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Research Article

DERMATOLOGICAL TOXICITY OF CANCER PATIENTS RECEIVING SMALL MOLECULE EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS – A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objectives: The objectives of the study are as follows: (1) To study the incidence of dermatological toxicity in patients receiving small molecule epidermal growth factor receptor inhibitors. (2) To assess the severity of dermatological toxicity.

Methods: This prospective observational study of 66 cancer patients carried out in the Department of Radiotherapy, Government Medical College, Thiruvananthapuram. Patients with histopathological evidence of cancer receiving small molecule epidermal growth factor receptor inhibitors and satisfying inclusion criteria were taken up in the study after obtaining written informed consent. History and clinical examination before initiation of treatment done. Data regarding the occurrence of developing dermatological toxicities were obtained by questioning for symptoms and with the help of structured proforma. Severities of dermatological toxicities were assessed, and toxicity grading was done.

Results: Sixty-six cancer patients enrolled in the study. The mean age of the patients was 62.4 years. The prevalence was higher in men (53%). Sixty-three patients (95.5%) developed at least one dermatological toxicity. The most common dermatological toxicity observed was papulopustular rash (68.2%), followed by xerosis (66.7%) and pruritus (59.1%).

Conclusion: The present study has thus determined the incidence and severity of dermatological toxicity of cancer patients receiving small molecule epidermal growth factor receptor inhibitors.

Keywords: Epidermal growth factor receptor, Papulopustules, Paronychia, Regulatory abnormalities of hair growth , Itching and dryness due to EGFR inhibitors, National Cancer Institute-Common Terminology Criteria for Adverse Events.

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INTRODUCTION

Epidermal growth factor receptor inhibition is an effective treatment of various cancers such as non-small cell lung cancer, colorectal cancer, pancreatic cancer, and squamous cell carcinoma of the head and neck. EGFR belongs to tyrosine kinase receptors which regulate tumor cell differentiation, survival, and proliferation [1].

The EGFR is expressed in various normal tissues, such as epithelial tissue, skin, hair follicles, and gastrointestinal tract. In malignancy downregulation or upregulation of receptors can result in avoidance from invasion, proliferation, metastasis, tumor-induced angiogenesis, and apoptosis [2].

Small molecule EGFR tyrosine kinase inhibitors that target the intracellular domain are Gefitinib and Erlotinib. When the expression of EGFR reduced, stopping of downstream signaling occurs in oncogenic cells [3] which results in the blocking of, growth, proliferation, differentiation, metastasis, and angiogenesis, causing programmed cell death of oncogenic cells. Erlotinib and gefitinib are oral tyrosine kinase inhibitors targeting human epidermal growth factor receptor Type I.

Usage of EGFR inhibitors leads to dermatological side effects termed as "PRIDE complex" – Papulopustules and, or Paronychia, Regulatory abnormalities of hair growth, Itching, and Dryness due to EGFR inhibitors [4]. EGFR inhibitors lack systemic toxicity. This study focuses on the incidence and severity of dermatological side effects, mainly papulopustular rash. The grading of cutaneous done [5,6].

METHODS

Ethical clearance

Ethics clearance was obtained from the Institutional Ethics Committee, Government Medical College, Thiruvananthapuram (IEC No. 05/16/2015/MCT).

Study tools

1. Written informed consent form
2. Structured Proforma
3. National Cancer Institute- Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0)
4. Hospital cancer registry

Study procedure

Patients with histopathological evidence of cancer receiving small-molecule epidermal growth factor receptor inhibitors were included in the study. Detailed history of the patient was taken. Clinical examination was done before initiating treatment. This prospective observational study was done at the Department of Radiotherapy, Government Medical College, Thiruvananthapuram, for 1 ½ years. Patients who received EGFR inhibitor therapy were provided with a pro forma to note down the occurrence of any dermatological toxicity. They had to report to the doctor at the time of event of any toxicity. They were instructed to return the pro forma to the investigator on the follow-up visit.

