ONLINE EXCLUSIVE

Targeted Therapy– and Chemotherapy-Associated Skin Toxicities: Systematic Review and Meta-Analysis

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PROBLEM IDENTIFICATION: Preventing and managing skin toxicities can minimize treatment disruptions and improve well-being. This systematic review aimed to evaluate the effectiveness of interventions for the prevention and management of cancer treatment–related skin toxicities.

LITERATURE SEARCH: The authors systematically searched for comparative studies published before April 1, 2019. Study selection and appraisal were conducted by pairs of independent reviewers.

DATA EVALUATION: The random-effects model was used to conduct meta-analysis when appropriate.

SYNTHESIS: 39 studies (6,006 patients) were included; 16 of those provided data for meta-analysis. Prophylactic minocycline reduced the development of all-grade and grade 1 acneform rash in patients who received erlotinib. Prophylaxis with pyridoxine 400 mg in capecitabine-treated patients lowered the risk of grade 2 or 3 hand-foot syndrome. Several treatments for hand-foot skin reaction suggested benefit in heterogeneous studies. Scalp cooling significantly reduced the risk for severe hair loss or total alopecia associated with chemotherapy.

IMPLICATIONS FOR RESEARCH: Certainty in the available evidence was limited for several interventions, suggesting the need for future research.

KEYWORDS chemotherapy; skin toxicity; systematic review; meta-analysis; cancer

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Skin toxicities due to systemic cancer treatment are a significant problem for many patients and can greatly affect their quality of life. Preventing and managing skin-related toxicities can minimize treatment disruptions and improve patient well-being. Treatments that cause skin toxicities are used across most cancer diagnoses (e.g., colorectal, breast, lung, pancreatic, head and neck) and affect a high percentage of patients. Adverse skin reactions can involve skin barrier function, hair, and nails. Preventing and managing skin toxicities is an important clinical priority for oncology healthcare providers.

Epidermal growth factor receptor inhibitors (EGFRIs) are an important class of anticancer agents. Although these agents have a more favorable toxicity profile than other anticancer therapies, they have unique adverse events (Lucchini et al., 2014). The primary toxicity associated with EGFRIs are cutaneous (acneform rash) reactions that can occur in more than 80% of patients receiving these agents (Lacouture et al., 2018; Ocvirk & Cencelj, 2010; Segaert & Van Cutsem, 2005). The rash associated with EGFRIs is mild in most cases, but it can lead to treatment cessation or dose modifications (Lacouture, 2009). Patients with moderate to severe cutaneous adverse events will frequently change or stop treatment (Lacouture & Lai, 2006). Patients who experience an EGFRI rash experience negative effects on physical, functional, emotional, and social well-being (Coleman et al., 2010).

Hand-foot syndrome, also known as palmar-plantar erythrodysesthesia, is a skin toxicity most often seen on the palms of the hands or the soles of the feet, but it can also be found on other pressure points, such as the waistline or bra line (Lipworth et

al., 2009). Hand-foot syndrome is a distinctive adverse event related to certain chemotherapeutic treatments, such as capecitabine, taxanes, 5-fluorouracil, and doxorubicin (Hoesly et al., 2011). The clinical presentation includes an initial altered sensation on the palms of the hands and soles of the feet that is followed by painful, symmetrical swelling and redness (Gressett et al., 2006). The pathogenesis of hand-foot syndrome is not yet known but may be a direct result of transport of the active agent to the skin surface via sweat (Templeton et al., 2014). Patients with colorectal cancer often receive treatments that are high risk for hand-foot syndrome. In a study by Zhao et al. (2013), about 67% of patients receiving chemotherapy for colorectal cancer developed hand-foot syndrome, and the majority reported they were unaware of management strategies. Hand-foot syndrome is also a common toxicity with liposomal doxorubicin treatment, with almost 50% of patients experiencing some form of hand-foot syndrome (Lorusso et al., 2007). Severe hand-foot syndrome can negatively affect quality of life, with some patients unable to wear shoes, walk, or use their hands to hold items (Brant et al., 2005).

