ONS Guidelines™ for Cancer Treatment–Related Skin Toxicity

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BACKGROUND: Management of cancer treatment–related skin toxicities can minimize treatment disruptions and improve patient well-being.

OBJECTIVES: This guideline aims to support patients and clinicians in decisions regarding management of cancer treatment–related skin toxicities.

METHODS: A panel developed a guideline for management of cancer treatment–related skin toxicities using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) for certainty of evidence and the National Academies of Sciences, Engineering, and Medicine criteria for trustworthy guidelines. The Cochrane risk-of-bias tool assessed risk of bias. A quantitative or narrative synthesis of the evidence was completed.

RESULTS: The panel issued seven conditional recommendations for epidermal growth factor receptor inhibitor rash, hand-foot skin reaction, hand-foot syndrome, and chemotherapy-induced alopecia. The panel suggested strategies for prevention and treatment for all toxicities except hand-foot syndrome, which only has a prevention recommendation.

IMPLICATIONS FOR NURSING: Cancer treatment–related skin toxicities can significantly affect quality of life. Incorporation of these interventions into clinical care can improve patient outcomes.

KEYWORDS skin toxicities; alopecia; GRADE; guidelines; side effect management
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Side effects of treatment that cause changes in appearance can be some of the most distressing toxicities to patients with cancer (Salzmann et al., 2019). The incidence of skin toxicities to systemic cancer therapies is reported to be as high as 90% for some systemic therapies (Salzmann et al., 2019). Patients often feel that these changes stigmatize them as patients with cancer and are a constant reminder of their disease (Salzmann et al., 2019). In addition, these side effects may be uncomfortable or painful, limit normal daily functioning, and leave permanent changes. Differing skin toxicities are caused by a variety of standard chemotherapies, targeted agents, and immunotherapies.

Common skin toxicities that will be covered by these guidelines include epidermal growth factor receptor inhibitor (EGFRI) rash, hand-foot skin reaction, hand-foot syndrome or palmar-plantar erythroderma, and chemotherapy-induced alopecia.

Epidermal Growth Factor Receptor Inhibitor Rash

Acneform rash is the most common dermatologic adverse event (AE) that occurs with EGFRIs, with an incidence as high as 90% (Tan & Chan, 2009). This type of rash is often painful or pruritic and most commonly presents on the upper part of the body and head where sebaceous glands are dense (Braden & Anadkat, 2016). The rash develops within the first one to two weeks of the initiation of EGFRI therapy, peaks at around four to six weeks of therapy, and resolves by three to four months after the start of therapy (Lacouture et al., 2011). Patients may be left with residual erythema or hyperpigmentation (Lacouture et al., 2011). The severity of the rash varies and can lead to dose adjustments or treatment discontinuation in severe cases (Lacouture, 2006).

EGFRI rashes affect the quality of life (QOL) and psychosocial well-being of patients and places patients at risk for secondary skin infections (Joshi et al., 2010; Lacouture et al., 2011). However, evidence exists that better response to treatment is correlated with the development of rash (Abdel-Rahman & Fouad, 2015).

Hand-Foot Skin Reaction

Hand-foot skin reaction describes an array of side effects involving the hands and/or feet and is associated with multikinase inhibitor (MKI) treatment. It is distinct from hand-foot syndrome. Hand-foot skin reaction has an incidence of about 9%–62%, depending on the drug (Lacouture et al., 2008). Hand-foot skin reaction typically presents during the first two to six weeks of therapy with erythema, tenderness, paresthesias, dysesthesia, and intolerance to contact with hot objects (De Wit et al., 2014; McLellan & Kerr, 2011). Eventually, blisters followed by hyperkeratotic skin may appear on areas of skin that are exposed to friction or weight bearing. These areas are frequently painful and may impair function, thereby affecting the patient's QOL and possibly leading to dose modification or therapy discontinuation (Lacouture et al., 2008).

Hand-Foot Syndrome

Hand-foot syndrome, also known as palmar-plantar erythroderma, is most often associated with pyrimidine analog and anthracycline chemotherapy agents (Nikolaou et al., 2016). It should not be confused with hand-foot skin reaction, which occurs with MKIs (Chu et al., 2008). The incidence is reported to be 6%–62% for single agents, and as high as 89% for combinations of agents associated with hand-foot syndrome (Gabra et al., 1996; Twelves et al., 2005; Wardley et al., 2010). Hand-foot syndrome typically develops within days to several weeks of initiation of chemotherapy (Degen et al., 2010). It initially presents with numbness, paresthesias, and erythema on the palms and sometimes the soles of the feet (Nikolaou et al., 2016). Patients with darker skin may develop hyperpigmentation rather than erythema (Nikolaou et al., 2016). Lesions are sharply demarcated, painful, and edematous (Degen et al., 2010). Eventually, blisters develop that peel and become painful, limiting daily functioning, decreasing patient QOL, and significantly affecting treatment schedules (Scheithauer & Blum, 2004).

Chemotherapy-Induced Alopecia

Along with myelosuppression and gastrointestinal side effects, chemotherapy-induced alopecia is one of the most common adverse effects of cancer therapy (Boyle et al., 2018). The reported incidence of chemotherapy-induced alopecia ranges from 10% to 100%, depending on the chemotherapeutic agent and dose, and the average incidence is estimated at 65% (Rossi et al., 2017). Route of administration, combinations of agents, and patient-related factors can also influence the occurrence of chemotherapy-induced alopecia (Paus et al., 2013). Because of its effects on appearance, self-esteem, and sexuality, it is one of the most distressing side effects to patients, even causing a small number to decline treatment (Balagula et al., 2011). Chemotherapy-induced alopecia is also seen as a stigmatizing sign highlighting a patient's cancer status (Trüeb, 2009; Trusson & Pilnick, 2017).

Hair loss typically begins within one to three weeks of initial chemotherapy administration and becomes noticeable when about 50% of the hair on the scalp is lost (Rossi et al., 2017). Alopecia is usually reversible, and hair regrows three to six months after completion of chemotherapy. However, hair may have a different color and/or texture when it returns, and regrowth may not be complete, depending on the amount of damage to hair follicle stem cells (Paus et al., 2013). Patients may perceive alopecia as one of the most devastating effects of cancer therapy (Rossi et al., 2017).

