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The Efficacy and Safety of Captopril in Preventing Capecitabine-induced Hand-foot Syndrome: A Randomized Double-blinded Placebo-controlled Clinical Trial

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Abstract

Background: Hand-foot syndrome (HFS) is a prevalent skin reaction to cytotoxic systemic therapy, mainly Capecitabine.

The present study aimed to determine etiologies of HFS in addition to its prevention in colorectal cancer patients with Capecitabine-containing chemotherapy regimen.

Method: In this randomized double-blinded study, we recruited 66 eligible patients. The first 33 patients received 25 mg captopril twice daily, while the other 33 were given two placebo tablets.

Results: All the patients were assessable for safety and efficacy. Captopril demonstrated a favorable safety profile. The participants in the two groups did not have any significant differences in terms of the median age and the level of hemoglobin ($P = 0.45$, $P = 0.06$, respectively). However, the CEA tumor marker was significantly higher in those with HFS ($P < 0.05$). The incidence of HFS in men and women were 8 (18.6%) and 3 (13%) cases, respectively, and the patients' sex did not affect the incidence of this syndrome ($P = 0.73$).

Furthermore, according to the stage of colorectal cancer, the difference between the two groups was significant ($P < 0.05$). Meanwhile, there were no significant differences concerning the grade of colorectal cancer ($P = 0.2$).

Conclusion: The results herein revealed that administration of captopril in colorectal cancer patients with Capecitabine-containing chemotherapy regimen reduced the symptoms and incidence of HFS.

On the other hand, CEA tumor marker and the stage of colorectal cancer were in correlation with incidence of HFS.

Keywords: Hand-foot syndrome, Capecitabine, Captopril

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Introduction

Hand-foot syndrome (HFS) is also known as palmar-plantar erythrodysesthesia syndrome, acral erythema, Burgdorf's syndrome, and more recently, grouped with the so-called toxic erythema of chemotherapy syndromes. It is a relatively prevalent skin reaction to chemotherapy.[1]

This syndrome is a common side-effect of several chemotherapy drugs, including Capecitabine.[2, 3]

Capecitabine, an oral prodrug of 5-fluorouracil, is a chemotherapeutic often used for the treatment of breast and colorectal cancers. This drug is usually well-tolerated owing to the absence of systemic 5-FU exposure. Nonetheless, a substantial proportion of patients suffer from one of several severe adverse drug reactions (ADRs), with the most prevalent being HFS; it is the most common adverse event of Capecitabine-containing chemotherapy, any grade of which was reported to affect 43 to 71% of the patients treated with single-agent Capecitabine chemotherapy.[4-6]

The onset of HFS can range from within 24 hours to 10 months of the initiation of chemotherapy, but Capecitabine-related HFS usually appears within the first three cycles of treatment.[7]

After the commencement of therapy, patients first experience palmoplantar dysesthesia and tingling in the hands and feet, which usually appear 2-12 days following the administration of chemotherapy. These symptoms may progress, 3-4 days later, into symmetrical demarcated edema and erythema of the palms and soles. Erythematous plaques with violaceous and edematous patches in the palms, soles, and other high-pressure areas are usually mild and resolve in 1-2 weeks. HFS; however, may evolve into blistering desquamation, crusting, ulceration, and epidermal necrosis, if the next chemotherapy cycle is not delayed or the dose is reduced (Figure 1).[8]

The spectrum of HFS symptoms can be mild, with erythema of the distal extremities, or severe enough to interfere with routine activities. These symptoms may occur on several body surfaces, especially in areas where pressure or increased warmth occur.[8]

Research reported the factors related to HFS incidence to be the hemoglobin levels with a 12 mg / dl cut-off, which is significantly associated with this syndrome.[9] Other HFS-associated causes in other studies are age, sex, performance status ECOG, number and location of metastasis, findings of physical examination, the cancer type,

