ONS SKIN TOXICITY SYMPTOM MANAGEMENT GUIDELINE

Supplementary Material

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1. Guideline panel conflict of interest disclosures

Panel Member	Conflict of Interest Disclosures

Loretta A. Williams, PhD, APRN, AOCN®, OCN®
Associate Professor
Departments of Symptom Research and Nursing
The University of Texas MD Anderson Center, Houston
	• *Consultant or Advisory Role:*
	  ○ Agile Pharma Solutions, myself, compensated
	  ○ Bristol-Meyers Squibb, myself, uncompensated
	• *Research Funding:*
	  ○ Astellas
	  ○ AstraZeneca, myself
	  ○ Bayer, myself – *Avelox/Avalox (moxifloxacin)* an antibiotic for pneumonia, skin, stomach infections; Cipro (ciprofloxacin) an antibiotic; Desonate® (desonide gel) treats atopic dermatitis; *Finacea® (azelaic acid)* foam for papules & pustules of rosacea
	  ○ Eli Lilly, myself
	  ○ Genentech, myself
	  ○ Merck, myself-- *DIPROLENE® AF cream (augmented betamethasone dipropionate)* corticosteroid cream; *DIPROLENE® lotion, ointment*; *ELOCON® cream, lotion, ointment (mometasone furoate)* corticosteroid; LOTRISONE® cream (clotrimazole and betamethasone dipropionate), antifungal & corticosteroid; *PROPECIA® tablets (finasteride)* for male pattern hair loss; *SIVEXTRO tablet (tedizolid phosphate)* treatment of acute bacterial skin and skin structure infections (ABSSSI); CELESTONE® SOLUSPAN® Injectable Suspension (betamethasone sodium phosphate and betamethasone acetate) corticosteroid; CUBICIN® & CUBICIN® RF (daptomycin for injection) for complicated skin and skin structure infections (cSSSI) antibacterial; *INVANZ® (ertapenem for injection)* antibacterial for skin and skin structure infections; PRIMAXIN® for Injection (imipenem and cilastatin) combination of imipenem, a penem antibacterial, and cilastatin, a renal dehydropeptidase inhibitor, for skin and skin structure infections

Kathryn Ciccolini, DNP, MSN, AGACNP-BC, OCN®, DNC CAR T-cell Clinical Program Manager Mount Sinai Hospital, New York, NY	*Employment*: Mount Sinai Hospital

George Ebanks, BSN, RN, OCN® Primary Nurse Cutaneous Oncology Program Moffitt Cancer Center, Miami, FL	*Honoraria:* Array Biopharma – Self; USF (Univ. of S. FL) Health – Self
Karren Ganstwig Patient Advocate	No conflicts listed
Bernice Y. Kwong, MD Clinical Associate Professor, Department of Dermatology Director, Supportive Dermato-Oncology Program Director of Inpatient Dermatology Consultation Stanford University, Palo Alto, CA	*Consultant or advisory:* Genetech, self, compensated; Oncoderm, self, compensated; H2B, self, compensated
Jeanene (Gigi) Robison, MSN, APRN-CNS, AOCN® Oncology Clinical Education Specialist St. Elizabeth Healthcare, Cincinnati, OH	*Consultant Role:* Teach an Oncology Nursing Certification Review Course 2X / year
Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP® Self-employed Oncology Clinical Nurse Specialist and Adult Nurse Practitioner New York, NY	*Honoraria:* Kyowa Kirin speakers bureau
Jenna Strelo, FNP-BC, MSN, BSN Nurse Practitioner III, Department of Dermatology Cutaneous Oncology/Supportive Dermato-Oncology Stanford Health Care, San Francisco, CA	No conflicts listed

2. PICO questions

Informal Question	PICO Question			
	Population	**Intervention(s)**	**Comparator**	**Patient Important Outcomes**
Acneiform rash prevention	Patients receiving EGFR inhibitors	Oral antibiotics (doxycycline, tetracycline and minocycline) and usual care (Usual care is assumed to include education on general skin care at the beginning of treatment--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)).	Usual care	Quality of life Development of acneiform rash Pruritis Adverse events from intervention Time to development of rash
Acneiform rash treatment	Patients receiving EGFR inhibitors who have developed a grade 1 - 3 acneiform rash	Topical corticosteroids with oral antibiotics and usual care (Usual care is assumed to include education on general skin care at the beginning of treatment--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)).	Usual care	Quality of life Infection Pruritis Adverse events from intervention Severity/change in rash Treatment interruption/discontinuation

Hand-foot syndrome (or PPE – palmar-plantar erythrodysesthesia) prevention	Patients receiving taxane-based chemotherapy who are at risk for hand-foot syndrome	Cooling procedures	No cooling procedures	Development of Hand Foot Syndrome Quality of life (functional limitations) Adverse events from intervention Treatment interruption/discontinuation
Hand-foot syndrome (or PPE – palmar-plantar erythrodysesthesia) prevention	Patients receiving capecitabine	Oral pyridoxine HCL (vitamin B_6 oral)	No treatment	Development of Hand Foot Syndrome Quality of life (functional limitations) Adverse events from intervention Treatment interruption/discontinuation
Hand-foot skin reaction (HFSR) prevention	Patients receiving multikinase inhibitors who are at risk for HFSR	Topical urea and topical corticosteroids and usual care (Usual care is assumed to include education on general skin care at the beginning of treatment--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)).	Usual care	Development of HFSR Quality of life (functional limitations) Adverse events from intervention Treatment interruption/discontinuation

Prevention of chemotherapy-induced alopecia	Patients receiving cytotoxic agents who are at risk for alopecia	Scalp cooling	No scalp cooling	Quality of life Development of alopecia Scalp metastasis Patient comfort Adverse events from intervention Self-estimated hair loss (Dean scale) Cost (patient and institutional)
Prevention of chemotherapy-induced alopecia	Patients receiving cytotoxic agents who are at risk for alopecia	Minoxidil	Usual care (Usual care is assumed to include education on general skin care at the beginning of treatment--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)).	Quality of life Resolution of alopecia Adverse events from intervention Self-estimated hair loss (Dean scale) Cost

3. Evidence-to-Decision frameworks (Developed using GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.)

- EGFR inhibitor rash prevention—oral antibiotics and usual care
- EGFR inhibitor rash treatment—topical corticosteroids with oral antibiotics and usual care
- Hand-foot skin reaction prevention—topical urea and topical corticosteroids
- Hand foot syndrome prevention—oral pyridoxine HCL (vitamin B_6)
- Hand foot syndrome prevention—cooling procedures
- Chemotherapy-induced alopecia prevention—scalp cooling
- Chemotherapy-induced alopecia prevention--minoxidil

EGFR inhibitor rash prevention—oral antibiotics (doxycycline, tetracycline, minocycline) and usual care vs. usual care

RECOMMENDATION

Should oral antibiotics (doxycycline, tetracycline, minocycline) and usual care rather than usual care alone be used in the prevention of skin rash in individuals taking EGFRIs?	
POPULATION:	Prevention of skin rash in patients on EGFR inhibitors
INTERVENTION:	Oral antibiotics (doxycycline, tetracycline, minocycline) and usual care
COMPARISON:	Usual care alone
MAIN OUTCOMES:	Quality of life; Development of acneiform rash; Pruritis; Adverse events from intervention; Time to development of rash
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective

BACKGROUND:	The severity of the acneiform rash varies and can lead to dose adjustments or treatment discontinuation in severe cases (Lacouture, 2006). EGFRI rashes affect the quality of life and psychosocial well-being of patients, as well as placing patients at risk for secondary skin infections (Joshi et al., 2010; Lacouture et al., 2011).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Papulopustular rash is the most common dermatologic adverse event that occurs with EGFRIs with an incidence as high as 90% (Tan & Chan, 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For evidence tables and forest plots, see Ding, J., Farah, M., Nayfeh, T., Malandris, K., Manolopoulos, A., Ginex, P., … Murad, H. (2020). Chemotherapy-associated skin toxicities: Systematic review and meta-analysis. *Oncology Nursing Forum, 47*(5). In Jatoi et al., 2008, quality of life benefits were seen in patients treated with tetracycline. Patients reported better scores on quality of life items such as skin burning or stinging, skin irritation, and being bothered by the skin condition (as measured on the SKINDEX-16); 15 patients in the tetracycline arm and 12 in the placebo arm completed the protocol. In Jatoi et al., 2011, there were no differences in quality of life (as measured on the SKINDEX-16) between the tetracycline and placebo groups; 16 patients in each arm completed the protocol.	The panel decided to separate their judgments based on the treatment being considered. Tetracycline - Moderate The panel's decision was based on the relative risk reduction of developing all grade rash. Additional considerations included quality of life because it was seen as a benefit if there is a reduction in development of rash. There was indirectness from use with acne literature. Minocycline - Moderate The panel prioritized prevention of grade 3 acneiform rash as of clinical importance for minocycline vs no. When comparing prophylactic use versus deferred use, the panel

