TOXIC EFFECTS OF MULTIPLE ANTICANCER DRUGS ON SKIN

NOOR KAMIL*, SABA KAMIL[1], SHAHIDA P. AHMED[2], RIZWAN ASHRAF[3], MOHAMMAD KHURRAM AND MUHAMMAD OBAID ALI[4]

Department of Pharmacology, Dow International Medical College & Institute of Basic Medical Sciences . Dow University of Health Sciences. Karachi, Pakistan
[1]Aga Khan University Hospital. Karachi, Pakistan
[2]Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Pakistan
[3]King Khalid University, Abha, Kingdom of Saudi Arabia
[4]Central Drug Laboratories, Ministry of Health, Karachi, Pakistan

ABSTRACT

In this study, cutaneous toxicities associated with the administration of chemotherapy in combination are discussed. Rapidly growing cells are the targets of chemotherapy, so the skin, hair follicles, and nail matrix are frequently affected by chemotherapy. Chemotherapy skin reactions are more likely toxic than allergic reactions. There are numerous chemotherapy-induced cutaneous reactions that have been described in the literature. In addition to a variety of miscellaneous reactions, 19 major cutaneous reactions were discussed in current study.

This study was designed to evaluate the clinical spectrum of all cutaneous toxicities over two years in hospitalized and ambulatory patients in the Department of Pediatric oncology and to establish probable relationship between the reaction and suspected anticancer protocol with the help of WHO (World Health Organization) Common Toxicity Criteria by Grade.

The data on the cutaneous toxicities were analyzed by percentile and ranking method. The minimal (0.8%) cutaneous adverse effects monitored during the study were Petechiae, photosensitivity, pruritis, urticaria, wound-infection, erythema multiforme, hand-foot skin reaction, injection site reaction, dry skin.

Alopecia was the single most common (64.3%) adverse effect observed during the study, where as the pigmentary changes were the second most common (18.2%) adverse effect monitored.

While these side effects are generally not life threatening, they can be a source of significant distress to patients, especially alopecia.

Keywords: Anticancer chemotherapy, alopecia, hyperpigmentation, cytotoxicity, cutaneous toxicity.

INTRODUCTION

Antincancer chemotherapy induced side effects affects nearly every structure of the skin especially skin adnexes such as hair cause alopecia (Guillot *et al*., 2004). Involvement of nails is frequent too but the sebaceous and eccrine sweat glands are rarely involved (Alley *et al*., 2002). Mouth is frequently affected by various mechanisms like direct cytotoxicity, infections and lower levels of white blood count or thrombocytes. As far as the dermatological side effects are concerned hyperpigmentation is very much prevalent with a number of different clinical presentations like generalized, figurated or localized. Dose related acryl erythema is another type of dermatological complication specific to anticancer drugs use (Branzan *et al*., 2005). Some dermatological untoward effects are occurred when anticancer drugs are combined with radiotherapy such as phototoxicity.

Some dermatological adverse effects only appeared with the use of specific drugs like hydroxyurea which can cause skin ulcers and dermatomyositis after prolong use (Koppel and Boh, 2001).

Chemotherapy induced mucocutaneous complications are common and in some cases more serious ones, but the cessation of causative agent is not necessary. Some times prevention of these untoward reactions might be necessary (Nakane, 2006).

In very few cases cessation of therapy is sometimes required due to the severity of adverse reactions (Svensson *et al*., 2001). In the current study only anticancer drugs were focused not any other biological agents were included like interlukins, colony stimulating factors or monoclonal antibodies for cancer therapy.

Chemotherapy is treatment with anticancer drugs to treat the different types of cancers. Most of the pediatric cancers (DeVita *et al*., 1997) need chemotherapy in first instance depending upon the stage and severity.

Although single-agent therapy is sometimes employed, the more common approach to chemotherapy involves administration of multiple agents to overcome factors for

Corresponding author: e-mail: noorkamil@hotmail.com

decreased patient response noted previously (Chabner 2006).

