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Advances in the mechanisms and prevention of chemotherapy-induced hand–foot syndrome

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Abstract. Hand–Foot Syndrome (HFS) is a dose-limiting dermatologic toxicity commonly associated with conventional chemotherapy, significantly constraining antitumor efficacy and impairing patients' quality of life. This paper systematically elucidates the pathogenic mechanisms underlying chemotherapy-induced HFS, highlighting that it is primarily driven by the synergistic effects of localized high drug accumulation, microvascular endothelial injury, inflammatory cascade activation, and oxidative stress, with notable modulation by genetic polymorphisms of metabolic enzymes. In terms of clinical management, an integrated prevention and treatment framework has been established, encompassing basic physical protection, localized targeted therapies, and dynamic dose adjustment strategies. In light of the limitations of the current evidence base, this review further provides a forward-looking discussion on precision-oriented approaches, including genetic prediction and novel transdermal drug delivery systems. The aim is to offer high-level evidence to optimize clinical diagnosis and treatment, and to provide both theoretical guidance and practical references for the prevention and management of HFS.

Keywords: hand–foot syndrome, chemotherapeutic agents, pathogenesis, review

1. Introduction

Hand–Foot Syndrome (HFS) represents one of the most common dose-limiting cutaneous toxicities associated with conventional chemotherapeutic agents such as capecitabine and liposomal doxorubicin. Its characteristic clinical manifestations include painful erythema, edema, and, in severe cases, ulceration and desquamation on the palmar and plantar surfaces. HFS not only markedly compromises patients' quality of life and functional capacity in daily activities, but also frequently necessitates dose reduction, treatment delay, or even discontinuation of antitumor therapy, thereby directly jeopardizing long-term survival benefits [1, 2]. In recent years, advances in modern medicine have shifted the understanding of HFS pathogenesis from the traditional single hypothesis of "localized drug accumulation" to a more intricate pathological network involving multiple molecular signaling pathways and genetic determinants. Multi-omics studies have demonstrated that chemotherapeutic agents can activate key signaling pathways such as P38 MAPK and NF-κB within the local microenvironment, leading to the upregulation of pro-inflammatory cytokines (e.g., IL-6 and IL-8) and the

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initiation of inflammatory cascades [3]. Concurrently, genetic polymorphisms in drug-metabolizing enzymes, including TYMS, exert a profound influence on individual susceptibility to HFS. Driven by these mechanistic insights, the clinical management of HFS is transitioning from passive symptomatic treatment toward proactive, precision-based prevention. For instance, a phase III D-TORCH study has definitively demonstrated that prophylactic topical application of 1% diclofenac gel can safely and significantly reduce the incidence of moderate-to-severe HFS, as well as the risk of chemotherapy dose modification, by selectively inhibiting epidermal COX-2 activity [4]. Against this backdrop, the present review aims to systematically synthesize the epidemiology, pathogenic mechanisms, and comprehensive intervention strategies for chemotherapy-induced HFS, while also addressing current research limitations and future directions. The ultimate objective is to provide robust evidence-based support for standardized clinical management, thereby achieving the dual goals of improving patients' quality of life and preserving optimal antitumor efficacy.

2. Definition

Hand–Foot Syndrome (HFS), also referred to as Palmar–Plantar Erythrodysesthesia (PPE), is a dose-limiting, localized cutaneous toxic reaction [5]. Clinically, it is characterized by diffuse erythema, progressive edema, sensory disturbances, and severe pain affecting the distal extremities, particularly the palms and soles. In advanced cases, the condition may progress to blistering, desquamation, epidermal necrosis, and ulceration [6, 7]. In modern medicine, HFS is primarily attributed to the effects of conventional cytotoxic chemotherapeutic agents. The most commonly implicated drugs include capecitabine, Pegylated Liposomal Doxorubicin (PLD), 5-Fluorouracil (5-FU), taxane-based compounds, and high-dose cytarabine [8, 9].

3. Incidence and epidemiology

The incidence of HFS varies considerably depending on the type of chemotherapeutic agent, route of administration, dose intensity, and treatment cycle [5]. Among conventional chemotherapy drugs, oral capecitabine is associated with the highest incidence of HFS. According to the literature, the overall incidence of all-grade HFS ranges from 42% to 77%, while the incidence of severe (grade 3) HFS can reach as high as 21% to 28% [10]. In contrast, the incidence associated with continuous intravenous infusion of 5-FU is significantly lower, typically ranging from 2.6% to 18% [5]. The occurrence of HFS with PLD is also clinically significant, with an overall incidence of approximately 15% to 50%, often peaking during the second to third chemotherapy cycles and substantially impairing patients' quality of life [7, 11]. When multiple chemotherapeutic agents are used in combination, the risk of cutaneous toxicity demonstrates a pronounced additive effect.