		noted the reductions for all grades and grade 1 development of acneiform rash. Doxycycline vs. deferred - Moderate The panel considered the improvement of quality of life in the treatment arm but recognized the indirectness of the trial participants also having received hydrocortisone cream, sunscreen, moisturizer.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	For evidence tables and forest plots, see Ding, J., Farah, M., Nayfeh, T., Malandris, K., Manolopoulos, A., Ginex, P., … Murad, H. (2020). Chemotherapy-associated skin toxicities: Systematic review and meta-analysis. *Oncology Nursing Forum, 47*(5). In a systematic review (Smith & Leyden, 2005), the literature reporting on the adverse events (AEs) of oral doxycycline and oral minocycline was summarized and then compared with US prescription data to create a profile of the general risk of these medications relative to exposure. The most-commonly reported AEs in US and non-US case reports for doxycycline were esophageal erosion (55%) and photosensitivity (36%). In clinical trials, the most- commonly reported AEs were gastrointestinal issues (other than heartburn/gastritis and nausea/vomiting) (up to 51.7%) and photosensitivity (30.5%). The most-commonly reported AEs in US and non-US case reports for minocycline were lupus-like syndrome (28%) and hyperpigmentation (15%). In clinical trials. the most-commonly reported were vestibular (not otherwise specified) (up to 67%), lightheadedness (up to 53%), disassociation (up to 50%), and nausea/vomiting (up to 50%). Based on the number of new prescriptions dispensed in the US (about 47,630,000 for doxycycline and about 15,234,000 for minocycline) and the number of AEs in the US recorded in MedWatch between January 1, 1998, and August 31, 2003, Smith & Leyden determined that the incidence of doxycycline AEs in the US was 2.3 per million per year and minocycline AEs, 13 per million per year.	Tetracycline vs. no - Moderate The panel decided that the undesirable effects were moderate based on gastrointestinal upset. They noted no difference between adverse events reported in each arm across the three studies. Minocycline vs. no - Moderate The panel deemed the undesirable effects to be moderate because of small risk of severe adverse events including dizziness, fatigue, drowsiness, pruritis, arthralgia, tinnitus. There is some risk of pigmentation and gastrointestinal upset. Doxycycline vs. no - Moderate The panel deemed the undesirable effects to be moderate because of gastrointestinal upset and phototoxicity, both adverse events considered frequent but manageable and typically do not lead to treatment discontinuation. The panel considered information about the treatment side-effects from Lexicomp via UpToDate: www.uptodate.com

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty in the evidence was rated as very low across the evidence for prophylactic use of antibiotics for prevention of acneiform rash.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% had chemotherapy and radiotherapy. When asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent of females and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if they had had ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs. In a study (Rosen et al., 2013) on the quality of life impact of dermatologic events in 283 patients receiving either targeted (mostly EGFR inhibitors and other small molecule kinase inhibitors or monoclonal antibodies) or non-targeted therapy, patients having papulopustular rash had higher Skindex-16 scores and higher scores in the symptom, emotion, and function subdomains than patients without the rash (High score has a negative connotation.). In a study (Joshi et al., 2010) of quality of life related to epidermal growth factor receptor inhibitor-induced dermatologic toxicities, 67 patients filled out the Skindex-16 questionnaire. Dermatologic toxicities were assessed using NCI-CTCAE. Papulopustular rash (PPR) was found in 82.1% of patients. Median symptom scores, emotion scores, and functioning scores increased as PPR grade increased in patients with PPR grades 0 – 3.	The panel decided that patient preference may be variable across the desirable and undesirable outcomes, e.g., some patients may be willing to accept additional treatment to avoid rash; however, others may place a higher value on avoiding additional treatments.

	A sub-analysis (Clabbers et al., 2016) of 77 patients from the BeCet study (NCT01136005) found that, during the first six weeks of epidermal growth factor receptor inhibitor treatment, for patients with acneiform rash, pruritus (24.2 %), xerosis (18.9 %), and papulopustular eruption (6.3 %) were found to be the adverse events having the most impact. All three symptoms showed a negative effect on health-related quality of life. In a qualitative study (Coleman, Kovtun, Nguyen, Pittelkow, & Jatoi, 2011) of 15 patients who had or had had EGFR-inhibitor-related rash, interviews with the patients were conducted. Patients discussed physical discomfort, concerns about their appearance, experiences of social isolation, and medical morbidity related to papulopustular rash. In a hermeneutic phenomenological study (Charalambous & Charalambous, 2016) in Cyprus of patients receiving EGFR-targeted agents and having treatment-induced skin toxicities, patients' responses about their experiences described negative effects of their skin toxicities on their self-images, social engagement, and intimate relationships. Of the 22 participants, 10 had grade 3 papulopustular eruptions and 12 had grade 2 skin eruptions.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel made a similar decision across all treatments, considering the potential for benefit over the potential for harms.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Skin Reactions Interventions Cost Example from GoodRx.com, Aug./Sept. 2019** **Intervention** / **Pittsburgh, PA price** / **Average retail price** Oral antibiotics / Ex.: Minocycline, 100 mg, 60 tablets: $34.91 w/ GoodRx.com coupon / $113.98 In a retrospective cohort study (Chen et al., 2018) of medical claims of patients treated with an EGFR inhibitor as recorded in the TruvenMarketScan® research database, 44,533 patients were eligible for the study. There were records of rash for 10.4% of the patients. Treatment persistence was longer among patients with rash than without rash. Annualized cost during treatment was $185,619 for patients without rash; $215,561 for patients receiving medication for rash; and $267,105 for patients with rash but not treated for rash.	The panel noted that many of these treatments are available as a generic brand with a reduced cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel decided that treatments used for prevention of rash may be less costly/more accessible than waiting for treatment and adding an extra office visit, possibly disadvantaging patients less.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel recognized the variability of acceptance of prophylactic antibiotics across stakeholders.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel recognized that there is the need for education.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

Recommendation

Among persons who are receiving EGFR inhibitors, the ONS guideline 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: Persons 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. Persons who place a higher value on avoiding unnecessary medication may prefer to not use antibiotics until the rash presents.

Justification

Patients who are starting treatment with EGFR inhibitors are at high risk of developing a rash (Tan & Chan, 2009). The evidence for a prophylactic antibiotic was judged to be of very low certainty. However, the ONS guideline 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.

Subgroup considerations

No subgroup considerations.

Implementation considerations

Clinical decision-making should happen when making decisions about EGFR inhibitors. Shared decision-making may also include a discussion of provision of antibiotics for reactive skin treatment, especially when access or coverage may be an issue. It is important to fully discuss options and side effects with patients. The clinician could give a script to the patient and tell the patient not to fill it or take it until symptoms present.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- In light of antibiotic stewardship, assess the benefit of good general skin care as prophylactic prior to the initiation of antibiotics
- Further assess the difference in prophylactic vs reactive antibiotics

IN-TEXT CITED REFERENCES

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EGFR inhibitor rash treatment—topical corticosteroids with oral antibiotics and usual care vs. usual care

RECOMMENDATION

Should topical corticosteroids with oral antibiotics and usual skin care rather than usual skin care alone be used in individuals taking EGFRIs inhibitors who have developed an acneiform rash?	
POPULATION:	Patients on EGFR who have developed an acneiform rash
INTERVENTION:	Topical corticosteroids with oral antibiotics and usual care
COMPARISON:	Usual care alone
MAIN OUTCOMES:	Quality of life; Infection; Pruritis; Adverse events from intervention; Severity/change in rash; Treatment interruption/discontinuation
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	The severity of the acneiform rash varies and can lead to dose adjustments or treatment discontinuation in severe cases (Lacouture, 2006). EGFRI rashes affect the quality of life and psychosocial well-being of patients, as well as placing patients at risk for secondary skin infections. (Joshi, Ortiz, Witherspoon, et al., 2010; Lacouture et al., 2011).

CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Papulopustular rash is the most common dermatologic adverse event that occurs with EGFRIs with an incidence as high as 90% (Tan & Chan, 2009).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For evidence tables and forest plots, see Ding, J., Farah, M., Nayfeh, T., Malandris, K., Manolopoulos, A., Ginex, P., … Murad, H. (2020). Chemotherapy-associated skin toxicities: Systematic review and meta-analysis. *Oncology Nursing Forum, 47*(5).	The panel based their judgment on the evidence for prevention and prevention of development of grade 3. Other desirable outcomes would include the measurable improvement of a rash once appeared.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	For evidence tables and forest plots, see Ding, J., Farah, M., Nayfeh, T., Malandris, K., Manolopoulos, A., Ginex, P., … Murad, H. (2020). Chemotherapy-associated skin toxicities: Systematic review and meta-analysis. *Oncology Nursing Forum, 47*(5). In a systematic review (Smith & Leyden, 2005), the literature reporting on the adverse events (AEs) of oral doxycycline and oral minocycline was summarized and then compared with US prescription data to create a profile of the general risk of these medications relative to	A shorter course of intervention would be required for treatment of the rash versus prophylaxis. The panel considered information about the treatment side-effects from Lexicomp via UpToDate: https://www.uptodate.com

	exposure. The most-commonly reported AEs in US and non-US case reports for doxycycline were esophageal erosion (55%) and photosensitivity (36%). In clinical trials, the most-commonly reported AEs were gastrointestinal issues (other than heartburn/gastritis and nausea/vomiting) (up to 51.7%) and photosensitivity (30.5%). The most-commonly reported AEs in US and non-US case reports for minocycline were lupus-like syndrome (28%) and hyperpigmentation (15%). In clinical trials, the most-commonly reported were vestibular (not otherwise specified) (up to 67%), lightheadedness (up to 53%), disassociation (up to 50%), and nausea/vomiting (up to 50%). Based on the number of new prescriptions dispensed in the US (about 47,630,000 for doxycycline and about 15,234,000 for minocycline) and the number of AEs in the US recorded in MedWatch between January 1, 1998, and August 31, 2003, Smith & Leyden determined that the incidence of doxycycline AEs in the US was 2.3 per million per year and minocycline AEs, 13 per million per year.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The panel used the research on prevention to inform their discussion on treatment and thus considered the certainty in the evidence of effects to be very low.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% had chemotherapy and radiotherapy. When asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent of females and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if	The panel decided that most people who have developed a rash would value treatment to minimize it.

	they had had ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Skin Reactions Interventions Cost Examples from GoodRx.com, Aug./Sept. 2019** **Intervention** / **Pittsburgh, PA price** / **Average retail price** Oral antibiotics / Ex.: Minocycline, 100 mg, 60 tablets: $34.91 w/ GoodRx.com coupon / $113.98 Topical corticosteroids / Ex.: Hydrocortisone, tube of cream, 28.4g of 1%: $3.89 / $14.27	The panel considered that the cost of steroids may be variable, with the upper end leading to moderate cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel decided that equity would be reduced because steroid vehicles (solution/foam/cream) may cause variability in coverage and accessibility. This may delay the receipt of the treatment, which would disadvantage patients.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The panel recognized the need for additional information about this to go to practitioners.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among persons who are receiving EGFR inhibitors who have developed grade 1–3 acneiform rash, the ONS guideline 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).

Justification

Patients who have developed a rash from EGFRi treatment are at risk for treatment delays and additional adverse events. The evidence for topical steroids and oral antibiotics was judged to be of very low certainty; however, the ONS guideline 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 EGFR inhibitors.

Subgroup considerations

No subgroup considerations.

Implementation considerations

Implementation can clarify:

- What a steroid vehicle is and why it is important according to the location of the skin rash.
- That this is for the treatment of the skin condition.
- The need to discuss with the clinician the length of treatment, i.e., when to stop.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- 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 vs reactive antibiotics.

IN-TEXT CITED REFERENCES

Gandhi, M., Oishi, K., Zubal, B., & Lacouture, M.E. (2010). Unanticipated toxicities from anticancer therapies: Survivors' perspectives. *Supportive Care in Cancer, 18*, 1461–1468. https://doi.org/10.1007/s00520-009-0769-1

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Tan, E.H., & Chan, A. (2009). Evidence-based treatment options for the management of skin toxicities associated with epidermal growth factor receptor inhibitors. *Annals of Pharmacotherapy, 43*, 1658–1666. https://doi.org/10.1345/aph.1M241

Hand-foot skin reaction prevention—topical urea and topical corticosteroids vs. usual care

RECOMMENDATION

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?	
POPULATION:	Patients receiving MKIs at risk for hand-foot skin reaction
INTERVENTION:	Topical urea and topical corticosteroids
COMPARISON:	Usual care
MAIN OUTCOMES:	Development of HFSR; Quality of life (functional limitations)
SETTING:	Clinical care

PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Hand-foot skin reaction (HFSR) describes symptoms affecting the hands and/or feet and is associated with multikinase inhibitor treatment. HSFR typically presents during the first 2 to 6 weeks of therapy with erythema, tenderness, paresthesia, 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 frequently are painful and may impair function, thus impacting the patient's quality of life and possibly leading to dose modification or therapy discontinuation (Lacouture et al., 2008).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	HFSR has an incidence of approximately 9% to 62% depending on the drug (Lacouture et al., 2008).	The intervention was considered for prevention and for treatment.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with usual care	Risk difference with topical urea and topical steroids (clobetasol 0.05%)
Prevention of any grade HFSR	871	-	**OR 0.46** (0.34 to 0.61)	Study population	
				704 per 1,000	**183 fewer per 1,000** (254 fewer to 113 fewer)

- Prevention of HFSR any grade OR: 0.457 (.344, 0.608)
- Mean time to development of HFSR HR: 0.658 (0.541, 0.799)

Table Reference:

Ren, Z., Zhu, K., Kang, H., Lu, M., Qu, Z., Lu, L., … Ye, S. L. (2015). Randomized controlled trial of the prophylactic effect of urea-based cream on sorafenib-associated hand-foot skin reactions in patients with advanced hepatocellular carcinoma. *Journal of Clinical Oncology*, *33*, 894–900. https://doi.org/10.1200/JCO.2013.52.9651

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with usual care	Risk difference with topical urea and topical steroids (clobetasol 0.05%)
Prevention of any grade HFSR	871	-	**OR 0.46** (0.34 to 0.61)	Study population	
				704 per 1,000	**183 fewer per 1,000** (254 fewer to 113 fewer)

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Table Reference:

Ren, Z., Zhu, K., Kang, H., Lu, M., Qu, Z., Lu, L., … Ye, S. L. (2015). Randomized controlled trial of the prophylactic effect of urea-based cream on sorafenib-associated hand-foot skin reactions in patients with advanced hepatocellular carcinoma. *Journal of Clinical Oncology*, *33*, 894–900. https://doi.org/10.1200/JCO.2013.52.9651

The intervention can have local side effects, including irritation of sensitive skin. The panel considered information about the treatment side-effects from Lexicomp via UpToDate: www.uptodate.com.

Prevention:

Because the skin hasn't thickened yet, the adverse events may be worse in the prevention stage, including with the addition of topical steroids. The panel determined that the undesirable effects are small.

Treatment:

Because the skin has thickened at this point, the panel determined the undesirable effects are trivial.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ● Low ○ Moderate ○ High ○ No included studies		The quality of evidence was low for the prevention of HFSR and very low for treatment of HFSR due to risk of bias and unclear randomization and allocation methods.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% had chemotherapy and radiotherapy. When asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent of females and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if they had had ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs.	Prevention: The panel decided there is possibly important uncertainty because of patient ideas regarding steroid use. Treatment: The panel decided there is probably no important uncertainty for treatment.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Prevention: The panel decided the balance of effects probably favors the intervention, though they recognized the variability in patient values. Treatment: The panel decided the balance of effects probably favors the intervention because of the lack of evidence on steroid cream.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Skin Reactions Interventions Costs Examples from GoodRx.com, Aug./Sept. 2019** **Intervention** / **Pittsburgh, PA price** / **Average retail price** Topical corticosteroids / Clobetasol, 60 gm tube of 0.05%: $57.88 w/GoodRx.com discount / $329.19 Urea / Urea cream, tube, 85g of 10%: $10.92 w/ GoodRx.com coupon / Not available	The panel determined there is a moderate cost for steroid. The panel decided urea cream has a small cost, so the decision would be driven by steroids.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		The panel determined that coverage and accessibility may be an issue regarding the steroid vehicle and potency. The panel noted that urea can be obtained over the counter but that it can still be a cost.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		The panel decided that the length of treatment acceptability may vary among clinicians but that they would accept initiation of the intervention. The panel noted that insurance providers would accept the intervention, as demonstrated by their formularies.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In an adherence study (Sato et al., 2019) of the use of a urea-based ointment for prophylaxis of regorafenib-related hand-foot skin reaction (HFSR), working status had an association with poor adherence. The grade of HFSR and the regorafenib relative dose intensity had a negative correlation with poor adherence.	The panel determined there is a need for education and compliance with the intervention in its implementation.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

Prevention

Among persons receiving MKIs at risk for hand-foot skin reaction, the ONS guideline 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 persons receiving MKIs with hand-foot skin reaction, the ONS guideline panel *suggests* topical urea and topical steroids in addition to usual care rather than usual care alone. (Conditional recommendation, very low certainty of evidence).

Justification

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

Subgroup considerations

No subgroup considerations.