Summary

Dermatologic AEs can result in negative physical and psychosocial effects ranging from mild to severe and have even led to change in therapy schedules and forgoing effective treatment in fear of developing these side effects, ultimately affecting clinical outcomes. Skin toxicities have gained considerable attention during the past decade, with novel targeted agents, and have become a more focused topic as the field of oncodermatology has emerged. There is a relative lack of evidence for effective management of systemic cancer therapy skin toxicities. It is important that oncology nurses are knowledgeable about the current evidence for effective management of skin toxicities to improve QOL and the ability to receive the most effective treatment for patients. Clinical practice guidelines can support shared decision making and communication to support patients' values and preferences in treatment decision making.

Aim of the Guideline and Specific Objectives

The aim of this guideline is to provide evidence-based side effect management recommendations for individuals with cancer who are experiencing skin reactions

from cancer treatment. The guideline incorporates the most recently published research on interventions for the prevention and management of skin reactions during cancer treatment. The target audience includes oncology healthcare professionals, patients, and decision makers. Policymakers interested in this guideline include individuals and organizations developing local, national, or international protocols with

TABLE 1. GRADE Definitions on Strength of Recommendation and Guide to Interpretation

Strength of Recommendation	Wording in the Guideline	For the Patient	For the Clinician	For Policymakers	For Researchers
Strong	"The ONS Guidelines™ panel recommends . . ."	Most individuals in this situation would want the intervention, and only a small proportion would not.	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	In most cases, the recommendation can be adopted as policy. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	This recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide information that alters the recommendation.
Conditional	"The ONS Guidelines panel suggests . . ."	Most individuals in this situation would want the suggested intervention, but many would not.	Different choices will be appropriate for different individuals. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with individuals when working toward a decision.	Policymaking will require substantial debate and involvement of various stakeholders.	This recommendation is likely to be strengthened by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional recommendation will help to identify possible research gaps.
Research and/or knowledge gap	"The ONS Guidelines panel recommends the intervention only in the context of a clinical trial. . . ."	A discussion of benefits/harms and alternatives is warranted.	Clinicians should look for clinical trials testing this intervention, if individuals are interested.	–	Available evidence is insufficient to determine true effect, and this recommendation may be appropriate for research.

GRADE—Grading of Recommendations, Assessment, Development, and Evaluation; ONS—Oncology Nursing Society
Note. Based on information from Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, et al., 2011; Guyatt, Oxman, Sultan, et al., 2011.
Note. From "ONS Guidelines™ for Cancer Treatment–Related Hot Flashes in Women With Breast Cancer and Men With Prostate Cancer," by M. Kaplan, P.K. Ginex, L.B. Michaud, et al., 2020, *Oncology Nursing Forum, 47*(4), p. 376 (https://doi.org/10.1188/20.ONF.374-399). Copyright 2020 by Oncology Nursing Society. Reprinted with permission.

a goal of improving care of adults with cancer who are experiencing skin reactions. The guideline is based on a systematic review and meta-analysis that explored the following research question: What interventions are effective in the prevention or treatment of skin toxicities in patients receiving systemic therapy for cancer?

Guideline Development Methods

The Oncology Nursing Society (ONS) vetted and appointed individuals to the ONS Guidelines™ panel. The membership of the interprofessional panel included oncology nurses at all levels of practice, a medical oncologist, and a patient representative (see online Appendix). The panel was coordinated by the manager of evidence-based practice at ONS (P.K.G.) with collaboration from a GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodologist (R.L.M.). The evidence synthesis for this guideline was based on a recently completed rigorous systematic review and meta-analysis (Ding, Farah, et al., 2020). The panel completed its work using online and face-to-face meetings and web-based tools (www.gradepro.org), with a two-day in-person meeting to review the evidence and formulate recommendations.

The ONS Guidelines panel developed and graded the recommendations and assessed the certainty in the supporting evidence according to the GRADE approach (Guyatt, Oxman, Sultan, et al., 2011). The guideline development process—including panel formation, management of conflicts of interest, internal and external review, and organizational approval—was guided by policies and procedures derived from the Guideline International Network (GIN)-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and the National Academies of Sciences, Engineering, and Medicine (NASEM) criteria for trustworthy guidelines (Graham et al., 2011; Schünemann et al., 2014).

Financial and intellectual disclosures of interest of all participants were collected and managed according to ONS policies and the recommendations of NASEM and GIN (Graham et al., 2011; Schünemann et al., 2015). At the time of appointment and again at the recommendations meeting, disclosures were recorded and the ONS Guidelines panel had no relevant conflicts of interest (no material interest in any commercial entity with a product that could be affected by the guidelines) (see online Appendix).

Formulation of Specific Clinical Questions and Determining Outcomes of Interest

The ONS Guidelines panel met remotely to discuss and prioritize clinical questions for this guideline. Panelists were instructed to identify questions that were clinically relevant—questions about skin reactions that patients with cancer were asking and that clinicians had uncertainty regarding the answer. Questions were formulated into PICO (Patient, Intervention, Comparator, Outcome) components. The ONS Guidelines panel selected outcomes of interest for each question a priori. The panel discussed all possible outcomes and prioritized importance for patients and decision making using the GRADE approach (Guyatt, Oxman, Kunz, et al., 2011). The panel rated the following outcomes as critical for clinical decision making across the PICO questions: QOL, development of skin toxicity, AEs, and severity or change in skin toxicity.

Synthesis of Evidence and Development of Recommendations

The evidence for this guideline was developed in a systematic review of randomized controlled trials (RCTs) on interventions for skin toxicities (Ding, Farah, et al., 2020). The evidence from that review was summarized and assessed in a GRADE evidence profile. Within the evidence profile, the body of evidence across each outcome is assessed based on factors that either decrease or increase one's certainty: risk of bias, inconsistency, indirectness, imprecision, publication bias, large magnitude of effect, dose-response gradient, or opposing residual confounding (Balshem et al., 2011; Guyatt, Oxman, Akl, et al., 2011). In addition to the certainty of evidence, the panel formulated recommendations considering the balance of benefits and harms, patients' values and preferences, resource use, equity, acceptability, and feasibility. For each question, the panel entered judgments into the GRADE Evidence-to-Decision (EtD) framework using the GRADEpro Guideline Development Tool (www.gradepro.org).

Based on the evidence summarized in the EtD framework table, the panel developed clinical recommendations during the two-day in-person meeting. The panel arrived at consensus on the following for each recommendation: the certainty in the evidence, the balance of benefits and harms of the compared intervention options, and the assumptions about the values and preferences associated with the decision. The panel also discussed the extent of the use of alternative treatment options. The panel agreed on the recommendations (including direction and

strength), remarks, and qualifications by consensus vote based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the guideline panel.