Moreover, the incidence of HFS exhibits marked heterogeneity across different ethnicities and populations. Evidence suggests that Asian patients experience a higher incidence of HFS during capecitabine therapy compared to Caucasian populations, potentially due to differences in folate metabolism and pharmacogenomic backgrounds [10]. Additionally, recent real-world studies have indicated that African American patients undergoing capecitabine treatment exhibit a significantly higher rate of dose reduction attributable to HFS compared with White patients [12].

4. Risk factor

The risk factors for HFS are multifactorial and are generally conceptualized as the interaction between clinical characteristics and genetic susceptibility. Among these, cumulative drug dose and daily dosage represent the

most independent and significant risk factors for HFS development [3]. Recent competing risk analyses have demonstrated that when the daily dose of capecitabine exceeds 3,000 mg—and particularly when it reaches 4,000 mg—the risk of developing moderate-to-severe (grade 2–3) HFS increases sharply in a dose-dependent manner, accompanied by a significantly shortened latency period [13]. Epidemiological regression analyses further indicate that female sex, age over 60 years, larger Body Surface Area (BSA), and the presence of hypoalbuminemia or malnutrition are all associated with an elevated risk of severe HFS [6, 14]. Pre-existing microcirculatory disorders of the lower extremities (e.g., chronic venous insufficiency) or dermatologic conditions (such as dermatophytosis) can also significantly increase the likelihood of local lesions progressing to HFS [14].

At the molecular level, Single Nucleotide Polymorphisms (SNPs) in genes encoding key enzymes involved in 5-Fluorouracil (5-FU) metabolism play a decisive role in determining susceptibility to HFS [10, 15]. Among these, Dihydropyrimidine Dehydrogenase (DPYD) and Thymidylate Synthase (TYMS) are the most extensively studied genes. It has been demonstrated that specific loss-of-function variants in the DPYD gene (e.g., rs12132152 polymorphism) markedly increase the risk of life-threatening myelosuppression and severe HFS [15]. More recent large-scale Genome-Wide Association Studies (GWAS) have identified polymorphisms in the ENOSF1 gene, located near TYMS (e.g., rs2612091), as having greater sensitivity and clinical utility than traditional TYMS variants in predicting capecitabine-induced HFS toxicity [16, 17].

5. Pathophysiological mechanisms

The mechanisms underlying Hand–Foot Syndrome (HFS) induced by conventional chemotherapeutic agents such as capecitabine and liposomal doxorubicin remain incompletely elucidated. It is widely accepted that HFS arises from the synergistic interplay of multiple factors, including local anatomical and physiological characteristics, pharmacokinetics of drug metabolism, and molecular–cellular responses [2, 5].

5.1. Drug accumulation mechanism

The distinctive anatomical and physiological features of the palms and soles constitute the primary basis for the pronounced site specificity of HFS [18]. These regions lack sebaceous glands but possess an exceptionally high density of eccrine sweat glands. Hydrophilic chemotherapeutic agents—such as the active metabolites of capecitabine and free doxorubicin—are readily excreted onto the skin surface via active secretion in sweat following systemic circulation [19, 20]. Due to the rapid evaporation of sweat at the extremities, combined with the thick stratum corneum in palmar and plantar regions, which exhibits strong barrier and retention properties, cytotoxic drug components accumulate at high concentrations within the local stratum corneum and deeper epidermal layers [2, 18]. This localized drug concentration, far exceeding systemic plasma levels, exerts direct cytotoxic effects on basal epidermal cells and keratinocytes, disrupting DNA synthesis and cell division, and ultimately impairing normal epidermal turnover [21].

5.2. Microcirculatory disturbance and endothelial injury

Beyond direct epidermal toxicity, mechanical and chemical injury to the dermal microvascular network forms the pathological basis for early manifestations such as erythema and edema. The dense capillary networks in the distal extremities—particularly in weight-bearing areas of the soles and high-friction regions of the palms—are continuously subjected to elevated hydrostatic pressure and mechanical shear stress during daily activities [5]. In the case of Pegylated Liposomal Doxorubicin (PLD), its unique liposomal structure is prone to mechanical disruption when passing through compressed microvasculature in the extremities, resulting in

the localized release of high concentrations of free drug at the endothelial interface [23]. This localized drug exposure directly damages the cytoskeleton of vascular endothelial cells and disrupts intercellular junctions, leading to increased microvascular permeability and microcirculatory dysfunction [22, 23]. The resulting collapse of dermal microcirculation facilitates the extravasation of plasma components and inflammatory cells, contributing to tissue edema. At the same time, it accelerates the diffusion of chemotherapeutic agents into subcutaneous tissues, thereby establishing a self-perpetuating pathological cycle.