Combination chemotherapy is given to target as many types of cells in the tumor as possible. Selection of agents for combination chemotherapy regimens involves consideration of drug-specific factors such as mechanism of action, antitumor activity, and toxicity profile. Drugs that possess minimally overlapping mechanisms of action and toxicities are combined, when possible.

When two or more agents are used together, the development of resistance may be slowed, but increased toxicity may result (Calabresi 2001). The development of effective combination anticancer therapy was stimulated by the success of combinations of antimicrobial drugs in patients with infectious diseases in instances where single agents failed. This development is one of the major advances in cancer treatment over the past 25 years. It must be noted that most combinations are chosen empirically, although there are a few basic rules that are usually followed: Summarized in table 1.

1. Select drugs that are active when used as a single agents.
2. Select drugs that act synergistically or that enhance the activity of the other agents either by different modes of action or by pharmacological mechanisms.
3. Select drugs that have minimally overlapping toxicities.
4. Maximize the dose and schedule of the various agents with respect to specific tumor cell and drug kinetics.

Many combinations now in use increase the response rate over single agents by factors of two to four times. Different drug classes can cause a range of dermatological effects like as simple as muculopapular rash and as sever as like toxic epidermal necrolysis. Some severe cutaneous toxicities may result in serious morbidity and even death (Trojan and Borelli 2002).

All these drugs are able to cause cutaneous toxicities alone, but when used in combination in theory their combine toxicities could be enhanced (Valks *et al*., 2000). In this study we monitored the cutaneous toxicities of anticancer drugs when used in combinations.

MATERIALS AND METHODS

Current study was conducted in the Cancer Hospitals for children, Karachi, Pakistan. A total of 106 cancer patients were admitted out of which 75 were male and rest (31) were female. After their admission to the hospital history and examination was done by one medical officer and a physician. Consultants thoroughly examined the dermatological complications. The SPSS version 16.0-computer was used to analyze the possible correlation between the deramatological effects and anticancer drugs. All the skin toxicities were monitored according to the specifications modified from the following guidelines.

1. Common toxicity criteria (ctc) version 2.0,
2. NCI (National Cancer Institute) Common Toxicity Criteria Version 1
3. WHO (World Health Organization) Toxicity Criteria by Grade,
4. SWOG (Southwestern Oncology Group) Toxicity Criteria

Table 1: Summary of hematologic neoplasms and currently used treatment regimens†

Hematologic malignancy	Primary therapy	Alternate therapy
Acute Non-Lymphocytic Leukemia (ANLL)	Anthracycline (daunorubicin or idarubicin) and cytarabine	Add etoposide to primary therapy
Chronic Myelogenous Leukemia	Hydroxyurea and interferon-α	Bone marrow transplant
Chronic Lymphocytic Leukemia	Chlorambucil and corticosteriods	Fludarabine
Non-Hodgkin's Lymphoma (NHL) – aggressive	CHOP	ESHAP, DHAP or MINE
Hodgkin's Disease (HD) - Stage III and IV	ABVD	MOPP or EPOCH
Multiple Myeloma	VAD	Oral alkylating agents (e.g., melphan) and prednisone
Acute Lymphoblastic Leukemia of Childhood (ALL)	Vincristine, prednisone, asparaginase and/or daunorubicin and/or methotrexate	Mercaptopurine and methotrexate

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; ESHAP = etoposide, methylprednisone, high dose cytarabine, cisplatin; DHAP = dexamethasone, high dose cytarabine, cisplatin; MINE = mesna, ifosfamide, mitoxantrone, etoposide; ABVD = adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; MOPP = mechlorethamine, vincristine, procarbazine, prednisone; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; VAD = vincristine, adriamycin, dexamethasone.
†adapted from Finley RS, Treish IM, Lindley CM *et al*. (2001). Hematologic Malignancies. *In*: Applied Therapeutics: The Clinical Use of Drugs. Koda-Kimble MA, Young LY (eds.). Lippincott Williams & Wilkins, Philadelphia, pp.88-1-88-42

As suggested by Sacerdoti *et al*., (1993) history and clinical examination were done. The patients treated on an outpatient basis without any previous history of dermatological disorder or toxicity of either gender aged between one to eighteen years were included in the study. The patients with previous history of any skin disorder, or taking any drug which is known to cause skin toxicity were excluded from the study. In search of etiology of a particular adverse drug reaction on the skin drug history, possible correlation with anticancer agent, duration of rashes, incubation period, morphological features of eruptions, related involvement of mucosa or any system and healing of lesions on cessation of therapy. In the combination therapy most likely causative agent was marked and confirmed by cessation of treatment.

