3 HFS (Common Terminology Criteria for Adverse Events version 5), which was compared between the two groups using simple logistic regression.

RESULTS In total, 264 patients were randomly assigned to receive topical diclofenac gel (n = 131) or placebo (n = 133). Grade 2 or 3 HFS was observed in 3.8% of participants in the diclofenac group compared with 15.0% in the placebo group (absolute difference, 11.2%; 95% CI, 4.3 to 18.1; P = .003). Grade 1-3 HFS was lower in the diclofenac group than in the placebo group (6.1% *v* 18.1%; absolute risk difference, 11.9%; 95% CI, 4.1 to 19.6). Capecitabine dose reductions because of HFS were less frequent in the diclofenac group (3.8%) than in the placebo group (13.5%; absolute risk difference, 9.7%; 95% CI, 3.0 to 16.4).

CONCLUSION Topical diclofenac prevented HFS in patients receiving capecitabine. This trial supports the use of topical diclofenac to prevent capecitabine-associated HFS.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Capecitabine is extensively used in patients with breast and GI cancers.[1-6] Palmar-plantar erythrodysesthesia, also known as hand-foot syndrome (HFS), is a dose-limiting side effect of capecitabine and is characterized by painful erythema, edema, desquamation, and dysesthesias over hands and feet.[7] The incidence of HFS is highly variable, and as many as three fourths of patients receiving capecitabine develop HFS.[1,8-10] Although HFS is not life-threatening, it is associated with deterioration of the quality of life (QOL) and necessitates dose reduction of capecitabine.[11]

Several strategies have been evaluated for capecitabine-associated HFS.[12,13] Although urea-based cream is effective in preventing hand-foot skin reaction (HFSR) associated with sorafenib, its role in capecitabine-associated HFS is unclear.[14,15] The placebo-controlled trial did not demonstrate the efficacy of urea-based cream in preventing capecitabine-associated HFS; the other trial lacked a placebo control and reported superiority over an antioxidant cream (mapisal).[16,17]

Celecoxib is an effective agent to prevent HFS.[13,18] In an open-labeled randomized controlled trial of 139 patients, grade 2 or 3 HFS incidence was 14.7% with celecoxib compared with 29.6% in the control group.[18] The mechanism postulated was the inhibition of the cyclooxygenase-2 (COX-2) enzyme, which is upregulated because of underlying inflammation in HFS.[19] However, celecoxib is not

CONTEXT

Key Objective

Hand-foot syndrome (HFS) is a dose-limiting adverse event associated with capecitabine, which leads to dose reductions and impairs the quality of life (QOL). In this double-blind, placebo-controlled study, we assessed the efficacy of topical diclofenac in preventing capecitabine-associated HFS in patients with breast or GI cancer.

Knowledge Generated

Our study demonstrated that topical diclofenac application is associated with a significantly lower rate of HFS in patients with breast or GI cancer. It was also associated with a lower rate of capecitabine dose reduction and a better QOL at 12 weeks compared with placebo.

Relevance *(C. Zimmermann)*

Topical diclofenac should be considered when prescribing capecitabine-based treatment to patients with breast or GI cancer to prevent HFS. Further trials are needed to evaluate this treatment alongside other cancer treatments commonly associated with HFS.*

*Relevance section written by *JCO* Associate Editor Camilla Zimmermann, MD, PhD, FRCPC.

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widely used for this indication because of its associated safety concerns.[20,21]

Topical diclofenac gel, commonly used in osteoarthritis, acts by inhibiting the COX-2 enzyme locally with minimal systemic side effects.[22] We planned the Diclofenac Topical in Reducing Capecitabine-associated HFS (D-TORCH) study, with the hypothesis that topical diclofenac will prevent HFS.

METHODS

Study Design and Setting

The study protocol was published earlier.[23] This was an investigator-initiated, single-institution, phase III, randomized, double-blind, placebo-controlled study conducted from February 2021 to January 2023 at the All India Institute of Medical Sciences, New Delhi, India.

The trial was conducted in accordance with the amended Declaration of Helsinki and as per the Indian Council of Medical Research guidelines, and the protocol was approved by the Institutional Ethics Committee before its conduct (IECPG-82/27.01.2021). Written informed consent was obtained from all patients. The trial was prospectively registered with the Clinical Trials Registry of India (CTRI/202101/030592).

Participants and Eligibility Criteria

Patients with breast or GI cancer planned to receive capecitabine-based treatment were eligible for the study. Key exclusion criteria included preexisting skin conditions or peripheral neuropathy that could confound HFS assessment. Full eligibility criteria are available in the protocol.[23]

Random Assignment and Masking

Random assignment was stratified by sex and type of therapy (capecitabine monotherapy or combination) as previous studies reported a higher rate of HFS in females and those who received combination chemotherapy.[24,25] A computer-generated (Sealed Envelope[26]) permuted block (variable size [4-8] blocks) stratified randomization sequence was generated by the statistician to allocate participants in a 1:1 ratio to one of the four strata.

Sealed, opaque, and sequentially numbered envelopes were used in each stratum to ensure allocation concealment. An independent research staff member wrote the participant's name on the envelope that the patient subsequently opened. The alphanumeric code (eg, AA1) in the envelope was matched with a packet of gel tubes that a study nurse handed over to the patient.