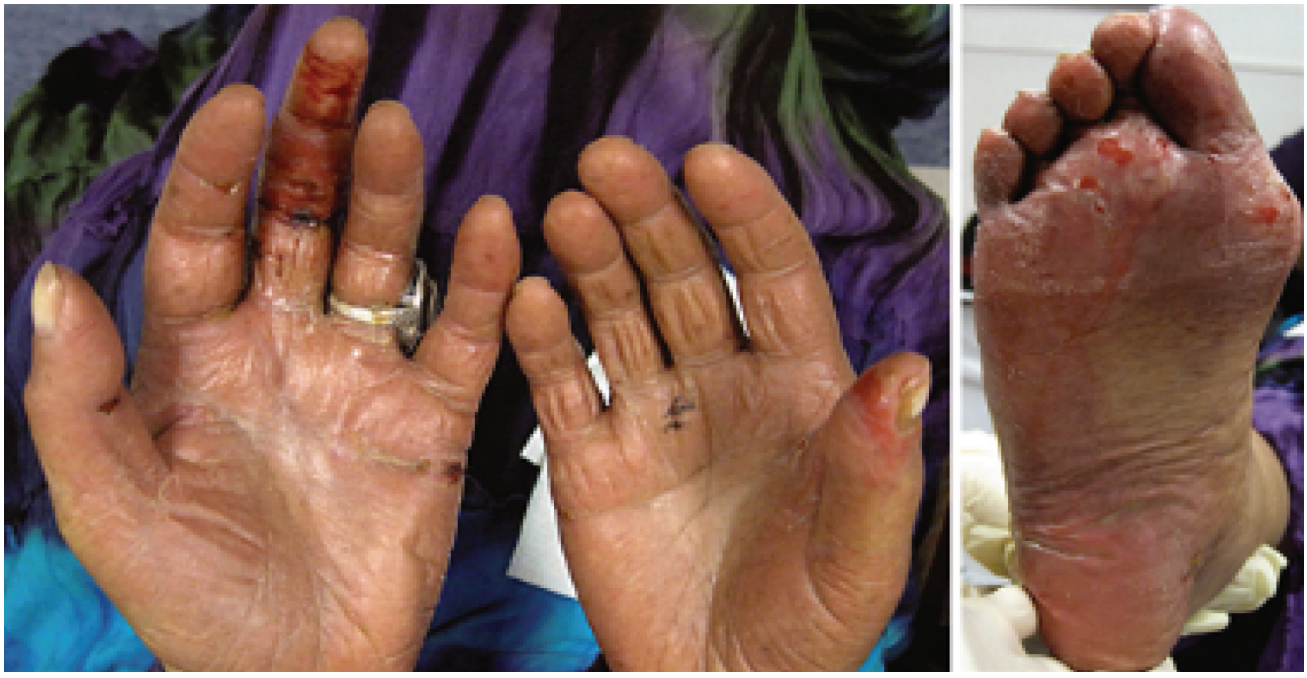

Figure 1. This figure shows the diffuse erythema and fissuring of the palms with focal erosions on the fingers (A) and the right foot (B).

Table 1. Grading of palmar-plantar erythrodysesthesia syndrome (HFS) according to the CTCAEv5.0

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

HFS: Hand-foot syndrome; ADL: Active daily living

and the previous occurrence of stomatitis caused by chemotherapy.[10]

HFS is unknown in its pathogenesis, although chemotherapeutic agents are thought to be the most likely mechanism. According to a number of authors, these medications contribute to local damages to the sweat ducts. In addition, HFS may be related to enzymes involved in Capecitabine metabolism, including thymidine phosphorylase and dihydropyrimidine dehydrogenase, causing inflammatory changes in the feet and palms. COX-2/PGES/EP signaling is involved in the inflammatory response. During day-to-day activities, mechanical pressure on the hands and feet may also lead to toxic skin damage through capillary damage.[11-13]

Of note, although HFS is non-life-threatening, it could often significantly affect a patient's quality of life (QoL); therefore, requiring therapeutic modifications or even discontinuation of treatments. The dose interruptions and reductions required after observation of HFS can also impact the dose intensity and treatment outcomes.[14,15]