An especial Performa was designed to record information carefully. The data of all the patients on cancer chemotherapy who experienced cutaneous toxicities were collected and analyzed on a daily basis by the principal investigator. A consultant dermatologist based on clinical and morphological grounds did the diagnosis of the cutaneous toxicity. Toxicity was defined as per the definition provided by WHO (Edwards and Aronson 2000). In every patient, the primary investigator collected a detailed history regarding drug intake, reaction time, previous allergic history, duration of reaction, type of cutaneous reaction, and relevant investigations (blood culture and/or serology to rule out infectious etiology).

Initially detailed drug history was taken regarding all the prescription and over the counter drugs during last month, with the date and dosages. Questions were asked from patients regarding any adverse effect observed with previous exposure of drugs. Physical examination provided information regarding hypersensitivity reaction caused by cytotoxic drug. Clear distinction between different skin reactions was necessary, because it give possible help in determining immunological orientation of chemotherapy drugs.

Identification of relevant literature The English and foreign-language medical literature was searched using the Medline (from January 1996 to January 2006) and Embase (from January 1988 to January 2006) databases. The search strategy employed the following keywords: (`Cutaneous adverse drug reaction' or `anticancer drug therapy/adverse effects' or `skin toxicities/cancer chemotherapy') and (`pediatric cancer treatment toxicities' or `anticancer drug toxicity') and `prospective studies'. The references of the retrieved studies and of published reviews on toxicities in pediatrics found via a manual search of various journals were examined in order to identify additional appropriate studies. The following criteria were used for considering studies in the review:

Selection of patients was not for any specific condition or drug exposure. Prospective monitoring was used to identify toxicities, and sufficient information was reported to calculate their incidence. Of the studies resulting from the screened electronic bibliographic search and the hand search, those that met previously defined inclusion criteria were selected and included in the analysis. Each study was carefully reviewed by two researchers on standard form, derived data on methods, results, and quality attributes. For each study the proportion of children who developed toxicities was extracted. The drugs which were used in the study are given below:

Asparaginase, Bleomycin, Carboplatin, *Cis*platin, Cyclophosphamide, Cytosine arabinoside, Dacarbazine, Dactinomycin, Daunorubicin, Doxorubicin, Etoposide, 5-Fluorouracil, Hydroxyurea, Ifosfamide,Lomustine, 6-Mercaptopurine, Prednisolone, Vinblastine, Vincristine

RESULTS

The current study based on the skin toxicities caused by the antineoplastic drugs specially when used in the different antineoplastic combinations revealed that the most common cutaneous adverse effects were alopecia and pigmentation changes.

The data on the cutaneous adverse effects were analyzed by percentile and ranking method. Table 2 (fig. 1) shows that chemotherapy drugs did not produce the cutaneous adverse effects like: Purpura, wound-non-infection, Bruising, Flushing after acute administration in either sex. The minimal (0.8 %) cutaneous adverse effects monitored during the study were petechiae, photosensitivity, pruritis, urticaria, wound-infection, erythema multiforme, hand-foot skin reaction, injection site reaction, and dry skin.

Table 2: Incidences of various skin toxicities

Skin toxicities	Cases recorded
Nail Changes	6
Petechiae	**1**
Photosensitivity	1
Pigmentation changes	21
Pruritus	1
Urticaria	1
Wound-infectious	1
Skin Peeling	1
Papular Rash	2
Skin Necrosis	2
Alopecia	74
Erythema multiforme	1
Hand-foot skin reaction	1
Injection site reaction	1
Dry Skin	1
Sum	115