Treatments

Participants received either 1% topical diclofenac (Enzoflam) or a placebo gel. Alkem Laboratories Ltd provided both gels as identical packets of 16 tubes of 30 g each, labeled a priori by the statistician.

The dose of diclofenac gel used in this study was extrapolated from osteoarthritis, where it is recommended to apply 2 g per hand up to four times per day.[22] This was a preventive trial; therefore, we empirically used 1 g diclofenac gel in each hand, applied twice daily.

Participants were instructed to apply one fingertip unit (FTU; one FTU, 0.5 g) each on the palmar and dorsal surfaces of both hands twice daily, starting concurrently with

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capecitabine for four cycles. An application period of 12 weeks was chosen because safety beyond 12 weeks has not been evaluated in osteoarthritis, and most patients develop HFS by this time point.[25,27] An investigator educated all participants about HFS and gel application (Appendix 1, online only).

End Points

The Common Terminology Criteria for Adverse Events (CTCAE) uses the term palmar-plantar erythrodysesthesia syndrome, which is also known as HFS. We have used HFS throughout the manuscript for simplicity. The CTCAE grades for HFS are defined from grades 1-3, with no grade 4 or 5 events (Appendix Table A1). We chose grade 2 or 3 HFS as the primary end point, as grade 1 is generally self-limiting, while grade 2 or 3 HFS significantly affects QOL.[28]

Secondary outcomes included the development of grade 1-3 of HFS, HFS-related dose changes of capecitabine, time to develop HFS (weeks), self-reported adherence with topical application, changes in the patient-reported outcomes using the HFS14 questionnaire from baseline to the end of the study, and adverse events.

Assessments

Participants were assessed clinically every 3 weeks for four cycles of capecitabine or until the development of grade 2 or 3 HFS, whichever occurred earlier. An investigator, blinded to treatment assignment, was trained to identify and grade the severity of HFS, and the investigator graded all patients at each clinical visit.

HFS-related QOL was assessed using the HFS14 questionnaire at baseline (after random assignment to one of the groups but before starting capecitabine) and at the development of grade 2 or 3 HFS or at 12 weeks if there was no evidence of HFS. HFS14 is a validated questionnaire specifically for patients with HFS.[28] The questionnaire contains 14 questions about activities that can be affected because of HFS. Each item was scored on a three-point Likert scale: 0, no, never; 1, yes, from time to time; 2, yes, always. The total HFS14 score was calculated by summing the scores of all items, which was adjusted to a 100-point scale. HFS14 score ranged from 0 to 100, with a higher score representing a more significant impairment of QOL.

Adherence to study medication was self-reported by patients in an adherence diary provided to the patients at random assignment.

Statistical Analysis

Descriptive statistics were used to present the baseline characteristics. Efficacy analyses included all randomly assigned patients and were conducted using the intention-to-treat principle. The primary end point was compared between the two study groups using Fisher's test. The primary outcome was reported as the absolute risk difference with 95% CIs and as an adjusted risk difference after adjusting for the stratification factors.

Regarding secondary outcomes, we did not apply any formal tests of significance to avoid multiplicity. Grade 1-3 of HFS and capecitabine dose reductions in both groups are reported as proportions and absolute risk differences with 95% CI. The widths of 95% CI were not adjusted for multiplicity; therefore, the intervals should not be used in place of hypothesis testing. Kaplan-Meier methods were used to calculate the median time to develop grade 2-3 HFS, and the Nelson-Aalen cumulative hazards graph was plotted for the two groups. The event for this analysis was defined as grade 2-3 HFS within 12 weeks. Participants who did not develop HFS until 12 weeks and those who stopped capecitabine earlier were censored at 12 weeks and at the date of stopping capecitabine, respectively. The reverse Kaplan-Meier method was used to calculate the median follow-up. Adherence was calculated by dividing the number of days patients applied topical medication by the number of days planned. The mean and standard deviation (SD) of adherence of both groups were calculated. For QOL, the mean change from baseline to development of HFS/end of the study period was calculated in both groups.

The minimum clinically important difference (MCID) was not prespecified. It was assessed post hoc using a distribution approach, wherein we calculated the pooled SD of the change in the HFS14 score in both groups. A cutoff range was taken as 0.4-0.5 SD.[29,30] Exploratory subgroup analyses were performed for sex, type of therapy, primary cancer, and performance status, using logistic regression, and the results were presented as relative risks with 95% CI.

The trial was designed to recruit 264 patients, which provided a power of at least 80% at a two-sided alpha of .05 to detect a difference of 15% in the incidence of grade 2 or 3 HFS in the two groups. For this, we assumed the grade 2 or 3 HFS rate to be 30% in the control group and 15% in the experimental group, and an attrition rate of 10%. These assumptions were made from the previously published trial of celecoxib in preventing capecitabine-induced HFS that reported 29.6% and 14.7% grade 2 or 3 HFS in placebo and celecoxib groups, respectively.[18]

The significance level was kept a priori at 0.05 (two-sided). All analyses were performed using Stata 14.0 (StataCorp, 2015. Stata Statistical Software: Release 14; StataCorp LP, College Station, TX) and R Statistical Software (v4.1.2; R Core Team 2021, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

From February 1, 2021, through September 30, 2022, 264 participants were randomly assigned to receive topical

diclofenac gel (n = 131) or placebo (n = 133; Fig 1). All participants in the study and placebo groups received the assigned treatments. At the time of efficacy analysis on January 15, 2023, the last enrolled patient completed the planned follow-up of 12 weeks. However, data of one patient randomly assigned to the study group were lost. Therefore, the final analysis was performed on 263 participants.