The data regarding the occurrence of rashes and other dermatological toxicities was collected from the patient's proforma. Dermatological

toxicity evaluation grading done with the help of NCI-CTCAE criteria version 4.0. The severity of toxicity graded as Grade 1-Grade 5.

The patients were followed at an interval of 2 weeks for the first 8 weeks, thereafter monthly follow-up, till the patient goes in for disease remission or stable disease or, for a minimum of 6 months or up to a maximum of 1 year.

Sample size calculation [1]

Sixty-six patients were assigned for the study with the help of a biostatistician using the formula:

$$n = \frac{z\alpha^2 \times \mathbf{p} \times \mathbf{q}}{\mathbf{d}^2}$$

Where,

n=Sample size

p=Proportion of patients with dermatological toxicity on EGFR inhibitor therapy = 62

q=100-p=38

d (precision)=20% of p

The significance level is 5%, zα is 1.96.

Using the above formula:

$$n = \frac{3.84 \times 62 \times 38}{(\mathbf{12.4})^2} = \sim 60$$

With a 10% dropout expected from patients, we finalized 66 patients for this study.

Therefore, n = 66.

Statistical analysis

Data collected were entered into Microsoft Excel 2007. Analysis was done using Microsoft Excel 2007 and Statistical Package for the Social Sciences version 22. Quantitative variables are expressed in Mean and Standard deviation. Qualitative variables were expressed in the frequency distribution. Descriptive statistics was done. Associations between different dermatological toxicities with age, gender, diagnosis, and drug were determined using the Chi-square test.

Inclusion criteria

The following criteria were included in the study:

1. All patients with histopathological evidence of cancer and receiving either Erlotinib or Gefitinib as treatment.
2. Patient age >18 years.
3. Patients are ready to provide written informed consent.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients are not willing to participate in the study.
2. Patients with uncontrolled infections or bleeding disorders.
3. Patients are on any concurrent radiation or medications that can interfere with skin toxicity assessments.
4. Patients with eczema, contact dermatitis, psoriasis, rosacea, severe photosensitivity, scleroderma, steroid-induced acne, or xerosis.
5. Patients with any known allergic manifestations to any drugs.

RESULTS

Out of 66 cancer patients who received small molecule EGFR inhibitors Gefitinib or Erlotinib, the pattern of results derived revealed:

1. Age distribution – Mean age of the patients was 62.44 years.
2. Gender distribution – Male – 53% and Female – 47%.
3. Smoking – Smokers – 25 and Non-smokers – 41.
4. Alcoholism – Alcoholics – 20 and Non-alcoholics – 46.