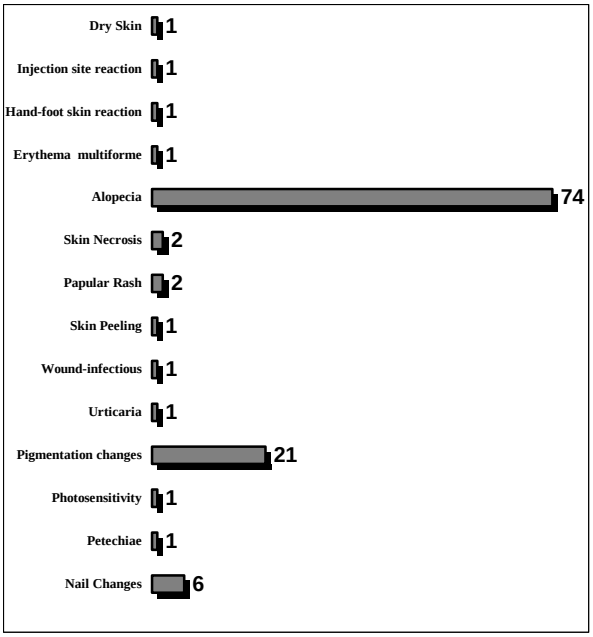

Fig. 1: Percentage of various skin toxicities.

Alopecia was the single most common (64.3%) adverse effect observed during the study, where as the pigmentary changes were the second most common (18.2%) adverse effect monitored. Nail changes were also found in 6 (5.2%) patients treated with the anticancer drugs.

DISCUSSION

Over the recent decades, the dermatological complications of cancer chemotherapy have become an increasingly significant subject in the management of cancer patients (Solensky, 2006) as the development of new antineoplastic drugs has continued to add to the arsenal of oncological treatment. The frequency of mucocutaneous complications in cancer chemotherapy is a reflection of the increased proliferative state of tissues, such as the mucous membranes, skin, hair, and nails, which renders them particularly susceptible to the actions of chemotherapeutic drugs. The diagnosis of cutaneous reactions in the cancer patient is especially difficult, given the complexity of their illnesses, and is complicated by the degree of their malignancy, other concomitant diseases, polypharmacy, and immunosuppression, with the development in bone marrow transplantation and graft rejection reaction is also being seen more frequently and may mimic and complicate the diagnosis of chemotherapy-induced reactions (Lutzow-Holm and Ronnevig 2005).

There are numerous chemotherapy-induced cutaneous reactions that have been described in the literature. Most common mucocutaneous reactions of the major classes of chemotherapeutic drugs are listed in Table 3, these reactions occur in varying degrees of frequency and severity within each class of chemotherapeutic drugs. Although dermatological complications are rarely fatal, it is important to recognize potential reactions in the management of the cancer patient, as they may result in significant morbidity, cosmetic disfigurement, and psychological distress. Proper treatment of potentially dose-limiting cutaneous toxicity may also allow achievement of ideal durations of chemotherapy administration, as well as the optimization of response rates.

Dermatological adverse reactions are more prevalent drug reactions (Magro and Crowson 1995; Magro *et al*., 1998). Early in drug-induced illness, prompt therapeutic intervention may limit toxicity. Chemotherapeutic agents usually associated with alopecia, of different types of dermatological adverse reaction, alopecia was most commonly seen in 74 (64.3%) patients, as recorded earlier (Chandah and Shenoi 2004). Also Consistent to the other studies (Pillans and Woods 1995; Hood, 1996; Fischer *et al*., 1997; Susser *et al*., 1999; Fitzpatrick *et al*., 1999) current study found most common causative agents of alopecia were Vincristine and Daunorubicin. Doxorubicin, Cyclophosphamide, Etoposide, Cytarabine, Carboplatin also produced the alopecia. In contrast to other studies Asparaginase and Prednisolone were also found to cause the alopecia in appreciable number of patients (Pillans and Woods 1995; Hood, 1996; Fischer *et al*., 1997; Susser *et al*., 1999; Fitzpatrick *et al*., 1999).