Baseline demographic and clinical characteristics were balanced in both groups (Table 1). Most participants were females (71.1%), and the most common diagnosis was breast cancer (56.3%). Among patients with GI cancers, the most common primary was colorectal cancer (55.6%). Overall, 58.9% received combination chemotherapy, and the remaining received capecitabine as a single agent. In the combination chemotherapy subgroup, oxaliplatin was the most common chemotherapeutic agent used with capecitabine (Appendix Table A2).

Efficacy

At the assessment cutoff of 12 weeks, 25 patients (9.5%) developed grade 2 or 3 HFS, of whom five (3.8%) were in the diclofenac group and 20 (15.0%) in the placebo group (P = .003). The absolute risk difference was 11.2% (95% CI, 4.3 to 18.1). After adjusting for stratification factors (sex and type of therapy), the adjusted risk difference was 11.3% (95% CI, 4.4 to 18.2).

Both grade 2 and grade 3 HFS were less frequent in the diclofenac group (Fig 2). In the diclofenac group, grade 2 and 3 HFS were observed in two (1.5%) and three (2.3%) patients, while in the placebo group, the distribution was 13 (9.8%) and seven (5.3%) patients, respectively.

Grade 1-3 HFS was observed in eight patients (6.1%) in the diclofenac group and 24 patients (18.1%) in the placebo

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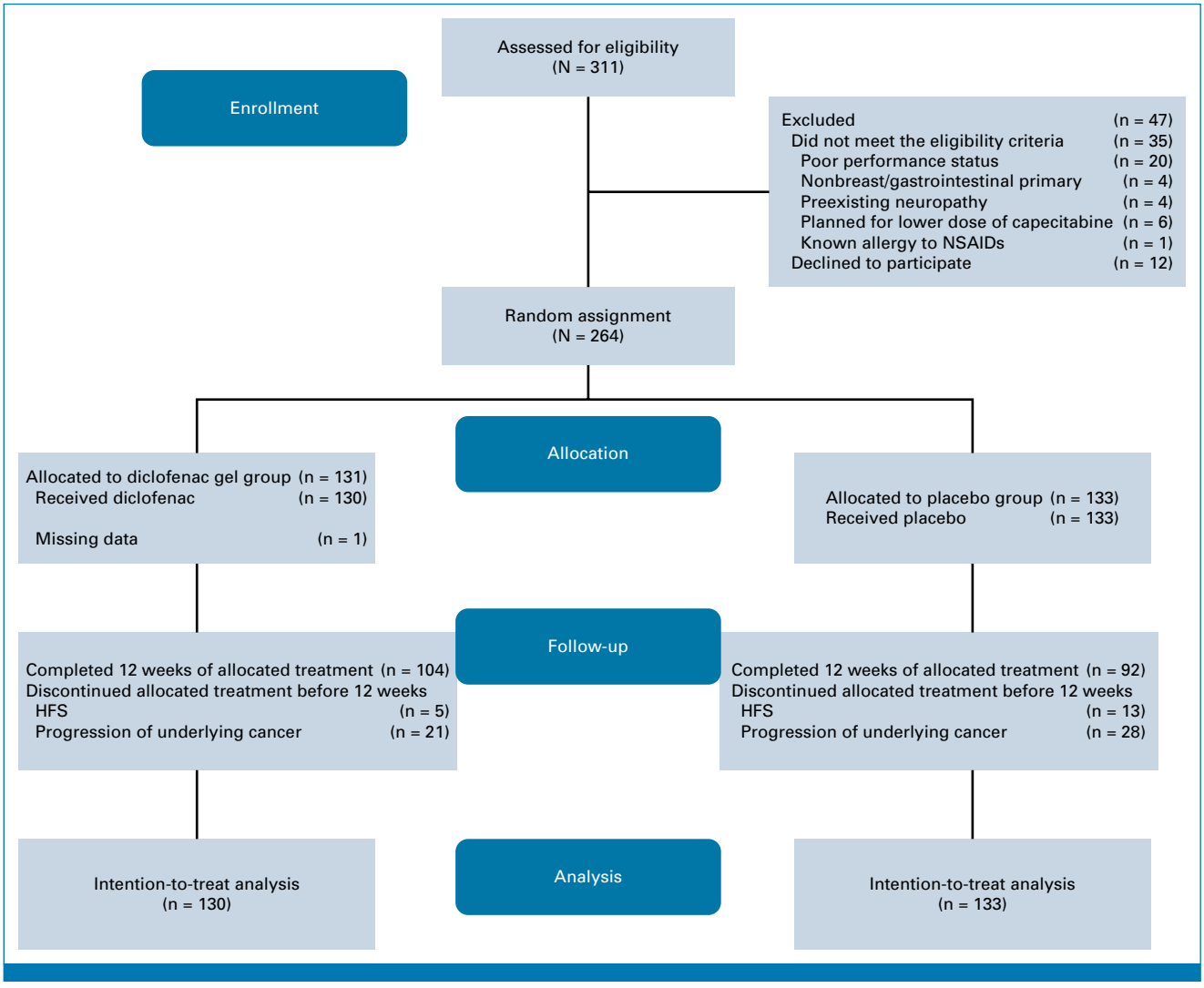