Implementation considerations

Education and compliance are needed.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Baseline folate levels on response to interventions

IN-TEXT CITED REFERENCES

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Sato, J., Ishikawa, H., Hamauchi, S., Yamawaki, Y., Mori, K., Kiyohara, Y., ... Shino, M. (2019). Adherence to a topical moisturizing preparation for regorafenib-related hand-foot skin reaction. *Journal of Oncology Pharmacy Practice*, 26, 361–367. https://doi.org/10.1177/1078155219849275

Hand-foot syndrome prevention—oral pyridoxine HCL (vitamin B_6) vs. no oral pyridoxine HCL (vitamin B_6)

RECOMMENDATION

Should oral pyridoxine HCL (Vitamin B_6) rather than no oral pyridoxine HCL (Vitamin B_6) be used in individuals receiving capecitabine who are at risk for hand-foot syndrome?	
POPULATION:	Patients receiving capecitabine at risk for hand foot syndrome
INTERVENTION:	Oral pyridoxine HCL (Vitamin B6)
COMPARISON:	No oral pyridoxine HCL (Vitamin B6)

MAIN OUTCOMES:	Development of HFS; Quality of life (functional limitations); Adverse events from intervention; Treatment interruption/discontinuation
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Palmar-plantar erythrodysesthesia, also known as Hand Foot Syndrome (HFS), is associated most often with pyrimidine analogue and anthracycline chemotherapy agents (Nikolaou, Syrigos, & Saif, 2016). PPE initially presents with numbness, tingling, and erythema on the palms and sometimes the soles of the feet (Nikolaou, Syrigos & Saif, 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 quality of life, and significantly impacting treatment schedules (Scheithauer & Blum, 2004).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The incidence of PPE is between 6% and 62% for single agents, and as high as 89% for combinations of agents associated with PPE (Gabra, Cameron, Lee, Mackay, & Leonard, 1996; Twelves, Wong, Nowacki, et al., 2005; Wardley et al., 2005).	The panel noted an additional consideration for patients with a B6 deficiency.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Pyridoxine HCL vs. placebo—Prevention of all grades of hand-foot syndrome: RR 1.02, 95% CI 0.85, 1.23, ARR 12 more per 1,000, from 89 fewer to 137 more **References:** Braik, T., Yim, B., Evans, A., Kassem, M., Mullane, M., Lad, T., . . . McDunn, S. (2014). Randomized trial of vitamin B6 for preventing hand-foot syndrome from capecitabine chemotherapy. *Journal of Community and Supportive Oncology, 12*, 65–70. https://doi.org/10.12788/jcso.0017 Corrie, P.G., Bulusu, R., Wilson, C., Armstrong, G., Bond, S., Hardy, R., . . . Daniel, F. (2012). A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. *British Journal of Cancer, 107*, 585–587. https://doi.org/10.1038/bjc.2012.318 Kang, Y.-K., Lee, S.S., Yoon, D.H., Lee, S.Y., Chun, Y.J., Kim, M.S., . . . Kim, T.W. (2010). Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: Results of a randomized, double-blind, placebo-controlled study. *Journal of Clinical Oncology, 28*, 3824–3829. https://doi.org/10.1200/JCO.2010.29.1807 Mortimer, J.E., Lauman, M.K., Tan, B., Dempsey, C.L., Shillington, A.C., & Hutchins, K.S. (2003). Pyridoxine treatment and prevention of hand-and-foot syndrome in patients receiving capecitabine. *Journal of Oncology Pharmacy Practice, 9*(4), 161–166. https://doi.org/10.1191/1078155203jp116oa Yap, Y.-S., Kwok, L.-L., Syn, N., Chay, W.Y., Chia, J.W.K., Tham, C.K., . . . Soong, R.C.T. (2017). Predictors of hand-foot syndrome and pyridoxine for prevention of capecitabine-induced hand-foot syndrome: A randomized clinical trial. *JAMA Oncology, 3*, 1538–1545. https://doi.org/10.1001/jamaoncol.2017.1269 Yoshimoto, N., Yamashita, T., Fujita, T., Hayashi, H., Tsunoda, N., Kimura, M., Tsuzuki, N., Yamashita, H., Toyama, T., Kondo, N., & Iwata, H. (2010). Impact of prophylactic pyridoxine on occurrence of hand-foot syndrome in patients receiving capecitabine for advanced or metastatic breast cancer. *Breast Cancer, 17*(4), 298-302. https://doi.org/10.1007/s12282-009-0171-3 In a double-blind, randomized trial (von Gruenigen et al., 2010) of the incidence of hand-foot syndrome in patients receiving pegylated liposomal doxorubicin chemotherapy and given pyridoxine or placebo (34 patients enrolled), no difference in global or domain quality of life scores between the intervention and placebo group and no difference between patients with grade 0/1 HFS and grade 2/3 HFS were reported. FACT-G was used with all patients, and women with ovarian cancer also completed FACT-Ovarian.	Prevention of PPE was considered here.

	In a randomized study (Corrie et al., 2012) of pyridoxine to reduce the incidence of capecitabine dose modifications (106 patients randomized), no significant differences were found in quality of life between the pyridoxine and placebo groups using the EORTC QLQ-C30 version 3 questionnaire including the modules dedicated specifically to colorectal and breast cancer.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	Pyridoxine HCL vs. placebo—Prevention of all grades of hand-foot syndrome: RR 1.02, 95% CI 0.85, 1.23, ARR 12 more per 1,000, from 89 fewer to 137 more **References:** Braik, T., Yim, B., Evans, A., Kassem, M., Mullane, M., Lad, T., . . . McDunn, S. (2014). Randomized trial of vitamin B6 for preventing hand-foot syndrome from capecitabine chemotherapy. *Journal of Community and Supportive Oncology, 12*, 65–70. https://doi.org/10.12788/jcso.0017 Corrie, P.G., Bulusu, R., Wilson, C., Armstrong, G., Bond, S., Hardy, R., . . . Daniel, F. (2012). A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. *British Journal of Cancer, 107*, 585–587. https://doi.org/ 10.1038/bjc.2012.318 Kang, Y.-K., Lee, S.S., Yoon, D.H., Lee, S.Y., Chun, Y.J., Kim, M.S., . . . Kim, T.W. (2010). Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: Results of a randomized, double-blind, placebo-controlled study. *Journal of Clinical Oncology, 28*, 3824–3829. https://doi.org/10.1200/JCO.2010.29.1807 Mortimer, J.E., Lauman, M.K., Tan, B., Dempsey, C.L., Shillington, A.C., & Hutchins, K.S. (2003). Pyridoxine treatment and prevention of hand-and-foot syndrome in patients receiving capecitabine. *Journal of Oncology Pharmacy Practice, 9*(4), 161–166. https://doi.org/10.1191/1078155203jp116oa Yap, Y.-S., Kwok, L.-L., Syn, N., Chay, W.Y., Chia, J.W.K., Tham, C.K., . . . Soong, R.C.T. (2017). Predictors of hand-foot syndrome and pyridoxine for prevention of capecitabine-induced hand-foot syndrome: A randomized clinical trial. *JAMA Oncology, 3*, 1538–1545. https://doi.org/10.1001/jamaoncol.2017.1269 Yoshimoto, N., Yamashita, T., Fujita, T., Hayashi, H., Tsunoda, N., Kimura, M., Tsuzuki, N., Yamashita, H., Toyama, T., Kondo, N., & Iwata, H. (2010). Impact of prophylactic pyridoxine on occurrence of hand-foot syndrome in patients receiving capecitabine for	The panel noted that minimal gastrointestinal issues could be experienced by patients but that those effects could be caused by the chemotherapy. They also said that the harms could be underreported. Peripheral neuropathy, dermatoses, photosensitivity, dizziness, and nausea have been reported in people taking over 250 mg per day over long periods of time. Chronic use of 100 – 200 mg per day seems to have caused neuropathy in a small number of cases (Pazirandeh & Burns, 2020).

	advanced or metastatic breast cancer. *Breast Cancer, 17*(4), 298-302. https://doi.org/10.1007/s12282-009-0171-3 In a double-blind, randomized trial (von Gruenigen et al., 2010) of the incidence of hand-foot syndrome in patients receiving pegylated liposomal doxorubicin chemotherapy and given pyridoxine or placebo (34 patients enrolled), no difference in global or domain quality of life scores between the intervention and placebo group and no difference between patients with grade 0/1 HFS and grade 2/3 HFS were reported. FACT-G was used with all patients, and women with ovarian cancer also completed FACT-Ovarian. In a randomized study (Corrie et al., 2012) of pyridoxine to reduce the incidence of capecitabine dose modifications (106 patients randomized), no significant differences were found in quality of life between the pyridoxine and placebo groups using the EORTC QLQ-C30 version 3 questionnaire including the modules dedicated specifically to colorectal and breast cancer.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies		The certainty in the evidence of effects was rated as low, due to imprecision and risk of bias.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% had chemotherapy and radiotherapy. When asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent of females and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if they had had	The panel decided that patients' aversion to PPE weighs more heavily than the burden of prophylactic treatment.

	ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel determined that there would be a greater potential for harm at higher levels of the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Intervention Cost from Walmart.com, September/October 2019** **Intervention** / **Product** / **Price** Pyridoxine (oral) / Spring Valley Vitamin B6 Supplement Tablets, 100 mg, 250 count / $4.88	The panel determined that B6 can be obtained over the counter and at a low cost.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced	No research evidence identified.	The panel noted that B6 is widely available.

● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel decided that this treatment adds burden to the patient and clinical team.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies

	JUDGEMENT						
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	●	○	○	○

CONCLUSIONS

Recommendation

Among persons receiving capecitabine, the ONS guideline panel *suggests* no treatment rather than prophylactic oral pyridoxine HCL for the prevention of hand foot syndrome. (Conditional against, low certainty of evidence).