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 (Susser *et al*., 1999). Agents commonly associated with oral mucosal hyper-pigmentation include busulfan, fluorouracil, tegafur, doxorubicin, hydroxyurea, cisplatin, and cyclo-phosphamide (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 Vincristine, Etoposide, Cyclophosphamide, Asparaginase, and Prednisolone and less common causative agents include Bleomycin, Carboplatin, Cytarabine, Doxorubicin, Daunorubicin, Ifosfamide, and Methotrexate, which were consistent with previous study (Branzan *et al*., 2005) except Prednisolone which was not included in previous studies. Among the antimetabolites, methotrexate may produce a characteristic "flag sign" on the hair: horizontal hyperpigmented bands alternating with normal hair color in light-haired individuals (Susser *et al*., 1999). Tegafur can induce hyperpigmentation of the palms, soles, nails, and glans penis in a third of patients receiving the drug. A "flagellate," band-like hyperpigmentation in areas of trauma also occurs with

high incidence in 8 to 20% of patients receiving bleomycin. Busulfan's hyper-pigmentation can mimic Addison's disease, with symptoms of weakness, weight loss, and diarrhea, but with normal melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH) serum levels (DeSpain, 1992).

Hyperpigmentation in areas of occlusion, such as cutaneous areas under electrocardiogram (EKG) pads, tape, or dressings, with or without preceding erythema has

Table 3: Skin toxicities associated with chemotherapeutic agents†

Chemotherapeutic Agent	Nail Changes	Petechiae	Photosensitivity	Pigmentation	Urticaria	Skin peeling	Rash	Erythema multiforme	Hand-foot skin reaction	Alopecia
Cell Cycle-Specific Agents										
Antimetabolites										
Methotrexate			✓	✓			✓			✓
5-Fluorouracil							✓	✓		✓
Purine Antagonists										
6-Mercaptopurine				✓			✓			
Pyrimidine Antagonists										
Cytosine arabinoside					✓	✓	✓			✓
Antitumor antibiotics										
Bleomycin				✓				✓	✓	
Topoisomerase inhibitors (Epipodophyllotoxins)										
Etoposide										✓
Antimicrotubular Agents (Vinca alkaloids)										
Vincristine							✓			✓
Vinblastine			✓				✓	✓		✓
Cell Cycle-Nonspecific Agents										
Alkylating Agents										
Cyclophosphamide	✓			✓			✓			✓
Ifosfamide	✓			✓			✓	✓		✓
Dacarbazine							✓			✓
Lomustine							✓			
Anthracycline Antibiotics										
Doxorubicin	✓				✓			✓		✓
Daunorubicin	✓				✓			✓		✓
Antitumor Antibiotics										
Dactinomycin				✓						✓
Platinum Analogs										
Carboplatin					✓		✓			✓
*Cis*platin										✓
Miscellaneous Agents										
Asparaginase					✓		✓			
Hydroxyurea				✓			✓	✓	✓	✓
Steroid Hormones										
Prednisolone				✓						

†adapted from Salmon SE, Sartorelli AC (2001). Cancer Chemotherapy. *In*: Basic & Clinical Pharmacology. Katzung BG (ed). McGraw-Hill, Toronto, pp.923-958.

been reported with ifosfamide, topical carmustine, thiotepa, docetaxel, and combinations of etoposide and carboplatin with either cyclophosphamide or ifosfamide (Burgin, 2005). Finally, localized, serpentine, supravenous hyperpigmentation is often seen at the intravenous administration sites of fotemustine, fluorouracil, vinorelbine, and various combined chemotherapy regimens. The underlying mechanism for cancer drug related hyperpigmentation is not currently understood but might be due to direct toxicity, stimulation of melanocytes and postinflammatory changes. Although sometimes may be permanent, but gradually subsides upon discontinuation of treatment.

The most common nail abnormality seen in dark-complexion patients is hyperpigmentation among various nail changes expected in these patients (Fischer *et al*., 1997). Vertical bands, horizontal bands, or diffuse hyperpigmentation of nails have been known to occur to some degree in the use of the following medications: 5-flurouracil, platinum compounds, nitrogen mustards, docetexal, bleomycin, antimetabolites, amino-glutethamide, antitumor antibiotics (Susser *et al*., 1999). In the current study same drugs caused the nail changes in 6 patients as reported in earlier studies (Susser *et al*., 1999) except Asparaginase, Carboplatin, Daunorubicin, Etoposide, Prednisolone, and Vincristine but these causative agents are structurally similar to that of other agents of same class except Prednisolone which was not included in the earlier studies. The reason of causing the nail changes by Vincristine is obviously due to its use in combination with other causative agents.