FIG 1. CONSORT diagram. HFS, hand-foot syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 1. Baseline Characteristics of Patients (N = 263)

Characteristic	All (N = 263)	Diclofenac (n = 130)	Placebo (n = 133)
Age, years, median (IQR)	47 (38-56)	47 (39-58)	47 (38-55)
Sex, No. (%)			
Female	187 (71.1)	91 (70.0)	96 (72.2)
Males	76 (28.9)	39 (30.0)	37 (27.8)
Performance status, No. (%)[a]			
0-1	164 (62.4)	84 (64.6)	80 (60.2)
2	99 (37.6)	46 (35.4)	53 (39.8)
Type of therapy, No. (%)			
Monotherapy	108 (41.1)	56 (43.1)	52 (39.1)
Combination	155 (58.9)	74 (56.9)	81 (60.9)
Dose of capecitabine, mg/m^2, mean (SD)	1,881.2 (186.5)	1,882.2 (197.0)	1,880.2 (176.5)
Type of cancer, No. (%)			
Breast	148 (56.3)	77 (59.2)	71 (53.4)
GI	115 (43.7)	53 (40.8)	62 (46.6)
Previous chemotherapy, No. (%)			
Received	98 (37.3)	53 (40.8)	45 (33.8)
Not received	165 (62.7)	77 (59.2)	88 (66.2)
Stage of cancer, No. (%)			
II	4 (1.5)	2 (1.5)	2 (1.5)
III	126 (47.9)	61 (46.9)	65 (48.9)
IV	132 (50.2)	67 (51.5)	65 (48.9)
Unknown	1 (0.4)	—	1 (0.7)
HFS14 score, mean	0	0	0

NOTE. Percentages may not total 100 because of rounding.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.
[a]Performance status was assessed by the ECOG performance status scale of 0-4.

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group (absolute risk difference, 11.9%; 95% CI, 4.1 to 19.6; Appendix Table A3).

Capecitabine dose reduction because of HFS was less frequent in the diclofenac group than in the placebo group (3.8% *v* 13.5%; absolute risk difference, 9.7%; 95% CI, 3.0 to 16.4). Overall, the dose of capecitabine was reduced in 21 patients (16.2%) in the diclofenac group compared with 41 patients (30.8%) in the placebo group (absolute risk difference, 14.7%; 95% CI, 4.6 to 24.7; Appendix Table A4).

The median follow-up period for the study participants was 12 weeks from random assignment, and the median time to develop HFS was not reached in both groups. The median time to detection of grade 2-3 HFS was 6 weeks (95% CI, 3 weeks to not reached) in the diclofenac group and 9 weeks (95% CI, 6 to 9 weeks) from random assignment to the respective group (Appendix Table A5). Cumulative hazard plots are shown in Appendix Figure A1. Adherence was over 90% in both the groups (mean ± SD, 96.7% ± 19.1% and 94.0% ± 28.3% in the diclofenac and placebo groups, respectively; Appendix Fig A2).

The HFS14 questionnaire was completed at baseline and the end of the study period by 110 patients (84.6%) in the diclofenac group and 106 patients (79.7%) in the placebo group. A higher score on the HFS14 tool indicates a worse HFS-related QOL. The mean increase in the HFS14 score was lower in the diclofenac group than in the placebo group (3.5 points *v* 12.4 points; difference, −8.9 points; 95% CI, −14.4 to −3.3; Appendix Fig A3). The MCID using the distribution approach for 0.4-0.5 SD was 8.2-10.2. This suggests a clinically meaningful difference in the HFS-related QOL.

Exploratory Analysis

In men, 2.6% of patients developed grade 2 or 3 HFS in the diclofenac group compared with 13.5% in the placebo group. In women, the corresponding percentages were 4.4% and 15.6%, respectively. In patients who received capecitabine monotherapy, 3.6% in the diclofenac group developed grade 2 or 3 HFS compared with 19.2% in the placebo group. The corresponding numbers for patients who received combination chemotherapy were 4.0% and 12.3%, respectively (Appendix Table A6).

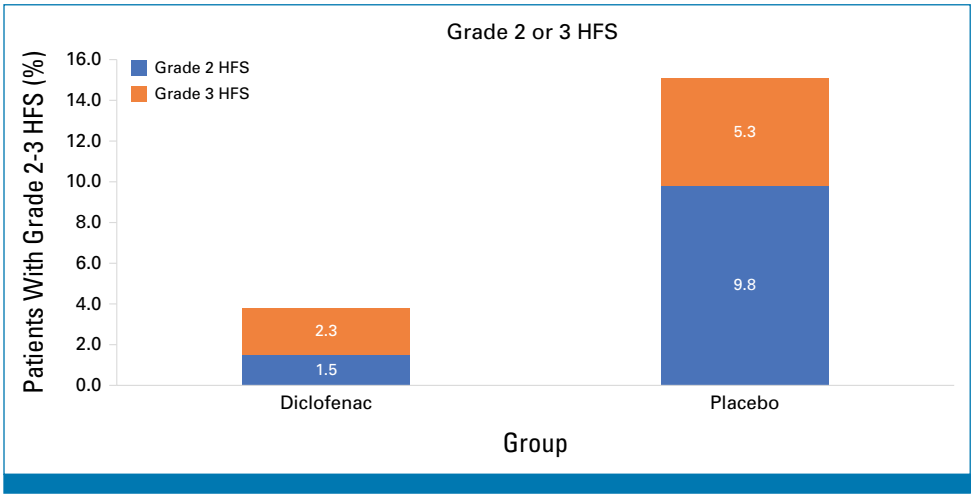

FIG 2. Grade 2 or 3 HFS within 12 weeks. HFS, hand-foot syndrome.

