

Development and Application of Procedures for the Management of Skin Toxicity Related to Immune Checkpoint Inhibitors in Patients with Lung Cancer

Qianru Xu*, Qiong Wen#

Department of Oncology, First People's Hospital of Jingzhou City, Jingzhou, China

Email: #18972161237@163.com

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Abstract

Objective: To establish the procedures for the management of skin toxicity related to immune checkpoint inhibitors in patients with lung cancer and explore the effect of application. **Methods:** A total of 24 evidence-based evidences were collected from 7 aspects, including risk factors, baseline screening, ICIs monitoring, daily skin care, multidisciplinary management, symptom management and health education. A total of 157 lung cancer patients and 94 nurses from 8 wards of the Oncology department of our hospital from November 2022 to May 2023 were selected by convenience sampling. A total of 77 patients and 46 nurses from ward 1 - 4 were divided into the baseline group. There were 80 patients and 48 nurses in Ward 5 - 8 as the evidence-based practice group. In the baseline group, patients were treated with routine methods such as assessing skin symptoms, taking medication according to symptoms, guiding to keep skin clean and moist, eating a light diet, and avoiding scratching. The evidence-based practice group adopts an evidence-based continuous improvement model for nursing. The differences in the severity of symptoms of skin toxicity in the second cycle of medication and the knowledge and practice of self-care of skin toxicity were compared between the two groups before and after the use of the syndrome, as well as the differences in the implementation rate of review indicators, evidence-based ability and knowledge and practice of skin toxicity care before and after the use of the syndrome. **Results:** The incidence and severity of cutaneous toxicity were significantly lower after treatment than before treatment ($P < 0.05$). The score of knowledge and practice on skin toxicity nursing of immune checkpoint inhibitor was higher after treatment than before treatment

*First author.

#Corresponding author.

($P < 0.05$). Conclusion: The implementation of immune checkpoint inhibitor-related skin toxicity management procedures can effectively reduce the incidence and severity of skin toxicity symptoms, optimize the clinical pathway, and improve the quality of care.

Keywords

Lung Cancer, Immune Checkpoint Inhibitors, Skin Toxicity, Process Management, Nurse

1. Introduction

Lung cancer is a malignant tumor originating from the bronchial mucosa or glands of the lungs. Traditional treatment methods include surgical radical resection, adjuvant chemoradiation and targeted therapy [1]-[3], etc. Although certain results have been achieved, the 5-year survival rate of patients is only 15% [4]. In recent years, with the rapid development of tumor immunology, immune checkpoint inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated protein 4, programmed cell death protein 1 or programmed cell death ligand 1 have been developed. The wide application of ICIs has improved the 5-year survival rate of lung cancer patients to 15.5% - 32.0% [5] [6]. However, while enhancing the anti-tumor effect of the body, ICIs may also change the normal immune response of the body and cause the imbalance of immune tolerance, resulting in immune-related adverse reactions, such as skin, endocrine, important organs and nervous system toxicity [7] [8]. Among them, skin toxicity with rash and pruritus as the main symptoms is the most common [9] [10]. It can affect the comfort, psychological state and quality of life of patients with lung cancer to varying degrees, and even lead to the interruption of treatment. At present, there is a lack of clinical studies on the best evidence aggregation and evidence translation for the care of ICIS-related skin toxicity in lung cancer patients. Therefore, this study intends to develop procedures for the management of ICIS-related skin toxicity in lung cancer patients and explore the effects of its application.

2. Development of Procedures for the Management of Skin Toxicity Associated with Immune Checkpoint Inhibitors in Patients with Lung Cancer

2.1. Establishment of ICIS-Related Skin Toxicity Management Group

The group consists of 15 members, including 3 deputy chief physicians of the department of Oncology, 3 head nurses, 6 chief nurses and 3 graduate nurses. The deputy chief physician of the Department of Oncology is responsible for the differential diagnosis of ICIS-related skin toxicity causes and the issuance of

medical advice; the head nurse is responsible for process training and quality control; the supervisor is the responsible team leader, responsible for the implementation and supervision of the responsible nurse procedures in each group; Nursing graduate students are responsible for literature search and evidence integration.