Hand-foot skin reaction refers to side effects patients experience from targeted therapy (multikinase inhibitors), which is distinct from hand-foot syndrome that occurs from traditional chemotherapy (Gomez & Lacouture, 2011). Hand-foot skin reaction symptoms start with a burning or tingling sensation that lasts for a few days, followed by the development of bilateral, painful erythema and large blisters that evolve into callous-like hyperkeratosis (McLellan et al., 2015). Pain related to the lesions can be significant to the patient. Symptoms typically occur at pressure points, such as the palms of the hands, soles of the feet, and elbows. The pathogenesis of hand-foot skin reaction is unclear, but targeted agents may disrupt the natural balance of vascular and epidermal trauma and repair at pressure points and with friction through changes to molecular signaling pathways (Lacouture et al., 2008). Hand-foot skin reaction is not life-threatening; however, similar to other skin toxicities, it can have a significant effect on patients' well-being, functional status, and quality of life (Nardone et al., 2012). If not identified or reported early enough, symptoms can become so severe that patients are unable or unwilling to continue therapy (McLellan et al., 2015).

Alopecia is a frequently occurring side effect of chemotherapy, characterized by partial or complete loss of hair that may be temporary or permanent. Alopecia makes cancer visible to the outside world and can have a negative effect on quality of life and well-being of many patients with cancer. Alopecia related to chemotherapy affects nearly 100% of patients with breast cancer receiving anthracycline- or taxane-containing chemotherapy (Watanabe et al., 2019). Patients report chemotherapy-induced alopecia as the most feared side effect of treatment (Kargar et al., 2011), with as many as 10% of women considering not receiving chemotherapy or choosing a less effective treatment to avoid hair loss (Roe, 2014).

Intervention strategies for these skin toxicities are often based on consensus data with limited research. Nurses are in an ideal position to effectively identify, assess, and intervene when patients are at risk for or experiencing skin toxicities related to their cancer treatment. Patient education and guideline-based care are important tools in successful management of skin toxicities (Wallner et al., 2016). Assessment, early identification, and intervention can prevent severe toxicities and the disabilities that result with them, as well as reduce treatment discontinuation related to toxicity. In the current systematic review, the authors evaluate interventions aiming to prevent or treat skin toxicities (i.e., acneform rash, hand-foot skin reaction, hand-foot syndrome, pruritis, and alopecia).

Methods

The current authors conducted a systematic review to address the prevention, treatment, and management of patients with cancer at risk for or already experiencing skin toxicities. This systematic review was performed following a protocol developed by a committee from the Oncology Nursing Society (ONS) charged with developing the ONS Guidelines™ to inform the management of symptoms related to targeted therapy– and chemotherapy-associated skin toxicities. The ONS Guidelines panel considered potential skin toxicities and narrowed the focus to five toxicities that were identified as prevalent for all patients with cancer (i.e., acneform rash, hand-foot skin reaction, hand-foot syndrome, pruritis, and alopecia). Other toxicities that are not addressed in this review and the accompanying guideline will be considered in future research. The systematic review and meta-analysis methodology are consistent with the approach of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2011). The reporting of the results followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009).

Development of Research Questions

The ONS Guidelines panel, in collaboration with methodologists, developed and prioritized symptom management questions according to the PICO (population, intervention, comparison, and outcomes) framework (Guyatt, Oxman, Kunz, et al., 2011) (see Appendix). The panel identified up to seven outcomes for each PICO question to consider in the review of the evidence. Across many of the PICO questions, several of the same outcomes were deemed critical for review.

Data Sources and Searches

A comprehensive search of databases, including MEDLINE®, Embase®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus, was conducted from database inception to April 1, 2019, by an experienced librarian with input from the ONS Guidelines panel and the principal investigator. Reference mining from relevant systematic reviews, conference proceedings, and clinical trial registries were applied to identify additional studies. The details of the search strategy are in the Appendix.