Interpretation of Recommendations

The strength of the recommendations in this guideline is labeled as strong or conditional. In some situations, the panel deemed the available evidence insufficient to determine a true effect and identified

TABLE 2. Summary of Recommendations: ONS Guidelines™ for Skin Toxicities in Patients With Cancer

Recommendation	Strength of Recommendation	Certainty of Evidence
EGFRI rash		
Recommendation 1 (prevention): Among individuals who are receiving EGFRIs, the ONS Guidelines™ panel suggests either prophylactic oral antibiotics or no prophylactic oral antibiotics for the prevention of skin rash. **Remarks:** Individuals who place a higher value on prevention of rash and a lower value on possible side effects of antibiotics may prefer to start oral antibiotics prophylactically. Individuals who place a higher value on avoiding unnecessary medication may prefer to not use antibiotics until symptoms present.	Conditional	Very low
Recommendation 2 (treatment): Among individuals who are receiving EGFRIs who have developed grade 1–3 acneform rash, the ONS Guidelines panel suggests topical corticosteroids and oral antibiotics in addition to usual skin care rather than usual skin care alone.	Conditional	Very low
Hand-foot skin reaction		
Recommendation 3 (prevention): Among individuals receiving MKIs at risk for hand-foot skin reaction, the ONS Guidelines panel suggests topical urea and topical steroids in addition to usual care rather than usual care alone.	Conditional	Moderate/low
Recommendation 3 (treatment): Among individuals receiving MKIs with hand-foot skin reaction, the ONS Guidelines panel suggests topical urea and topical steroids in addition to usual care rather than usual care alone.	Conditional	Very low
Hand-foot syndrome		
Recommendation 4: Among individuals receiving capecitabine, the ONS Guidelines panel suggests no treatment rather than prophylactic oral pyridoxine (vitamin B_6) for the prevention of hand-foot syndrome.	Conditional	Low
Recommendation 5: Among individuals receiving taxane-based chemotherapy regimens, the ONS Guidelines panel suggests cooling procedures rather than no cooling procedures for prevention of hand-foot syndrome.	Conditional	Very low
Chemotherapy-induced alopecia		
Recommendation 6: Among individuals with cancer receiving cytotoxic agents associated with chemotherapy-induced alopecia who are concerned about alopecia, the ONS Guidelines panel suggests scalp cooling rather than no scalp cooling for the minimization or reduction in severity of alopecia. **Remarks:** If an individual is seen at a facility without a cooling system, a cap can be used because they have similar efficacy.	Conditional	Very low
Recommendation 7: Among individuals with cancer on cytotoxic treatment at risk for alopecia, the ONS Guidelines panel suggests topical minoxidil rather than no treatment for the shortening or minimization of alopecia. **Remarks:** Individuals preferring to minimize or shorten hair loss may wish to use minoxidil.	Conditional	Very low

EGFRI—epidermal growth factor receptor inhibitor; MKI—multikinase inhibitor; ONS—Oncology Nursing Society

the area as an evidence gap. Table 1 provides the interpretation of the recommendations by patients, clinicians, healthcare policymakers, and researchers. The recommendations are summarized in Table 2.

Document Review

Draft recommendations were reviewed and approved by all members of the ONS Guidelines panel and then opened for public comment from January 27 to February 7, 2020. In addition, a targeted peer review was conducted with three clinical or research experts on the dermatologic effects of cancer therapy. The goal of public comment and targeted peer review was to obtain direct feedback on the draft recommendations, as well as feedback to facilitate dissemination of the final guideline to practitioners. Following public and targeted comment, the document was revised to address pertinent comments and clarify text where needed; however, no changes were made to the recommendations. The ONS Board reviewed and approved the guideline methodology and process. The guidelines were then submitted to the *Oncology Nursing Forum* for peer review.

How to Use These Guidelines

ONS Guidelines are intended to assist clinicians in making decisions about treatment interventions for common symptoms and other side effects experienced by patients with cancer throughout the treatment trajectory. ONS Guidelines are intended to inform education, identify research gaps, and promote policy and advocacy. They may also be used by patients in collaboration with their healthcare team. ONS Guidelines are not medical advice and do not replace care by a cancer care clinician. Using a shared decision-making process, clinicians make decisions with patients, including discussion of patients' values and preferences with respect to their current situation. ONS Guidelines may not include all available treatments for an individual patient. Treatments described in the ONS Guidelines may not be appropriate for all patients or in all scenarios. Following these ONS Guidelines does not guarantee improvement or a successful outcome. ONS does not warrant or guarantee any products described.

Implementation of ONS Guidelines will be facilitated by forthcoming dissemination tools and patient education resources. The use of ONS Guidelines will also be facilitated by the links to the EtD frameworks and summary-of-findings tables in each section.

Recommendations, Key Evidence, and Qualifying Statements

The systematic review for this guideline included 40 studies (25 RCTs and 15 comparative observational studies) with 6,181 patients with a history of cancer. Twenty studies (13 RCTs and 7 comparative observational studies) are included in quantitative synthesis (Ding, Farah, et al., 2020). The ONS Guidelines panel recommendations are grouped by toxicity: EGFRI rash, hand-foot skin reaction, hand-foot syndrome, and chemotherapy-induced alopecia. Each recommendation includes a description of the total analysis (network meta-analysis, pairwise meta-analysis, and narrative summaries) in the GRADE EtD frameworks. The narrative following each recommendation parallels the organization of the GRADE EtD framework. First, a summary of the evidence is presented, followed by a description of the benefits and harms considered by the panel members, including a statement about the certainty of the evidence. Additional factors from the EtD framework are then summarized in a section labeled "other EtD framework criteria and considerations." Lastly, a final summary of the recommendation is presented, considering any overarching remarks made by the panel. The EtD framework for each recommendation is available in the online Appendix.

Although there is no universally accepted definition of usual care for patients at risk for skin side effects, general skincare management and advice are available. Patients who are at risk for skin side effects should receive education about general skin care at the beginning of treatment. This education should include advice to avoid topical products with fragrances or alcohol, mild soap and water for routine bathing, a cream-based moisturizer, and a broad-spectrum sunscreen (SPF 30 or higher). When considering usual care in the following PICO questions, the ONS Guidelines panel assumed usual care to include these general skincare recommendations.