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There was no interaction between sex, type of chemotherapy, performance status, and primary cancer on the effect of diclofenac in preventing HFS (Fig 3).

Adverse Events

Overall, 132 patients (50.2%) reported adverse events of any grade during the study period. There were 64 (49.2%) and 68 (51.1%) patients who reported adverse events in the diclofenac and placebo groups, respectively (Table 2). Grade 3 adverse events were reported in 11.5% and 13.5% of patients in the diclofenac and placebo groups, respectively. The most common adverse event was mucositis, whereas the most common grade 3 adverse event was diarrhea in both groups. Capecitabine was discontinued in six patients (4.6%) in the diclofenac group and 11 patients (8.3%) in the placebo group after two cycles because of the progression (Appendix Table A7). Likewise, 15 (11.5%) and 17 (12.8%) patients discontinued capecitabine after the third cycle. No patient discontinued capecitabine because of adverse events. No cardiovascular events were reported.

There were five deaths in the study: one in the diclofenac group and four in the placebo group. The death in the diclofenac group was due to intracranial bleeding. In the placebo group, one death was due to febrile neutropenia and refractory septic shock, one due to diabetic ketoacidosis, and two due to cancer progression.

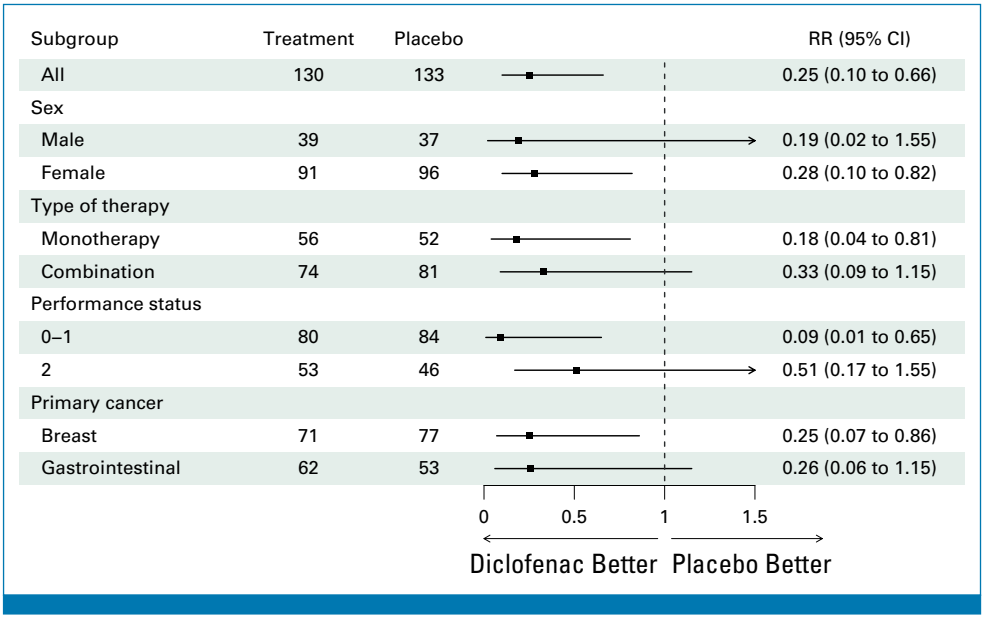

FIG 3. Forest plot showing subgroup analysis. RR, relative risk.

TABLE 2. Adverse Events in the Diclofenac and Placebo Groups

	Diclofenac (n = 130), No. (%)				Placebo (n = 133), No. (%)			
Adverse Event	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
Any event	64 (49.2)	6 (4.6)	43 (33.1)	15 (11.5)	68 (51.1)	6 (4.5)	44 (33.1)	18 (13.5)
Diarrhea	33 (25.3)	2 (1.5)	21 (16.1)	10 (7.7)	37 (27.8)	0	27 (20.3)	10 (7.5)
Mucositis	42 (32.3)	5 (3.8)	33 (25.4)	4 (3.1)	44 (33.1)	6 (4.5)	30 (22.6)	8 (6.0)
Myelosuppression	3 (2.3)	0	1 (0.8)	2 (1.5)	6 (4.5)	1 (0.7)	5 (3.8)	0

DISCUSSION

In the D-TORCH trial, we found that topical diclofenac was significantly associated with lower grade 2 or 3 HFS rates. This was associated with less frequent dose reductions of capecitabine and a better HFS-related QOL.