Selection Criteria

Comparative studies, including comparative observational studies and randomized/nonrandomized clinical trials, were included if they studied the prevention and/or treatment of (a) acneform rash, (b) hand-foot syndrome, (c) hand-foot skin reaction, (d) pruritis, or (e) alopecia in patients with cancer treated with chemotherapy who were at risk for or already developed one of the skin side effects. All included studies were comparative studies that evaluated at least one of the primary outcomes (development and/or alleviation of skin side effects) according to the protocol (see Appendix). Noncomparative studies, abstracts, reviews, and guidelines were excluded. Studies without the primary outcomes and foreign language studies were also excluded. The studies were screened by two independent reviewers, and any discrepancies were resolved by consensus through discussion with a third reviewer.

Data Extraction and Risk-of-Bias Assessment

The data extraction and methodologic quality assessment were performed by two independent reviewers. The authors developed a standardized data extraction form to extract relevant data, including baseline characteristics, intervention and comparison groups, duration, primary outcomes, and other relevant outcomes. To assess the risk of bias, the authors used items from the Newcastle-Ottawa Scale (Wells et al., 2017) for observational studies and nonrandomized clinical trials, and Cochrane Collaboration risk-of-bias tool (Higgins & Green, 2011) for randomized clinical trials in the context of primary outcomes.

Outcome Measures

The outcomes were measured at the point of termination of the interventions or at the earliest follow-up time point. The primary outcome was the development of the listed skin toxicities. The authors also extracted other relevant secondary outcomes, including quality of life (overall, patient comfort, and functional limitations), infection, adverse events, and treatment interruption or discontinuation. The World Health Organization (WHO, 1979) criteria for alopecia was chosen as the outcome measure for chemotherapy-induced alopecia.

Data Synthesis and Analysis

The random-effects model was used to pool the outcomes of interest from studies reporting the number of patients with rash, hand-foot syndrome, and alopecia, and to generate relative risks (RRs) and 95% confidence intervals (CIs). Other outcomes were summarized narratively.

Subgroup analysis was performed based on the types of the interventions. For statistical heterogeneity, the I^2 index was used, with values greater than 50% suggesting substantial heterogeneity (Higgins, 2003). Publication bias was not evaluated because fewer than 10 studies were included in any analysis. All statistical analyses were performed with Stata, version 15.1.

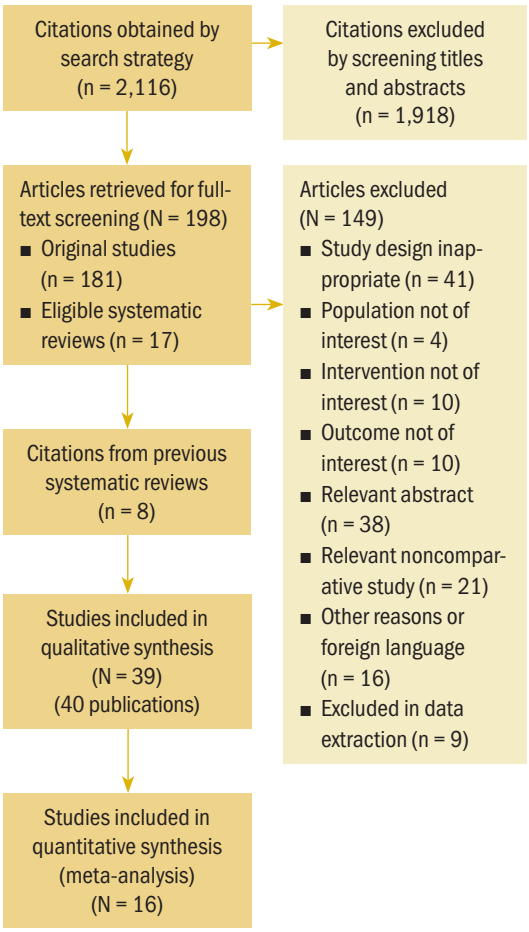
Grading the Certainty of Evidence

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was applied to rate the certainty of evidence. Evidence from randomized clinical trials start at high initial certainty, and those from observational studies and nonrandomized clinical trials start at low initial certainty. The body of evidence across each outcome was then rated down for risk of bias, inconsistency (i.e., heterogeneity), indirectness, imprecision, or publication bias (Guyatt, Oxman, Akl, et al., 2011).