Prevention of Epidermal Growth Factor Receptor Inhibitor Rash

Should oral antibiotics (doxycycline, tetracycline, and minocycline) and usual care rather than usual care alone be used in the prevention of skin rash in individuals taking EGFRIs?

Recommendation 1

Among individuals who are receiving EGFRIs, the ONS Guidelines panel suggests either prophylactic oral antibiotics or no prophylactic oral antibiotics for

the prevention of skin rash (conditional recommendation, very low certainty of evidence).

Remarks: Individuals who place a higher value on prevention of rash and a lower value on possible side effects of antibiotics may prefer to start oral antibiotics prophylactically. Individuals who place a higher value on avoiding unnecessary medication may prefer to not use antibiotics until the rash presents.

Summary of the Evidence

The evidence for this question was informed by three studies for prophylactic tetracycline (Arrieta et al., 2015; Jatoi et al., 2008, 2011), three studies for prophylactic minocycline (Melosky et al., 2016; Shinohara et al., 2015; Yamada et al., 2015), and one study for prophylactic doxycycline (Lacouture et al., 2010). Development and staging of acneform rash were measured using the Common Terminology Criteria for Adverse Events.

Benefits

There is some evidence that prophylactic tetracycline may reduce development of all grades of acneform rash collectively (relative risk [RR] = 0.79; 95% confidence interval [CI] [0.41, 1.52]), as well as grades 1, 2, and 3 independently over no treatment with tetracycline (RR = 0.72; 95% CI [0.4, 1.29]; RR = 0.69; 95% CI [0.3, 1.58]; and RR = 0.25; 95% CI [0.03, 2.15], respectively), but the evidence is uncertain. QOL benefits were seen in patients treated with prophylactic tetracycline. Patients reported better scores on symptom items in QOL scales such as skin burning or stinging, skin irritation, and being bothered by the skin condition (as measured on the Skindex-16) (Jatoi et al., 2008). Prophylactic minocycline may reduce development of grade 3 acneform rash over no treatment (RR = 0.49; 95% CI [0.23, 2.15]), but the evidence is uncertain. Prophylactic doxycycline may reduce development of any stage of acneform rash (RR = 0.67; 95% CI [0.38, 1.2]), but the evidence is uncertain.

Patients who received doxycycline treatment prophylactically (preemptive group) had improved QOL compared to patients who were treated after rash developed (reactive group) (Lacouture et al., 2010). At week 3, when EGFRI rash often peaks, mean QOL score changes from baseline for patients in the preemptive and reactive treatment groups were 1.3 points and 4.2 points, respectively, indicating less QOL impairment when treated prophylactically (measured with the Dermatology Life Quality Index) (Lacouture et al., 2010). A study of prophylactic or reactive minocycline found no statistical difference in QOL between the groups or at any time point during the study (Melosky et al., 2016).

Harms and Burden

Patients treated with prophylactic minocycline have an increased risk of developing any stage of acneform rash (RR = 1.02; 95% CI [0.86, 1.22]; absolute risk reduction [ARR] 16 more per 1,000, from 115 fewer to 180 more), and an even greater risk of developing stage I and II acneform rash (stage I RR = 1.94; 95% CI [0.25, 15.23]; ARR 433 more per 1,000, from 345 fewer to 6,550 more and stage II RR = 1.04; 95% CI [0.2, 5.49]; ARR 11 more per 1,000, from 216 fewer to 1,212 more), but the evidence is uncertain. Each antibiotic also has undesirable side effects, with serious side effects being rare but significant when they occur.

Certainty in the Evidence of Effects

The certainty in the evidence was rated as very low across the evidence for prophylactic use of antibiotics for prevention of acneform rash.

Other Evidence-to-Decision Framework Criteria and Considerations

The panel judged the desirable anticipated effects to be moderate for all antibiotics and considered not only the reduction in risk of developing a rash but the benefit to QOL. The undesirable anticipated effects were judged to be moderate with concern of gastrointestinal upset, phototoxicity (with doxycycline), and the possibility of a small risk of dizziness, fatigue, drowsiness, pruritus, arthralgia, and tinnitus seen with minocycline. The panel considered there to be possibly important variability in how much people value the main outcomes. Some patients may prefer to prevent the rash, and others may have a preference to avoid additional treatments until they are needed (when the rash occurs). The panel judged that the balance of effects probably favors antibiotics for prevention of rash and prioritized the moderate benefits of preventing the rash over the harms. The panel judged that costs would be negligible, but no cost-effectiveness studies were identified. The panel discussed that preventing the rash may negate additional office visits, may prevent a specialty consultation if an infection occurs, and may prevent discontinuation of treatment if grade 3 rash develops. The panel judged that equity would probably be increased because prevention may be less costly than treatment of rash and the antibiotics are low cost and covered by insurance. The panel considered that acceptability may vary because clinicians may have concerns about antibiotic resistance,

antibiotic stewardship, and the utility of prophylactic treatment, but that the intervention is feasible.

Conclusions

Patients who are starting treatment with EGFRIs are at high risk for developing a rash (Tan & Chan, 2009). The evidence for a prophylactic antibiotic was judged to be very low certainty. However, the ONS Guidelines panel balanced the desirable and undesirable health effects to make a conditional recommendation for either prophylactic antibiotics or to wait until the rash appears. The discussion about when or if to start antibiotics is an important one. Patients may value prevention of the rash, or they may value not taking additional medications with additional side effects. Patient participation in clinical decision making and goal setting is an important consideration for this patient population.

Treatment of Epidermal Growth Factor Receptor Inhibitor Rash

Should topical corticosteroids with oral antibiotics and usual skin care rather than usual skin care alone be used in individuals taking EGFRIs who have developed an acneform rash?

Recommendation 2

Among individuals who are receiving EGFRIs who have developed grade 1–3 acneform rash, the ONS Guidelines panel suggests topical corticosteroids along with oral antibiotics in addition to usual skin care rather than usual skin care alone (conditional recommendation, very low certainty in the evidence).

Summary of the Evidence

The panel considered that almost all patients receiving an EGFRI would develop a rash, so this question was informed by evidence addressing grade 3 rash, considering that a benefit among patients developing grade 3 rash could demonstrate a treatment effect. In addition, the panel also considered studies that included a preemptive (prevention) as well as a reactive (treatment) group. Topical steroids are included in some studies and in usual care to benefit the symptoms and appearance of the rash once it has developed.