5.3. Inflammatory cascade response

Drug-induced cytotoxicity and endothelial injury rapidly disrupt local immune homeostasis, triggering a robust inflammatory cascade [24]. Damaged keratinocytes and activated macrophages release substantial amounts of pro-inflammatory cytokines, including Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), thereby amplifying local inflammatory cell infiltration [2]. Within this process, the Cyclooxygenase-2 (COX-2) and Prostaglandin E2 (PGE2) signaling pathway plays a central regulatory role [24, 25]. Recent molecular epidemiological studies have demonstrated that Single Nucleotide Polymorphisms (SNPs) within the COX-2/PGES/EP signaling axis are closely associated with the risk of severe capecitabine-induced HFS [26]. Furthermore, exploratory analyses from the D-TORCH study have shown significantly elevated levels of COX-2 in both serum and local tissues of patients with HFS. The excessive release of its downstream product, PGE2, not only induces pronounced inflammatory erythema but also directly sensitizes peripheral nociceptive neurons, providing a molecular explanation for the severe burning pain experienced by patients [27].

5.4. Oxidative stress and apoptosis

In recent years, the critical role of oxidative stress in the progression to tissue necrosis in HFS has been increasingly recognized, particularly in models involving PLD and fluoropyrimidine-based agents. Excessive local accumulation of chemotherapeutic drugs disrupts mitochondrial respiratory chain function, leading to a burst of Reactive Oxygen Species (ROS) generation and overwhelming the local antioxidant defense system [7]. Elevated ROS levels directly damage cellular membranes through lipid peroxidation, compromising membrane integrity [2]. Concurrently, oxidative stress induces irreversible DNA double-strand breaks, thereby activating the ATM/Chk/p53 DNA damage response and apoptotic signaling pathways [28]. Persistent DNA damage ultimately drives epidermal cells and dermal fibroblasts toward irreversible apoptosis and necrosis. Clinically, this process manifests as severe desquamation, deep blistering, skin exfoliation, and chronic non-healing ulcers observed in patients with high-grade HFS [21].

6. Treatment and prevention strategies

The management of HFS emphasizes a comprehensive approach characterized by "prevention as the priority, early intervention, and grade-based treatment". This framework encompasses non-pharmacological measures, topical therapies, systemic pharmacologic interventions, and chemotherapy dose modification. In recent years, the accumulation of high-quality clinical evidence has substantially strengthened the evidence-based foundation for standardized HFS management.

6.1. Physical protection and basic care

6.1.1. Basic prevention

Avoidance of friction, pressure, and exposure to heat or chemical irritants on the hands and feet constitutes the cornerstone of HFS prevention. Kwakman et al. highlighted that patient education is central to non-

pharmacological interventions, recommending the use of soft cotton gloves and socks to absorb pressure and reduce mechanical friction [5]. Routine application of moisturizers containing ceramides or urea can help restore the skin barrier. Basic research by Uchino et al. demonstrated significant alterations in ceramide and free fatty acid composition within the stratum corneum of patients with capecitabine-induced HFS, thereby providing direct mechanistic support for the clinical use of lipid-replenishing barrier repair agents [29].

6.1.2. Local cryotherapy

The use of ice gloves or ice socks during chemotherapy infusion represents a highly evidence-supported preventive strategy. By inducing vasoconstriction in peripheral microvasculature, local cooling reduces drug exposure in distal tissues. A study by Bun et al. involving 96 ovarian cancer patients receiving PLD demonstrated a significantly reduced incidence of HFS in the cryotherapy group, with a compliance rate of 96% [30]. Similarly, a cohort study by Zheng et al. in 101 breast cancer patients showed that cooling patches reduced the incidence of PLD-induced HFS to extremely low levels (grade 1 incidence: 38% in the control group vs. 2% in the cooling group, with no grade 2 cases observed) [31]. Furthermore, research by Nara et al. confirmed that regional cryotherapy combined with oral dexamethasone reduced the incidence of ≥ grade 3 HFS induced by PLD to as low as 1.4% [32].

6.2. Topical pharmacologic interventions

6.2.1. Corticosteroids

Topical high-potency corticosteroid ointments are effective for controlling inflammatory responses during the acute erythematous phase. A phase II T-CRACC study conducted by Iimura et al. evaluated the prophylactic efficacy of 0.1% hydrocortisone butyrate cream in 47 patients receiving capecitabine plus oxaliplatin. The results demonstrated a ≥ grade 2 HFS incidence of only 6.4%, with no systemic adverse events related to topical steroid use [33].