2.2. Literature Retrieval

According to the 6S evidence pyramid, Search BMJ Best Clinical Practices, UpToDate, JBI Library, PubMed, Web of Science, Embase, CINAHL, Elsevier, Medline, Cochrane Library, WHO website, NCCN, ASCO, GIN, NICE, SIGN, RNAO, SITC, MASCC, CSCO, CNKI.cn, Wanfang, Vipu, China Biomedical Literature Database, Evidence on ICIS-related skin toxicity Care for lung cancer patients in Jiemitong. The search period is up to October 1, 2022. A total of 867 literatures were obtained in the search. After excluding the literatures that could not obtain the full text, guideline interpretation and repeated publication, 14 literatures were finally included after eliminating the duplicated literatures and literatures that did not meet the criteria.

2.3. Evidence Summary and Process Development

Three nursing graduate students read and screened the literature to extract relevant evidence for the management of skin toxicity related to immune checkpoint inhibitors. 5 guidelines [11]-[14], 3 systematic reviews [15] [16] and 6 expert consensus articles [17]-[22] are evaluated by using AGREE II [23], JBI Evidence-Based Health Care Center and JBI expert consensus quality evaluation tools [24] [25], respectively. JBI Evidence pre-grading and evidence recommendation system (2014 edition) was adopted for evidence pre-grading and evidence recommendation [26]. This study summarized 24 best evidence from 7 aspects, and deleted 11 pieces of evidence after FAME evaluation to form 13 best evidence summaries. See **Table 1**

Table 1. Summary of nursing evidence for ICIS-related dermal toxicity in lung cancer patients.

Category	Content of evidence	Evidence level (level)	Recommended Level (Level)
High risk factor	1) The occurrence of skin toxicity of immunosuppressants is related to the type, dose, allergy history, and duration of ICIs drug use [16]	4	A
	2) Excessive skin cleansing, combination of CTLA-4 with anti-PD-1 and PD-L1 drugs, chemotherapy, sun exposure, and a history of autoimmune can aggravate skin toxicity [11] [27]	4	A
Baseline screening	3) Before starting treatment, the doctor must evaluate the patient's susceptibility to skin toxicity, including: current history, past history (especially autoimmune disease, immune deficiency history, special infection history), family history, general condition, etc., and conduct a whole body skin examination (including mucosa) [20] [21]	5	A

Continued

	4) Routine tests are required before immunotherapy, including a complete blood count, eosinophil count, and liver and kidney function tests. Specific serological tests if autoimmune disease is suspected [9] [20]	5	A
ICIs Monitoring during treatment	5) Early identification, diagnosis, intervention and adequate monitoring are important measures to maintain drug dose intensity and reduce the severity of skin adverse reactions. [15] [28]	5	A
	6) Close monitoring of the patient's entire skin and mucosa is required at the beginning of medication. In the course of ICIs treatment, the functional status of the body or the function of human organs is regularly monitored, so as to detect toxicity early [16]	4	A
Daily skin care	7) It is recommended to use emollients and sunscreens regularly, avoid alcohol-based over-the-counter lotions and harsh products, use a mild cleanser (pH neutral), and use a moisturizer with 5% - 10% urea [19]	5	B
	8) Reduce contact with water and wear cotton gloves under plastic or rubber gloves in wet work [19]	5	B
	9) Avoid using skin irritants (e.g., over-the-counter anti-acne medications, solvents, or disinfectants) and procedures that damage the skin structure (e.g., manicures) [19]	5	A
	10) Avoid scratching and hot washing, limit bath time; Close-fitting cotton underwear; Avoid spicy food; Regulate emotions, avoid fatigue [21]	5	B
Multidisciplinary management	11) It is suggested to adopt a multidisciplinary model to manage ICIs treatment for lung cancer patients, set up a skin toxicity management team at the hospital level, and set up a skin toxicity prevention and treatment management team in the oncology treatment department, so as to improve the ability of oncologists to deal with skin toxicity, improve the quality of life of patients, maximize the survival of patients, and improve the prognosis [22] [29]	5	A
	12) The multidisciplinary team members include medical oncologists, dermatologists, pathology specialists, nurses and other clinical experts [22]	5	A
Symptom management	13) When skin symptoms occur, a full-body skin examination should be performed immediately, including the severity, size, shape, comorbidities, and mucosal involvement. If there are abnormalities, biopsy should be considered [21]	5	A
	14) Identification with other causes (such as infections, the effects of other drugs) or unrelated primary skin disorders [14]	5	B
	15) Topical anti-itch drugs (menthol, pramoxine) are recommended for pruritus patients without rashes [14]	5	B
	16) It is recommended to use patient-reported tools to measure its severity and impact on quality of life, such as: The National Cancer Institute developed Adverse Event Evaluation Criteria 5.0 (CTCAEV5.0) to grade skin toxicity [9] [12] [28]	5	A