The evidence for this question was informed by three studies (Arrieta et al., 2015; Lacouture et al., 2010; Shinohara et al., 2015). Antibiotics included tetracycline, minocycline, and doxycycline, with sample sizes ranging from 90 to 96. Patients with a variety of cancer diagnoses were included.

Benefits

Tetracycline may reduce the development of grade 3 acneform rash compared to no treatment (RR = 0.25; 95% CI [0.03, 2.15]; ARR 67 fewer per 1,000, from 86 fewer to 102 more). Minocycline may reduce the development of grade 3 acneform rash compared to no treatment (RR = 0.49; 95% CI [0.23, 1.06]; ARR 130 fewer per 1,000, from 196 fewer to 15 more).

For the development of any grade acneform rash, prophylactic compared to deferred treatment with minocycline has moderate benefits (RR = 0.59; 95% CI [0.42, 0.83]; ARR 336 fewer per 1,000, from 476 fewer to 139 fewer) and prophylactic compared to deferred treatment with doxycycline has moderate benefits (RR = 0.67; 95% CI [0.38, 1.2]; ARR 133 fewer per 1,000, from 251 fewer to 81 more).

Harms and Burden

AEs were reported in the studies but were noted to be events commonly observed after treatment with the anticancer therapy. In addition to rash, paronychia (17% versus 36%) was reported less frequently in the preemptive compared to deferred treatment group in one study of usual care, topical steroids, and doxycycline (Lacouture et al., 2010).

Certainty in the Evidence of Effects

The panel used the research on prevention to inform its discussion on treatment and thereby considered the certainty in the evidence of effects to be very low.

Other Evidence-to-Decision Framework Criteria and Considerations

The panel judged the desirable and undesirable anticipated effects to be moderate. The prevention evidence informed this question and is indirect to the specific question of treatment when a rash is present. The desirable effects include measurable improvement in the rash once it has appeared, and the undesirable effects include AEs related to the antibiotics or steroids. The panel judged there to be no important uncertainty or variability in how much individuals value the main outcomes because patients do not want the rash to progress once it has occurred. The panel considered that the balance of effects probably favors treatment with topical steroids and oral antibiotics when a rash is present. Topical steroids can be costly, so the panel judged there to be moderate costs with no cost-effectiveness studies found. Equity would probably be reduced because of coverage and accessibility. Some topical steroids are prescribed in

foam, solution, or cream and may have coverage or accessibility constraints for some patients. The panel considered that topical steroids and oral antibiotics are acceptable to key stakeholders and probably feasible to implement.

Conclusions

Patients who have developed a rash from EGFRI treatment are at risk for treatment delays and additional AEs. The evidence for topical steroids and oral antibiotics was judged to be of very low certainty; however, the ONS Guidelines panel balanced the desirable and undesirable health effects to make a conditional recommendation for topical steroids and oral antibiotics for patients with cancer who have developed a rash while taking EGFRIs.

Prevention of Hand-Foot Skin Reaction

Should topical urea and topical corticosteroids rather than usual care be used for individuals taking MKIs who are at risk for hand-foot skin reaction?

Recommendation 3

Prevention: Among individuals receiving MKIs who are at risk for hand-foot skin reaction, the ONS Guidelines panel suggests topical urea and topical steroids in addition to usual care rather than usual care alone (conditional recommendation, moderate/low certainty of evidence).

Treatment: Among individuals receiving MKIs with hand-foot skin reaction, the ONS Guidelines panel suggests topical urea and topical steroids in addition to usual care rather than usual care alone (conditional recommendation, very low certainty of evidence).

Summary of the Evidence

The evidence for this question was informed by a study of urea-based cream as prophylaxis for sorafenib-associated hand-foot skin reaction in patients with hepatocellular carcinoma (Ren et al., 2015). In this trial, 871 patients were randomized to 10% urea-based cream three times a day in conjunction with best supportive care or best supportive care alone. Treatment started on the first day of sorafenib therapy and continued for as many as 12 weeks. Best supportive care was not defined by the authors.

Benefits

Prophylactic use of urea-based cream had a moderate effect on the prevention of any grade hand-foot skin reaction (odds ratio [OR] = 0.46; 95% CI [0.34, 0.61]; ARR 183 fewer per 1,000; from 254 fewer to 113 fewer) (Ren et al., 2015). Urea cream may increase the hand-foot skin reaction–free time (i.e., time to development of hand-foot skin reaction) (hazard ratio [HR] = 0.66; 95% CI [0.54, 0.8]) (Ren et al., 2015).

Harms and Burden

The authors assessed for 26 preselected common AEs at each visit. Except for the differences in hand-foot skin reaction, no significant differences were found between treatment groups in the incidence of treatment-related AEs. The most common AE (after hand-foot skin reaction) was diarrhea, which occurred in 10.5% of patients in the intervention group and 10.2% of patients in the usual care group (Ren et al., 2015).

Certainty in the Evidence of Effects

The quality of evidence was low for the prevention of hand-foot skin reaction and very low for the treatment of hand-foot skin reaction because of risk of bias and unclear randomization and allocation methods.

Other Evidence-to-Decision Framework Criteria and Considerations

The ONS Guidelines panel judged the desirable anticipated effects to be moderate and the undesirable anticipated effects to be small for prevention and trivial for treatment because of the difference in steroid effect on skin prior to or after hand-foot skin reaction has developed. The panel considered that there is uncertainty or variability in how much people value the main outcomes for prevention but that, for treatment, there would probably be no important uncertainty. The difference in values is related to a patient's values and preferences for preventing hand-foot skin reaction over the potential burden and AEs from the steroids and urea treatment. The panel judged that the balance of effects probably favors the intervention and that moderate costs may be involved because of the cost for steroids. No cost-effectiveness studies were identified. The panel judged that equity would probably be reduced for patients who do not have coverage for steroids and that the urea cream, even though it is over-the-counter, can be costly to patients. The panel considered that urea and steroids are acceptable to key stakeholders and would be feasible to implement.

Conclusions

The ONS Guidelines panel determined that there was very low certainty in the evidence that the desirable effects of topical urea and topical steroids outweigh the undesirable effects in patients with cancer who are on MKIs and are at risk for or have developed hand-foot skin reaction. The ONS Guidelines panel issued a conditional recommendation for topical urea and topical steroids for the management of hand-foot skin reaction in patients with cancer on MKIs.