6.2.2. Topical Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Topical 1% diclofenac gel has strong evidence supporting its role in preventing capecitabine-induced HFS. In the double-blind randomized controlled D-TORCH trial conducted by Santhosh et al., the incidence of grade 2–3 HFS in the diclofenac group was 3.8%, significantly lower than 15.0% in the placebo group ($p = 0.003$). Moreover, the need for chemotherapy dose reduction due to HFS was markedly decreased (3.8% vs. 13.5%) [4]. A network meta-analysis by Huang et al., incorporating 16 randomized controlled trials, further confirmed that topical diclofenac and urea-based creams are among the most effective interventions for reducing the overall incidence of HFS and minimizing chemotherapy regimen modifications [34].

6.2.3. Novel tissue repair approaches (ozone therapy)

Emerging evidence suggests that topical ozone therapy can effectively promote skin repair. It has been shown to significantly upregulate the expression of Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-β (TGF-β), and Vascular Endothelial Growth Factor (VEGF), thereby facilitating microvascular regeneration and epidermal reconstruction [35]. A randomized controlled trial by Chen Xiaowei et al. (n = 91) demonstrated that medical ozone oil was significantly more effective than conventional urea ointment in both preventing and treating kinase inhibitor–associated hand–foot skin reactions; these pro-healing mechanisms are likewise applicable to chemotherapy-induced HFS [36]. In addition, Song Linlin et al. reported a case in which major autohemotherapy with ozone successfully treated grade III capecitabine-induced HFS. Following three days of combined topical ozonated water dressing and autohemotherapy, severe blistering resolved without recurrence, allowing continuation of chemotherapy [37].

6.2.4. Other interventions

According to the European Society for Medical Oncology (ESMO) clinical practice guidelines on dermatologic toxicities, when HFS progresses to the ulcerative stage with erosion and open lesions, antiseptic agents such as polyhexanide solution or silver sulfadiazine cream are recommended to prevent secondary infections [38]. For patients with severe tenderness, topical lidocaine gel may be used for analgesia to improve quality of life.

6.3. Systemic pharmacologic therapy

6.3.1. COX-2 inhibitors

Oral Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), such as celecoxib, can inhibit the inflammatory cascade mediated by Cyclooxygenase-2 (COX-2). A landmark phase II prospective randomized study conducted by Zhang et al. demonstrated that oral celecoxib (200 mg, twice daily) can safely and significantly reduce the incidence of ≥ grade 2 capecitabine-induced HFS [25]. This finding has been consistently validated in multiple recent network meta-analyses, confirming its efficacy as a systemic agent for preventing moderate-to-severe HFS [34].

6.3.2. Vitamin B6

High-dose vitamin B6 (pyridoxine) has shown some adjunctive benefit in HFS induced by PLD. A randomized controlled trial by Xiaozhe et al. reported that it reduced the incidence of HFS in patients with multiple myeloma from 20.8% to 5.8% [9]. However, in the context of capecitabine-induced HFS, a large double-blind randomized controlled trial conducted by Yap et al. (n = 386) demonstrated no significant difference between high-dose pyridoxine and placebo in preventing HFS or delaying its onset [39]. Therefore, vitamin B6 should not be considered a routine prophylactic agent across all HFS subtypes.

6.3.3. Corticosteroids

For severe and rapidly progressive HFS, short-term systemic corticosteroid therapy may be employed. Prospective studies by Nara et al. [32] and Drake et al. [40] have shown that short courses of oral dexamethasone (e.g., 8 mg/day with tapering) can effectively alleviate or resolve severe PLD-induced HFS and help prevent treatment delays.

6.4. Dose management

Dose modification of chemotherapeutic agents remains the most direct and critical intervention for controlling severe HFS. HFS induced by conventional chemotherapy is highly dose-dependent, with both peak plasma concentration and cumulative dose determining the toxicity threshold. Kwakman et al. emphasized that once grade 3 HFS occurs, chemotherapy must be immediately interrupted. Treatment may be resumed only after symptoms have improved to ≤ grade 1, and the causative drug dose should be mandatorily reduced by 25%–50% to avoid irreversible peripheral nerve and tissue damage [5].