The absolute risk reduction for grade 2 or 3 HFS was 11.2%; therefore, the number needed to prevent one event was approximately 9. The absolute reduction is similar to that reported in the oral celecoxib study (29.6% *v* 14.7%).[18] We did not find any safety issues with topical diclofenac, and it has been used in patients with osteoarthritis for more than two decades without any significant safety signals.[22] The duration of use in our study was limited to 12 weeks, as most patients develop HFS by this time.[25,27]

Although capecitabine is extensively used in oncology and HFS leads to dose reduction and permanent discontinuation in up to 26% and 10%, respectively, there is no standard prophylactic measure to prevent HFS.[31,32] Two recently published meta-analyses concluded that celecoxib is the only effective preventive measure. However, celecoxib has not been clinically adopted for HFS prevention because of concerns regarding cardiac and GI side effects.[20] Pyridoxine has failed to prevent HFS in several studies.[9,12,13,33] Although some institutions use urea-based cream as a prophylactic measure with capecitabine, its efficacy has been demonstrated only in clinical trials assessing HFSR associated with vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI).[14,15] Whether diclofenac is effective in VEGF TKI-associated HFSR is not currently known. However, it is unlikely to be effective, as the mechanism of HFSR is distinct from capecitabine-associated HFS.[34]

Most secondary outcomes aligned and suggested the efficacy of topical diclofenac. The incidence of grade 1-3 HFS was lower with diclofenac, although most of the effect was attributed to the reduction in grade 2 or 3 HFS. This was associated with a lower deterioration in HFS-related QOL in patients who applied topical diclofenac. Counterintuitively, the median time from random assignment to development of grade 2-3 HFS was shorter in the diclofenac group compared with the placebo group. We believe that this is a chance finding because of a low number of events observed in the diclofenac group. Notably, patients required less frequent dose reductions of capecitabine, which may potentially improve cancer outcomes. We did not assess outcomes of underlying cancer as the study duration was short, and this was not defined as an objective of the study.

The proportion of patients who developed grade 2 or 3 HFS in the control group was less than our assumption and lower than previously reported rates, ranging from 22% to 77%.[1,35-39] This may be attributed to the moisturizing effect of the gel base used as a placebo and general education of patients regarding HFS and its prevention. Furthermore, the median dose of capecitabine was <2,000 mg/m² divided in twice a day dose in both groups. However, the treating physician decided this, and the study investigators had no role in prescribing the capecitabine dose.

The study had a few limitations, including this being a single-center study. The dose of topical diclofenac used in this study was empirically halved of that used in osteoarthritis. Diclofenac application and HFS assessment were limited to hands in our study. Capecitabine-associated HFS is more common in hands because of a high concentration of thymidine phosphorylase in palms, the enzyme responsible for the conversion of capecitabine to its active form, fluorouracil, postulated in the pathophysiology of HFS.[40] We lost data of one patient after random assignment to the diclofenac group; therefore, the final analysis was performed on 263 patients. This resulted in having one fewer patient than the recommended sample size (n = 264). We did not assess participants for the development of HFS beyond 12 weeks. Despite these limitations, diclofenac had a significant effect in reducing the incidence of HFS.

In the D-TORCH study, topical diclofenac gel significantly reduced the incidence of HFS in patients receiving oral capecitabine for breast and GI malignancies compared with placebo. Therefore, we recommend topical diclofenac gel as the new standard of care to prevent HFS in this patient population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Topical Diclofenac for Prevention of Capecitabine-Associated Hand-Foot Syndrome: A Double-Blind Randomized Controlled Trial

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APPENDIX 1. SUPPLEMENTARY METHODS

Inclusion Criteria

1. Age 18 years and older
2. Starting capecitabine for breast and GI malignancies, either in adjuvant/neoadjuvant or palliative setting
3. Commencing capecitabine at a planned dose of ≥1,000 mg/m^2 twice daily every 2 of 3 weeks as single-agent chemotherapy or in combination with other systemic therapy
4. Life expectancy >12 weeks
5. Eastern Cooperative Oncology Group performance status 0-2
6. Study treatment both planned and able to start within 14 days of random assignment
7. Willing and able to comply with all study requirements, including treatment (applying diclofenac gel), timing, and/or nature of required assessments
8. Signed, written informed consent

Exclusion Criteria

1. Preexisting grade 2 or higher neuropathy confounding assessment of hand-foot syndrome
2. Other dermatologic condition, that, in the opinion of the physician, may affect the hands or feet or may complicate evaluation during study treatment
3. Concurrent or planned use of pyridoxine
4. Allergy or anaphylactic reactions with nonsteroidal anti-inflammatory drugs (NSAIDs)
5. History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs
6. Patients receiving oral or topical NSAIDs for other conditions
7. Concurrent illness, including severe infection that may jeopardize the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety.
8. Serious medical or psychiatric conditions that might limit the ability of the patient to comply with the protocol.
9. Pregnant or lactating women

Detailed Instructions for Gel Application

Store the gel tubes in the packet at room temperature 20°C-25°C. Do not freeze.

When you want to use a new tube of gel for the first time, open the seal that covers the tube opening by using the spiked top of the cap.

Apply the gel to clean, dry skin of both hands on both the palmar and dorsal surfaces that do not have any cuts, open wounds, infections, or rashes. Use one-fingertip unit for each side of the hand.

Do not use heating pads or apply bandages to where you have applied the gel.

Avoid exposing skin where you apply the gel to sunlight and artificial light, such as tanning booths. Do not use sunscreens, cosmetics, lotions, creams, insect repellants, or other topical medicines on the same skin areas where you have applied the gel.

Do not get the gel in your eyes, nose, or mouth. The gel is only to be used on your skin (topical use). If you get the gel in your eyes, rinse your eyes right away with water or saline. Talk with your health care provider if eye irritation lasts for more than 1 hour.

APPENDIX 2.