Prevention of Hand-Foot Syndrome

Should oral pyridoxine (vitamin B_6) rather than no oral pyridoxine (vitamin B_6) be used in individuals receiving capecitabine who are at risk for hand-foot syndrome?

Recommendation 4

Among individuals receiving capecitabine, the ONS Guidelines panel suggests no treatment rather than prophylactic oral pyridoxine (vitamin B_6) for the prevention of hand-foot syndrome (conditional recommendation against, low certainty of evidence).

Summary of the Evidence

The evidence for this question was informed by six studies (Braik et al., 2014; Corrie et al., 2012; Kang et al., 2010; Mortimer et al., 2003; Yap et al., 2017; Yoshimoto et al., 2010). All were inpatients receiving capecitabine as treatment for their cancer. The panel made the decision to limit this question to capecitabine therapy but acknowledged that hand-foot syndrome may occur with other treatments. Sample sizes ranged from 77 to 360 and included a variety of cancer diagnoses. Pyridoxine (vitamin B_6) was compared to placebo or to urea cream.

Benefits

Pyridoxine (vitamin B_6) appears to have no benefit for the prevention of all grades of hand-foot syndrome when compared to placebo (RR = 1.02; 95% CI [0.85, 1.23]; ARR 12 more per 1,000, from 89 fewer to 137 more).

Harms and Burden

No harms related to pyridoxine (vitamin B_6) were reported in the studies.

Certainty in the Evidence of Effects

The certainty in the evidence of effects was rated as low because of imprecision and risk of bias.

Other Evidence-to-Decision Framework Criteria and Considerations

The panel judged the desirable anticipated effects as trivial and the undesirable anticipated effects as small for the prevention of hand-foot syndrome with pyridoxine (vitamin B_6). Although no harms were reported in the studies of pyridoxine (vitamin B_6) to prevent hand-foot syndrome, the panel considered that there are known toxicities associated with pyridoxine (vitamin B_6), particularly at higher doses. The panel judged there to be probably no important variability in how much individuals value the main outcomes and that the balance of effects probably favors no treatment because of the greater potential for harms with pyridoxine. There would be negligible costs, with no studies on cost effectiveness. No impact on equity was considered because pyridoxine is widely available and low-cost. The panel considered that pyridoxine is probably not acceptable to key stakeholders because of the unknown efficacy and potential for harms.

Conclusions

Limited consistent evidence exists to support a recommendation for pyridoxine for the treatment of hand-foot syndrome in patients with cancer who are on capecitabine. Based on the potential for harms and limitations of evidence, the ONS Guidelines panel recommended no treatment rather than pyridoxine for the treatment of hand-foot syndrome in patients taking capecitabine for cancer treatment.

Prevention of Hand-Foot Syndrome

Should cooling procedures rather than no cooling procedures be used in patients receiving taxane-based chemotherapy who are at risk for hand-foot syndrome?

Recommendation 5

Among individuals receiving taxane-based chemotherapy regimens, the ONS Guidelines panel suggests cooling procedures rather than no cooling procedures for prevention of hand-foot syndrome (conditional recommendation, very low certainty in the evidence)

Summary of the Evidence

The evidence for this question was informed by two studies (Scotté et al., 2005, 2008). Both were case-control studies with the patients serving as their own control. In Scotté et al. (2005), 45 patients with a mix of cancer diagnoses wore a frozen glove on one hand and no treatment on the opposite hand. In Scotté et al. (2008), 50 patients with a mix of cancer diagnoses wore a frozen sock on one foot and had no

treatment on the opposite foot. Cancer treatments in these studies were limited to taxanes alone or taxane-based therapies, so the panel made the decision to limit this question to individuals receiving taxane-based chemotherapy. Nail toxicity is also a side effect of taxane therapy and is included in the treatment with cooling procedures. A study by McCarthy et al. (2014) assessed taxane-induced hand and fingernail toxicity in 53 patients who wore a frozen glove on one hand with no treatment on the other.

Benefits

Cooling procedures were found to be protective of the development of hand-foot syndrome (RR = 0.44; 95% CI [0.25, 0.77]; ARR 264 fewer per 1,000, from 354 fewer to 108 fewer) and the development of nail toxicity (RR = 0.31; 95% CI [0.06, 1.54]; ARR 310 fewer per 1,000, from 423 fewer to 243 more (Ding, Farah, et al., 2020). However, McCarthy et al. (2014) did not find that cooling procedures offered benefits to nail toxicity.

Harms and Burden

The burden that cooling procedures presents to patients is mixed. One study reported 60% of patients withdrawing because of discomfort with the frozen gloves (McCarthy et al., 2014), and another study reported one patient (2%) reporting discomfort and more than half of patients reporting they were satisfied (58%) or very satisfied (19%) with the frozen sock protection (Scotté et al., 2008)

Certainty in the Evidence of Effects

The panel considered the certainty in the evidence of effects to be very low.

Other Evidence-to-Decision Framework Criteria and Considerations

The ONS Guidelines panel judged the desirable anticipated effects to be moderate because of the reduction in the development of hand-foot syndrome or nail changes. The undesirable anticipated effects were judged to be small, with localized discomfort and the potential to diminish QOL while cooling. The panel considered there to be probably no important uncertainty or variability in how much individuals value the main outcomes. The variability was considered because patients need to start the cooling before and maintain it after cancer treatment and may need to relocate to a different area. The panel considered that, with the appropriate understanding of the severity of the harm (the development of hand-foot syndrome), most patients would choose the cooling procedure and judged that the balance of effects favored cooling. Resources required would vary. There are direct costs to cooling of additional clinician and chair time, and cooling can be done in a variety of ways—from ice and plastic bags to specialized frozen gloves and boots. No cost-effectiveness studies were identified. The effect on health equity would vary with the different cooling procedures that could be used and the accessibility issues with additional chair time. However, equity could be improved by allowing simple, low-cost interventions, such as ice packs for cooling. The panel considered that cooling procedures are acceptable to key stakeholders and probably feasible to implement. The panel acknowledged the burden on clinical space and time and that the cooling procedure should be applied during the infusion of the taxane agent for patients on combination regimens.

Conclusions

The ONS Guidelines panel determined that there was very low certainty in the evidence and that the moderate desirable effects of cooling procedures outweigh the small undesirable effect in patients with cancer who are on taxanes and are at risk for or have developed hand-foot syndrome. The ONS Guidelines panel issued a conditional recommendation for cooling procedures for the prevention of hand-foot syndrome in patients with cancer receiving taxanes.