Justification

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 guideline panel recommended no treatment rather than pyridoxine for the treatment of hand foot syndrome in patients taking capecitabine for cancer treatment.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

IN-TEXT CITED REFERENCES

Corrie, P.G., Bulusu, R., Wilson, C.B., Armstrong, G., Bond, S., Hardy, R., ... Hill, M. (2012). A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications. *British Journal of Cancer*, *107*, 585–587. https://doi.org/10.1038/bjc.2012.318

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von Gruenigen, V., Frasure, H., Fusco, N., DeBernardo, R., Eldermire, E., Eaton, S., & Waggoner, S. (2010). A double-blind, randomized trial of pyridoxine versus placebo for the prevention of pegylated liposomal doxorubicin-related hand-foot syndrome in gynecologic oncology patients. *Cancer*, *116*, 4735–4743. https://doi.org/10.1002/cncr.25262

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Hand-foot syndrome prevention—cooling procedures vs. no cooling procedures

RECOMMENDATION

Should cooling procedures rather than no cooling procedures be used in patients receiving taxane-based chemotherapy who are at risk for hand-foot syndrome?	
POPULATION:	Patients receiving taxane-based chemotherapy who are at risk for hand-foot syndrome
INTERVENTION:	Cooling procedures
COMPARISON:	No cooling procedures
MAIN OUTCOMES:	Development of HFS; Quality of life (functional limitations); Adverse events from intervention; Treatment interruption/discontinuation
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Hand Foot Syndrome initially presents with numbness, tingling, and erythema on the palms and sometimes the soles of the feet (Nikolaou Syrigos, & Saif, 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 quality of life, and significantly impacting treatment schedules (Scheithauer & Blum, 2004).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The incidence of PPE is reported between 6% and 62% for single agents, and as high as 89% for combinations of agents associated with HFS (Gabra, Cameron, Lee, Mackay, & Leonard, 1996; Twelves, Wong, Nowacki, et al., 2005; Wardley et al., 2005). In a review (Sibaud et al., 2016) of the dermatological adverse events with taxanes, incidence of HFS was reported as 5–10%. It was noted that HFS was relatively more common with docetaxel than paclitaxel.	

In a systematic review and meta-analysis (Capriotti et al., 2015) of the risk of nail changes with taxane chemotherapy, incidence of all-grade nail changes with docetaxel was 34.9%. Incidence of all-grade nail changes with paclitaxel and nab-paclitaxel was 43.7%. The literature for docetaxel included RCTS, and the relative risk of nail changes, compared with controls, was 77.74 (95% CI 41.88–144.32; P < 0.001).

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know		Effects considered are only for taxane-based treatments. Scotté et al., 2005, and Scotté et al., 2008, report skin toxicity, which is used in the analysis for PPE development. Scotté 2005, 2008, and Can 2012 reported nail change/toxicity grades 1–3. Tanyi et al., 2009, was removed from consideration because the study did not report on the correct intervention (Tanyi et al. cooled the wrists and ankles, not the hands and feet). In addition, Tanyi et al. reported on liposomal doxorubicin. The panel determined the desirable effects to be moderate because of the reduction in the development of PPE or nail changes.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no cooling procedures	Risk difference with cooling procedures
Development of HFS	146 (2 observational studies)	⨁◯◯◯ VERY LOW[a,b,c]	RR 0.44 (0.25 to 0.77)	Study population	
				472 per 1,000	**264 fewer per 1,000** (354 fewer to 108 fewer)
Development of nail toxicity	386 (3 observational studies)	⨁◯◯◯ VERY LOW[b,c,d]	RR 0.31 (0.06 to 1.54)	Study population	
				450 per 1,000	**310 fewer per 1,000** (423 fewer to 243 more)

a. Substantial heterogeneity (I^2=90%)
b. Scotté 2005 & 2008 were match case-control studies with patients serving as their own controls. Patients and outcome assessors were not blinded.
c. Wide CI may suggest the potential of benefit and harm. Not meeting OIS.
d. Substantial heterogeneity (I^2=88%)

	Six of the patients were dissatisfied with global comfort—5 (11%) patients withdrew because of cold intolerance (Scotté et al., 2005). Sock contact, temperature tolerance, and immobilization constraints were some aspects of the assessment of patients' global comfort. Fifty-eight percent of patients were satisfied with the frozen sock protection; 19%, very satisfied. One patient (2%) reported dissatisfaction due to cold intolerance (Scotté et al., 2008). **Table References:** Can, G., Aydiner, A., & Cavdar, I. (2012). Taxane-induced nail changes: Predictors and efficacy of the use of frozen gloves and socks in the prevention of nail toxicity. *European Journal of Oncology Nursing*, *16*, 270–275. https://doi.org/10.1016/j.ejon.2011.06.007 Scotté, F., Banu, E., Medioni, J., Levy, E., Ebenezer, C., Marsan, S., ... Oudard, S. (2008). Matched case-control phase 2 study to evaluate the use of a frozen sock to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. *Cancer*, *112*, 1625–1631. https://doi.org/10.1002/cncr.23333 Scotté, F., Tourani, J.M., Banu, E., Peyromaure, M., Levy, E., Marsan, S., ... Oudard, S. (2005). Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *Journal of Clinical Oncology*, *23*, 4424–4429. https://doi.org/10.1200/JCO.2005.15.65	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no cooling procedures	Risk difference with cooling procedures
Development of HFS	146 (2 observational studies)	⨁◯◯◯ VERY LOW[a,b,c]	RR 0.44 (0.25 to 0.77)	Study population	
				472 per 1,000	**264 fewer per 1,000** (354 fewer to 108 fewer)
Development of nail toxicity	386 (3 observational studies)	⨁◯◯◯ VERY LOW[b,c,d]	RR 0.31 (0.06 to 1.54)	Study population	
				450 per 1,000	**310 fewer per 1,000** (423 fewer to 243 more)

a. Substantial heterogeneity (I^2=90%)
b. Scotté 2005 & 2008 were match case-control studies with patients serving as their own controls. Patients and outcome assessors were not blinded.
c. Wide CI may suggest the potential of benefit and harm. Not meeting OIS.
d. Substantial heterogeneity (I^2=88%)

Scotté et al. (2005) reported that 6 of the patients were dissatisfied with global comfort—5 (11%) patients withdrew because of cold intolerance.

Scotté et al. (2008) reported that sock contact, temperature tolerance, and immobilization constraints were some aspects of the assessment of patients' global comfort. Fifty-eight percent of patients were satisfied with the frozen sock protection; 19%, very satisfied. One patient (2%) reported dissatisfaction due to cold intolerance.

Table References:

Effects considered are only for taxane-based treatments.

Tanyi et al., 2009, was removed from consideration because the study did not report on the correct intervention (Tanyi et al. cooled the wrists and ankles, not the hands and feet). In addition, Tanyi et al. reported on liposomal doxorubicin.

The panel noted that localized discomfort (2–11% discomfort from the studies) may decrease quality of life for patients in the moment, though the severity of the potential outcomes was lower than it could have been.

	Can, G., Aydiner, A., & Cavdar, I. (2012). Taxane-induced nail changes: Predictors and efficacy of the use of frozen gloves and socks in the prevention of nail toxicity. *European Journal of Oncology Nursing*, *16*, 270–275. https://doi.org/0.1016/j.ejon.2011.06.007 Scotté, F., Banu, E., Medioni, J., Levy, E., Ebenezer, C., Marsan, S., ... Oudard, S. (2008). Matched case-control phase 2 study to evaluate the use of a frozen sock to prevent docetaxel-induced onycholysis and cutaneous toxicity of the foot. *Cancer*, *112*, 1625–1631. https://doi.org/10.1002/cncr.23333 Scotté, F., Tourani, J.M., Banu, E., Peyromaure, M., Levy, E., Marsan, S., ... Oudard, S. (2005). Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *Journal of Clinical Oncology*, *23*, 4424–4429. https://doi.org/10.1200/JCO.2005.15.65	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The panel considered the certainty in the evidence of effects to be very low.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% had chemotherapy and radiotherapy. When asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent of females and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if they had had ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs.	The panel noted variability in values given the time commitment and discomfort—15 minutes before and after infusion. The patient may need to be relocated from the chair to a different area. The panel considered the unknown pain involved, the knowledge of the benefits of the prevention of PPE, and the severity of the PPE outcome.

		The panel decided that, with an appropriate understanding of the severity of the harm (the development of PPE), the majority of patients would choose the cooling procedure.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know		The panel considered the moderate benefit of the intervention versus the small harm. The incidence of PPE is reported between 6% and 62% for single agents, and as high as 89% for combinations of agents associated with PPE (Gabra, Cameron, Lee, Mackay, & Leonard, 1996; Twelves, Wong, Nowacki, et al., 2005; Wardley et al., 2005). In a systematic review and meta-analysis (Capriotti et al., 2015) of the risk of nail changes with taxane chemotherapy, incidence of all-grade nail changes with docetaxel was 34.9%. Incidence of all-grade nail changes with paclitaxel and nab-paclitaxel was 43.7%. The literature for docetaxel included RCTS, and the relative risk of nail changes, compared with controls, was 77.74 (95% CI 41.88–144.32; P < 0.001). In a review (Sibaud et al., 2016) of the dermatological adverse events with taxanes, incidence of HFS was reported as 5–10%. It was noted that HFS was relatively more common with docetaxel than paclitaxel.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	No research evidence identified.	Direct costs of cooling procedures include additional clinical time/chair time. However, patients would be there for pre-treatment anyway, so some time could be consolidated. The cost varies from negligible (sealable bag with ice) to large cost (specific frozen gloves for hands and feet, dry ice, cooler). The panel determined that the cost could be variable depending on the products and modalities used.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The development of PPE would require additional clinical visits, medication, DALYs (cost per disability-adjusted life year) and would affect daily functioning for an extended period of time.

