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RESEARCH ARTICLE

Nail Toxicity Induced by Cancer Chemotherapy Patients: Data from the Two Multispecialty Hospital

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ABSTRACT:
Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems. The objectives of our study is to assessed the nail toxicity induced by cancer chemotherapy in outpatient clinical setting of two multispecialty hospital. This is a prospective observational study for a period of 12 months. Clinical variables included type of cancer, stage, treatment modalities and type of skin toxicity. Skin toxicities were graded by a dermatologist according to the National Cancer Institute Common Toxicity Criteria (NCICTC), version 3. We included all patients age (more than 16 yrs) attending oncology clinic for a period of 24 weeks. The patients with a history of cutaneous reactions, nail changes and other adverse effects. Our results shows that (Male/Female, 08/92) with Male to Female ratio of 0.08:1 who were treated with chemotherapy. The mean age of our study population was found to be 49.47±11.59 years. However, 58(58%) were from rural background and 42(42%) from urban areas. Whereas, 65% patients were farmers and 09%, Private employee. Most of the belongs to Hindu religion (62%). Our study conclude that a significant nail changes with AC-T (Cyclophosphamide Doxorubicin followed by Paclitaxel) and alopecia with FAC (5-fluorouracil Cyclophosphamide doxorubicin) are the most commonly seen adverse event in cancer patients.

KEYWORDS: Cancer, Alopecia, Gender, Place, Chemotherapy, and Nail changes.

INTRODUCTION
In present scenario, newer cancer drugs are continuously emerging in world- wide. Unfortunately, most anticancer drugs used today are highly toxic [1]. However, researchers understanding of the cellular and molecular regulatory processes involved in cancer growth and spread. But even though, adverse drug reaction may also be influenced by genetic predisposition and environmental factors. Among the potential determinants of susceptibility are age, gender, co-existing disease, co-exposure to other xenobiotic agents, nutritional status, tissue reserve capacity and drug metabolism differences. [2] Chemotherapy is associated with a number of potentially serious adverse drug reactions, clinical pharmacist who work with these drugs must carefully verify the chemotherapy dosage prescription, monitor patients for potential ADRs, and educate patients regarding drug therapy and diet.

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This process, however, is often complicated by the fact that many chemotherapy protocols employ a wide range of dosages and most anti-cancer drugs administered in combination therapy .In addition, to that shortage of clinical pharmacists especially in government and private hospitals, India. However, management of drug related adverse effect are early recognition of symptoms, withdrawal of the causative agent and prompt initiation of symptomatic treatment [3]. Moreover, drug related nail changes are the result of acute toxicity to the nail epithelium, Nail changes may appear several weeks after drug intake, due to the kinetics of nail formation and the slow growth rate of the nail plate. Cancer chemotherapeutic agents are a cause of drug-induced nail changes as the continuously dividing nail matrix cells are easily perturbed by antimitotic activity . [4] therefore our study is to assessed the nail toxicity induced by cancer chemotherapy in outpatient clinical setting of two multispecialty hospital

MATERIALS AND METHODS:

Study site:

This is a prospective observational study conducted in a two hospitals government i.e. M.G.M Hospital and private i.e. St. Anns General and cancer hospital, Kazipet, A.P, India. Mahatma Gandhi Memorial Hospital (MGMH) is a large government health facility located in northern area of Warangal which is 1200 bed strength with an area of 13 acres (53,000 m^2) which provides teaching facility to Kakatiya Medical College. St. Ann's Cancer and General hospital is 40-50 bedded hospital providing general and oncology services. This both hospitals had a very active oncology services with a busy practice covering hundreds of patient in a day attending outpatient clinic of chemotherapy/radiotherapy. In MGMH the department of radiotherapy was open from 8 A.M to 2 P.M and in St.Anns 24hrs services were provided. The physician in both oncology departments were informed about the aim of the studies.

Study Design:

The study period was 12 months, patients' demographic and clinical data were recorded at the initial visit. Demographic variables included age, gender, occupation, place etc. Clinical variables included type of cancer, stage, treatment modalities and nail toxicity.

Inclusion Criteria:

We included all adult patients age (more than 16 yrs) attending oncology clinics for a period of 24 weeks. The patient with a history of cutaneous reactions, nail changes and other adverse effects.