Results

The authors identified 2,116 unique publications from database searching, and 198 studies were screened for inclusion after full-text retrieval. Forty publications were identified, including 39 unique studies

FIGURE 1. PRISMA Flow Chart



(24 randomized controlled trials [RCTs]) with 6,006 patients, that were included in the review. Sixteen studies (11 RCTs) were included in the quantitative synthesis (meta-analysis). The PRISMA flow chart of study selection is shown in Figure 1. Figures and tables for acneform rash and chemotherapy-induced alopecia are presented in the current article. Figures and tables for hand-foot skin reaction and hand-foot syndrome are presented in the Appendix.

Characteristics and Risk of Bias of Included Studies

The characteristics of the included studies are summarized in the Appendix. Seven studies reported patients with or at risk for acneform rash from cancer treatment with EGFRIs. Three studies reported chemotherapy-induced alopecia. Seven studies reported patients with or at risk for hand-foot syndrome from chemotherapy, and three with or at risk for hand-foot skin reaction from chemotherapy. No included studies reported on prevention or management of pruritus related to programmed cell death protein 1 (PD-1) inhibitors or other immunotherapies in the absence of dermatitis. The studies involved in the meta-analysis are shown in the Appendix, stratified by the type of chemotherapeutic skin side effect.

The overall risk of bias was considered to be moderate to low owing to lack of blinding of outcome assessors, participants and personnel, allocation concealment, and adequate sequence generation (see Appendix).

Acneform Rash

Risk for acneform rash from EGFRIs: A total of seven studies informed this question and included 595 patients (Arrieta et al., 2015; Jatoi et al., 2008, 2011; Lacouture et al., 2010; Melosky et al., 2016; Shinohara et al., 2015; Yamada et al., 2015). Studies included patients with lung cancer, colorectal cancer, pancreatic cancer, or mixed diagnoses. Sample size ranged from 38 to 150 patients. Interventions studied included minocycline, tetracycline, and doxycycline, and comparisons were either placebo or control. One study compared prophylactic minocycline to deferred minocycline (Shinohara et al., 2015), and one compared preventive doxycycline to reactive treatment (Lacouture et al., 2010). Cancer treatment included EGFRIs with or without chemotherapy (see Appendix).

Meta-analysis results, grouped by comparisons, and the certainty of evidence are summarized in Table 1 and in the Appendix. One observational study (Shinohara et al., 2015) demonstrated that prophylactic minocycline significantly reduced the development of all-grade (RR = 0.59, 95% CI [0.42, 0.83], certainty of evidence: very low) and grade 1 (RR = 0.53, 95% CI [0.3, 0.91], certainty of evidence: very low) acneform rash using the Common Terminology Criteria for Adverse Events in patients with cancer who received erlotinib as compared to deferred minocycline (U.S. Department of Health and Human Services, 2017). The authors did not find a significant difference in other analyzed intervention groups. Table 2 summarizes the certainty of evidence related to the effectiveness of tetracycline.

Other outcomes: Quality of life was evaluated in five studies (Hofheinz et al., 2018; Jatoi et al., 2008; Lacouture et al., 2010, 2016; Melosky et al., 2016). Two studies (Lacouture et al., 2010; Melosky et al., 2016) applied the Dermatology Life Quality Index (DLQI) at baseline and at subsequent visits. The European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 (EORTC QLQ-C30) and DLQI were administered at

the same time by Hofheinz et al. (2018), whereas quality of life was reported with Skindex-16 by Jatoi et al. (2008) and Lacouture et al. (2016).