Equity

What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No research evidence identified.	Different cooling procedures may be used, ranging from plastic bags of ice to patients needing to bring in specialty gloves/dry ice/coolers. There would be accessibility issues at public hospitals due to extra chair time. There is no insurance coverage for regional cooling, and the out-of-pocket costs varies. The panel determined that equity may be improved by allowing simple/accessible/low cost interventions for cooling; however, if using specialty cooling interventions, equity would be reduced based on cost, accessibility, and burden.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The guideline panel determined that Infusion nurses would probably accept regional cooling, but it would depend on education surrounding the intervention and how much it competed for time with their other responsibilities. The panel determined that hospital administrators and caregivers would probably accept regional cooling. The panel determined that the clinical team, oncology team, and specialists would accept regional cooling. The panel decided that, with well-informed persons/groups, regional would be acceptable for the stakeholders involved.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no	No research evidence identified.	There would be a burden because of the clinical space needed and the regulations surrounding the needed materials.

● Probably yes ○ Yes ○ Varies ○ Don't know		Patients would have to be selected for the intervention because not all patients would need the regional cooling. Clinical, patient, and caregiver time would be required. The panel noted that there could be "created infeasibility" if there is not enough space in the clinic to accommodate coolers brought by patients. However, they determined that regional cooling could be very feasible if staff and patients could use the supplies already in the institution or if the intervention could be integrated with pre-treatment appointments.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among persons receiving taxane-based chemotherapy regimens, the ONS guideline panel *suggests* cooling procedures rather than no cooling procedures for prevention of hand-foot syndrome. (Conditional recommendation, very low certainty in the evidence)

Justification

The ONS guideline 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 guideline panel issued a conditional recommendation for cooling procedures for the prevention of hand foot syndrome in patients with cancer receiving taxanes.

Subgroup considerations

No subgroup considerations.

Implementation considerations

Education and training are needed for the clinical team regarding the benefit of prevention of PPE versus the time/clinical burden of regional cooling.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

Use of cooling procedures for chemotherapy beyond taxanes

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Chemotherapy-induced alopecia prevention—scalp cooling vs. no scalp cooling

RECOMMENDATION

Should scalp cooling rather than no scalp cooling be used for individuals receiving cytotoxic agents who are at risk for alopecia?	
POPULATION:	Patients receiving cytotoxic agents at risk for alopecia
INTERVENTION:	Scalp cooling
COMPARISON:	No scalp cooling
MAIN OUTCOMES:	Quality of life; Development of alopecia; Scalp metastasis; Patient comfort; Adverse events from intervention; Self-estimated hair loss (Dean scale); Cost (patient and institution)
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Because of its effects on appearance, self-esteem, and sexuality, alopecia is one of the most distressing side effects to patients, even causing a small number to decline treatment (Balagula, Rosen, & Lacouture, 2011). Alopecia also is seen as a stigmatizing sign that a person is a cancer patient (Trueb, 2009).

CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The reported incidence of 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).	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	See table below	The discussion pertains only to hair on the scalp. Alopecia is a distressing side effect and can occur in 20–100% of cancer patients undergoing chemotherapy treatment (Freites-Martinez, Shapiro, et al., 2019). Over 40% of patients can experience permanent chemotherapy-induced alopecia (Kang et al., 2019). Rugo et al., 2017, and Nangia et al., 2017, were not included in the meta-analysis based on the measurement of the primary outcome. They demonstrate a significant difference in loss of hair/presence of alopecia. Nangia et al., 2017, had risk of bias concerns due to the role of the funder in the study and the fact that it was stopped early for benefits observed.

Outcomes	**№ of participants (studies) Follow up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects* (95% CI)**	
				Risk with no cooling caps	**Risk difference with cooling caps**
Development of alopecia assessed with: WHO criteria for severe hair	889 (7 studies)	-	**RR 0.59** (0.46 to 0.76)	Study population	
				843 per 1,000	**346 fewer per 1,000** (455 fewer

	loss or total alopecia					to 202 fewer)
	Significant alopecia (assessed with: >50% of Alopecia, Generally Requiring a Wig)	296 (5 studies)	⨁⨁⨁◯ MODERATE	**RR 0.54** (0.46 to 0.63)	-	**426 fewer per 1,000** (from 500 fewer to 343 fewer)

A 40% RRR and the magnitude in absolute terms were determined to be moderate.

Table References:

Betticher, D.C., Delmore, G., Breitenstein, U., Anchisi, S., Zimmerli-Schwab, B., Müller, A., ... Bühler, V. (2013). Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. *Supportive Care in Cancer*, *21*, 2565–2573. https://doi.org/10.1007/s00520-013-1804-9

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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no cooling caps	Risk difference with cooling caps
Development of alopecia assessed with: WHO criteria for severe hair loss or total alopecia	889 (7 studies)	-	**RR 0.59** (0.46 to 0.76)	Study population	
				843 per 1,000	**346 fewer per 1,000** (455 fewer to 202 fewer)
Significant alopecia (assessed with: >50% of Alopecia, Generally Requiring a Wig)	296 (5 studies)	⨁⨁⨁◯ MODERATE	**RR 0.54** (0.46 to 0.63)	-	**426 fewer per 1,000** (from 500 fewer to 343 fewer)

Table References:

Betticher, D.C., Delmore, G., Breitenstein, U., Anchisi, S., Zimmerli-Schwab, B., Müller, A., ... Bühler, V. (2013). Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. *Supportive Care in Cancer*, *21*, 2565–2573. https://doi.org/10.1007/s00520-013-1804-9

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Rugo, Melin, and Voigt (2017) reported scalp metastasis in the scalp cooled group was 0.61% (95% CI 0.32–1.1%); whereas in the group without scalp cooling, it was 0.41% (95%CI 0.13–0.94%). P=0.43

Rugo et al., 2017, and Nangia et al., 2017, were not included in the meta-analysis based on the measurement of the primary outcome. They demonstrate a significant difference in loss of hair/presence of alopecia.

Nangia et al., 2017, had risk of bias concerns due to the role of the funder in the study and the fact that it was stopped early for benefits observed.

Scalp cooling involves burdens in terms of cold tolerance and time in the infusion center. The panel determined that expectations of what scalp cooling can and cannot provide need to be established. Patients may endure distress if the intervention is not successful, but this may be mitigated by patient education.

	Mols, F., van den Hurk, C.J., Vingerhoets, A.J., & Breed, W.P. (2009). Scalp cooling to prevent chemotherapy-induced hair loss: Practical and clinical considerations. *Supportive Care in Cancer, 17*(2), 181–189. https://doi.org/10.1007/s00520-008-0475-4 Protière, C., Evans, K., Camerlo, J., d'Ingrado, M.P., Macquart-Moulin, G., Viens, P., ... Genre, D. (2002). Efficacy and tolerance of a scalp-cooling system for prevention of hair loss and the experience of breast cancer patients treated by adjuvant chemotherapy. *Supportive Care in Cancer*, *10*, 529–537. https://doi.org/10.1007/s00520-002-0375-y Rostom, Y., El-Husseiny, G., Salama, A., & El-Saka, R. (2012). Scalp cooler efficacy to reduce anthracycline-induced alopecia and its psycho-social impact in breast cancer patients. *Pan Arab Journal of Oncology*, *5*, 6–10. Smetanay, K., Junio, P., Feißt, M., Seitz, J., Hassel, J. C., Mayer, L., ... Sohn, C. (2019). COOLHAIR: A prospective randomized trial to investigate the efficacy and tolerability of scalp cooling in patients undergoing (neo) adjuvant chemotherapy for early breast cancer. *Breast Cancer Research and Treatment*, *173*, 135–143. https://doi.org/10.1007/s10549-018-4983-8 Van den Hurk, C.J.G., Breed, W.P.M., & Nortier, J.W.R. (2012). Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia. *Supportive Care in Cancer*, *20*, 3255–3260. https://doi.org/10.1007/s00520-012-1465-0 van den Hurk, Corina J., Peerbooms, M., van de Poll-Franse, Lonneke V., Nortier, J.W., Coebergh, J.W.W., & Breed, W.P. (2012). Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients - Results of the Dutch Scalp Cooling Registry. *Acta Oncologica, 51*, 497–504. https://doi.org/10.3109/0284186x.2012.658966 Van den Hurk, C.J.G., Van den Akker-van Marle, M.E., Breed, W.P.M., Van de Poll-Franse, L.V., Nortier, J.W.R., & Coebergh, J.W.W. (2013). Impact of scalp cooling on chemotherapy-induced alopecia, wig use and hair growth of patients with cancer. *European Journal of Oncology Nursing*, *17*, 536–540. https://doi.org/10.1016/j.ejon.2013.02.004 **Adverse events:**	