Continued

	17) G1 grade continued immunotherapy, topical emollients, oral antihistamines, and treatment of the affected area with moderate-potency topical steroids [9]	5	A
	18) G2 grade consideration of suspension of immunotherapy, topical emollients, oral antihistamines, treatment of the affected area with highly potent topical steroids, and/or prednisone treatment [9] [13]	5	A
	19) G3 grade suspension of immunotherapy, treatment of the affected area with strong local steroids, prednisone 0.5 - 1 mg/(kg.d) if no improvement can be increased to 2 mg/(kg.d), emergency dermatology consultation, consider hospitalization [9] [12]	5	A
	20) When Stevens-Johnson syndrome and toxic epidermal necrolysis occur, immunotherapy should be permanently discontinued, hospitalization should be performed, and multidisciplinary consultation such as dermatology should be requested immediately [12]	5	A
	21) Healthcare professionals should conduct special education on skin toxicity to patients, which can be carried out through multimedia, information cards or pamphlets. Patients should be followed up and monitored for at least one year after ICIs treatment [11] [13]	4	A
	22) The contents of health education include: immunotherapy, its mechanism of action, manifestations and monitoring of possible complications [14] [21]	5	B
Health education	23) It is suggested that medical staff should provide health education on skin toxicity to patients and their families before starting treatment, throughout treatment and survival period, and in the event of adverse reactions, patients should report symptoms directly to the tubebed doctor [14] [21] [28]	5	A
	24) It is suggested that medical staff should be regularly organized to participate in special training on ICIS-related toxicity, and nurses in oncology treatment departments should be strengthened to enhance their ability to identify and care for ICIS-related toxicity [29]	5	A

3. Application of ICIS-Related Skin Toxicity Management Procedures in Lung Cancer Patients

3.1. Research Object

A total of 157 lung cancer patients and 94 nurses from 8 wards of the Oncology department of our hospital from November 2022 to May 2023 were selected by convenience sampling. A total of 77 patients and 46 nurses from ward 1 - 4 were divided into the baseline group. There were 80 patients and 48 nurses in Ward 5 - 8 as the evidence-based practice group. Inclusion criteria: 1) Patients aged 18 - 75 years; 2) Patients undergoing ICIs therapy. Exclusion criteria: 1) Patients with impairment of perception, understanding and expression; 2) Patients with skin diseases, diabetes and immune system diseases before treatment; 3) Patients with

severe skin reactions such as bullous dermatitis after treatment. Inclusion criteria: Nurses engaged in cancer nursing for ≥ 1 year and volunteered to participate in this study. Exclusion criteria: studying and rotating nurses. There was no significant difference in general data between the two groups ($P > 0.05$). The ethics approval number for this study is 2022HL08.

3.2. Research Method

3.2.1. Routine Care

The medical staff in the two groups were fixed, and the patients were treated and cared for in accordance with the 2023CSCO Immune Checkpoint Inhibitor-related Toxicity Management Guidelines. Before treatment, the skin and mucosa of the whole body of the patient were evaluated to understand the patient's allergy history, medication cycle and blood test results. The patients' mental state and sleep condition were evaluated. Explain in detail to the patient and his family the action of the drug, the dosage, the course of treatment, and the symptoms of skin toxicity that may occur after the drug. During treatment, patients may suffer from fear, anxiety and other adverse reactions such as rashes and pruritus. The baseline group should check the skin condition regularly and pay special attention to abnormal symptoms such as redness, swelling, pruritus and ulcers. Strengthen the shift, carefully check the patient's skin, find abnormal, should inform the doctor in time for treatment; assist patients to trim nails regularly to avoid skin scratches; instruct patients to pay attention to sun protection when going out, choose soft, comfortable, breathable clothing, and avoid wearing rough or too tight clothing and other conventional methods of care.

