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Subjective evaluation of skin toxicity and quality of life in patients undergoing anti-cancer treatment at the Department of Cancer Chemotherapy

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ABSTRACT

Introduction: Skin complications are a frequent side effect of oncological treatment, which may impair patients' quality of life. The aim of this study is a subjective assessment of skin toxicity and life quality during anticancer treatment.

Material and methods: We analysed patients with malignant cancer, receiving conventional chemotherapy, molecularly targeted drugs, or both, between January 2019 and February 2020, for at least six weeks. The researchers' questionnaire assessed the type and intensity of skin toxicity, its impact on the emotional state and life quality. Subjective needs concerning education about the potential toxicity of treatment and dermatological care were analysed. Global quality of life was assessed using the EORTC QLQ-C30 scale.

Results: We analysed 78 patients, aged 27–78 years (41 men; 37 women). Twelve patients received anti-EGFR antibody. Skin toxicity influence on emotional state and life quality was assessed by age, gender, duration and type of therapy. Skin complications were reported by 95% of patients, 53% confirmed the influence of skin toxicity on emotional state and 32% on everyday functioning. The inverse correlation between life quality and skin lesions' severity was found (correlation coefficient = 0,33, $p < 0,0001$). 31% of patients were willing to have a dermatologist in the team of leading doctors. 28% reported a total lack of possible skin side effects information. 82% declared total skin toxicity acceptance in case of the good effect of anti-cancer therapy.

Conclusions: Dermal toxicity negatively affects various areas of patient functioning. Improvement can be made by proper education of patients, effective prevention and treatment.

Key words: skin toxicity, quality of life, systemic treatment, monoclonal antibodies, epidermal growth factor receptor

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Introduction

Systemic anticancer treatment may cause skin side effects in 40–90% of patients [1–3]. This mainly concerns molecularly targeted drugs. Monoclonal antibodies and tyrosine kinase inhibitors directed against the epidermal growth factor receptor (EGFR) cause skin toxicity in almost all treated patients [4, 5]. Immunotherapy in more than a third [6].

Skin toxicity may impair the quality of life, and if severe, lead to discontinuation of anticancer therapy. Patients should be properly prepared for potential adverse effects which allow to effectively minimize the level of anxiety in the situation of their occurrence as well as improve compliance with medical recommendations.

This study aims to subjectively evaluate skin toxicity in patients undergoing systemic treatment, its impact on their emotional state and quality of life. Moreover, the study assesses the extent to which patients are informed about potential complications as well as their needs for the prevention and treatment of these side effects.