Exclusion Criteria:

Paediatric cases were not taken into our study. Old cases i.e., patient who were already on chemotherapy were not selected. Patients were considered ineligible for this analysis if they had reported fever (body temperature $>38.0^0$c) during the last week before study entry, in order to avoid confounding factors influencing the presence and the severity of side effects, or had receive any radiotherapy, chemotherapy, immunotherapy, or growth factors during the last 4 weeks before the analysis. Patients recently (<1 week) or simultaneously treated with chronic steroid based therapy, affected by acute (or) chronic infection (or) inflammatory disease (or) with a previous medical history suggestive of chronic rashes were considered ineligible for the study.

Ethical Approval:

The research obeyed resolution 196/96 on research involving human beings. This resolution incorporates under the ethics of the individual and the collectivities the four basic references of bioethics; autonomy; non-malficience; beneficience and justice. It seems to ensure the rights and duties that respect the scientific community; the research subject and the state. This study was reviewed and approved by Institutional Review Board (IRB)/ Human Ethical Committee (HEC) of Kakatiya Medical College (KMC) affiliated to Dr. NTR University of Health Sciences, Andhra Pradesh, India and permission to collect data were given by the Medical Superintendent of the both hospital.

Data Collection:

All the skin toxicities were monitored according to the specifications modified from the guidelines of NCI (National Cancer Institute) Common Toxicity criteria version 3. In every case a detailed history was elicited and a through clinical examination was carried out as suggested by sacedoti et al., (1993). This study was carried out during the period of January to December 2013. We included all adult patient (age more than 16yrs) attending oncology clinic for a period of 24 weeks.

Patient Informed Consent Form:

A patient informed consent form was also prepared; written consent was obtained from all the patients included in the study or from the caregivers by using patient consent form after providing the information. The form contains details like address, date, place, provision for signature of the patient or caregivers, investigator and supervisor. The same is given in the Data Entry Form . A separate data entry form for incorporating patient details was also designed. The format contains the details such as Name, Age, Gender, Height, Weight, IP/OP number, DOA, Patient past medical and medication history, laboratory investigations like RBC, TWBC, Platelet count, Neutrophils, Lymphocytes, Eosinophils, Monocyte counts and Serum creatinine, Diagnosis, Drug chart.

Drugs:

The drugs which were used in the study are given below: Anthracycline antibiotics (Doxorubicin), Alkylating agents (Cyclophosphamide), Anti metabolites (5- Fluorouracil, Methotrexate), Antimicrotubular agents(Paclitaxel), platinum analogues (Cisplatin, Carboplatin, Oxaliplatin), Topoisomerase inhibitors (Etopside), Adjuvant (Leucovorin).

Participants:

Indian medical association for supporting care in cancer (IMASCC) skin toxicity study group i.e., principal investigator assembled national interdisciplinary and supportive oncology, health related quality of life and pharmacovigilance. Title review the literature and develop the guidelines for the following dermatologic toxicities: papulopustular (acneiform), rash, hair changes, radiation dermatitis, pruritis, mucositis, xerosis/fissures, and paronychia.

Statistical Analysis:

The data collected were entered into MS- Excel sheets and analysis was carried out. The information obtained was tabulated and all analysis was performed with statistical package graph pad prism for windows (version 5.0- 2007). Results were represented as a mean ± standard deviation (SD) (continuous variable). The data on the cutaneous

adverse effects were analyzed by percentage and ranking method.

RESULTS:

The current study based on the cutaneous reactions caused by the anti-neoplastic drugs especially when used in the different anti-neoplastic combinations and revealed that the most common cutaneous adverse effect were alopecia and pigmentation, nail changes. The data on the cutaneous adverse effects were analyzed by percentage and ranking methods.