3.2.2. Evidence-Based Practice Group Intervention Methods

1) Select assessment tools and build information platform

In order to standardize the information management and tracking of high-risk patients, the project team, relying on the hospital Information Department, implanted the CTCEA5.0 adverse event report into the nursing information system of our hospital to help implement evidence-based practice plans and improve work efficiency.

2) Develop standardized nursing procedures

Based on the evidence and clinical experience, the nursing flowchart of ICIS-related skin toxicity was developed. In the process of medication, should strictly follow the doctor's advice, and pay attention to observe the drug reaction; Symptoms and management of dermal toxicity: Continued immunotherapy for primary dermal toxicity, topical emollients, oral antihistamines, topical medium acting steroids to treat the affected area; secondary skin toxicity consider discontinuation of immunotherapy, topical emollients, oral antihistamine, topical high-potency steroids, and/or prednisone treatment of the affected area; suspend immunotherapy for tertiary skin toxicity, treat the affected area with local strong steroids or prednisone 0.5 - 1 mg/(kg·d), increase the dose to 2 mg/(kg·d) if there is no improvement, and consult the dermatologist urgently for timely treatment;

instruct the patient to use mild, non-irritating soap or detergent to clean the skin, and ask the patient to avoid using hot water; Act gently during the nursing operation, keep the sheet flat and clean, avoid skin irritation and friction; psychological care: Necessary psychological counseling for patients and their families, listening, music therapy, mindfulness-based stress reduction and other ways can be used to encourage patients to speak out their feelings, help establish confidence in overcoming the disease, and promote the successful completion of treatment. And the flow chart is made into a nursing car table, convenient for nurses to view.

3) Optimize processes and facilitate multidisciplinary collaboration

Improve ICIS-related skin toxicity assessment, diagnosis and treatment, consultation, referral, follow-up and other procedures. Promote the multi-disciplinary cooperative management model including oncology, dermatology, pathology and specialist nurses.

4) Multi-channel personalized precision health education

On the basis of existing education, personalized and accurate health education for patients is conducted according to the best evidence and combined with the age and education level of patients, including face-to-face communication with patients, two-dimensional code of health education video placed in the hospital, paper version of education manual, online public account learning, online live interaction of medical care and small training meetings of departments.

5) Intensive discharge education

The contents of health education for hospital discharge were made into mind maps. A paper self-care knowledge questionnaire related to ICIs was issued to assess patients the day before discharge. Those who fail to pass will continue education and be discharged after passing.

6) Deepen continuity of care

Establish a home Wechat management group for immunotherapy, and invite doctors and nurses with rich clinical experience and specialist knowledge to join the group. Patients report their symptoms by sending pictures, videos and other means to promote doctor-patient communication.

4. Result

Statistical analysis was performed using SPSS22.0 software. The severity of skin toxicity symptoms in the second cycle of medication and the knowledge and practice of self-care of skin toxicity were compared between the two groups before and after treatment. The ability of evidence-based nursing and the knowledge and practice of skin toxicity nursing were compared before and after using the evidence.

4.1. Patient Level

1) The incidence and severity of skin toxicity after treatment were significantly lower than those before treatment ($P < 0.05$), as shown in **Tables 2-4**.

Table 2. Comparison of occurrence of skin toxicity before and after treatment.

group	Cutaneous toxicity (example)	
	Take place	unoccurred
Preapplication of evidence ($n = 77$)	32	45
Postapplication of evidence ($n = 80$)	21	59
χ^2 value	4.112	
P value	0.043	

Table 3. Comparison of pruritus degree before and after treatment.

group	The number of pruritus cases	pruritus		
		G1	G2	G3
Preapplication of evidence	26	5	11	10
Postapplication of evidence	15	8	5	2
Z value	-2.317			
P value	0.019			

Table 4. Comparison of rash degree before and after treatment.

group	Number of cases of rash	rash		
		G1	G2	G3
Preapplication of evidence	18	2	5	11
Postapplication of evidence	9	6	1	2
Z value	-2.535			
P value	0.012			

2) The self-designed ICIs self-care questionnaire was used to investigate skin toxicity. The total score of the questionnaire was 78 points, including 3 dimensions, namely knowledge (8 items), attitude (8 items) and behavior (6 items). Cronbach's α coefficient was 0.89, and content validity was 0.91. It was concluded that the score of self-care knowledge and practice of skin toxicity was higher after treatment than before treatment ($P < 0.05$), as shown in **Table 5**.