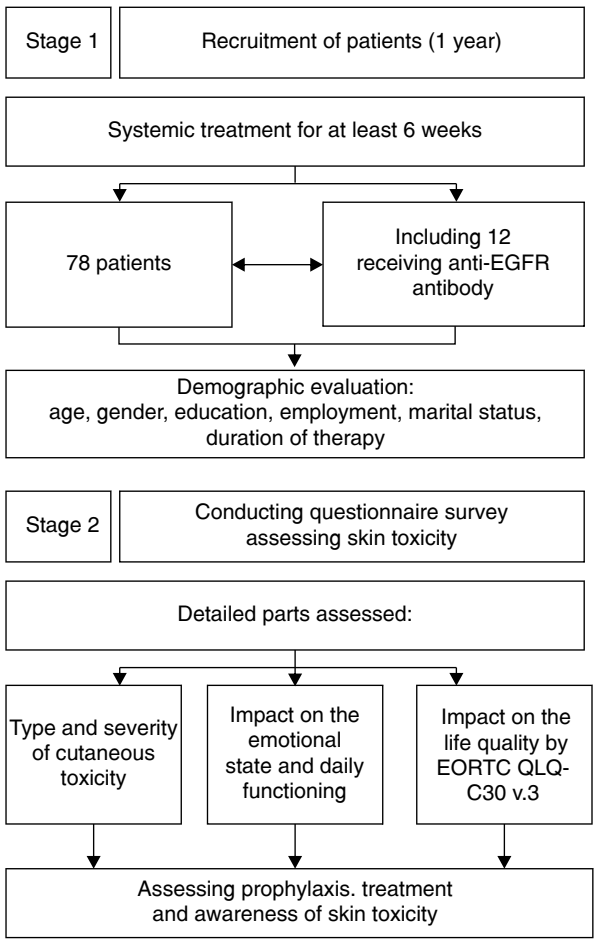

Figure 1. The scheme of the course of the study

Material and methods

This questionnaire survey was conducted between January 2019 and February 2020 in a group of cancer patients who received either palliative or adjuvant systemic treatment for at least 6 weeks at the Department of Chemotherapy, Nicholas Copernicus Hospital, Lodz, Poland. Each patient gave informed consent for the survey. Bioethics committee approval for the study was obtained.

An original questionnaire, consisting of three parts, was used to assess the type and severity of cutaneous toxicity and its impact on the emotional state and quality of life. In the first part — demographic: age, gender, education, employment, marital status and duration of therapy were analysed. In the second part patients' global quality of life was assessed according to the standardized EORTC (European Organization for Research and Treatment of Cancer) QLQ-C30 (Quality of Life Questionnaire Core 30) version 3. In the third part of the study adverse effects of skin and its appendages, occurring in the last month were analysed (in the initial version of the questionnaire 18 patients were asked about complaints occurring during the last week, but such a time interval was considered not representative of skin complications and was changed in subsequent questionnaires). Moreover, the influence of skin toxicity on emotional state and daily functioning was analysed. Prophylaxis and treatment of dermatological complications were assessed. The patients were asked about their knowledge of the possibility of dermal side effects and the possible need for dermatological consultation. The scheme of the course of the study is shown in Figure 1.

Statistical significance of selected parameters was determined by chi-square test, Mann-Whitney U test and Kendall correlation, all tests were two-sided, no correction for multiple testing was applied.

Results

78 patients (41 men, 37 women) were included in the study. Demographic data of the patients, information about the types of cancer and systemic treatment are presented in Table 1. 78% of the patients claimed that their feelings during cancer treatment should have the least negative impact on their daily life. 90% agreed that quality of life during chemotherapy was very important to them. The specific results of the quality of life using the EORTC QLQ-C30 questionnaire (version 3) are presented in Table 2.

93% of patients reported the occurrence of side effects affecting the skin, its appendages and mucous membranes during systemic treatment. The results of the severity of these lesions are shown in Table 3.

There was a positive correlation between the total quality of life scores and skin lesion severity (Kendall's tau b = 0.33; $p < 0.0001$), indicating an association between worsening quality of life and greater severity of skin side effects. The relationship was confirmed by the chi-square test (analysis of subgroups separated by a median of total points), which showed that lower skin lesion severity was more likely to coexist with better quality of life (chi-square test $p = 0.0003$). The negative impact of skin toxicity on the emotional state was reported by 53% of patients, while 32% reported its impact on daily functioning. The results of examining the severity of this impact according to gender are shown in Table 4. The male group reported a statistically significant greater negative impact of skin side effects on emotional state compared to females (chi-square test $p = 0.0007$; Mann-Whitney test $p = 0.0034$). In the group of women, it is noteworthy that the adverse effect of skin lesions on daily functioning was numerically greater compared to men, but this difference was not statistically significant.

Table 1. Patient demographic data, information on types of cancer and applied systemic treatment