7. Discussion and perspectives

With the widespread application of chemotherapeutic agents in oncology, HFS has emerged as a key dose-limiting toxicity that significantly affects treatment adherence and dose tolerance. Current clinical management primarily relies on physical cooling, topical urea-based creams or NSAIDs, and dynamic dose adjustment of chemotherapy, aiming to alleviate symptoms by restoring the skin barrier and suppressing local inflammatory cascades. Although these strategies provide certain clinical benefits, the overall prevention and management of HFS in modern medicine remain constrained by gaps in high-level evidence, incomplete

elucidation of pathogenic targets, and the lack of highly specific therapeutic interventions. These limitations hinder the advancement of guideline recommendation levels. To address these challenges, future research should focus on in-depth exploration across the following three key dimensions:

7.1. Establishment of a high-quality evidence base

Current studies on the prevention and management of HFS are often characterized by substantial heterogeneity in design, and several interventions remain controversial due to the lack of high-level evidence. Future research should prioritize the implementation of multicenter, large-sample, double-blind Randomized Controlled Trials (RCTs), with the comprehensive integration of Patient-Reported Outcomes (PROs). By adopting a dual-dimensional evaluation framework that combines objective clinical signs with subjective assessment scales, the precise therapeutic benefit of various systemic and topical interventions can be delineated. This approach will provide the highest level of scientific evidence to support the standardization of HFS clinical management and the updating of clinical guidelines.

7.2. Exploration of specific pathogenic targets

Current mechanistic studies on chemotherapy-induced HFS predominantly focus on macroscopic processes such as Reactive Oxygen Species (ROS) accumulation and aberrant activation of DNA damage pathways (e.g., ATM/Chk/p53). However, in-depth investigation into drug-specific microscopic toxicity targets remains insufficient, which has directly impeded the development of HFS-specific "antidotes". With advances in pharmacogenomics, future research should aim to elucidate the core regulatory networks driven by genetic polymorphisms in drug-metabolizing enzymes. On this basis, early risk prediction models can be constructed at the genetic level, facilitating a transition toward individualized and precision-based prevention and treatment strategies.

7.3. Advancement of novel drug delivery systems

Although emerging drug delivery technologies—such as nanoliposomes, microneedle arrays, and thermosensitive hydrogels—have demonstrated substantial potential in enhancing local bioavailability and enabling targeted, controlled release, their translational application in HFS prevention and treatment remains limited. Future pharmaceutical research should focus on the development of innovative carriers capable of intelligently penetrating the dense stratum corneum and achieving deep targeted delivery. Through fundamental innovation in drug delivery systems, anti-inflammatory and antioxidant agents can be effectively concentrated within the local microenvironment of the hands and feet, thereby maximizing local therapeutic efficacy while minimizing systemic adverse effects. Ultimately, this will optimize both patient experience and clinical outcomes.

8. Conclusion

In summary, HFS is a critical dose-limiting cutaneous toxicity associated with conventional chemotherapy, characterized by a complex pathogenesis involving the synergistic effects of localized high drug accumulation, microvascular endothelial injury, inflammatory cascade activation, and oxidative stress, with significant modulation by genetic polymorphisms in metabolic enzymes. At present, a preliminary integrated management framework has been established in clinical practice, centered on physical protection, topical pharmacologic interventions, and dynamic dose adjustment. However, existing strategies remain limited in terms of target specificity and the availability of high-level evidence. Future optimization of HFS management

strategies will require the deep integration of oncology, pharmaceutical sciences, and multi-omics technologies. On the one hand, pharmacogenomics should be leveraged to develop precise risk prediction models; on the other, novel transdermal drug delivery systems should be actively advanced to achieve efficient, targeted treatment of localized skin lesions. In conclusion, transitioning the clinical management of HFS from empirical symptomatic treatment toward standardized, evidence-based, and precision-oriented approaches represents an essential pathway to overcoming chemotherapy dose limitations. Such progress is crucial for safeguarding overall antitumor efficacy while meaningfully improving patients' quality of life.

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References

[1] King, T. L., Voon, P. J., Yuen, K. H., & Mohamed Noor, D. A. (2024). Hand-foot syndrome in cancer patients on capecitabine: examining prevalence, impacts, and associated risk factors at a cancer centre in Malaysia. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 32*(6), 345.

[2] Chen, B., Wang, X., & Meng, L. (2025). Advancements in the diagnosis and management of capecitabine-induced hand-foot syndrome. *Journal of cancer research and clinical oncology, 151*(10), 265.

[3] He, X., Wang, J., Wang, Q., Liu, J., Yang, X., He, L., Hu, H., Zeng, S., Yu, L., Qiu, Y., & Lou, Y. (2022). P38 MAPK, NF-κB, and JAK-STAT3 Signaling Pathways Involved in Capecitabine-Induced Hand-Foot Syndrome via Interleukin 6 or Interleukin 8 Abnormal Expression. *Chemical research in toxicology, 35*(3), 422–430.