No effective methods have been yet established for HFS treatment, but the following measures can be considered: an early diagnosis, modification of dose or dosing intervals, supportive measures, including cooling methods, wearing loose-fitting clothes, and using topical agents, such as potent topical steroids and emollients, lotions, and moisturizing creams occasionally, to reduce pain and discomfort and protect against infections. When extreme, HFS may necessitate cessation of therapy.[16-19]

In this study, we hypothesized that according to the anti-inflammatory properties, prescribing ACEIs, including captopril, can be accompanied by a reduction in HFS in colorectal cancer patients with Capecitabine-containing chemotherapy regimen (articles about this relation are mentioned in the discussion section).[20, 21]

Materials and Methods

This study is a randomized double-blinded placebo-controlled study, conducted in an academic center affiliated to “Blinded for peer review” from 2016 to 2018. The population included colorectal cancer patients with Capecitabine-containing chemotherapy regimen (only CAPEOX regimen in this study). The exclusion criteria were patient's dissatisfaction with participation in the study, allergic reactions to captopril or other ACEIs, an age of over 75, patients with hypertension or those using other antihypertensive or drugs that have interaction with ACEIs (including second generation antipsychotic, barbiturate, Allopurinol, Ciprofloxacin, Imatinib, Temsirolimus, Denosomab, systemic diclophenac, phenytoin, warfarin), and a history of metabolic disease (diabetes, renal disease).

The design protocol was approved by the University Ethics Committee (IR.MUI.MED.REC.1397.025) and Iranian Registry of Clinical Trials (IRCTID: IRCT20130311012782N50). Informed consent was obtained from the patients prior to their participation.

We estimated the sample size as 66 patients, with a 95% confidence interval, considering the first target with the formula of mean estimation ($n = (z \hat{} 2 \llbracket SD \rrbracket \hat{} 2) / d \hat{} 2$) according to the results of Gressett et al. The sampling method was simple and 66 patients were distributed via random allocation software in two groups of 33, namely captopril and placebo groups. Figure 2 illustrates these results.

The method of blinding was as follows: The medication was prescribed by an examiner, and the patients’ treatment and examination were done by another doctor who was unaware of the prescribed medication. The participants were also unaware of the type of medication they received.

After obtaining a license from the College of

Medical Ethics, the patients were assigned randomly to groups A or B. Group A was given 25 mg captopril twice daily, while Group B was given two placebo tablets with similar forms and doses to captopril 25 mg tablets, from one week before the beginning of the treatment until the completion of the third course of chemotherapy.

The chemotherapy regimen was used for all the participants as a CAPEOX regimen with a dose of 130 mg per meter squared of Oxaliplatin on day 1 and the mean cumulative dose of 1000 mg per meter squared of Capecitabine twice a day from day 1 to 14, every 21 days for six months (or eight cycles).

All the patients were examined three and six weeks after the beginning of the treatment and four weeks following the completion of the third course of chemotherapy. The incidence and severity of HFS, sex, age, hemoglobin level, CEA tumor marker, as well as grade and stage of