According to Hofheinz et al. (2018), quality of life was comparable in both arms (doxycycline plus vitamin K1 versus doxycycline plus vehicle solution). Jatoi et al. (2008) reported that patients treated with tetracycline had better scores on Skindex-16 on multiple quality-of-life domains. Lacouture et al. (2016) reported that doxycycline was associated with less deterioration in quality of life as compared to placebo, and alclometasone (a steroid) was associated with less deterioration in quality of life as compared to placebo.

Three studies (Lacouture et al., 2016; Melosky et al., 2016; Shinohara et al., 2015) reported the rate of treatment interruption or discontinuation because of adverse events. Shinohara et al. (2015) reported time to development of acneform rash.

Lacouture et al. (2016) showed that doxycycline as compared to placebo decreased the incidence of permanent discontinuation of dacomitinib because of treatment-emergent adverse events (7.1% with doxycycline versus 13.8% with placebo).

Adverse events associated with the interventions were assessed in seven studies (Jatoi et al., 2008, 2011; Lacouture et al., 2016; Li et al., 2015; Melosky et al., 2016; Shacham Shmueli et al., 2019; Shinohara et al., 2015). Doxycycline, minocycline, and tetracycline were confirmed to be associated with a certain degree of skin toxicities and/or gastrointestinal adverse events (Jatoi et al., 2008, 2011; Lacouture et al., 2016; Melosky et al., 2016; Shacham Shmueli et al., 2019; Shinohara et al., 2015). Li et al. (2015) reported that vitamin K cream in the treatment of cetuximab-induced skin toxicity had no observed adverse events or reported discomfort from patients.

Hand-Foot Syndrome

A total of seven studies informed this question and included 1,067 patients with primarily breast or colorectal cancer (Braik et al., 2014; Chalermchai et al., 2010; Corrie et al., 2012; Kang et al., 2010; Mortimer et al., 2003; Ota et al., 2014; Yap et al., 2017). Sample size ranged from 56 to 360 patients. Interventions studied consisted of pyridoxine, and comparisons were placebo or control. Cancer treatment was capecitabine alone or in combination with chemotherapy (see Appendix). No studies reporting cooling procedures for hand-foot syndrome were included.

Risk for hand-foot syndrome from chemotherapy: As compared to pyridoxine 200 mg, prophylaxis with pyridoxine 400 mg in capecitabine-treated patients

TABLE 1. Risk for Acneform Rash From Cancer Treatment With EGFRIs

			Treatment Group		Control Group		
Study	RR	95% CI	Events	Total	Events	Total	% Weight
Tetracycline versus no tetracycline							
Arrieta et al., 2015 (RCT)	0.59	[0.41, 0.85]	20	45	34	45	33.32
Jatoi et al., 2008 (RCT)	0.79	[0.46, 1.43]	13	31	16	30	29.87
Jatoi et al., 2011 (RCT)	1.03	[0.93, 1.15]	32	33	30	32	36.81
Subtotal (I^2 = 92.1%, p = 0.000)	0.79	[0.41, 1.52]	65	109	80	107	100
Minocycline versus no minocycline							
Melosky et al., 2015 (RCT)	1.02	[0.86, 1.22]	42	50	41	50	100
Prophylactic minocycline versus deferred minocycline							
Shinohara et al., 2015 (observational)	0.59	[0.42, 0.83]	21	44	42	52	100
Preemptive versus reactive skin treatment							
Lacouture et al., 2010 (RCT)	0.67	[0.38, 1.2]	13	48	19	47	100

CI—confidence interval; EGFRI—epidermal growth factor receptor inhibitor; RCT—randomized controlled trial; RR—relative risk
Note. Weights are from random-effects analysis. EGFRIs were all grade, as defined by Common Terminology Criteria for Adverse Events (U.S. Department of Health and Human Services, 2017).