[4] Santhosh, A., Sharma, A., Bakhshi, S., Kumar, A., Sharma, V., Malik, P. S., Pramanik, R., Gogia, A., Prasad, C. P., Sehgal, T., Gund, S., Dev, A., Cheung, W. Y., Pandey, R. M., Kumar, S., Gupta, I., Batra, A., & D-TORCH Trial Investigators (2024). Topical Diclofenac for Prevention of Capecitabine-Associated Hand-Foot Syndrome: A Double-Blind Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 42*(15), 1821–1829.

[5] Kwakman, J. J. M., Elshot, Y. S., Punt, C. J. A., & Koopman, M. (2020). Management of cytotoxic chemotherapy-induced hand-foot syndrome. *Oncology reviews, 14*(1), 442.

[6] de Queiroz, M. V. R., de Medeiros, A. C. T. R., Toledo, S. P., de Abreu Sarmenghi, K. D., & de Vasconcellos, V. F. (2022). Hand-foot syndrome caused by capecitabine: incidence, risk factors and the role of dermatological evaluation. *Ecancermedicalscience, 16*, 1390.

[7] Hu, X., Dong, M., Liang, X., Liu, Z., & Li, Q. (2021). Reactive Oxygen Species-Mediated Inflammation and Apoptosis in Hand-Foot Syndrome Induced by PEGylated Liposomal Doxorubicin. *International journal of nanomedicine, 16,* 471–480.

[8] Santhosh, A., Kumar, A., Pramanik, R., Gogia, A., Prasad, C. P., Gupta, I., Gupta, N., Cheung, W. Y., Pandey, R. M., Sharma, A., & Batra, A. (2022). Randomized double-blind, placebo-controlled study of topical diclofenac in the prevention of hand-foot syndrome in patients receiving capecitabine (the D-TORCH study). *Trials, 23*(1), 420.

[9] Xiaozhe, L., Meilan, C., Beihui, H., Junru, L., Jingli, G., Lifen, K., & Juan, L. (2022). Pyridoxine Is Effective for Preventing Hand-Foot Syndrome Induced by Pegylated Liposomal Doxorubicin for Multiple Myeloma: The Results of a Randomized Study. *Integrative cancer therapies, 21*, 15347354221140402.

[10] Dong, S. Q., Wang, T. M., Zhang, J. B., He, Y. Q., Xue, W. Q., Wu, Z. Y., Yang, D. W., Cao, L. J., Huang, J. W., Li, X. Z., Zhang, P. F., Zheng, X. H., & Jia, W. H. (2021). Polymorphisms in TYMS for Prediction of Capecitabine-Induced Hand-Foot Syndrome in Chinese Patients with Colorectal Cancer. *Cancer research and treatment, 53*(3), 724–732.

[11] Li, Y., Huang, W. W., Zhang, L. J., Jiang, L. J., Lin, X. H., Wu, H. T., Huang, Y. T., & Li, N. (2022). Evaluation of the preventive effect of regional cooling nursing on hand foot syndrome caused by doxorubicin hydrochloride liposome. *Open Journal of Nursing, 12*(11), 772–781..

[12] Brazelton, A., Yande, S., Pope, R., Johnson, M. L., Musher, B., & Trivedi, M. V. (2022). Racial and ethnic differences in capecitabine toxicity in patients with gastrointestinal tract cancers. *Annals of gastroenterology, 35*(2), 182–186.

[13] Chantharakhit, C., & Sujaritvanichpong, N. (2023). Predictive factors for the development of capecitabine-induced hand-foot syndrome: a retrospective observational cohort study. *Annals of medicine and surgery (2012), 86*(1), 73–77.

[14] Hanafi, T., Titou, H., Kerrouch, H., & Boui, M. (2020). Palmoplantar erythrodysesthesia associated with capecitabine, epidemiological mapping and risk factors in Morocco. *International Journal of Cancer and Clinical Research, 7*, 131.

[15] Palles, C., Fotheringham, S., Chegwidden, L., Lucas, M., Kerr, R., Mozolowski, G., Rosmarin, D., Taylor, J. C., Tomlinson, I., & Kerr, D. (2021). An Evaluation of the Diagnostic Accuracy of a Panel of Variants in DPYD and a Single Variant in ENOSF1 for Predicting Common Capecitabine Related Toxicities. *Cancers, 13*(7), 1497.