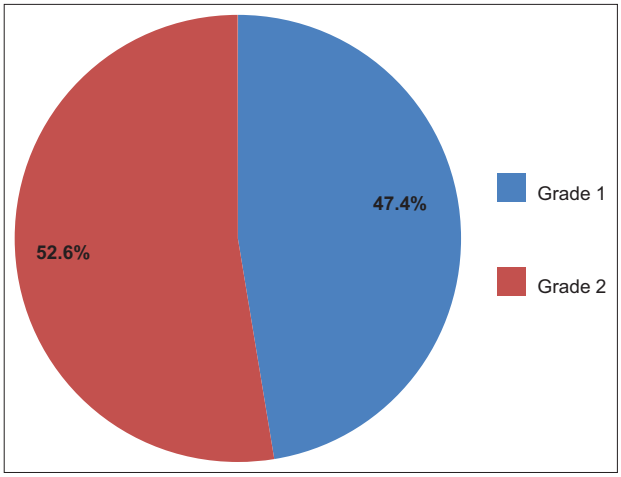

Fig. 1: Severity of maculopapular rash

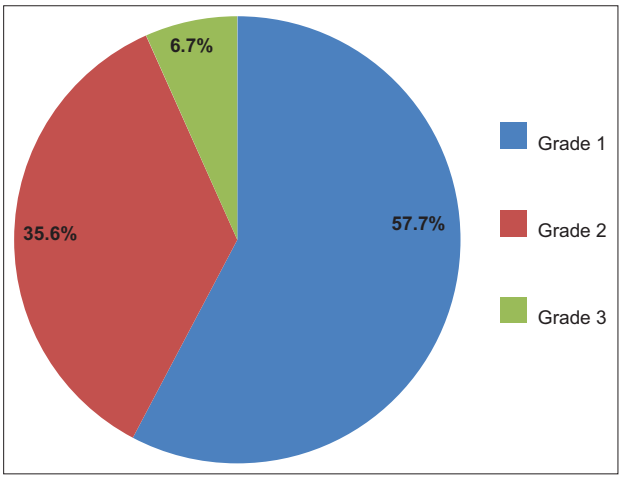

Fig. 2: Severity of papulopustular rash

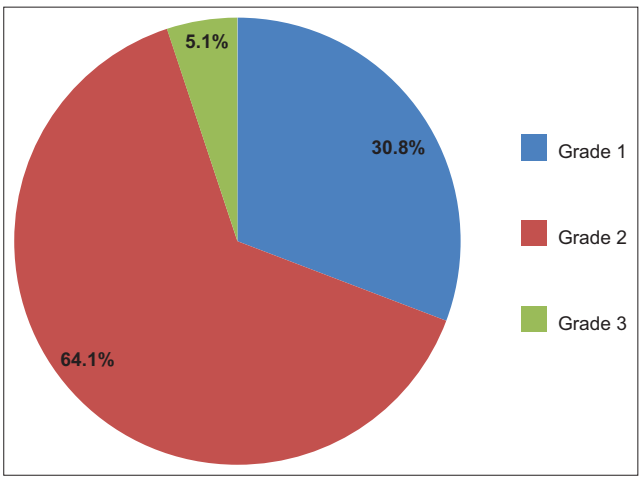

Fig. 3: Severity of pruritus

5. Pan chewing – Pan chewers – 5 and Non-pan chewers – 61.
6. Comorbidities – With comorbidities – 29 and Without comorbidities – 37.
7. Types of cancers – Lung – 43, Pancreas – 10, Head and Neck – 13.
8. Types of EGFR inhibitors – gefitinib – 45 and erlotinib – 21.