Age	**Median: 66 y.o. Range: 27–78 y.**	**Number of patients (n)%**
Sex	male	n = 41 (≈53%)
	female	n = 37 (≈47%)
Education	primary/ vocational	n = 34 (≈44%)
	secondary	n = 30 (≈39%)
	higher	n = 14 (≈18%)
Marital status	Living alone	n = 15 (≈19%)
	Living with partner/ children/grandchildren/ parents	n = 63 (≈81%)
Length of oncological therapy	Less than 12 months	n = 34 (≈44%)
	More than 12 months	n = 44 (≈56%)
Duration of current treatment	Less than 3 months	n = 34 (≈44%)
	3–12 months	n = 31 (≈40%)
	1–3 years	n = 10 (≈13%)
	More than 3 years	n = 3 (≈4%)
Type of malignant neoplasm	colorectal cancer	n = 38 (≈49%)
	breast cancer	n = 11 (≈14%)
	ovarian cancer	n = 5 (≈6%)
	pancreatic cancer	n = 5 (≈6%)
	lung cancer	n = 4 (≈5%)
	stomach cancer	n = 4 (≈5%)
	testicular cancer*	n = 2 (≈3%)
Scheme of systemic treatment	chemotherapy	n = 57 (≈73%)
	chemotherapy with anti-EGFR antibody**	n = 11 (≈14%)
	olaparyb	n = 2 (≈3%)
	abiraterone	n = 1 (≈1%)
	anti-HER2 antibodies	n = 5 (≈6%)
	pembrolizumab	n = 1 (≈1%)
	panitumumab	n = 1 (≈1%)

* In addition, single patients with diagnosed cancer of: prostate, cervix, fallopian tube, oesophagus, nasopharynx, anus and pleural mesothelioma, uterine sarcoma, melanoma.
**chemotherapy + cetuximab: n = 10; chemotherapy + panitumumab: n = 1)

Table 2. The results of the quality of life study according to the EORTC QLQ-C30 (version 3) questionnaire

Quality of life of patients according to the EORTC QLQ-C30 questionnaire (version 3)	
Questions number 1–28, regarding the severity of factors impairing quality of life	
Possible worsening of the quality of life with scores:	Possible range of point totals: 28–112
1 — Slightly 2 — Moderately 3 — Considerably 4 — Extremely	Achieved range of total points: 29–80 Median: 53 Mean: 52.5
Question 29: How would you rate your general health over the past month?	
Badly — 2.6% of patients (n = 2) Rather bad — 3.8% (n = 3) Average — 52.6% (n = 41) Fairly well — 23.1% (n = 18) Good — 17.9% (n = 14)	
Question 30: How would you rate your overall quality of life over the past month?	
Badly — 1.3% of patients (n = 1) Rather bad — 7.7% (n = 6) Average — 53.8% (n = 42) Fairly well —16.7% (n = 13) Good — 20.5% (n = 16)	

Table 3. The results of the severity of adverse effects on the skin, its appendages and mucous membranes

The severity of adverse effects on the skin, its appendages and mucous membranes — 17 questions	
Possible severity of side effects with scores:	Possible range of severity sum scores for side effects: 0–68
No change — 0 A little — 2 Moderately — 3 Very much — 4	Achieved range of total points: 0–37 Median: 11 Mean: 13.29 No skin side effects: 7.7% of patients (n = 6)

As many as 28% of respondents reported being completely uninformed about possible skin-related side effects of anticancer treatment. Figure 2 shows data on the sources from which patients drew information about possible skin complications, for all respondents and according to the type of systemic treatment received. Only 44% of patients felt completely informed about possible skin toxicity. Among patients treated with EGFR inhibitors, the level of awareness was higher, with all of them reporting that they were completely (9/12) or moderately (3/12) informed about potential cutaneous side effects of anticancer treatment. In comparison, 58% of patients felt completely informed about the life-threatening side effects of anticancer treatment.

As many as 82% of the respondents admitted that they were able to completely accept cutaneous side effects of treatment in case of a favourable result of the therapy and 18% of the patients would be able to accept them partially. As many as 55% declared that they did not receive recommendations from their doctor on how to prevent cutaneous side effects. In addition, 40% of patients who experienced skin toxicity said that their physician did not recommend them any treatment for skin lesions or did not inform them of the need to avoid factors that exacerbate symptoms. Figure 3 shows data on the frequency and type of recommendations given by the oncologist for prevention (3A) and treatment

Table 4. The influence of skin toxicity on the emotional state and functioning of patients