This kind of hyperpigmentation commonly grows out with nail. Others include horizontal depression of nail plate (Beau's line), white horizontal discoloration of nail plate over whole nail width (Mee's line), and white horizontal discoloration on partial nail width (leukonychia), onycolysis and onychodystrophy. Associations between bleomycin and nail loss, hydroxyurea and brittle nails, and etoposide and nail bed pigmentation have also been reported in the literature (Fischer *et al*., 1997 & Susser *et al*., 1999). Patients can be reassured about these nail changes, which are generally benign and eventually resolve once administration of the causative agent ceases and the affected nails grow out.

In the current study pruritus, purpura, urticaria, and papular rash were also studied. The results were consistent with the previous studies (Weiss, 1996). Bleomycin, Carboplatin, Cyclophosphamide, Cytarabine, Daunorubicin, Etoposide, Prednisolone, and Vincristine produced the different allergic skin reactions ranges from pruritus to papular rashes in the pediatric patients.

Urticaria is the second most common Chemotherapy induced adverse drug reaction (Breathnach, 1998). The main feature of urticaria is the development of red wheals on the skin having pruritus. When urticaria affected deep in subcutaneous tissues angioedema could occur. Drug related urticaria can not be distinguished from urticaria induced by other causes.

In the present study only one case of urticaria was found, which is statistically insignificant. Desire to scratch elicited by the unpleasant sensation is prurutis or itching. Pruritus endangered the skin's protective function and due to its subjective nature, lacks exact definition and non availability of appropriate animal models pruritus has not properly researched. Allergic reactions of antineoplastic agents can be appeared in the form of pruritus, edema, urticaria and erythema. Allergic reactions vary in their symptoms based on the drug, dosage, and drug allergy history of patient.

Hypersensitivity reactions most commonly caused by antitumor antibiotics, platinuium compounds, cytosine arabinoside, asparaginase and paclitaxel.Most of these reactions limited to the site of injection and vanished within 30-90 minutes (Pejsa *et al*., 2004 and Huang *et al*., 2004).

In the present study pruritus was found only in one patient which is insignificant and difficult to explain which particular agent cause that reaction when more than one anticancer agent was used. Cutaneous reactions related to chemotherapy and UV light exposure have been well documented, though they are relatively infrequent. Generally, most of these reactions involve exogenous phototoxicity with the agents acting as chromophores (Gould *et al*., 1995). Dacarbazine, fluorouracil, methotrexate, and vinblastine are the cytotoxic agents, which are commonly associated with phototoxicity(Gould *et al*., 1995). Present study showed only one case of photosensitivity reaction, which is consistent with the other such studies (Gould *et al*., 1995).

Interpretation of the histological changes in cutaneous drug eruptions is always difficult. The biopsy is generally not done except for last longer and severe ones otherwise most of the reaction are temporary (Stephens and Dalziel 1998). When biopsy performed the provided clinical history is not sufficient. This problem become more complicated when other drugs were also used by patient which caused rash and inflammatory process same in clinical and histological ground as of cytotoxic drugs (Prommer, 2005). The diagnosis of a drug eruption is more difficult in patients that have a systemic disease with skin involvement and are on multiple drugs (Crowson and Magro 1999; Crowson and Magro 1999; Crowson *et al*., 2003). The example of this is a patient in which the early stage of graft versus host disease is suspected. The changes are often subtle and distinction from a drug eruption or overlap between both processes

may be impossible unless internal involvement is presented (usually indicative of graft versus host disease). On histological grounds a more prominent infiltrate with eosinophils tends to favor a drug eruption but this is by no means absolute.