Dermatological toxicities associated with EGFR inhibitors

1. Maculopapular rash – 19 out of 66 patients experienced maculopapular rash, with Incidence being 28.8%.

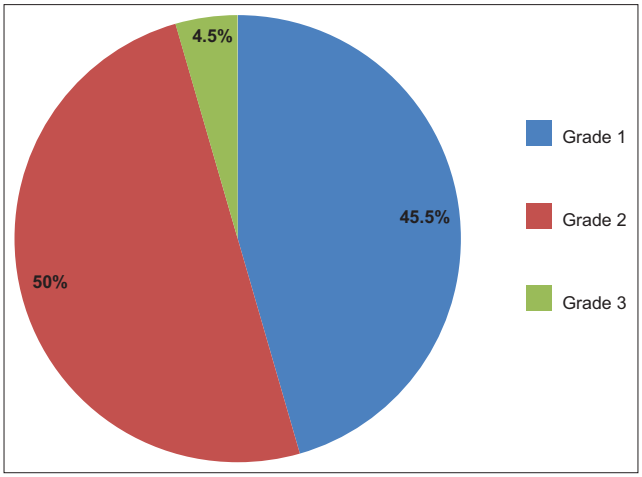

Fig. 4: Severity of xerosis

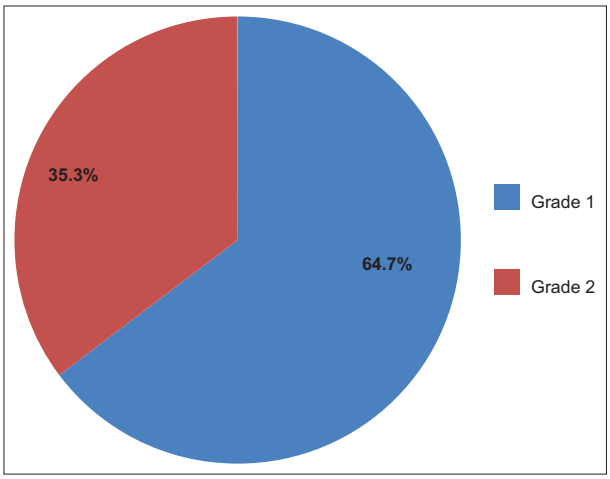

Fig. 5: Severity of nail change (paronychia)

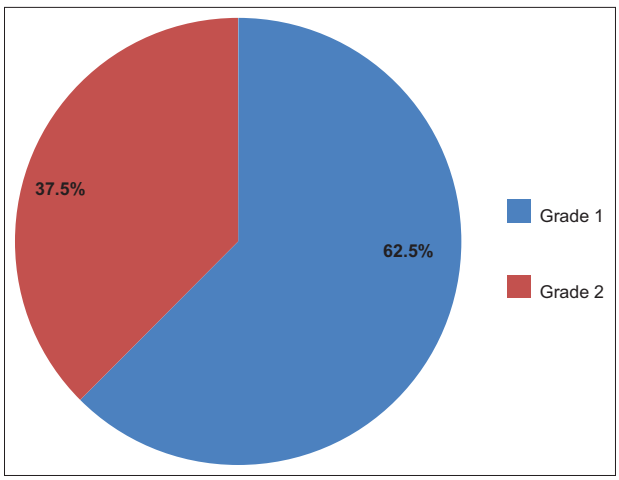

Fig. 6: Severity of skin hyperpigmentation

2. Papulopustular rash – 45 out of 66 patients experienced papulopustular rash, with incidence being 68.2%.
3. Pruritus – 39 out of 66 patients experienced pruritus, with incidence being 59.1%.
4. Xerosis – 44 out of 66 patients experienced Xerosis, with incidence being 66.7%.
5. Photosensitivity – 12 out of 66 patients experienced photosensitivity, with incidence being 18.2% Table 1

Table 1: Severity of photosensitivity

Grade (NCI-CTCAEv4.0)	Percentage
1	91.7
2	8.3
3	0
4	0
5	0
Total	100.0

NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events Version 4.0

Table 2: Severity of hair loss

Grade (NCI-CTCAEv4.0)	Frequency (%)
1	34 (100.0)
2	0
Total	34 (100.0)

NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events Version 4.0

6. Hair Loss – 34 out of 66 patients experienced hair loss, with incidence being 51.5% Table 2.
7. Nail change (paronychia) – 17 out of 66 patients experienced nail change (paronychia), with incidence being 25.8%.
8. Skin hyperpigmentation – 16 out of 66 patients experienced skin hyperpigmentation, with incidence being 24.2%.

DISCUSSION

This prospective observational study aimed to determine the incidence and severity of dermatological toxicity of cancer patients receiving small molecule EGFR inhibitors. Dermatological toxicity was slightly predominant in males (53%). Among the 66 patients observed in the study, the overall incidence of dermatological toxicity was 95.5%, similar to a retrospective study done by Yoshida *et al.* [7], where the incidence of dermatological toxicity with EGFR inhibitors Gefitinib or Erlotinib was within the range of 62 to 94%. The most common dermatological toxicity observed in the patients was papulopustular rash, followed by Xerosis, pruritus, hair loss, maculopapular rash, nail change like paronychia, photosensitivity, and skin hyperpigmentation. The dermatological toxicities of patients associated with EGFR inhibitors were assessed and their severity was graded using NCI – CTCAE v4.0.