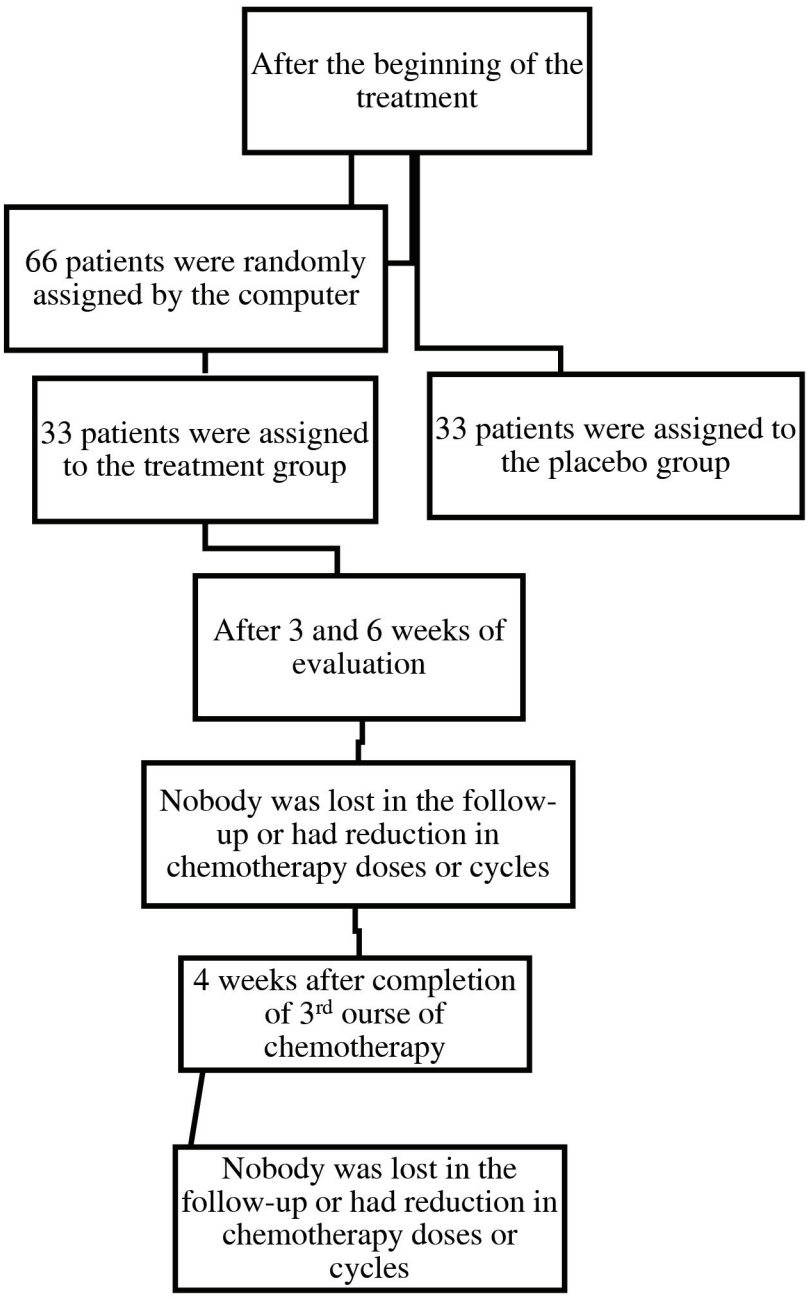

Figure 2. 66 patients were distributed in two groups of 33 patients, namely captopril and placebo groups, via random allocation software.

Table 2. Patients' characteristics

Characteristic	Captopril group (n=33) No.	% score SD	Placebo group (n=33) No.	% score SD	*P* value
Mean age years	59.9 ± 8.9		62.7 ± 10.1		0.24
Sex					0.2
Male	19	57.6	24	72.7	
Female	14	42.4	9	27.3	
Colorectal cancer grade					0.47
Good Diff.	5	15.2	7	21.2	
Moderate Diff.	19	57.6	14	42.4	
Poor Diff.	9	27.3	12	36.4	
Colorectal cancer stage					0.48
Stage2	4	12.5	6	18.2	
Stage3	28	87.5	26	78.8	
Stage4	0	0	1	3	
Hemoglobin level	12.69 ± 1.28		12.74 ± 1.25		0.88

SD: Standard deviation; Diff.: Differentiation

colorectal cancer were determined and recorded.

During the treatment, they were also questioned concerning the common side-effects of captopril, including hypertension, dizziness, dry cough, frequency, nucturia, nausea, vomiting, and diarrhea; no cases were observed.

Evaluation of HFS incidence and severity was carried out via CTCAE criteria version 5.0 that is based on clinical examination and skin symptoms distributed in three degrees (Table 1).

The data were finally entered into SPSS 21 software and analyzed using frequency tables, graphs, and mean and standard deviation indices. Pearson or Spearman correlation coefficients were utilized for determination of the relationship between HFS incidence and other variables. Through the use of independent t-test or Mann-Whitney test, we compared the quantitative and ranking data between the two groups. Vertical linear models were used for controlling the confounding variables. A *P* value of less than 0.05 was considered to be significant.