Patient Characteristic Features:

In the present study, we included 100 cancer patients (Male/Female, 8/92) with Male to Female ratio of 0.08:1 who were treated with chemotherapy. The mean age of our study population was found to be 49.47±11.59 years. The region wise distribution of study population was assessed and found that 58(58%) were from rural background and 42(42%) from urban background. Among the study population, 65% patients were farmers and 9% working as private employee in different organization of Warangal. Most of the patients belongs to hindu religion (62%), followed by christians (26%) and muslims (12%). Furthermore, among the study group 79% were found to be married and 21% divorced/ separated/ widowed. Table 1 shows demographic details of our study population. The patients were categorized into different groups based on their age. The adult patient were the majority of the study population and accounted for 45(45%) of 100 cases. Followed by old adult patients were 25(25%), young adult patients were 16(16%) and younger older patients were 13(13%). Minimum cases (01%) were seen in old age group patients. Table 2 shows the Distribution of patients according to age group and gender. In overall adult patients, 31% were diagnosed with breast cancer, 8% cervical cancer, 2% stomach cancer and 01% with gastro-esophageal junction. Our study found that most of the patients (58%) were having rural background since the rural population is more in this area. Occupationally most of the patients were farmers 65% and housewives 14%. The reasons behind may be uncertain. The gender distribution of the study population revealed that females were mostly effected (92%) by cancer in this area. The study population was thoroughly screened to identify the problems. The results revealed that 67% (67) of the study population had breast cancer, 16% (16) had cervical cancer, 08%(08) were having stomach cancer and 03%(03) were having ovarian cancer.

Table1. Patient Features and Base Line Characteristic of the Study population

Patient characteristics	N	Percentage (%)
Number of patients included	100	100
Total mean age (Range)	49.47±11.59	-
Mean age Male (Range)	62.50±9.040	-
Mean age Female(Range)	48.34±11.59	-
Gender		
Female	92	92
Male	08	08
Region		
Rural	58	58
Urban	42	42
Occupation		
Farmer	65	65
Business	08	08
Govt. Employee	04	04
Private Employee	09	09
House wife	14	14
Religion		
Hindu	62	62
Christian	26	26
Muslim	12	12
Marital status		
Unmarried	00	00
Married	79	79
Divorced /Separated /Widowed	21	21

'N' indicates number of patients

Table .2 Age-Wise Distribution of Different Types of Cancer in Patients

Age (in years)	Br	Cx	St	Ovary	Rec	Lung	G.E.J	H.C.C	M.C
Young adult(19-35)	09	04	01	02	-	-	-	-	-
Adult (36-50)	31	08	02	-	01	01	01	01	-
Old adult (51-64)	19	03	03	-	-	-	-	-	-
Younger adult (65-74)	07	01	02	01	01	-	-	-	01
Old (75-84)	01	-	-	-	-	-	-	-	-
Total	67	16	08	03	02	01	01	01	01

Table 3 shows that chemotherapy drugs produce the cutaneous adverse effects; nail changes (75%), Pigmentation changes (26%) and Minimal (06%) as a Serpentine changes.

Table 3. Incidences of various skin toxicities

Skin toxicities	Events recorded (%)
Nail changes	75 (75)
Pigmentation changes	26 (26)
Serpentine changes	06 (6)
Total	107

Table 4. Shows that chemotherapy dermatogical changes of patients in the both hospital. However, we observe that 5-FU Cyclo doxo combination chemotherapy patients shows nail changes (80%) and least number observed in monotherapy patients.

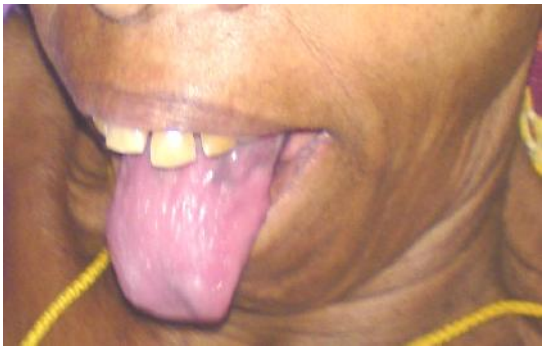
Table 4. Chemotherapy dermatological changes of patients