	Females (n = 37)	**Males (n = 41)**	
6 questions regarding the negative impact on patients' emotional state:			
Possible negative impact scoring: 0 — No impact 1 — Slightly 2 — Moderately 3 — Considerably 4 — Extremely	Possible range of point totals: 0–24 • Achieved range of total points: 0–16 • Average point totals: 2.08 • No negative impact in 67.6% of women (n = 25)	Possible range of point totals: 0–24 • Achieved range of total points: 0–19 • Average point totals: 4.76 • No negative impact in 29.3% of men (n = 12)	chi-square test p = 0.0007; Mann-Whitney test p = 0.0034
5 questions regarding the negative impact on patient functioning			
Possible negative impact scoring: 0 — No impact 1 — Slightly 2 — Moderately 3 — Considerably 4 — Extremely	Possible range of point totals: 0–20 • Achieved range of total points: 0–12 • Average point totals: 2.78 • No negative impact in 59.5% of women (n = 22)	Possible range of point totals: 0–20 • Achieved range of total points: 0–18 • Average point totals: 2.20 • No negative impact in 75.6% of men (n = 31)	chi-square test p = 0.127; Mann-Whitney test p = 0.1939

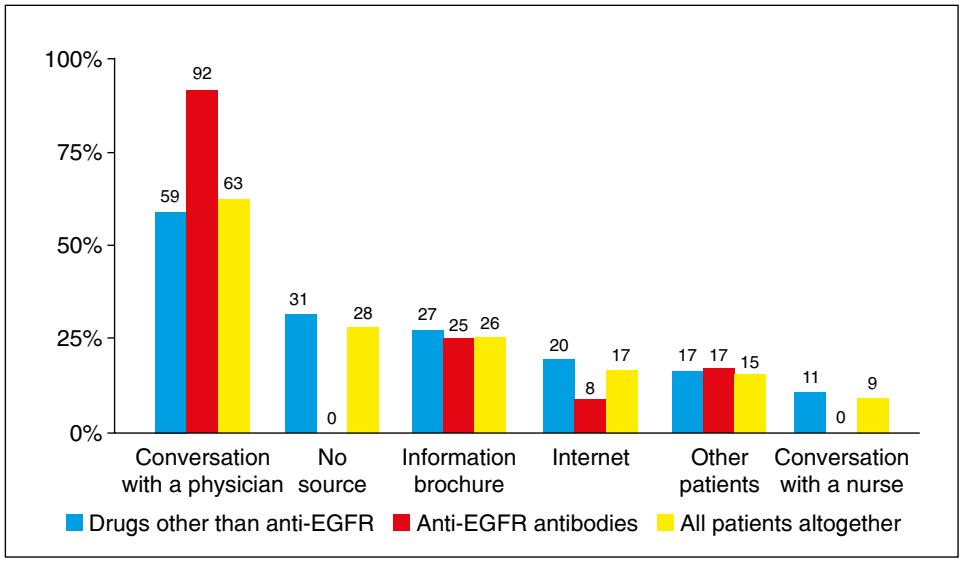

Figure 2. Patients' information sources about potential skin toxicity of the treatment, among patients with different types of treatment

(3B) of cutaneous side effects, according to the type of systemic therapy as well as data about the frequency of using preventive measures, if applied (3C).

58% of respondents agreed that they could use an antibiotic long-term if it reduced the severity of skin lesions, and 83% expressed acceptance of long-term use of skin care creams or medicated ointments. Among those who experienced skin side effects, 6% considered intermittent interruption or termination of anticancer treatment because of high lesion severity. Dermatological consultation was ordered only once. Four patients (5%) saw a dermatologist regardless of the oncologist's recommendation. 31% of respondents expressed the need for a dermatologist in the oncological treatment team.

Discussion

The nature of cutaneous toxicity of systemic treatment depends on the type of drugs and differs in pathomechanism.

Baldness is most commonly caused by paclitaxel (> 80%), doxorubicin (60–100%), cyclophosphamide (> 60%) and fluorouracil (10–50%) [7].