CONCLUSION

The study showed that toxicities in children are a significant health issue for public. The reporting of prescription and clinical information was a rarity and create difficulties for a health provider to use preventive strategies on the bases of evidences. Further methodologically strong drug surveillance studies are required to promote safe use of drugs in pediatrics cancer patients. Very few studies done on neonates, infants, children and adolescents (Impicciatore *et al*., 1999 & Bonati *et al*., 1990). Pediatric patients constitute a vulnerable group with regard to dermatological adverse drug reactions of anticancer chemotherapeutic agents of limited experience in this age group (Impicciatore *et al*., 1999). This deficiency causes oncologists to prescribe the drug in combination in different anticancer protocols without knowing their ADR in combination, thereby increasing the risk of drug toxicity (Conroy *et al*., 2001). Adequate controlled clinical trials in children are lacking, mainly because of issues of cost and responsibility, and to regulations that frequently act as major obstacles (Bonati *et al*., 1990). Although paediatric pharmacotherapy has recently come to the fore both in Europe and USA (Bonati *et al*., 1999), so far no meta-analytical review has been performed to assess the cutaneous toxicities of drugs in the pediatric population. Recently published drug surveillance studies allow an estimation of the overall incidence of toxicities in pediatric cancer patients. In this study systematically review prospective studies on dermatological toxicities in children and provide a summary quantitative estimate of their occurrence.

REFERENCES

Alley E, Green R and Schuchter L (2002). Cutaneous toxicities of cancer therapy. *Curr Opin. Oncol.*, **14**(2): 212-216.

Bonati M, Choonara I, Hoppu K, Pons G and Seyberth H (1999). Closing the gap in drug therapy. *Lancet*., **355**: 1625.

Branzan AL, Landthaler M, Szeimies RM. (2005). Skin changes with chemotherapy. *Hautarzt*., **56**(6): 591-602.

Breathnach SM (1998). Drug reactions, in Rook/Wilkinson/Ebling Textbook of Dermatology (Champion RH, Burton JL, Burns DA and Breathnach SM eds.), Blackwell Science, Malden, MA. Pp.3349-3517.

Calabresi P and Chabner BA (2001). Chemotherapy of neoplastic disease. In: Hardman JG, Limbird LE, Molinoff PB, (eds.). Goodman & Gilman's, The Pharmacologic Basis of Therapeutics, 10th ed. McGraw-Hill, New York, pp.1381-1388.

Chabner BA. (2006). Clinical strategies for cancer treatment: The role of drugs. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy. Principles and Practice, 4th ed. Lippincott Williams & Wilkins, Philadelphia, pp.1-14.

Chandha V and Shenoi SD (2004). Hair loss in cancer chemotherapeutic patients. *Indian J. Dermatol. Venereol. Leprol*., **69**: 131-132.

Conroy S, *et al*. (2000). Unlicensed and off-label drug use in paediatric wards in different European countries. *Br. Med. J.*, **320**: 79-82.

Crowson AN, Brown TJ and Magro CM (2003). Progress in the understanding of the pathology and pathogenesis of cutaneous drug eruptions: implications for pathogenesis. *Am. J. Clin. Dermatol.*, **4**: 407-428.

Crowson AN and Magro CM. (1999). Lichenoid and subacute cutaneous lupus erythematosus-like dermatitis associated with antihistamine therapy. *J. Cutan. Pathol*., **26**: 95-99.

Crowson AN and Magro CM (1999). Recent advances in the pathology of cutaneous drug eruptions. *Dermatol. Clin*., **17**: 537-560.

DeSpain JD (1992). Dermatologic toxicity of chemotherapy. *Semin Oncol*. **19**: 501-507.

DeVita VT Jr, Hellman S and Rosenberg SA (eds.) (1997). Cancer: Principles & Practice of Oncology. 5th ed. Lippincott-Raven, Philadelphia, PA, pp.1201-1209.

Edwards IR and Aronson JK (2000). Adverse drug reactions: Definitions, diagnosis and management. *Lancet*, **356**: 1255-1259.