	• Betticher et al., 2013: 3.3% of persons in intervention groups experienced AEs (sensation of cold). 12.6% of patients in cooling arms discontinued treatment after cycle 1 • Rugo, Melin, & Voight, 2017: (n=106): 4/106 (3.85) headache, pruritis, skin pain, head discomfort. 3/106 (2.8%): discontinued due to cold • Nangia et al., 2017: no SAEs, 54 grade 1/2 AE (n=119); 46 anticipated/8 unanticipated (dry skin, scalp pain) • Kargar et al., 2011: NR • van den Hurk, Breed, & Nortier, 2012: 4 (2.4%) discontinued because of cold In a systematic review (Marks et al., 2019) of scalp cooling's effect on chemotherapy-induced alopecia-related quality of life in breast cancer patients, 13 studies were reviewed. Four of the studies reported no significant improvements in quality of life measures; 8 reported non-significant or no improvement, and 1 reported improvement in some domains and worsening in other domains. In a review (Ross & Fisher-Cartlidge, 2017) of the efficacy, safety, and tolerability of scalp cooling for chemotherapy-induced alopecia, five studies were examined. The review authors concluded that, given the patient-reported data and the discontinuation rates, scalp cooling was well-tolerated.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The panel considered the certainty in the evidence of effects to be very low due to publication bias, risk of bias, and selective reporting.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% received chemotherapy and radiotherapy. When asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent of females and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if they had had ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs. In an overview (Breed, van den Hurk, & Peerbooms, 2011) of chemotherapy-induced alopecia and scalp cooling, the authors note that chemotherapy-induced alopecia is a reason some patients refuse chemotherapy or choose potentially less-effective regimens that do not cause severe hair loss. In a selective review (Dua, Heiland, Kracen, & Deshields, 2015) of the psychosocial impact of cancer-related hair loss in survivors, 36 peer-reviewed articles were included. The authors of the review found that alopecia was among the most distressing side effects of cancer treatment. They found that for many of the survivors, it is a traumatic experience. They reported that concerns and distress can accompany the physical appearance of alopecia and some patients engaged in social avoidance. In a retrospective, multicenter cohort study (Freites-Martinez et al., 2019) of women having persistent chemotherapy-induced alopecia (pCIA) or endocrine therapy-induced alopecia after chemotherapy (EIAC), multivariate analysis of 41 patients with pCIA and 58 patients with EIAC showed a negative emotional effect in both groups.	The panel noted that there would be a greater burden with use of the devices and a potential for greater benefit if using a cooling system as opposed to a cap. Additionally, cooling caps may have more burden on the patient because of the need for patient-provided coolers.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The view for this question was focused on those patients looking to minimize or stop hair reduction. The panel noted the large desirable effects and small and temporary undesirable effects in determining that the balance probably favors the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Scalp cooling ranged between 1,500 and 3,000 USD per patient depending on treatment regimen and number of treatment cycles (Rubio-Gonzalez 2018). (Cooling system) In a Dutch cost effectiveness analysis (van den Hurk et al., 2014) of scalp cooling comparing the cost of the cooling machine and nursing care versus the cost of hair dressers, wigs, and head covers, the average societal costs decreased by €269. The willingness of the Dutch to pay for a QALY is generally 20,000 to 40,000 Euros.	Resources required differ between a cooling system and cooling caps.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	In the Dutch Scalp Cooling Registry study (van den Hurk, Peerbooms, et al., 2012) of satisfaction with scalp cooling in patients treated with chemotherapy, data were collected on 1411 scalp-cooled patients from 28 Dutch hospitals. Satisfaction with scalp cooling was determined by whether the patients wore a head cover during their last chemotherapy session. The wearing of head covers varied by type and dose of chemotherapy from 8% to 94% of patients. Higher chemotherapy dose and shorter infusion time, older age, female gender, and Asian type of hair decreased satisfaction (Types of hair were classified as African, Asian, West European, South European.).	The panel determined that the cost and accessibility of the intervention would place a burden for equity.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The panel noted that the oncology team would need proper education on the risk of scalp metastasis for acceptance of the intervention. The panel determined that the infusion staff and caregivers would probably accept the intervention.

Feasibility

Is the intervention feasible to implement?

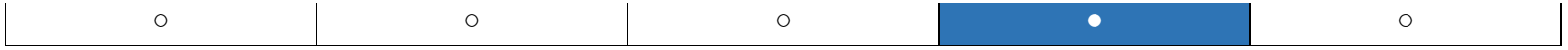
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	In an overview (Breed, van den Hurk, & Peerbooms, 2011) of chemotherapy-induced alopecia and scalp cooling, a variety of methods of scalp cooling are described: bags with crushed ice, frozen cryogel packs, packs with an endothermic cooling reaction, precooled caps, caps cooled by fluid or chilled air, liquid circulation, and chilled air. Pre-cooled caps need frequent cap changes and can be uncomfortable because of their weight. With the chilled air system, there are no concerns about a properly fitting cap. In the discussion section of a Japanese multicenter, controlled trial (Kinoshita et al., 2019) on the safety and efficacy of the Paxman Hair Loss Prevention System for chemotherapy-induced alopecia in patients with breast cancer, the authors stated that the Paxman system had been designed for Caucasian heads and that the Japanese head is more brachycephalic.	The panel noted that the cooling systems would be more feasible than the cooling caps. However, setting up a program with the cooling systems would require a great deal of work and of training the infusion nurses.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention



CONCLUSIONS

Recommendation

Among persons with cancer receiving cytotoxic agents associated with chemotherapy-induced alopecia who are concerned about alopecia, the ONS guideline 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 a patient is seen at a facility without a cooling system, an ice cap can be used as they have similar efficacy.

Justification

The ONS guideline 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 guideline panel issued a conditional recommendation for cooling caps for the prevention or minimization of chemotherapy-induced alopecia.

Subgroup considerations

No subgroup considerations.

Implementation considerations

The training of infusion nurses and a large amount of work to set up the system would be required.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

- Quality of life among responders and non-responders of scalp cooling
- Economic outcomes for hospitals that offer scalp cooling programs
- Response to scalp cooling across a diverse patient population

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Chemotherapy-induced alopecia prevention—minoxidil vs. usual care

RECOMMENDATION

Should minoxidil rather than usual care be used for individuals receiving cytotoxic agents who are at risk for alopecia?	
POPULATION:	Patients on cytotoxic treatment at risk for alopecia
INTERVENTION:	Minoxidil
COMPARISON:	Usual care
MAIN OUTCOMES:	Quality of life; Resolution of alopecia; Adverse events from intervention; Self-estimated hair loss (Dean scale); Cost
SETTING:	Clinical care
PERSPECTIVE:	Clinical recommendation – Population perspective
BACKGROUND:	Because of its effects on appearance, self-esteem, and sexuality, alopecia is one of the most distressing side effects to patients, even causing a small number to decline treatment (Balagula, Rosen, & Lacouture, 2011). Alopecia also is seen as a stigmatizing sign that a person is a cancer patient (Trüeb, 2009).
CONFLICT OF INTERESTS:	ONS conflict of interest declaration and management policies were applied and the following panel members were voting panel members (determining the direction and strength of the recommendation): Loretta A. Williams, PhD, APRN, AOCN®, OCN®, Kathryn Ciccolini, DNP, AGACNP-BC, OCN®, DNC, George Ebanks, BSN, RN, OCN®, Karren Ganstwig, Bernice Y. Kwong, MD, Gary Shelton, DNP, MSN, NP, ANP-BC, ACHPN, AOCNP®, Jenna Strelo, FNP-BC, MSN, BSN Panel members recused as a result of risk of conflicts of interest: None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The reported incidence of 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). In a Korean 3-year prospective cohort study (Kang et al., 2019) of permanent chemotherapy-induced alopecia in 61 patients with breast cancer, 39.5% experienced the effect at 6 months and 42.3% at 3 years. At 3 years, the most common problems reported were thinning hair (75.0%), less hair volume (53.9%), loss of hair (34.6%), and gray hair (34.6%). In a retrospective, multicenter cohort study (Freites-Martinez et al., 2019), 98 women with persistent chemotherapy-induced alopecia (pCIA) and 94 with endocrine therapy-induced alopecia after chemotherapy (EIAC) were characterized as to quality of life and treatment outcomes. The Hairdex	The question is a priority but needs to be split into oral and topical for treatment. There is an ongoing study with oral minoxidil (https://clinicaltrials.gov/ct2/show/NCT03831334?cond=minoxidil&draw=3&rank=12). The guidelines will be updated once results from that trial are presented.