Results

In this study, 66 colorectal cancer patients with Capecitabine-containing chemotherapy regimen were distributed in two groups of 33 subjects. The first (captopril) and second (placebo) groups received 50 mg of captopril daily with similar forms and doses to captopril from one week before the beginning of the treatment until the completion of the third course of chemotherapy. The patients in both groups were evaluated for the incidence of HFS, CEA tumor marker, level of hemoglobin, sex, age, as well as the stage and grade of colorectal cancer.

They both had a mean age of 61.3 ± 9.6 years (37-84 years). In this study, there were 43 (65.2%) male and 23 (34.8%) female patients.

Colorectal cancer grade was found to be well-differentiated in 12 (18.2%), moderately-differentiated in 33 (50 %), and poorly-differentiated in 21 cases (31.8%). We found that 11 patients (16.7 %) were at colorectal cancer stage 2, 54 (81.8 %) at stage 3, and 1 (1.5 %) at stage 4. Table 2 lists the individual queried symptoms.

HFS prevalence of the first and seconds groups was respectively three and five cases (9.1% vs. 15.2%) 6 weeks after the beginning of the treatment ($P = 0.45$), and two and eight cases, 4 weeks after the completion of the third course of chemotherapy (6.1% vs. 24.2%) ($P = 0.039$).

HFS incidence, based on other variables, indicated that the patients in the groups did not have any significant differences in terms of the mean age and level of hemoglobin ($P = 0.45$ and $P = 0.06$, respectively). However, CEA tumor marker was significantly higher in the patients with HFS ($P = 0.001$).

HFS severity was not significantly different between the two groups ($P = 0.07$). Table 3 represents the results.

HFS incidence in men and women were eight

Table 3. Incidence and severity of HFS in the two groups

HFS	Captopril group (n=33) No.	%	score	SD	Placebo group (n=33) No.	%	score	SD	*P* value
Incidence(time)									
Three weeks after the beginning of the treatment	0		0		0		0		*
6 weeks after the beginning of the treatment	3		9.1		5		5.2		0.45
4 weeks after the completion of the third course of chemotherapy	2		6.1		8		24.2		0.039
Severity(time)									
Three weeks after the beginning of the treatment									**1**
None	33		100		33		100		
Mild	0		0		0		0		
Moderate	0		0		0		0		
Severe	0		0		0		0		
6 weeks after the beginning of the treatment									**0.45**
None	30		90.9		28		84.8		
Mild	3		9.1		5		15.2		
Moderate	0		0		0		0		
Severe	0		0		0		0		
4 weeks after the completion of the third course of chemotherapy									**0.07**
None	31		93.9		25		75.8		
Mild	2		6.1		3		9.1		
Moderate	0		0		5		15.2		
Severe	0		0		0		0		

HFS: Hand-foot syndrome; SD: Standard deviation

(18.6%) and three (13%) cases, respectively; thus, the patients' sex did not affect the incidence of this syndrome ($P = 0.73$).

Moreover, concerning the stage of colorectal cancer, the difference between the two groups was significant ($P = 0.044$). Nonetheless, there were no significant differences in terms of the grade of colorectal cancer ($P = 0.2$). Table 4 demonstrates the results about these parameters.

There were not any captopril-related side-effects in the two study groups and everyone tolerated captopril drug.

Discussion

There is no article about captopril efficacy in prevention of HFS, but herein, we hypothesized that according to the anti-inflammatory properties, prescribing ACEIs, including captopril, can be accompanied by a reduction in HFS in colorectal cancer patients with Capecitabine-containing chemotherapy regimen.[22, 23]

HFS is unknown in its pathogenesis although chemotherapeutic agents are thought to be the most likely mechanism. According to certain authors, these medications contribute to the symptomatology of the disease by causing local damages to the sweat ducts, which explains how they are distributed anatomically. In addition, HFS may be related to the enzymes involved in Capecitabine metabolism, including thymidine phosphorylase and dihydropyrimidine dehydrogenase, causing inflammatory changes in the feet and palms. COX-2/PGES/EP signaling is involved in the inflammatory response. During day-to-day activities, mechanical pressure on the hands and feet may also lead to toxic skin damage through capillary damage.[12-14]