[16] Rosmarin, D., Palles, C., Pagnamenta, A., Kaur, K., Pita, G., Martin, M., Domingo, E., Jones, A., Howarth, K., Freeman-Mills, L., Johnstone, E., Wang, H., Love, S., Scudder, C., Julier, P., Fernández-Rozadilla, C., Ruiz-Ponte, C., Carracedo, A., Castellvi-Bel, S., Castells, A., … Tomlinson, I. (2015). A candidate gene study of capecitabine-related toxicity in colorectal cancer identifies new toxicity variants at DPYD and a putative role for ENOSF1 rather than TYMS. *Gut, 64*(1), 111–120.

[17] Hamzic, S., Kummer, D., Froehlich, T. K., Joerger, M., Aebi, S., Palles, C., Thomlinson, I., Meulendijks, D., Schellens, J. H. M., García-González, X., López-Fernández, L. A., Amstutz, U., & Largiadèr, C. R. (2020). Evaluating the role of ENOSF1 and TYMS variants as predictors in fluoropyrimidine-related toxicities: An IPD meta-analysis. *Pharmacological research, 152*, 104594.

[18] Lou, Y., Wang, Q., Zheng, J., Hu, H., Liu, L., Hong, D., & Zeng, S. (2016). Possible Pathways of Capecitabine-Induced Hand-Foot Syndrome. *Chemical research in toxicology, 29*(10), 1591–1601.

[19] Jacobi, U., Waibler, E., Schulze, P., Sehouli, J., Oskay-Ozcelik, G., Schmook, T., Sterry, W., & Lademann, J. (2005). Release of doxorubicin in sweat: first step to induce the palmar-plantar erythrodysesthesia syndrome?. *Annals of oncology : official journal of the European Society for Medical Oncology, 16*(7), 1210–1211.

[20] Janssen, J. M., Jacobs, B. A. W., Roosendaal, J., Derissen, E. J. B., Marchetti, S., Beijnen, J. H., Huitema, A. D. R., & Dorlo, T. P. C. (2021). Population Pharmacokinetics of Intracellular 5-Fluorouridine 5'-Triphosphate and its Relationship with Hand-and-Foot Syndrome in Patients Treated with Capecitabine. *The AAPS journal, 23*(1), 23.

[21] Takano-Mochizuki, M., Nakajima, K., Ishida, T., Ohta, E., Moriyama, T., & Asakura, S. (2024). A novel animal model of tegafur-induced hand-foot syndrome. *Toxicology and applied pharmacology, 487*, 116977. https://doi.org/10.1016/j.taap.2024.116977

[22] Martschick, A., Sehouli, J., Patzelt, A., Richter, H., Jacobi, U., Oskay-Ozcelik, G., Sterry, W., & Lademann, J. (2009). The pathogenetic mechanism of anthracycline-induced palmar-plantar erythrodysesthesia. *Anticancer research, 29*(6), 2307–2313.

[23] Yokomichi, N., Nagasawa, T., Coler-Reilly, A., Suzuki, H., Kubota, Y., Yoshioka, R., Tozawa, A., Suzuki, N., & Yamaguchi, Y. (2013). Pathogenesis of Hand-Foot Syndrome induced by PEG-modified liposomal Doxorubicin. *Human cell, 26*(1), 8–18.

[24] Zhang, R. X., Wu, X. J., Lu, S. X., Pan, Z. Z., Wan, D. S., & Chen, G. (2011). 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. *Journal of cancer research and clinical oncology, 137*(6), 953–957.

[25] Zhang, R. X., Wu, X. J., Wan, D. S., Lu, Z. H., Kong, L. H., Pan, Z. Z., & Chen, G. (2012). 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. *Annals of oncology : official journal of the European Society for Medical Oncology, 23*(5), 1348–1353.

[26] Liao, X., Huang, L., Yu, Q., He, S., Li, Q., Huang, C., & Yuan, X. (2020). SNPs in the COX-2/PGES/EP signaling pathway are associated with risk of severe capecitabine-induced hand-foot syndrome. *Cancer chemotherapy and pharmacology, 85*(4), 785–792.

[27] Tansir, G., Santhosh, A., Kumar, A., Baskarane, H., Divakar, M. K., Hooda, V., Dev, A. J. R., Prasad, C. P., Gupta, I., Kumar, S., Tanwar, P., Sharma, A., Bakhshi, S., & Batra, A. (2025). Association of serum cyclooxygenase-2 levels with hand-foot syndrome in patients receiving capecitabine: an exploratory analysis of D-TORCH study. *Ecancermedicalscience, 19*, 1967.

[28] Yang, J., Qiao, L., Zeng, Z., Wang, J., Zhu, T., Wei, J., Wu, M., Ye, S., Huang, X., Ma, D., Liu, R., & Gao, Q. (2017). The role of the ATM/Chk/P53 pathway in mediating DNA damage in hand-foot syndrome induced by PLD. *Toxicology letters, 265*, 131–139.