Drug regimen	Total number of pts 'n' (%)	Patients with nail changes (%)	Patients with pigmentation (%)	Patients with serpentine changes
5-FU	01 (01)	01 (100)	00 (0)	00 (0)
5-FU Cyclo doxo	20 (20)	16 (80)	04 (20)	00 (0)
5-FU adriamycin	01 (01)	01 (100)	00 (0)	00 (0)
5-FU leuco	08 (08)	04 (50)	00 (0)	1 (12.5)
Cisplatin	16 (16)	00 (0)	00 (0)	00 (0)
Cisplatin 5-FU	02 (02)	02 (100)	00 (0)	00 (0)
Cyclo 5-FU Metho	01 (01)	01 (100)	00 (0)	00 (0)
Cyclo Doxo pacli	46 (46)	45 (98)	22 (48.8)	3 (6.6)
Etop Cisplatin	01 (01)	01 (100)	00 (0)	0 (0)
Oxali 5-Fu leuco	01 (01)	01 (100)	00 (0)	1 (100)
Paclitaxel Carboplatin	03 (03)	03 (100)	00 (0)	0(00)

DISCUSSION:

The nail plate is made up of the hard keratin cover of the dorsal portion of the distal phalanx and as it grows the distal part of the naimjul matrix generates the deeper layer of the plate. The epithelium of the nail matrix is made up of rapidly proliferating cells that differentiate and keratinize to generate the nail plate, making it susceptible to the toxicities of chemotherapy. Nail changes seen with the use of chemotherapy or both cosmetically displacing (nail discoloration) and can result in Oncholysis (separation of the nail plate from the nail bed)- which can be painful and may lead to infection [5]. Taxanes (e.g. docetaxel and paclitaxel) are most notorious for causing Oncholysis [6]. These nail changes have been attributed to a cessation of mitotic activity in the nail matrix, which produces a horizontal depression of the nail plate or complete separation of the nail plate from the nail bed . After several weeks of chemotherapy, beaus's and mees lines move with normal nail growth and disappear within six months. [7,8] Chemotherapeutic agents that cause nail changes include 5-fluorouracil, Bleomycin, Cyclophosphamide, Daunorubicin, Docetaxel, Doxorubicin, Epirubicin, Hydroxy urea and Paclitaxel [9]. No current pharmacological therapies are available for the treatment of chemotherapy induced nail changes and only one non-pharmacological therapy is available.

Hyperpigmentation is a common cutaneous toxicity, which may be of cosmetic concern to patients. The skin, mucous membranes, hair, teeth, and nails may be affected and the reaction may be diffuse or localized. Alkylating agents and anticancer antibiotics commonly cause hyperpigmentation [10]. Agents commonly associated with oral mucosal hyperpigmentation include Busulfan, Fluorouracil, Tagafur, Doxorubicin, Hydroxyl urea, Cisplatin and Cyclophosphamide (Susser et al., 1999). In the current study the most common causative anticancer agents of the pigmentation changes including the nail changes after the alopecia were Cyclophosphamide, doxorubicin, paclitaxel regimen (AC followed by T) with 49% and less common causative agents include 5-fluorouracil, carboplatin. It has been depicted in Figure.1

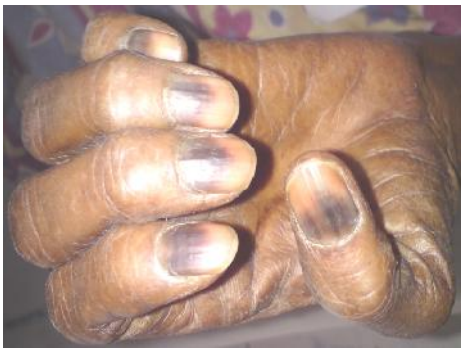


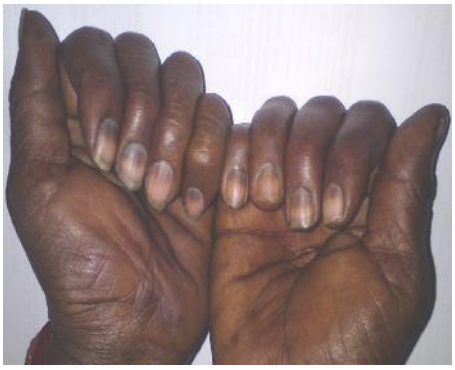
The age distribution indicated that the adult and elderly people were commonly getting affected. The similar findings were reported by other literature (USC health magazine, 2005) [11]. Region is also a contributing factor for the cancer incidence. Bird et al reported the occurrence of white transverse lines on the left hand of a patient treated with combination doxorubicin and cyclophosphamide chemotherapy for metastatic breast cancer. Her right hand was spared, but nerve conduction studies showed a complete branchial plexopathy with extensive denervation in all three trunks of the branchial plexus in that hand. In our study, out of the 100 patients who were under drug