4.2. Nurse Level

1) The questionnaire of knowledge and practice of skin toxicity related to ICIs was used to investigate. The questionnaire, with a total score of 86, contained three dimensions, namely knowledge (18 items), attitude (7 items) and behavior (10 items). Cronbach's α coefficient was 0.83 and the structural validity was 0.85. It was concluded that the score of knowledge and practice of nursing for skin toxicity of ICIs was higher after the use of the certificate than before the use of the certificate ($P < 0.05$), as shown in **Table 6**.

Table 5. Comparison of knowledge and practice scores of self-care for cutaneous toxicity before and after treatment ($c \pm s$).

time	knowledge	faith	behavior
Preapplication of evidence ($n = 77$)	2.48 ± 1.57	22.85 ± 7.96	12.12 ± 3.95
Postapplication of evidence ($n = 80$)	6.10 ± 1.46	32.79 ± 4.44	21.81 ± 5.37
t value	13.195	8.550	11.322
P value	<0.001	<0.001	<0.001

Table 6. Comparison of knowledge and practice scores of nurses on ICIS-related skin toxicity before and after use ($c \pm s$).

time	knowledge	faith	behavior
Preapplication of evidence ($n = 46$)	7.57 ± 2.25	24.70 ± 4.44	29.83 ± 8.24
Postapplication of evidence ($n = 48$)	10.18 ± 2.97	26.35 ± 2.72	34.24 ± 6.31
t value	12.772	23.89	10.178
P value	<0.001	<0.001	0.002

5. Discuss

5.1. The Management Procedure of ICIS-Related Skin Toxicity in Lung Cancer Patients Is Scientific and Feasible

This study comprehensively searched relevant literature and extracted the best evidence, combined with clinical practice, and finally formulated the management process of ICIS-related skin toxicity in lung cancer patients, reflecting the scientific formulation of the process. Through comprehensive assessment, identification of high-risk factors, analysis of skin toxicity symptoms and severity, daily care is given first, and symptomatic treatment such as local use of drugs or dermatology consultation is given after no obvious effect, which reduces the number of aggravation of skin toxicity symptoms or interruption of treatment due to skin toxicity symptoms, and better guarantees the continuity of treatment for patients. In the process of application, the communication and cooperation between the doctors and nurses are enhanced, and the value of nurses as the leading personnel is recognized and has good feasibility.

5.2. The Implementation of ICIS-Related Skin Toxicity Management Procedures Can Reduce the Incidence and Severity of Skin Toxicity in Patients

The results of this study showed that the implementation of ICIS-related dermal toxicity management procedures could reduce the incidence and severity of patients' dermal toxicity ($P < 0.05$), and the evidence-based ability of nurses and the knowledge and practice of ICIS-related dermal toxicity care were significantly improved, based on the evidence-based construction of the standardized

procedures of ICIS-related dermal toxicity care for lung cancer patients. Improve the connotation construction and service level of nursing.

6. Conclusion

The widespread use of ICIs has improved the 5-year survival rate of lung cancer patients. However, while enhancing the anti-tumor effect of the body, the immune-related adverse reactions caused by ICIs, skin toxicity with rash and pruritus as the main symptoms, have varying degrees of impact on the comfort, psychological state and quality of life of lung cancer patients, and even lead to treatment interruption. The ICIS-related skin toxicity management process for lung cancer patients established in this study has good scientific and feasibility, which can reduce the incidence of skin toxicity in patients, improve its occurrence degree, cultivate nurses' evidence-based thinking, and promote continuous improvement of nursing quality based on evidence, which has clinical practical significance. However, the sample size of this study is small and the observation time is short, which needs to be verified by high-quality research with large samples.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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