Finley RS, *et al*. (2001). Hematologic Malignancies. In: Applied

Therapeutics: The Clinical Use of Drugs. Koda-Kimble MA, Young LY (eds.). Lippincott Williams & Wilkins, Philadelphia, pp.88-1-88-42

Fischer D, Knobf M and Durivage H (1997). The cancer chemotherapy handbook. St. Louis: Mosby. pp.514-526.

Fitzpatrick JE, Yokel BE and Hood AF (1999). Mucocutaneous complications of antineoplastic therapy. In: Fitzpatrick's Dermatology in general medicine, 5th Ed. Freedberg IM, Eisen AZ, Wolff K, *et al*. editors. McGraw-Hill, New York, pp.1642-1653.

Guillot B, Bessis D and Dereure O (2004). Mucocutaneous side effects of antineoplastic chemotherapy. *Expert Opin Drug Saf*., **3**(6): 579-587.

Gould JW, Mercurio MG and Elmets CA (1995). Cutaneous photosensitivity diseases induced by exogenous agents. *J. Am. Acad. Dermatol*., **33**: 551-573.

Hood AF (1996). Dermatologic toxicity. In: The chemotherapy source book, 2nd ed. Perry MC (editor). Williams & Wilkins, Baltimore, pp.595-606.

Huang JY, Wu CH, Shih IH and Lai PC (2004). Complications mimicking lupus flare-up in a uremic

patient undergoing pegylated liposomal doxorubicin therapy for cervical cancer. *Anticancer Drugs*, **15**(3): 239-241.

Impicciatore P and Choonara I (1999). Status of new medicines approved by the European Medicines Evaluation Agency regarding paediatric use. *Br. J. Clin. Pharmacol.,* **48**: 15-18.

Koppel RA and Boh EE (2001). Cutaneous reactions to chemotherapeutic agents. *Am. J. Med. Sci*., **321**(5): 327-235.

Lutzow-Holm C and Ronnevig JR (2005). Cutaneous drug reactions. *Tidsskr Nor Laegeforen*,. **125**(18): 2483-2487.

Magro CM, Crowson AN and Schapiro BL (1998). The interstitial granulomatous drug reaction: a distinctive clinical and pathological entity. *J. Cutan. Pathol*., **25**: 72-78.

Magro CM and Crowson AN (1995). Drugs with antihistaminic properties as a cause of atypical cutaneous lymphoid hyperplasia. *J. Am. Acad. Dermatol. M.*, **32**: 419-428.

Nakane M (2006). Neurotoxicity and dermatologic toxicity of cancer chemotherapy. *Gan To Kagaku Ryoho*., **33**(1): 29-33.

Pejsa V, et al., (2004). No adverse effect of ABVD chemotherapy in a patient with chronic hepatitis C and Hodgkin's disease. *Wien Klin Wochenschr*., **116**(19-20): 695-697.

Pillans P and Woods D (1995). Drug-associated alopecia. *Int. J. Dermatol*., **34**: 149-158.

Prommer E. (2005). Pruritus in patients with advanced cancer. *J. Pain Symptom. Manage*, **30**(3): 201-202.

Stephens A and Dalziel K (1998). The histopathology of drug rashes. *Curr. Diagn. Pathol*., **5**: 138-149.

Susser WS, Whitaker-Worth DL and Grant-Kels JM (1999). Mucocutaneous reactions to chemotherapy. *J. Am. Acad. Dermatol.,* **40**: 367-398.

Sacerdoti G, Vozza A and Ruocco V (1993). Identifying skin reactions to drugs. *Int. J. Dermatol.,* **32**: 469-479.

Solensky R (2006). Drug hypersensitivity. *Med. Clin. North Am*., **90**(1): 233-260.

Svensson CK, Cowen EW and Gaspari AA (2001). Cutaneous drug reactions. *Pharmacol Rev.*, **53**(3): 357-379.

Trojan A and Borelli S (2002). Adverse chemotherapy effects on skin and mucous membranes. *Schweiz Rundsch Med. Prax*., **91**(24): 1078-1087.

Valks R, Garcia-Diez A and Fernandez-Herrera J (2000). Mucocutaneous reactions to chemotherapy. *J. Am. Acad. Dermatol.*, **42**(4): 699.