Papulopustular rash accounted for the significant dermatological toxicity. Fourty-five out of 66 patients were affected, taking the incidence to 68.2%. In a review article by Chu *et al.* [8], the incidence of papulopustular rash seen in patients treated with EGFR inhibitors ranges from 66% to 89%. Severity analysis of papulopustular rash showed the majority of papulopustular rash were mild (Grade 1–57.7%), moderate (Grade 2–35.6%), and severe (Grade 3–6.7%) in nature Fig. 2. In a study by Chanprapaph *et al.* [9], the majority of patients treated with EGFR inhibitors developing papulopustular rash were mild to moderate in severity. The second most common dermatological toxicity was Xerosis. 44 out of 66 patients experienced xerosis, the incidence being 66.7%. In a study by Chanprapaph *et al.* [9], dermatological toxicity associated with EGFR inhibitors having an Incidence of Xerosis was 52.5%. Severity analysis of Xerosis showed mild (Grade 1–45.5%), moderate (Grade 2–50%), and severe (Grade 3–4.5%). The third most common dermatological toxicity observed was pruritus Fig. 4. 39 out of 66 patients experienced pruritus, the Incidence being 59.1%. According to Eaby–Sandy *et al.* [10] study, pruritus can occur in nearly half of patients receiving EGFR inhibitors, and according to Califano *et al.* [11], the Incidence of pruritus in patients treated with EGFR inhibitors ranges from 18% to 54%. Severity analysis of pruritus showed the majority of pruritus were mild (Grade 1–30.8%), moderate (Grade 2–64.1%), and severe (Grade 3–5.1%) Fig. 3. Concerning to maculopapular rash, 19 out of 66 patients experienced this dermatological toxicity, the

Incidence being 28.8%. In a similar study by Chanprapaph *et al.* [9], an incidence of 11.1% was seen in the case of maculopapular rash. Analysis of maculopapular rash denoted that the majority were mild (Grade 1–47.4%) to moderate (Grade 2–52.6%) in severity Fig. 1.

In the case of photosensitivity, 12 patients experienced it, the incidence being 18.2%. Severity analysis showed mild (Grade 1–91.7%) and moderate (Grade 2–8.3%). Hair loss was experienced by 34 out of 66 patients, the incidence being 51.5%. According to Chia-Yu Chu *et al.* [8], the incidence of hair changes in patients treated with EGFR inhibitors increases to approximately 80% after 6 months of continuous use. Severity analysis showed all patients experiencing mild (Grade 1–100%) hair loss. The other dermatological toxicity observed was nail change (Paronychia) – 17 out of 66 patients experienced it, the Incidence being 25.8%. In Chanprapaph *et al.* [9] study, the incidence of Paronychia was 5.1%. And according to Chu *et al.* [8], the Incidence of Paronychia in patients treated with EGFR inhibitors ranges from 4% to 56.8%. Severity analysis showed the majority of patients experiencing mild (Grade 1–64.7%) and moderate (Grade 2–35.3%) changes Fig. 5. Skin hyperpigmentation seen in 16 out of 66 patients, the incidence being 24.2%. Severity analysis showed most of patients with skin hyperpigmentation experienced mild (Grade 1–62.5%) compared to moderate (Grade 2–37.5%) changes Fig. 6.

CONCLUSION

The major conclusions derived from this study were:

- The overall incidence of dermatological toxicities due to EGFR inhibitors was 95.5%.
- Among the dermatological toxicities observed in the study, papulopustular rash (68.2%) was the most frequent, followed by xerosis (66.7%) and pruritus (59.1%).
- Patients also presented with maculopapular rash (28.8%), photosensitivity (18.2%),
- Nail change (paronychia) (25.8%), skin hyperpigmentation (24.2%), and hair loss (51.5%).
- Dermatological toxicities were ranging from mild to moderate in severity.

AUTHORS' CONTRIBUTIONS

All authors have contributed critically to the preparation of the manuscript.

CONFLICTS OF INTEREST

None declared.

AUTHOR FUNDING

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ETHICAL APPROVAL

The study approved by the Institutional Ethics Committee, Government Medical College, Thiruvananthapuram (IEC No. 05/16/2015/MCT).

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