Nail damage during the systemic treatment most commonly includes onycholysis, leukonychia and paronychia. These complications affect almost half of patients treated with taxoids and 1/3 of patients receiving anti-EGFR antibodies [8]. In our study, brittleness, ingrown nails, inflammation and cracking of the skin

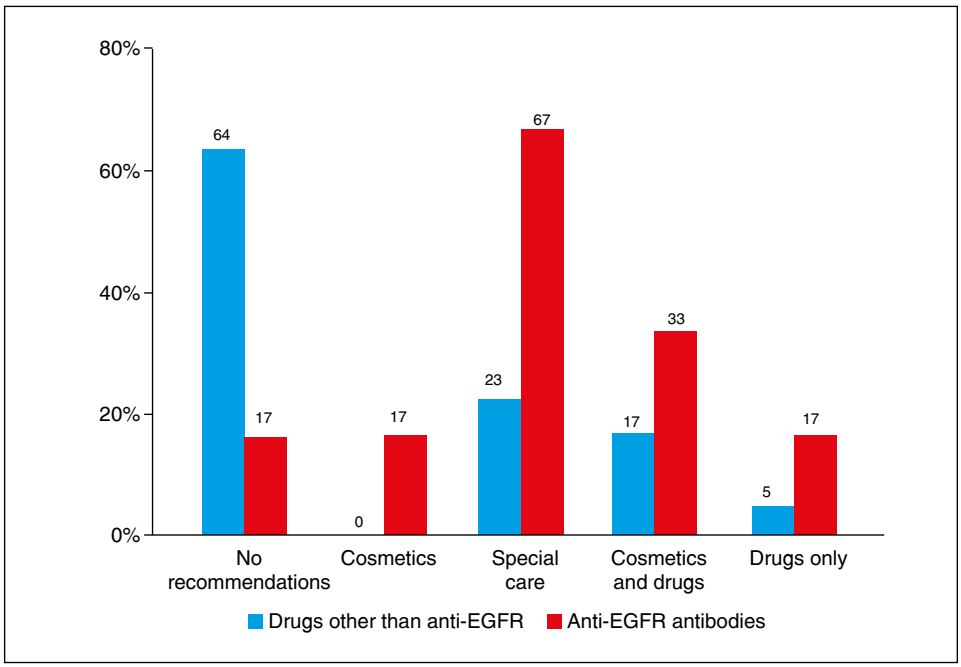

Figure 3A. Frequency of various recommendations for prophylaxis against skin toxicity depending on the type of systemic treatment

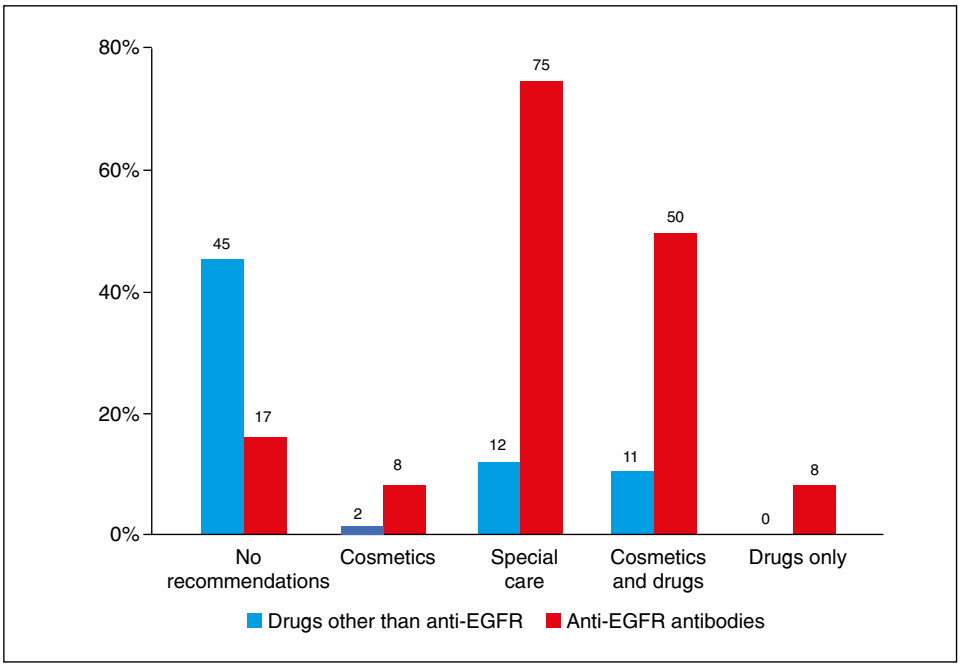

Figure 3B. Types and frequency of recommendations for prophylaxis against skin toxicity, depending on the type of systemic treatment