According to the guidelines of ACC-AHA, from 2005 to date, patients with coronary artery diseases (and other vascular diseases) have been recommended to use ACEIs (including captopril) to reduce the risk of cardiovascular accidents. Additionally, Hirsch. et al. showed in their trial that endothelial dysfunction is an initial step towards physiological development. They also demonstrated that hypertension leads to endothelial dysfunction, with the result that treatment with ACEI drugs caused the alleviation of endothelial dysfunction.[22]

Yusuf et al. reported hypertension as one of the major risk factors for the development of diabetic retinopathy, and that ACEI drugs have

Table 4. HFS incidence based on the demographic characteristics

HFS	Yes		No		*P* value
Suffering	**No.**	**% score SD**	**No.**	**% score SD**	
Colorectal cancer grade					**0.2**
Good Diff.	4	36.4	8	14.5	
Moderate Diff.	5	45.5	28	50.9	
Poor Diff.	2	18.2	19	34.5	
Colorectal cancer stage					**0.044**
Stage 2	0	0	11	20	
Stage 3	10	90.9	44	80	
Stage 4	1	9.1	0	0	
Sex					**0.73**
Male	8	72.7	35	63.6	
Female	3	27.3	20	36.4	
Mean age (years)	59.3 ± 9.6		61.7 ± 9.6		**0.45**
Hemoglobin level	12.06 ± 1.1		12.58 ± 1.25		**0.06**
CEA tumor marker	19.15 ± 5.51		12.04 ± 6.1		**0.001**

HFS: Hand-foot syndrome; CEA tumor marker: Carcinoembryonic antigen; SD: Standard deviation

beneficial effects on vascular diseases caused by diabetes in hemodynamic and vascular permeability. Similarly, Ramipril reduced the risk of clinical outcomes in patients with a clinical history of peripheral arterial disease (PAD) as well as those with subclinical PAD in one study. Ramipril belongs to a class of drugs called angiotensin converting enzyme inhibitors, used for treating high blood pressure and heart failure as well as preventing kidney failure due to high blood pressure and diabetes.[23]

However, given the limitations of our study, including small sample size bias and having found no previous articles about captopril efficacy, we could suggest randomized controlled trials with a larger sample size to prove its efficacy.

Conclusion

Administration of captopril in colorectal cancer patients with Capecitabine-containing chemotherapy regimen reduced the symptoms and incidence of HFS four weeks after the completion of the third course of chemotherapy, similar to (ACEIs) effect on other vascular disorders. On the other hand, CEA tumor marker and the stage of colorectal cancer were correlated with HFS incidence.

These results further support clinical evaluations regarding ACE inhibitors for reducing HFS.

Acknowledgments

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Conflict of Interest

None declared.

References

1. Kwakman JJM, Elshot YS, Punt CJA, Koopman M. Management of cytotoxic chemotherapy-induced hand-foot syndrome. *Oncol Rev.* 2020;14(1):442. doi: 10.4081/oncol.2020.442.
2. Komatsu H, Yagasaki K, Hirata K, Hamamoto Y. Unmet needs of cancer patients with chemotherapy-related hand-foot syndrome and targeted therapy-related hand-foot skin reaction: A qualitative study. *Eur J Oncol Nurs.* 2019;38:65-9. doi: 10.1016/j.ejon.2018.12.001.
3. Nikolaou V, Syrigos K, Saif MW. Incidence and implications of chemotherapy related hand-foot syndrome. *Expert Opin Drug Saf.* 2016;15(12):1625-33. doi: 10.1080/14740338.2016.1238067.
4. 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;142(12):2567-77. doi: 10.1002/ijc.31269.
5. 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;3(11):1538-45. doi: 10.1001/jamaoncol.2017.1269.
6. Wheeler HE, González-Neira A, Pita G, de la Torre-Montero JC, Alonso R, Lopez-Fernandez LA, et al. Identification of genetic variants associated with