TABLE A1. NCI CTCAE Grading of Hand-Foot Syndrome

NCI Grade	Description
Grade 1	Minimal skin changes or dermatitis (redness, swelling, hyperkeratosis) without pain
Grade 2	Skin changes (peeling, blisters, bleeding, fissures, swelling, hyperkeratosis) with pain, limiting instrumental ADL
Grade 3	Severe skin changes (peeling, blisters, bleeding, fissures, swelling, hyperkeratosis) with pain. Limiting self-care ADL

Abbreviations: ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

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TABLE A2. Additional Baseline Characteristics of Patients (N = 263)

Characteristic	All (N = 263), No. (%)	Diclofenac (n = 130), No. (%)	Placebo (n = 133), No. (%)
Additional chemotherapeutic agent used[a]			
Oxaliplatin	93 (60.0)	39 (52.7)	54 (66.7)
Vinorelbine	11 (7.1)	3 (4.1)	8 (9.9)
Lapatinib	42 (27.1)	25 (33.8)	17 (21.0)
Gemcitabine	8 (5.2)	6 (8.1)	2 (2.5)
Irinotecan	1 (0.6)	1 (1.3)	0
Type of GI cancer[b]			
Colorectal	64 (55.6)	27 (50.9)	37 (59.7)
Stomach	18 (15.6)	8 (15.1)	10 (16.1)
Pancreas/periampullary	14 (12.2)	10 (18.9)	4 (6.4)
Gallbladder	6 (5.2)	4 (7.5)	2 (3.2)
Esophagus	3 (2.6)	0	3 (4.8)
Urachal	4 (3.5)	1 (1.9)	3 (4.8)
Pseudomyxoma peritonei	6 (5.2)	3 (5.7)	3 (4.8)
Comorbidities			
Nil	147 (55.9)	71 (54.6)	76 (57.1)
Diabetes	36 (13.7)	21 (16.1)	15 (11.3)
Hypertension	46 (17.5)	21 (16.1)	25 (18.8)
Hypothyroidism	34 (12.9)	17 (13.1)	17 (12.8)

NOTE. Percentages may not total 100 because of rounding.
[a]n = 155 (combination chemotherapy); diclofenac group (n = 74), placebo group (n = 81).
[b]n = 115 (GI cancers); diclofenac group (n = 53), placebo group (n = 62).

TABLE A3. Distribution of Grades of HFS

HFS	Diclofenac Arm (n = 130), No. (%)	Placebo Arm (n = 133), No. (%)
Grade 0	122 (93.8)	109 (81.9)
Grade 1	3 (2.3)	4 (3.0)
Grade 2	2 (1.5)	13 (9.8)
Grade 3	3 (2.3)	7 (5.3)

Abbreviation: HFS, hand-foot syndrome.

TABLE A4. Causes of Capecitabine Dose Reduction

Cause of Dose Reduction	Diclofenac Arm (n = 130), No. (%)	Placebo Arm (n = 133), No. (%)
No dose reduction	109 (83.8)	92 (69.2)
Hand-foot syndrome	5 (3.8)	18 (13.5)
Mucositis	5 (3.8)	10 (7.5)
Diarrhea	8 (6.1)	8 (6.0)
Myelosuppression	3 (2.3)	5 (3.8)

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TABLE A5. Time of Development of HFS

Time Point	Diclofenac Arm		Placebo Arm	
	Grade 1-3 (n = 8)	Grade 2/3 (n = 5) (Grade 2+ Grade 3)	Grade 1-3 (n = 24)	Grade 2/3 (n = 20) (Grade 2+ Grade 3)
3 weeks			2	1
6 weeks	4	3 (1 + 2)	6	5 (2 + 3)
9 weeks	4	2 (1 + 1)	8	7 (5 + 2)
12 weeks	—		8	7 (6 + 1)

Abbreviation: HFS, hand-foot syndrome.

TABLE A6. Subgroup Analysis by Sex and Type of Therapy

Subgroup	Absolute Risk Difference in Incidence of Grade 2 or Higher HFS, %	95% CI
Sex		
Male (n = 76)	10.9	1.1 to 23.0
Female (n = 187)	11.2	2.8 to 19.6
Type of therapy		
Monotherapy (n = 108)	15.6	3.9 to 27.4
Combination (n = 155)	8.2	0.2 to 16.7

Abbreviation: HFS, hand-foot syndrome.

TABLE A7. Total Number of Capecitabine Cycles Completed by Patients in the Study

No. of Cycles	Diclofenac Arm (n = 130), No. (%)	Placebo Arm (n = 133), No. (%)
1	0	1 (0.8)
2	9 (6.9)	16 (12.0)
3	17 (13.1)	24 (18.0)
4	104 (80.0)	92 (69.2)