around the nails were observed in 31% of all patients and 83% of patients treated with anti-EGFR antibodies.

Hand-foot syndrome is observed in approximately 10–60% of patients undergoing anticancer treatment and is most commonly a complication of treatment with capecitabine, liposomal doxorubicin, docetaxel and fluorouracil [9]. Grade G1-2 hand-foot syndrome presents with erythema, hyperkeratosis and swelling of the palmar surface of the hands and soles of the feet. Grade G3 is associated with skin exfoliation,

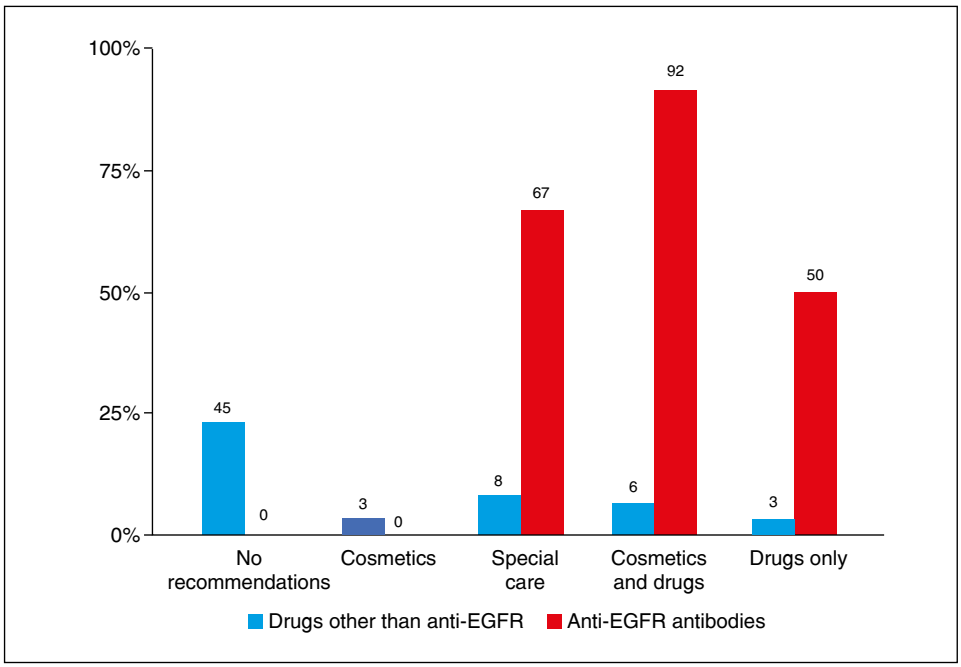

Figure 3C. Types and frequency of prophylaxis used against skin toxicity among patients on different systemic treatments

blistering, ulceration and pain which make self-care difficult [10].

Taxoids, in addition to affecting hair and nails, can also cause erythema and skin rash [11]. Anti-EGFR antibodies, panitumumab and cetuximab, interfere with keratinocyte function and stimulate a non-specific immune response in the skin [12, 13]. Skin toxicity affects up to 97% of patients receiving these drugs together with chemotherapy and most commonly manifests as acne-like rash, dry and pruritic skin, periungual dermatitis and erythematous lesions. A G3/4 grade rash is observed in approximately 20–40% of patients receiving chemotherapy and anti-EGFR antibody, and G3/4 grade nail toxicity in approximately 15% [12, 14]. All patients included in the present study who underwent combination chemotherapy with anti-EGFR antibody reported an acne-like rash of varying severity (G ≥ 3 in 27% of subjects), consistent with the expected frequency of this complication.