Prevention of Chemotherapy-Induced Alopecia

Should scalp cooling rather than no scalp cooling be used for individuals receiving cytotoxic agents who are at risk for alopecia?

Recommendation 6

Among individuals with cancer receiving cytotoxic agents associated with chemotherapy-induced alopecia who are concerned about alopecia, the ONS Guidelines panel suggests scalp cooling rather than no scalp cooling for the minimization or reduction in severity of alopecia (conditional recommendation, very low certainty of evidence).

Remarks: If an individual is seen at a facility without a cooling system, an ice cap can be used because they have similar efficacy.

Summary of the Evidence

The evidence for this question was informed by eight studies (Betticher et al., 2013; Kargar et al., 2011; Mols et al., 2009; Nangia et al., 2017; Rugo et al., 2017; Van

den Hurk, Breed, et al., 2012; Van den Hurk et al., 2013; Van den Hurk, Peerbooms, et al., 2012). Rugo et al. (2017) and Nangia et al. (2017) were not included in the meta-analysis based on the measurement of the primary outcome of hair loss. Sample sizes ranged from 63 to 246 and included patients with a variety of cancer diagnoses. One study was an RCT (Nangia et al., 2017), and the remaining had prospective cohort, quasi-experimental, or observational designs.

Benefits

Scalp cooling has a moderate benefit on preventing hair loss (RR = 0.54; 95% CI [0.46, 0.63]; ARR 426 fewer per 1,000, from 500 fewer to 343 fewer) (Ding, Farah, et al., 2020). A systematic review of 13 studies found uncertain benefits to QOL, with 4 (31%) concluding that scalp cooling was associated with significant improvements in QOL measures, 8 (62%) determining that there was either nonsignificant or no improvement in QOL measures, and 1 (7.7%) finding mixed results among specific QOL domains (Marks et al., 2018).

Harms and Burden

Scalp cooling is not tolerated by all patients, with rates of discontinuation because of AEs ranging from 3% to 40%. Most AEs were discomfort from the cold, headaches, or scalp discomfort and were reported as mild or grade 1 or 2. Mols et al. (2009) reported that, in a trial with 98 participants using a cooling system, 39% reported that it was cold, 33% reported that it was a burden, 29% reported that the cap was heavy, 27% reported that they felt bored during the cooling, and 20% reported that they got dizzy.

Scalp metastasis has been reported as a potential AE from scalp cooling. Two systematic reviews addressed this question. In a meta-analysis of scalp cooling (N = 3,197 participants with breast cancer undergoing chemotherapy), a small percentage of patients in the cooling and the noncooling groups developed scalp metastases, with no statistical significance found between groups (0.06% and 0.4%, respectively; p = 0.43) (Rugo et al., 2017). A review of 20 studies on cooling found that cooling was stopped because of the detection of scalp skin metastasis in one patient (Marks et al., 2018) but recommended that further research to find the association between scalp cooling and metastases is warranted.

Certainty in the Evidence of Effects

The panel considered the certainty in the evidence of effects to be very low because of publication bias, risk of bias, and selective reporting.

Other Evidence-to-Decision Framework Criteria and Considerations

The panel judged the desirable anticipated effects to be large, with a relative response rate of 40% and a baseline risk of alopecia of 20%–100% and alopecia being considered a distressing effect that patients want to avoid. The undesirable anticipated effects were judged to be small, with a risk of scalp metastasis of 0.61 (Rugo et al., 2017) and the potential for distress if the scalp cooling was not successful. The panel considered there to possibly be important uncertainty or variability in how much individuals would value the main outcome of hair loss and that the balance of effects probably favors scalp cooling. The panel considered that patients who place a strong value on minimizing or preventing hair loss would place high value on scalp cooling. The costs for a scalp cooling system (single patient use cap and refrigeration system) would be large, with costs of a cooling system ranging from $1,500 to $3,000 per patient (Rubio-Gonzalez et al., 2018); however, no studies on cost effectiveness were identified. Equity would be reduced because of the cost and accessibility; however, ice caps could be used in place of expensive cooling systems. The panel judged scalp cooling to be probably acceptable to key stakeholders and probably feasible to implement. The panel acknowledged that setting up a program with scalp-cooling devices would require significant time and effort, but once the program is operational, the burden would decrease.

Conclusions

The ONS Guidelines panel determined that there was very low certainty in the evidence and that the large desirable effects of cooling caps outweigh the small undesirable effects in patients with cancer who are receiving cytotoxic agents that cause alopecia. The ONS Guidelines panel issued a conditional recommendation for cooling caps for the prevention or minimization of chemotherapy-induced alopecia.

Prevention of Chemotherapy-Induced Alopecia

Should minoxidil rather than usual care be used for individuals receiving cytotoxic agents who are at risk for alopecia?

Recommendation 7

Among individuals with cancer on cytotoxic treatment who are at risk for alopecia, the ONS Guidelines panel suggests topical minoxidil rather than no treatment for the shortening or minimization of alopecia

(conditional recommendation, very low certainty of evidence).

Remarks: Individuals preferring to minimize or shorten duration of hair loss may wish to use topical minoxidil.

Summary of the Evidence

The evidence for this question was informed by four studies (Duvic et al., 1996; Freites-Martinez et al., 2019; Granai et al., 1991; Rodriguez et al., 1994). All studies were in women with cancer, and sample sizes ranged from 10 to 192. Two studies were RCTs (Duvic et al., 1996; Rodriguez et al., 1994), one was a retrospective cohort (Freites-Martinez et al., 2019), and one was a nonrandomized cohort study (Granai et al., 1991).

Benefits

Topical minoxidil has a modest benefit for chemotherapy-induced alopecia, but findings have been mixed. A cohort study included 54 patients with persistent chemotherapy-induced alopecia who were treated with topical minoxidil (45 received only minoxidil, 9 received minoxidil and oral spironolactone). Thirty-six patients (67%) had a moderate to significant improvement, and for 18 (33%) the alopecia was stable or progressed. Duvic et al. (1996) compared topical minoxidil to placebo for alopecia prevention in a sample of patients with breast cancer and found that the duration of complete alopecia was reduced by 50 days for patients using minoxidil compared to placebo. In this study, patients applied the topical minoxidil throughout chemotherapy and four months post-treatment. Other studies (Granai et al., 1991; Rodriguez et al., 1994) found no benefit with topical minoxidil.