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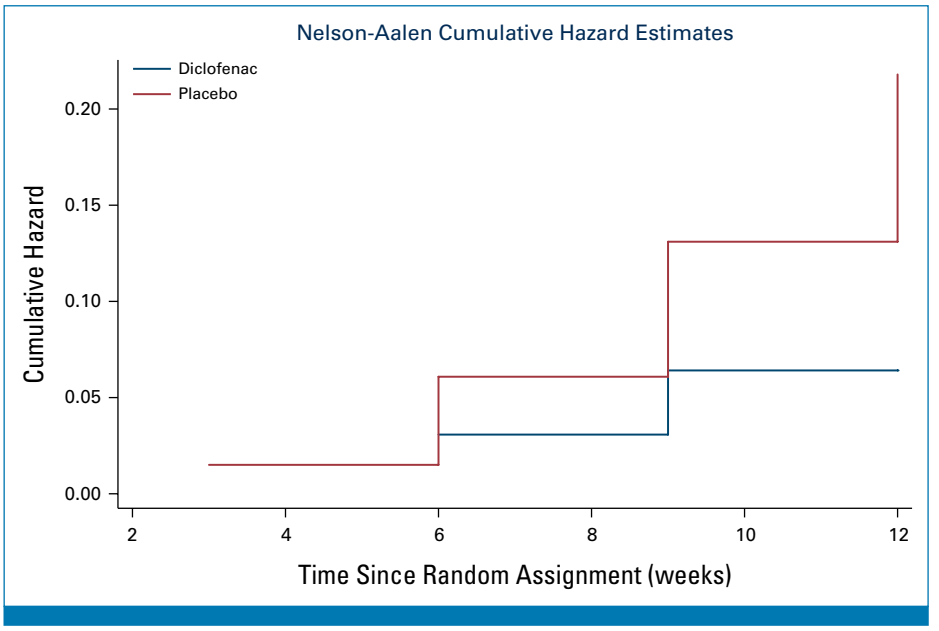

FIG A1. Cumulative hazard estimates of developing grade 1-3 hand-foot syndrome in the diclofenac arm and placebo arm.

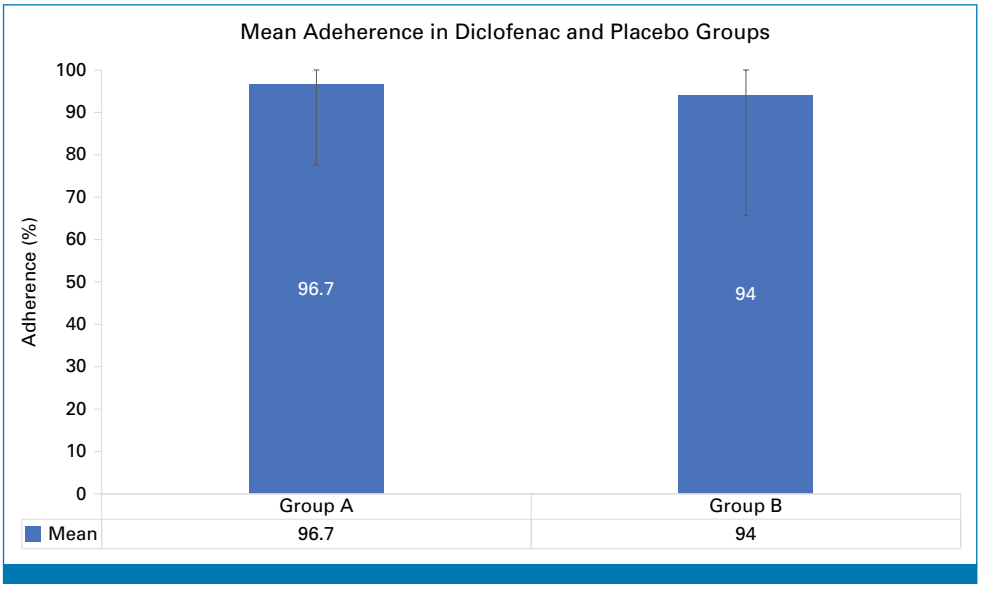

FIG A2. Self-reported adherence for diclofenac and placebo gel.

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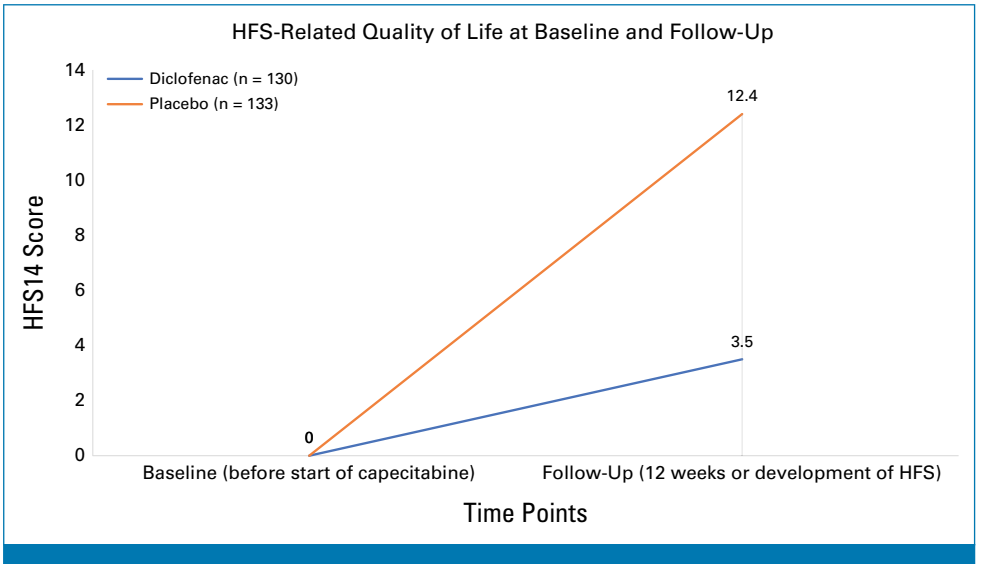

FIG A3. HFS14 score at baseline and at 12 weeks or development of HFS. HFS, hand-foot syndrome.

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