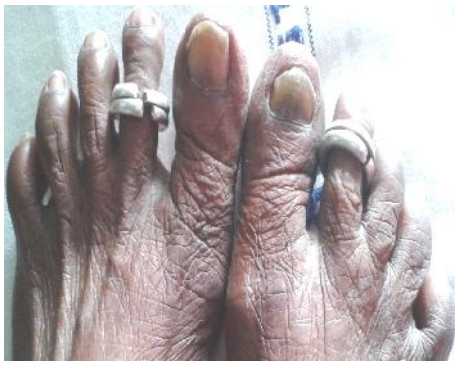
regimen AC (Cyclophosphamide, Doxorubicin) followed by T (Paclitaxel) the nail changes occurred 97% . This may indicate a similar to wasner et al reported the neurogenic mechanism for anthracycline-induced nail changes as was proposed for docetaxel [12,13].

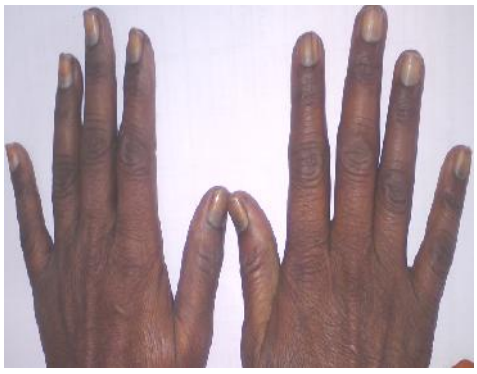
Joyce M and Susan N reported that during final cycle of docetaxel and capecitabine (cycle 6), the patient reported to the oncology office with extreme nail changes. All of the nails of her fingers were bulging, whitish-green in color, and very foul smelling. This was interfering with the patient's activities of daily living and caused embarrassment because of the odor. The physician was consulted, and the patient was instructed to soak her fingers in water with an antibacterial soap. The patient made a self-referral to a podiatrist. Here in our study we did not observed that nail bulging and foul smell of the nail who were under chemotherapy of taxene group [14]. Physician, Clinical pharmacist and nurse should counsel the patients that their nail changes are temporary and will resolve after chemotherapy administration is completed (Piraccini and Tosti, 1999). However, complete resolution is not immediate and may take as long as six months. Patients on chemotherapy should be instructed to keep nails short, maintain proper personal hygiene, and avoid exposure to harmful chemicals or detergents. Fragile nails may be improved by the administration of biotin, a water-soluble B-complex vitamin, at 5 mg per day. Additionally, patients should use moisturizer for hands and nails, wear gloves when completing household tasks, and avoid injury (Breast Care Site, n.d.). Wearing artificial nails is not recommended, but nail polish may be used. However, patients should be advised to be cautious when using nail polish remover. Frequent use can make nails fragile or brittle. However, Clinical research studies should investigate potential remedies for chemotherapy-induced nail changes. Scotte et al. (2004) described the results of a case-controlled study using an Elasto-Gel (Akromed, France) frozen glove during docetaxel infusion. Patients were a specially designed frozen glove on the right hand while the left hand remained ungloved for control purposes. The investigators reported that occurrences of onycholysis and cutaneous reactions were reduced in the gloved hand. Although not statistically significant, the onset of onycholysis occurred later in the gloved hand (Scotte et al.) [15-17]

However in other studies vassallo et al and susser et al reported that, a number of different nail toxicities have been attributed to fluorouracil including diffuse hypermelanosis, transverse bands, onycholysis, paronychial inflammation and pain, thickening of the nail beds, and hyperpigmentation. In addition to that, chen et al. described a case of single transverse apparent leukonychia, with bands corresponding to the number and duration of cycles, following combination chemotherapy with fluorouracil and high-dose leucovorin. In our study finding reveals that, combination drugs like FAC (5-fluorouracil, cyclophosphamide and doxorubicin) the nail changes occurred in 80% patients. These regimens were used for breast cancer treatment. In addition to that a least percentage 20% nail changes occurred in those patients who were received 5-fluorouracil leucovorin for stomach cancer. [18-20] Figure 1, 2, 3 and 4. Nail changes occurred in combination chemotherapy