capecitabine-induced hand-foot syndrome through integration of patient and cell line genomic analyses. *Pharmacogenet Genomics.* 2014;24(5):231-7. doi: 10.1097/FPC.0000000000000037.
7. Lou Y, Wang Q, Zheng J, Hu H, Liu L, Hong D, et al. Possible pathways of capecitabine-induced hand-foot syndrome. *Chem Res Toxicol.* 2016;29(10):1591-601. doi: 10.1021/acs.chemrestox.6b00215.
8. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Ann Intern Med.* 1984;101(6):798-9. doi: 10.7326/0003-4819-101-6-798.
9. 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. doi: 10.1159/000445866.
10. Kanbayashi Y, Hosokawa T, Yasui K, Hongo F, Yamaguchi K, Moriguchi M, et al. Predictive factors for sorafenib-induced hand-foot skin reaction using ordered logistic regression analysis. *Am J Health Syst Pharm.* 2016;73(1):e18-23. doi: 10.2146/ajhp150129.
11. Lassere Y, Hoff P. Management of hand-foot syndrome in patients treated with capecitabine (Xeloda). *Eur J Oncol Nurs.* 2004;8 Suppl 1:S31-40. doi: 10.1016/j.ejon.2004.06.007.
12. Saif MW. Capecitabine and hand-foot syndrome. *Expert Opin Drug Saf.* 2011;10(2):159-69. doi: 10.1517/14740338.2011.546342.
13. Liao X, Huang L, Yu Q, He S, Li Q, Huang C, et al. SNPs in the COX-2/PGES/EP signaling pathway are associated with risk of severe capecitabine-induced hand-foot syndrome. *Cancer Chemother Pharmacol.* 2020;85(4):785-92. doi: 10.1007/s00280-020-04053-9.
14. Zhao C, Chen J, Yu B, Wu X, Dai C, Zhou C, et al. Effect of modified taohongsiwu decoction on patients with chemotherapy-induced hand-foot syndrome. *J Tradit Chin Med.* 2014;34(1):10-4. doi: 10.1016/s0254-6272(14)60047-9.
15. Hoesly FJ, Baker SG, Gunawardane ND, Cotliar JA. Capecitabine-induced hand-foot syndrome complicated by pseudomonal superinfection resulting in bacterial sepsis and death: case report and review of the literature. *Arch Dermatol.* 2011;147(12):1418-23. doi: 10.1001/archdermatol.2011.320.
16. von Gruenigen V, Frasure H, Fusco N, DeBernardo R, Eldermire E, Eaton S, et al. A double-blind, randomized trial of pyridoxine versus placebo for the prevention of pegylated liposomal doxorubicin-related hand-foot syndrome in gynecologic oncology patients. *Cancer.* 2010;116(20):4735-43. doi: 10.1002/cncr.25262.
17. Zhou Y, Peng L, Li Y, Chen L. Prophylactic pyridoxine was not able to reduce the incidence of capecitabine-induced hand-foot syndrome: A meta-analysis. *Biomed Rep.* 2013;1(6):873-8. doi: 10.3892/br. 2013.161.
18. Lal HS. Hand and foot syndrome secondary to capecitabine. *Indian J Dermatol Venereol Leprol.* 2014;80(5):427-30. doi: 10.4103/0378-6323.140302.
19. Nagore E, Insa A, Sanmart'n O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand-foot') syndrome. Incidence, recognition and management. *Am J Clin Dermatol.* 2000;1(4):225-34. doi: 10.2165/00128071-200001040-00004.
20. Zhang JZ, Xi X, Gao L, Kern TS. Captopril inhibits capillary degeneration in the early stages of diabetic retinopathy. *Curr Eye Res.* 2007;32(10):883-9. doi: 10.1080/02713680701584123.
21. Coppola G, Romano G, Corrado E, Grisanti RM, Novo S. Peripheral artery disease: potential role of ACE-inhibitor therapy. *Vasc Health Risk Manag.* 2008;4(6):1179-87. doi: 10.2147/vhrm.s3096.
22. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation.* 2006;113(11):e463-654. doi: 10.1161/CIRCULATIONAHA.106.174526.
23. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342(3):145-53. doi: 10.1056/NEJM200001203420301. Erratum in: *N Engl J Med*. 2000;342(10):748.