[29] Uchino, T., Nakajo, M., Hatta, I., Suzuki, I., Okada, M., Terada, R., Miyazaki, Y., Osawa, M., Taku, K., Yokoyama, T., Tsuji, D., & Kagawa, Y. (2026). Analysis of intercellular lipids in the stratum corneum of patients with capecitabine-induced hand-foot syndrome: comparison with the stratum corneum of healthy individuals. *Cancer chemotherapy and pharmacology, 96*(1), 8.

[30] Bun, S., Yunokawa, M., Tamaki, Y., Shimomura, A., Shimoi, T., Kodaira, M., Shimizu, C., Yonemori, K., Fujiwara, Y., Makino, Y., Terakado, H., & Tamura, K. (2018). Symptom management: the utility of regional cooling for hand-foot syndrome induced by pegylated liposomal doxorubicin in ovarian cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 26*(7), 2161–2166.

[31] Zheng, Y. F., Fu, X., Wang, X. X., Sun, X. J., & He, X. D. (2021). Utility of cooling patches to prevent hand-foot syndrome caused by pegylated liposomal doxorubicin in breast cancer patients. *World journal of clinical cases, 9*(33), 10075–10087.

[32] Nara, K., Taguchi, A., Yamamoto, T., Tsuruga, T., Tojima, Y., Miyamoto, Y., Tanikawa, M., Sone, K., Mori, M., Takada, T., Suzuki, H., & Osuga, Y. (2023). Efficacy of regional cooling + oral dexamethasone for primary prevention of hand-foot syndrome associated with pegylated liposomal doxorubicin. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 31*(5), 283.

[33] Iimura, Y., Baba, K., Furukawa, N., Ishibashi, M., Sasuga, C., Ahiko, Y., Monma, S., Sakuyama, N., Aikou, S., Shida, D., Nojima, M., Kuroda, S., & Boku, N. (2025). A phase II study evaluating the preventive effect of topical hydrocortisone for capecitabine-induced hand-foot syndrome in patients with colorectal cancer receiving adjuvant chemotherapy with capecitabine plus oxaliplatin (T-CRACC study). *International journal of clinical oncology, 30*(11), 2316–2324.

[34] Kao, Y. S., Lo, C. H., Tu, Y. K., & Hung, C. H. (2022). Pharmacological prevention strategy for capecitabine-induced hand-foot syndrome: A network meta-analysis of randomized control trials. *Dermatologic therapy, 35*(10), e15774.

[35] Kim, H. S., Noh, S. U., Han, Y. W., Kim, K. M., Kang, H., Kim, H. O., & Park, Y. M. (2009). Therapeutic effects of topical application of ozone on acute cutaneous wound healing. *Journal of Korean medical science, 24*(3), 368–374.

[36] Chen, X., Jiang, Y., Zhang, Y., Dai, W., Fan, R., Weng, X., He, P., Yan, F., & Guo, Y. (2020). Medical ozone oil for the prevention and treatment of sorafenib-induced hand–foot skin reaction: A randomized controlled clinical trial of 91 cases. *Journal of Southern Medical University, 40*(10), 1488–1492.

[37] Song, L., Gu, D., Li, J., Han, Y., Yang, X., & Huang, X. (2020). Ozonated autohemotherapy for capecitabine-induced grade III hand–foot syndrome: A case report. *China Pharmaceuticals, 29*(3), 96–97.

[38] Lacouture, M. E., Sibaud, V., Gerber, P. A., van den Hurk, C., Fernández-Peñas, P., Santini, D., Jahn, F., Jordan, K., & ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org (2021). Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines☆. *Annals of oncology : official journal of the European Society for Medical Oncology, 32*(2), 157–170.

[39] Yap, Y. S., Kwok, L. L., Syn, N., Chay, W. Y., Chia, J. W. K., Tham, C. K., Wong, N. S., Lo, S. K., Dent, R. A., Tan, S., Mok, Z. Y., Koh, K. X., Toh, H. C., Koo, W. H., Loh, M., Ng, R. C. H., Choo, S. P., & Soong, R. C. T. (2017). Predictors of Hand-Foot Syndrome and Pyridoxine for Prevention of Capecitabine-Induced Hand-Foot Syndrome: A Randomized Clinical Trial. *JAMA oncology, 3*(11), 1538–1545.

[40] Drake, R. D., Lin, W. M., King, M., Farrar, D., Miller, D. S., & Coleman, R. L. (2004). Oral dexamethasone attenuates Doxil-induced palmar-plantar erythrodysesthesias in patients with recurrent gynecologic malignancies. *Gynecologic oncology, 94*(2), 320–324. .