TABLE 2. Development of Acneform Rash: Tetracycline Versus No Tetracycline

Outcome	Studies and Design	RR	95% CI	I^2	Risk Difference	Certainty of Evidence
Development of acneform rash (all grade)	3 studies, 3 RCTs (n = 216)	0.79	[0.41, 1.52]	92%	157 fewer per 1,000 (441 fewer to 389 more)	Very low; rated down twice because of imprecision[a], inconsistency[b], and risk of bias[c]
Development of acneform rash (grade 1)	1 study, 1 RCT (n = 90)	0.72	[0.4, 1.29]	–	112 fewer per 1,000 (240 fewer to 116 more)	Very low; rated down twice because of imprecision[a] and risk of bias[c]
Development of acneform rash (grade 2)	3 studies, 3 RCTs (n = 216)	0.69	[0.3, 1.58]	74%	125 fewer per 1,000 (281 fewer to 233 more)	Very low; rated down twice because of imprecision[a], inconsistency[b], and risk of bias[c]
Development of acneform rash (grade 3)	1 study, 1 RCT (n = 90)	0.25	[0.03, 2.15]	–	67 fewer per 1,000 (86 fewer to 102 more)	Very low; rated down twice because of imprecision[a] and risk of bias[c]

[a] Without known thresholds, the authors rated down once for either events less than 300 or 95% CI including appreciable benefits and harm (binary outcomes).
[b] Without known thresholds, the authors rated down for I^2 greater than 50% (binary outcomes).
[c] For RCTs, the authors used the Cochrane Collaboration risk-of-bias tool and evaluated according to the two most important domains that may cause bias: random sequence generation and blinding of outcome assessment. For non-RCTs, the authors used the Newcastle-Ottawa scale and evaluated according to the two most important domains that may cause bias: the representative of patients, reported as a consecutive sample of patients and comparability of patients. RCTs and non-RCTs are evaluated as follows: (a) 2 domains of low risk = low risk, (b) 1 low risk plus 1 high risk or unclear/2 unclear = unclear, or (c) 1 unclear plus 1 high risk/2 high risk = high risk.
CI—confidence interval; RCT—randomized controlled trial; RR—relative risk
Note. When greater than 50% of studies were RCTs with no inconsistency, the authors started at high quality; otherwise, they started at low. Grades were defined using Common Terminology Criteria for Adverse Events (U.S. Department of Health and Human Services, 2017).

lowered the risk for grade 2 or 3 hand-foot syndrome (RR = 0.26, 95% CI [0.08, 0.79], certainty of evidence: low) as demonstrated in one RCT (Chalermchai et al., 2010). No significant difference was found in a meta-analysis of four studies comparing pyridoxine (any dose) versus no pyridoxine (see Appendix).

Other outcomes: Two studies (Li et al., 2015; Yap et al., 2017) assessed quality of life using EORTC QLQ-C30 and functional limitations using the EuroQol EQ-5D-3L questionnaire. Chalermchai et al. (2010) reported the rate of treatment interruption or discontinuation from adverse events. Potential adverse events from pyridoxine were assessed in two RCTs (Toyama et al., 2018; von Gruenigen et al., 2010). In these studies, the authors assessed the adverse events overall but were not able to determine if the adverse events were from the interventions only or partially from the chemotherapeutic agents used to treat the patients' cancer. According to Toyama et al. (2018), adverse events were similar in the pyridoxine and no pyridoxine groups, except for leukopenia, which was more common in the pyridoxine group. In the study by von Gruenigen et al. (2010), the most common adverse events in both groups were blood- or bone marrow-related symptoms, gastrointestinal symptoms, and constitutional symptoms.

Hand-Foot Skin Reaction

Three RCTs (Lin et al., 2017; Ren et al., 2015; Shinohara et al., 2014) reported hand-foot skin reaction in 967 patients with hepatocellular or renal cell cancer (see Appendix). Sample size ranged from 33 to 871 patients. Interventions studied consisted of urea-containing cream plus best supportive care, corticosteroid ointment, and hydrocolloid dressing containing ceramide. All patients were receiving sorafenib for cancer treatment.