Harms and Burden

Patient burden may be an issue with topical minoxidil treatment because it requires twice-a-day application or dosing; in one study, 40% of patients were not able to maintain that treatment schedule (Granai et al., 1991). Pruritus was reported in 60% of patients in another study (Duvic et al., 1996).

Certainty in the Evidence of Effects

The certainty in the evidence was rated to be very low certainty because of the unknown magnitude of the harms.

Other Evidence-to-Decision Framework Criteria and Considerations

The panel considered that this question includes oral and topical minoxidil for treatment. The only evidence for oral minoxidil was an ongoing study (ClinicalTrials.gov identifier: NCT03831334) that will be considered for a future guideline once completed. The panel judged the desirable anticipated effects to be large, with the high percentage of alopecia seen with some cytotoxic treatment regimens. The panel judged the undesirable anticipated effects to be small in that topical application may lead to some patient burden and minoxidil may need to be used for life. The panel considered that individuals preferring to minimize or shorten the duration of hair loss may wish to use topical minoxidil and may weigh a preference for hair regrowth with the burden and cost of minoxidil. The panel judged that the balance of effects probably favors topical minoxidil with moderate costs because of the potential for lifetime use, but no cost-effectiveness studies were identified. Equity may be reduced because topical minoxidil for this use may not be covered by insurance. The panel considered that topical minoxidil is acceptable to key stakeholders and feasible to implement.

Conclusions

The panel determined that there is evidence for a net benefit from topical minoxidil and that the balance of effect favors minoxidil over no treatment. Based on this evidence, the panel issued a conditional recommendation in favor of topical minoxidil in patients for the shortening or minimization of alopecia in patients receiving cytotoxic agents known to cause chemotherapy-induced alopecia.

Discussion

Other Guidelines on Skin Toxicities

Evidence-based treatment guidelines for skin toxicities from cancer treatment are limited primarily because of the lack of relevant RCTs. The Multinational Association of Supportive Care in Cancer (MASCC) published clinical practice guidelines for the prevention and treatment of EGFRI-associated dermatologic toxicities in 2011 (Lacouture et al., 2011). The MASCC guidelines were developed following a review of the literature and assigning level of evidence and grade to each recommendation. For prevention of EGFRI rash, MASCC recommends topical hydrocortisone 1% cream with moisturizer and sunscreen twice daily and oral antibiotic (minocycline or doxycycline) unless

SUPPLEMENTARY MATERIAL AVAILABLE ONLINE

Appendices mentioned within this article can be accessed online at https://bit.ly/3kLieUI.

there are contraindications. The ONS Guidelines suggest either oral antibiotics or no antibiotics, based on patients' preferences, values, and clinical situation following a discussion with their healthcare provider. For treatment of EGFRI rash, MASCC and ONS Guidelines recommend topical steroids and oral antibiotics (Lacouture et al., 2011). The U.K. Oncology Nursing Society (2020) has released oncology management guidelines, in draft form, that recommend topical steroid cream for prevention and oral antibiotics for treatment of EGFRI rash.

The 2011 MASCC guideline recommended topical minoxidil for chemotherapy-induced alopecia (Lacouture et al., 2011), which is consistent with the ONS Guidelines. Of note, cooling systems that are suggested for chemotherapy-induced alopecia in the ONS Guidelines were not approved by the U.S. Food and Drug Administration until 2015. The authors did not identify evidence-based guidelines for hand-foot skin reaction or hand-foot syndrome in the literature.

FIGURE 1. Research Priorities and Rationales Identified by the ONS Guidelines™ Panel

EGFRI Rash

- In light of antibiotic stewardship, assess the benefit of good general skin care as prophylactic prior to the initiation of antibiotics.
- Further assess difference in prophylactic versus reactive antibiotics.
- Effect on quality of life and clinical outcomes

Hand-Foot Skin Reaction

- Relationship between folate levels and response to interventions
- Incidence rates with multikinase inhibitors
- Effect on quality of life and clinical outcomes

Hand-Foot Syndrome

- Use of cooling procedures for chemotherapy beyond taxanes

Chemotherapy-Induced Alopecia

- Quality of life among responders and nonresponders of scalp cooling
- Economic outcomes for hospitals that offer scalp cooling programs
- Response to scalp cooling across a diverse patient population
- When to start and end minoxidil for maximum benefit

General Research Recommendations

- Cost-effectiveness studies for all interventions (to understand the effect on costs for patients and institutions—time, supplies, prevention of secondary referrals/infections, long-term effect on quality of life or body image)
- Quality improvement studies incorporating interventions into routine patient care

EGFRI—epidermal growth factor receptor inhibitor; ONS—Oncology Nursing Society

Clinical Implications

This guideline is the first evidence-based summary and recommendations for the prevention and management of skin side effects from cancer treatment in almost a decade. Skin side effects can have a significant effect on a patient's QOL and treatment course. Evidence-based recommendations for EGFRI acneform rash, hand-foot skin reaction, hand-foot syndrome, and chemotherapy-induced alopecia are included. For patients at risk for EGFRI rash, the decision whether to take oral antibiotics should be made following a discussion of the risks and benefits and individual preferences and values. For treatment of EGFRI rash, topical corticosteroids and oral antibiotics are recommended. For prevention or treatment of hand-foot skin reaction from MKIs, topical urea or topical steroid creams are recommended. Cooling procedures are suggested for patients on taxanes who are at risk for hand-foot syndrome. For patients at risk for chemotherapy-induced alopecia, the ONS Guidelines panel suggests scalp cooling or minoxidil.

Despite the prevalence of these skin side effects, research remains limited and of low certainty (see Figure 1 for Research Priorities). RCTs of standard interventions for skin side effects are unlikely to be conducted, but guidelines based on an evidence-based synthesis of available research by a panel of clinical experts provide recommendations that can be incorporated into clinical care. In addition, patients may be at risk for several of these side effects at the same time, and additional work on how to manage that in a clinical setting, and the effect on patients, is important. As part of good clinical care, patients should be educated at the start of treatment about the potential for skin toxicities and encouraged to use good skin care and preventive measures, where appropriate. Education, assessment, and treatment of skin toxicities are the responsibility of an interprofessional team, including nurses, oncologists, dermatologists, wound care specialists, and others, as needed. Collaboration and evidence-based recommendations incorporated into routine clinical care have the potential to prevent and manage these bothersome side effects.

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