Dry skin was the most common skin complication reported by the patients, occurring in 63% of them. In the group treated with anti-EGFR antibodies, dry skin affected all patients (G ≥ 3 in 27%). In addition, 82% of patients receiving anti-EGFR antibody reported damage of nails and nail area, and 55% reported features of hand-foot syndrome. This high incidence of these side effects may have been because patients were receiving fluorouracil infusions at the same time.

Trastuzumab and pertuzumab antibodies are directed against the HER2 receptor (human epidermal growth factor receptor, type 2) which is also expressed in keratinocytes. They may cause skin toxicity in the form of rash, dry skin and nail plate changes [15, 16].

Skin toxicity had a negative impact on the emotional state of more than half of the surveyed patients and daily functioning in more than one-third of them. The negative impact of skin lesions on the emotional state was twice higher in men compared to women (4.76 *vs.* 2.08). These findings suggest that male patients may need more support with education, prevention and treatment of skin toxicity compared to women.

However, in a study of 379 patients by Gandhi et al, it was women who were 5 times more likely (15% *vs.* 3%) than men to report negative effects of skin toxicity on their professional and private lives. This study also found that interpersonal relationships were mostly affected in patients receiving targeted treatment (26%) compared to chemotherapy (4%) and radiotherapy (5%). Similar results were obtained by Rosen et al. [5, 17].

According to Nikolaou et al. and Barrios et al. skin toxicity caused by targeted drugs is a more frequent reason for dose modification compared to standard chemotherapy. This poses a risk of premature termination of anticancer therapy [18, 19]. The increasing availability of targeted therapy causes the proper management of skin toxicity to become an important issue.

In our study, patients with poorer quality of life were more likely to report increased skin complaints. The analysis of data from American and European centers concerning skin toxicity during systemic treatment confirms that skin complications may worsen the quality of life of patients [2, 5, 17]. Hackbarth et al.

evaluated 91 patients, 70% of whom declared that the occurrence of skin toxicity in the course of systemic treatment significantly limited their daily activity [2]. In a study conducted on 283 patients in 2007–2008, Rosen et al. showed that skin side effects related to targeted therapy have a negative impact on patients' quality of life, especially on their emotions and daily functioning [5]. In a study by Gandhi et al. dry skin, nail changes and burning sensations had the greatest impact on the quality of life of patients undergoing systemic treatment [17]. Many studies that aimed to evaluate the relationship between skin toxicity or its severity and quality of life have yielded inconclusive results [20–22]. Unger et al. demonstrated worsening of quality of life in patients receiving anti-EGFR antibody together with chemotherapy when G ≥ 3 versus G1-2 complications occurred [23]. On the other hand, in a study by Peeters et al. paradoxically, patients with more severe skin toxicity during treatment with anti-EGFR antibody reported better quality of life [24]. In the case of anti-EGFR therapy, this paradoxical relationship between reported quality of life and severity of skin symptoms may be related to patients' awareness that the occurrence of skin toxicity is an expected effect of the drug proving its efficacy, which may be a supportive factor in the acceptance of side effects [25].

An important aspect is to properly inform patients about possible skin complications. In our center, only 44% of the patients felt completely informed about the expected cutaneous toxicity of the treatment. Patients who received anti-EGFR antibodies appear to be better informed about potential skin toxicity compared to the rest. All of these subgroups declared that they were completely or moderately informed about potential cutaneous side effects of anticancer treatment. This may be related to physicians' less awareness of the cutaneous toxicity of drugs other than anti-EGFR.

In a study by Gandhi et al., 67% reported that cutaneous side effects of therapy were more severe than they expected. They found that before treatment, 47% of patients expressed significant concern about possible hair loss, 14% about skin irritation and 13% about dry skin. These results differed from those obtained during treatment, where only 29% of patients were concerned about hair loss, while skin irritation and dryness were feared by 23% and 24% of patients, respectively [17]. The discrepancy may have resulted from the fact that patients did not receive sufficient information before treatment regarding possible cutaneous side effects.