Lin et al. (2017) reported that the risk for hand-foot skin reaction associated with sorafenib was not different between the corticosteroid cream–treated group and the non-corticosteroid group, but the median time to develop hand-foot skin reaction was longer in the

corticosteroid group (median = 41 days, range = 1–238 days) than that in the non-corticosteroid group (median = 22 days, range = 5–145 days), which was not statistically significant (p = 0.0639). However, in another RCT, Ren et al. (2015) found that urea-containing cream was significantly associated with a reduced risk of developing any-grade hand-foot skin reaction induced by sorafenib (odds ratio = 0.457, 95% CI [0.344, 0.608], p < 0.001). Similarly, the median time to first occurrence of hand-foot skin reaction was significantly longer in the urea-containing cream group (hazard ratio = 0.658, 95% CI [0.541, 0.799], p < 0.001).

Shinohara et al. (2014) conducted a randomized multicenter trial to investigate the efficacy of a hydrocolloid dressing with ceramide for the treatment of sorafenib-induced hand-foot skin reaction by comparing with 10% urea-containing cream. The results showed that the risk for grade 2 or higher hand-foot skin reaction on the soles was significantly lower with ceramide (29.4% with ceramide versus 68.8% without, p = 0.03), whereas no significant difference was observed between the two groups in terms of hand-foot skin reaction on the hands (p = 0.58). The median time to development of grade 2 or 3 hand-foot skin reaction was significantly longer with ceramide (greater than 28 days, 95% CI [13, greater than 28]) as compared to urea-containing cream (22 days, 95% CI [15, 27]) (p = 0.03). For adverse events, only a mild skin sore was observed in one patient treated with ceramide.

Alopecia

A total of six studies informed this question and included 774 patients (Betticher et al., 2013; Kargar et al., 2011; Protière et al., 2002; Rugo et al., 2017; van den Hurk et al., 2013, 2014). Sample size ranged from 63 to 246 patients. Patients included in the studies were primarily treated for breast cancer, with two studies including patients with other solid tumors (Betticher et al., 2013; van den Hurk et al., 2013, 2014). All patients received systemic chemotherapy as treatment for cancer. Interventions studied included scalp cooling systems, as well as cooling caps, and were compared to not receiving any sort of cooling. No studies reporting on the use of minoxidil were identified.

Meta-analysis of two studies (Kragar et al., 2011; van den Hurk et al., 2013) with 308 patients showed that scalp cooling significantly reduced the risk for developing severe hair loss or total alopecia using WHO criteria (RR = 0.8, 95% CI [0.67, 0.94], I^2 = 21.8%, certainty of evidence: low) (see Table 3). The risk difference was 183 fewer per 1,000 (302 fewer to 55 fewer).

Four studies (Deplanque et al., 2016; Nangia et al., 2017; Rugo et al., 2017; van den Hurk et al., 2014) reported on quality of life associated with the interventions for the prevention and/or treatment of alopecia. Three studies (Betticher et al., 2013; Protière et al., 2002; Rugo et al., 2017) assessed patient comfort by reported unpleasant feeling or satisfaction score. In three studies (Protière et al., 2002; Rugo et al., 2017; van den Hurk et al., 2013), researchers found that scalp cooling did not lead to scalp metastasis. Adverse events from the interventions were reported in four studies (Betticher et al., 2013; Deplanque et al., 2016; Nangia et al., 2017; Rugo et al., 2017). Adverse events included gastrointestinal, neural, and skin side effects. Rugo et al. (2017) evaluated hair loss with the Dean scale (Rugo & Melin, 2013) (score range from 0 with 0% hair loss to 4 with greater than 75% hair loss) and found that 67 of 101 patients demonstrated

SUPPLEMENTARY MATERIAL AVAILABLE ONLINE

Appendices mentioned within this article can be accessed online at https://bit.ly/31bDrPW.