	questionnaire was used to assess quality of life. QoL data was available for 41 of the pCIA patients and 58 of the EIAC patients. Negative emotional effect was reported in both groups. The chemotherapy-induced patients with grade 2 alopecia scored higher (higher score = greater negative result) than those with grade 1.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know		The guideline panel noted that there would be a difference in decisions regarding acute versus persistent alopecia. They also noted that hair regrowth is an important outcome.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Impact
Hair thinning or loss assessed with: Time to maximal hair loss, partial or complete hair loss	(3 observational studies)	⨁◯◯◯ VERY LOW[a,b]	Duvic et al., 1996: Minoxidil users had a longer time until maximal hair loss, a shorter time between baseline and maximal regrowth (p = 0.07). Granai et al., 1991: Five women had hair loss—either complete or severe symmetrically diffuse. One patient had no hair loss in the minoxidil or control areas. Rodriguez et al., 1994: In the minoxidil arm, 21 patients (88%) experienced grade 3 alopecia; in the placebo arm, 22 patients (92%).
Hair regrowth assessed with: time to hair regrowth, general measure of improvement	(2 observational studies)	⨁◯◯◯ VERY LOW[a,b]	Duvic et al., 1996: A statistically significant difference was found between the minoxidil and placebo groups in the time from maximal hair loss to initial hair regrowth. Freites-Martinez et al., 2019: Moderate to significant improvement was found in 36 patients (67%); stable or progressed alopecia was found in 18 patients (33%). Between the minoxidil and spironolactone groups, no outcomes differences were discovered.

Adverse events	(1 observational study)	⊕◯◯◯ VERY LOW[a]	Granai et al., 1991: No adverse events were reported from the drug. Rodriguez et al., 1994: No adverse events were reported from the drug.	

Table References

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Granai, C.O., Frederickson, H., Gajewski, W., Goodman, A., Goldstein, A., & Baden, H. (1991). The use of minoxidil to attempt to prevent alopecia during chemotherapy for gynecologic malignancies. *European Journal of Gynaecological Oncology*, *12*, 129–132.

Rodriguez, R., Machiavelli, M., Leone, B., Romero, A., Cuevas, M. A., Langhi, M., ... Vallejo, C. (1994). Minoxidil (Mx) as a prophylaxis of doxorubicin–induced alopecia. *Annals of Oncology*, *5*, 769–770. https://doi.org/10.1093/oxfordjournals.annonc.a058986

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Impact
Hair thinning or loss assessed with: Time to maximal hair loss, partial or complete hair loss	(3 observational studies)	⨁◯◯◯ VERY LOW[a,b]	Duvic et al., 1996: Minoxidil users had a longer time until maximal hair loss, a shorter time between baseline and maximal regrowth (p = 0.07). Granai et al., 1991: Five women had hair loss—either complete or severe symmetrically diffuse. One patient had no hair loss in the minoxidil or control areas. Rodriguez et al., 1994: In the minoxidil arm, 21 patients (88%) experienced grade 3 alopecia; in the placebo arm, 22 patients (92%).
Hair regrowth assessed with: time to hair regrowth, general measure of improvement	(2 observational studies)	⨁◯◯◯ VERY LOW[a,b]	Duvic et al., 1996: A statistically significant difference was found between the minoxidil and placebo groups in the time from maximal hair loss to initial hair regrowth. Freites-Martinez et al., 2019: Moderate to significant improvement was found in 36 patients (67%); stable or progressed alopecia was found in 18 patients (33%). Between the minoxidil and spironolactone groups, no outcomes differences were discovered.
Adverse events	(1 observational study)	⨁◯◯◯ VERY LOW[a]	Granai et al., 1991: No adverse events were reported from the drug. Rodriguez et al., 1994: No adverse events were reported from the drug.

Table References

The panel noted that the topical application may lead to some burden and may need to be used for life. The evidence for lifetime use is indirect, coming from non-cancer patients.

There is the possibility of the shedding of hair at start of minoxidil use and the possibility of localized skin irritation.

	Duvic, M., Lemak, N.A., Valero, V., Hymes, S.R., Farmer, K.L., Hortobagyi, G.N., ... Compton, L.D. (1996). A randomized trial of minoxidil in chemotherapy-induced alopecia. *Journal of the American Academy of Dermatology*, *35*, 74–78. https://doi.org/10.1016/S0190-9622(96)90500-9 Freites-Martinez, A., Chan, D., Sibaud, V., Shapiro, J., Fabbrocini, G., Tosti, A., ... Norton, L. (2019). Assessment of quality of life and treatment outcomes of patients with persistent postchemotherapy alopecia. *JAMA Dermatology, 155*, 724–728. https://doi.org/10.1001/jamadermatol.2018.5071 Granai, C.O., Frederickson, H., Gajewski, W., Goodman, A., Goldstein, A., & Baden, H. (1991). The use of minoxidil to attempt to prevent alopecia during chemotherapy for gynecologic malignancies. *European Journal of Gynaecological Oncology*, *12*, 129–132. Rodriguez, R., Machiavelli, M., Leone, B., Romero, A., Cuevas, M. A., Langhi, M., ... Vallejo, C. (1994). Minoxidil (Mx) as a prophylaxis of doxorubicin–induced alopecia. *Annals of Oncology*, *5*, 769–770. https://doi.org/10.1093/oxfordjournals.annonc.a058986	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies		The certainty in the evidence was rated to be very low certainty due to the unknown magnitude of the harms.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important	In a quantitative study (Gandhi, Oishi, Zubal, & Lacouture, 2010) of survivors' views on dermatologic, gastrointestinal, and constitutional toxicities, 379 survivors of various cancers answered questionnaires. Eighty-seven percent received chemotherapy; 57% received chemotherapy and radiotherapy. When	The panel determined that there is a general patient dislike of hair loss, so great weight would be placed on avoiding hair loss or on regrowth. They also noted that

uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	asked about skin irritation prior to and after treatment, there was a significant increase in concern. Twenty-five percent and 5% of males were very concerned about it after treatment; 59% of females and 40% of males were somewhat concerned after treatment. Of the 84% of respondents who had skin toxicity and were not referred to a dermatologist, 54% said they would have felt better during therapy if they had had ways to deal with the secondary skin issues. Sixty-seven percent of respondents said they felt their skin toxicities were worse than their initial beliefs. In an overview (Breed, van den Hurk, & Peerbooms, 2011) of chemotherapy-induced alopecia and scalp cooling, the authors note that chemotherapy-induced alopecia is a reason some patients refuse chemotherapy or choose potentially less-effective regimens that do not cause severe hair loss. In a selective review (Dua, Heiland, Kracen, & Deshields, 2015) of the psychosocial impact of cancer-related hair loss in survivors, 36 peer-reviewed articles were included. The authors of the review found that alopecia was among the most distressing side effects of cancer treatment. They found that for many of the survivors, it is a traumatic experience. They reported that concerns and distress can accompanying the physical appearance of alopecia and some patients engaged in social avoidance. In a retrospective, multicenter cohort study (Freites-Martinez et al., 2019) of women having persistent chemotherapy-induced alopecia (pCIA) or endocrine therapy-induced alopecia after chemotherapy (EIAC), multivariate analysis of 41 patients with pCIA and 58 patients with EIAC showed a negative emotional effect in both groups.	there may be variability in patients' willingness to use minoxidil if they are thinking about having to use it for life (potential high burden). Patients who place a higher value on the potential for improvement of hair growth may be willing to put up with the burden of use.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel decided that the balance of effects probably favors the intervention given the variability in how much patients value hair regrowth versus the burden of the intervention.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Skin Reactions Intervention Costs from Walmart.com, September/October 2019** **Intervention** / **Product** / **Price** Minoxidil / Equate Women's Minoxidil Topical Solution for Hair Regrowth, 3-Month supply / $18.76	The intervention is purchased over the counter at a low cost, but it would potentially need to be used for life.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact	No research evidence identified.	Access may be reduced because it would potentially be an out-of-pocket cost for life.

○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel determined that the clinical team, oncology team, and caregivers would accept the intervention.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	Feasibility issues involve the cost and burden discussed above.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important	No important uncertainty or variability			

	JUDGEMENT						
			uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

Among persons with cancer on cytotoxic treatment at risk for alopecia, the ONS guideline panel *suggests* minoxidil rather than no treatment for the shortening or minimization of alopecia. (Conditional recommendation, very low certainty of evidence).

Remark: Persons preferring to minimize or shorten duration of hair loss may wish to use minoxidil.

Justification

The panel determined that there is evidence for a net benefit from 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 minoxidil in patients for the shortening or minimization of alopecia in patients receiving cytotoxic agents known to cause chemotherapy-induced alopecia.

Subgroup considerations

No subgroup considerations.

Implementation considerations

No implementation considerations.

Monitoring and evaluation

No monitoring and evaluation considerations.

Research priorities

IN-TEXT CITED REFERENCES

Balagula, Y., Rosen, S.T., & Lacouture, M.E. (2011). The emergence of supportive oncodermatology: The study of dermatologic adverse events to cancer therapies. *Journal of the American Academy of Dermatology, 65*, 624–635. https://doi.org/10.1016/j.jaad.2010.06.051

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