Adequate education that reinforces a sense of control during developing complications may help maintain the quality of life of patients experiencing cutaneous toxicity. Frith et al. developed a 4-step strategy to improve patients' acceptance of cutaneous side effects. This consists of anticipating, coming to terms with the inevitable, becoming ready and taking control. A patient who is prepared for the side effects of systemic treatment may have lower levels of anxiety and psychological distress when complications occur [26]. Having specific information about possible cutaneous toxicity is additionally associated with more accurate adherence to recommendations for prevention and treatment of complications and with better-reported quality of life [11].

The effectiveness of the treatment of cutaneous side effects, and thus the tolerance of anticancer treatment as well as the patients' quality of life, can be improved by the collaboration between oncologists and dermatologists.

As many as 40% of the patients who reported skin side effects in this study stated that the oncologist neither initiated treatment of the lesions nor provided information on lifestyle modifications that could improve the skin condition. This is probably due to the high proportion of adverse reactions, such as dry skin, which patients may not have reported during a routine medical examination.

The occurrence of G ≥ 3 skin toxicity is an indication for dermatological consultation, especially if no improvement is obtained after 1–2 weeks of treatment [27]. Only one patient of the 78 included in this study was referred to a dermatologist. At the same time, more than one-third of the respondents expressed the need for the presence of a physician of this specialty in the therapeutic team.

In a study by Gandhi et al., 16% of all patients who experienced skin complications were referred to a dermatologist and 54% of patients admitted that they would feel better if they had this option [17]. A study by Guerrero et al. involving 127 patients with cutaneous complications of therapy, showed that 51% of them had a change in the diagnosis of skin symptoms after consultation with a dermatologist, and 64% were recommended with further dermatological interventions [28].

Dermatological consultation can be particularly helpful in cases of increased skin toxicity when the oncologist is inclined to discontinue systemic treatment for this reason. Barrios et al. analysed the medical data of 44 patients in whom discontinuation of anticancer treatment due to skin toxicity was considered. In the dermatological assessment, interruption of anticancer treatment was considered justified in only 6 of the 44 cases [18].

Another study showed that the assessment of cutaneous toxicity made by oncologists and dermatologists was consistent in only 62% of cases. Oncologists had the greatest difficulty in naming and assessing the severity of skin lesions, dermatologists in classifying skin toxicity according to the NCI CTCAE criteria [29].

Therefore, the presence of a dermatologist in the therapeutic team to diagnose and treat skin complications during anticancer therapy is justified. Moreover, the use of a consistent nomenclature and a scale for assessing the severity of skin lesions will further improve the management of cutaneous toxicity.

It has also been shown that skin toxicity, in addition to its impact on quality of life, is also associated with increased costs of patient hospitalization [27]. In a study by Phillips et al. at a US center, the median length of hospital stay for patients requiring dermatological consultation was 6 days greater compared with patients not requiring medical intervention in this regard [30].

In the USA we can observe the development of a branch of medicine called "supportive oncodermatology" which is an answer to the escalation of skin toxicity as a complication of systemic treatment. Similar actions in Polish conditions could positively influence the quality of life and effective therapy of patients.

Conclusions

This study shows that cutaneous toxicity is an important but underestimated side effect of systemic treatment, which is associated with a poorer quality of life and an adverse effect on a patient's emotional state.

We have demonstrated the need for greater involvement of medical (including nursing) staff in educating patients about possible skin toxicity, its prevention and treatment.

Patients' access to professional sources of information, such as information brochures and websites, should also be increased.

Although these goals seem to be satisfactorily achieved among patients treated with anti-EGFR antibodies, prevention and treatment of skin toxicity caused by chemotherapy and other targeted drugs remain a challenge.

Education reinforces patients' sense of control during the appearance of side effects and increases the chances of effective compliance, thus giving greater chances of successful treatment of skin toxicity.

Conflict of interest: *None.*

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