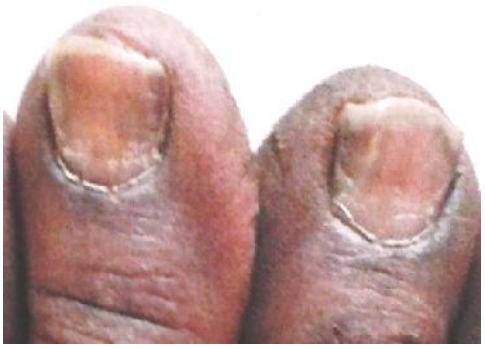








Mees' lines are signs of toxicity to the distal nail matrix, resulting in parakeratosis of the nail plate, which becomes white and opaque. Drug-induced true leukonychia (Mees' lines) appears as one or several parallel transverse white bands affecting all nails at the same level and moving distally with nail growth. Beau's lines are typical signs of acute toxicity to the nail matrix with transient arrest in nail plate production. The nail shows a transverse depression that migrates distally as the nail grows. But in our study we observe the mee's line signs of toxicity to the distal nail matrix. [21] (Figure 5) Mees lines in a patients treated with Paclitaxel



Hyperpigmentation can occur locally at site of infusion or diffusely (Alley E *et al*.,2002).the nails , mucous membranes and teeth have all been reported sites of discolouration (Alley E *et al*.,2002). Some of the mechanisms of chemotherapy induced hyperpigmentation that have been postulated include 1) drug diposition in certain areas that subsequently lead to increased pigmentation. 2) direct skin toxicity caused by secretion of drugs in sweat with accumulation of drug on the skin; 3) endocrinology abnormalities with increased adrenocorticotrophic hormone and melanocytes stimulating hormone causing hyperpigmentation as a results of suppressed adrenal function;4) deplation of tyrosinase inhibitors result in increased pigmentation; and 5)direct toxic effect on epidermal melanocytes stimulating increased melanin production [22]. Some hyperpigmentation may be irreversible, but often resolves after discontinuation of the chemotherapeutic agents. The pigmentation changes are mainly a cosmotic concern as they have not been associated with any negative clinical sequelae. There is no treatment available for this adverse effect.

However localized serpentine supravenous hyperpigmentation is often seen at the intravenous administration sites of 5- fluorouracil leucovorin 13%, where as less common in cyclophosphamide doxorubicin paclitaxel chemotherapeutic regimen is 7%,which were consistent with previous studies [23]. This pattern of hyperpigmentation has subsequently been associated with a number of agents, including fotemustine, bromodeoxyuridine, [24,25] vinorelbine, [26] and a number of multi-agent regimens, all of which employed vincristine [27].

Pigmentary changes typically fade over the course of months, although persistent reactions have been reported. [28,29]. The reaction is thought to occur due to local loss of vessel integrity and leaching of the drug into the neighboring soft tissue with possible direct effect on epidermal melanocytes[30]. The drug related hyperpigmentation changes sometimes may be permanent, but gradually subsides upon discontinuation of treatment.

CONCLUSION:

The study showed that dermatological toxicities are common side effects of chemotherapy of anticancer treatment. The reporting of the present study conclude that a significant nail changes with AC-T (Cyclophosphamide Doxorubicin followed by Paclitaxel). Although the dermatological toxicities due to anti-cancer therapy affect the dermatology-related QoL of cancer patients. Therefore, clinician should pay more attention to these side effects occurring in cancer patients, since cutaneous reactions attributable to anti-cancer therapy can result in patient morbidity and alteration of treatment plans. Also, health care professionals should pay attention to the psychological effects of skin problems and educate cancer patients to adapt proactive skin protective behavior to minimize dermatological toxicities of anticancer therapy and maximize QoL. In contrast, the absence of these side effects might suggest a lack of antitumor activity of the drug and Perhaps suggest a change in therapy. Early recognition and treatment of the toxicity facilitates good symptom control, prevents treatment-related morbidity, and allows continuation of anti-cancer therapy. However, co-operation between oncologist, dermatologist and patient is also fundamental in order to make the best decision for the patients and to implement preventive measures for cutaneous toxicities.

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