TABLE 3. Risk for Chemotherapy-Induced Alopecia With Scalp Cooling Versus No Scalp Cooling

			Treatment Group		Control Group		
Study	RR	95% CI	Events	Total	Events	Total	% Weight
van den Hurk et al., 2013 (observational)	0.82	[0.75, 0.89]	128	160	84	86	85.93
Kargar et al., 2011 (quasirandomized)	0.67	[0.44, 1]	15	30	24	32	14.07
Subtotal (I^2 = 21.8%, p = 0.258)	0.8	[0.67, 0.94]	143	190	108	118	100

CI—confidence interval; RR—relative risk
Note. Weights are from random-effects analysis. Alopecia was defined as severe hair loss or total alopecia as defined by World Health Organization (1979) criteria.

hair loss of 50% or less in the scalp-cooling group as compared to 0 of 16 patients in the control group ($p < 0.001$). In an observational study, van den Hurk et al. (2014) conducted a cost-effectiveness analysis of scalp cooling and reported on total patient costs and their influence on average societal costs. In that study, the authors reported that wigs were still purchased by 38% of patients despite scalp cooling reducing the use of a wig or head cover by 40%, which limited the decrease in societal costs (van den Hurk et al., 2014).

Discussion

This systematic review and meta-analysis investigated interventions for the prevention and treatment of skin toxicities following cancer treatment. Prophylactic oral minocycline was found to reduce the development of acneform rash in patients receiving EGFRIs, but this benefit did not extend to minocycline when used as a treatment after the rash has developed. Tetracycline offered moderate benefits as compared to no tetracycline for the development of all grades of acneform rash. The use of prophylactic treatment with doxycycline and 1% hydrocortisone had a moderate benefit for the reduction in the development of all grades of acneform rash as compared to initiating treatment after the rash has developed. Treatment of hand-foot syndrome with pyridoxine does not appear to be effective at either 200 mg or 400 mg doses. Identified studies for hand-foot skin reactions included different interventions (topical corticosteroids, urea-containing cream, and a hydrocolloid dressing with ceramide), which all showed some benefit. Because of the diversity of interventions, the results could not be pooled in a meta-analysis. For the development of alopecia, scalp cooling had a moderate benefit over no scalp cooling for the outcome of severe hair loss or total alopecia using WHO criteria.

Strengths and Limitations

The certainty of evidence is limited by heterogeneity of included patients and the interventions used to prevent skin reactions to chemotherapy. The strengths of this review include following a rigorous and transparent methodology for the identification of eligible studies, meta-analysis, and grading of the evidence. In addition, randomized and nonrandomized comparative studies were included to evaluate the totality of evidence.

Gaps in the Literature

Randomized trials and comparative studies involving cooling procedures for hand-foot syndrome, as well as those that involve minoxidil for alopecia, in patients treated with chemotherapy were lacking. This area remains in need of quality trials that would help answer these questions in the future.

Implications for Nursing

Skin toxicities can be disfiguring and lead to treatment delays, as well as diminished quality of life. Preventing and managing these unique reactions is of clinical importance. This review identifies some promising interventions, albeit with varying certainty, and serves as the evidence base for a clinical practice guideline on management of skin toxicities for patients undergoing cancer treatment. Healthcare providers managing patients at risk for or already experiencing cancer treatment–related skin toxicities have an opportunity to engage patients in shared decision making and elicit their values and preferences. This is also an opportunity for interprofessional collaboration among nurses, oncologists, and dermatologists to coordinate assessment, intervention, and follow-up, which would lead to treatments that fit the patient's context and goals. Future research and clinical practice can move the evidence base forward by using standardized instruments, such as those that grade symptom severity and assess quality of life, and conducting well-designed clinical trials to address gaps in the research literature.

Conclusion

Skin toxicities are prevalent side effects of cancer treatments that can be managed with appropriate treatment. This systematic review synthesized the available evidence on interventions for EGFRI acneform rash, hand-foot skin reaction, hand-foot syndrome, and chemotherapy-induced alopecia. Continued research on these side effects and other skin toxicities is needed to improve patient care.

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