Mucocutaneous Complications of Chemotherapy in 74 Patients from Maharaj Nakorn Chiang Mai Hospital

Siri Chiewchanvit MD*,
Khajornsakdi Noppakun MD*, Kittika Kanchanarattanakorn**

** Department of Internal Medicine, Faculty of Medicine, Chiang Mai University,*
*** Medical education section, Faculty of Medicine, Chiang Mai University*

Background : *There have been many reports about mucocutaneous complications of chemotherapy from western countries, but they are only small case series. Until now, there had been no such report in Thailand.*
Objective : *We assessed mucocutaneous complications in patients who received chemotherapy.*
Patients and Method : *A total of 74 patients, admitted for chemotherapy from October 2001 to January 2002 in the Internal Medicine Department, Maharaj Nakhon Chiang Mai Hospital, were studied.*
Results : *Of 74 patients (53 male and 21 female), we found a statistically significant relation between gemcitabine and alopecia (p = .020), bleomycin and hyperpigmentation (p = .030), and cytarabine and ichthyosis (< .001). The most common findings were alopecia (76.68%), hyperpigmentation (31.08%), transverse white bands of the nails (22.97%), and ichthyosis (20.27%). Other notable findings included oral mucositis, acne, acral erythema, flushing, onycholysis, urticaria, pruritus, phlebitis and cutaneous infections (including tinea corporis, tinea ungium, and warts).*
Conclusion : *Mucocutaneous complications are common in patients who have received chemotherapy. However, a further study with a larger sample size and specified chemotherapy regimen would be valuable.*

Keywords : *Mucocutaneous, Chemotherapy, Complication, Skin*

J Med Assoc Thai 2004; 87(5): 508-14

Chemotherapeutic agents have been used for a long time and have saved many lives, but they also have many complications. One of the most common is the mucocutaneous complication. Although it is not life threatening, it can cause cosmetic and psychological problems to patients. There have been many reviews and case reports of mucocutaneous complications in cancer patients from Western countries[1, 2], but there has been no such report in Thailand until now. In the present study, the authors researched the prevalence of mucocutaneous complications from chemotherapy, and the relationship between chemotherapeutic agents and their complications.

Patients and Method

From October 2001 to January 2003, 74 (53 male and 21 female) cancer patients were admitted to the Department of Medicine, Faculty of Medicine, Chiang Mai University. These patients had a mean age of 44.9 years (range 45-82 years), and lung cancer was the most frequent cancer found in, followed by leukemia (Table 1).

When the patients were admitted to Maharaj Nakorn Chiang Mai Hospital, their history of illness was recorded and they were examined by one physician. The treatment and skin biopsy were judged and performed by the primary physicians. The Chi-square and Fisher-exact test, and SPSS version 10.0 computer program analyzed the correlation between mucocutaneous complications and chemotherapy.

The median of chemotherapy cycles was 3 (range 1-13 cycles), and the median of chemotherapeutic agent numbers was 3 (30 patients received two and 25 received three chemotherapeutic agents). Table 2 shows the number of patients who received each chemotherapeutic agent. There were 17 patients who received radiation therapy, concomitant with chemotherapy.

Correspondence to : Chiewchanvit S, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. E-mail: schiewch@mail.med.cmu.ac.th

Table 1. Frequency of cancer in 74 patients

Cancer	Number of patients
Lung cancer	22
Cholangiocarcinoma	6
Breast cancer	2
Gastric cancer	2
Hematologic malignancies	
Leukemia	17
non Hodgkin Lymphoma	11
Hodgkin lymphoma	3
Multiple myeloma	2
Others	9

Table 2. Number of patients who received each chemotherapeutic agent

Chemotherapeutic agent	Number of patients
Alkylating agents	
Cyclophosphamide	17
Carboplatin	8
Ifosfamide	6
Mechlorethamine	2
Melphalan	1
Chlorambucil	1
Antimetabolites	
Doxorubicin	38
Cytarabine	20
Gemcitabine	11
Methotrexate	5
Fluorouracil	5
Mitoxanthrone	3
Antibiotics	
Bleomycin	5
Farmorubicin	3
Mitomycin	2
Dactinomycin	1
Idarubicin	1
Vinca alkaloids	
Vincristine	19
Docetaxel	11
Vinblastine	4
Others	
Cisplatin	28
Etoposide	14
Aminocamptothecin	6
Hydroxyurea	2
Amifostine	1

Results (Table 3 and 4)

Fifty-six patients (75.6%) developed alopecia, which was the most common mucocutaneous complication in the present study. The mean time of alopecia development was about 30 days (range 3-150 days). In the early phase, there was some hair loss on the entire scalp, which progressed until there was scanty hair. The hairs collected from 12 patients were in the anagen phase in 8 patients (66.7%), and their shafts were irregular and fragile. The rest of the patients had hairs in the telogen phase. There was a statistically significant correlation between alopecia and gemcitabine ($p = 0.02$), but there was no correlation between groups of chemotherapeutic agents and alopecia. Eighteen patients, who did not develop alopecia, had received chemotherapy for only 1-2 cycles. Besides scalp alopecia, the authors also found hair loss of the eyebrow and eyelashes (75.0%), beard (77.8%), axillary hair (76.7%), and pubic hair (69.6%). In one patient, the color of his beard changed to brown after 3 cycles of chemotherapy.

Twenty-three patients (31.3%) developed hyperpigmentation. Of these patients, 12 (52.2%) had skin hyperpigmentation, 14 (60.9%) had nail hyperpigmentation (Fig. 1), and 4 (17.4%) had oral, tongue or gum hyperpigmentation (Fig. 2). Two patterns of skin hyperpigmentation included generalized and localized hyperpigmentation along irritating areas, i.e. scratch marks (Fig. 3) or phlebitis. Bleomycin was significantly associated with skin hyperpigmentation ($p = 0.03$).

Seventeen patients (23.0%) developed transverse white bands of both the fingernails (Fig. 4) and toenails. Some patients developed both Beau's line and transverse white bands. The number of transverse bands and Beau's lines corresponded with chemotherapy cycles. There was no correlation between each chemotherapeutic agent and transverse white band, but when the chemotherapy group was analyzed, there was a significant correlation between vinca alkaloids and transverse white bands of the nails ($p = .0290$).

Fifteen patients (20.3%) developed acquired ichthyosis (Fig. 5), but only a few cases were severe. A significant correlation between acquired ichthyosis and cytarabine ($p < .001$) and antimetabolites ($p = .028$) were found.

Infectious diseases included 3 patients with tinea ungium, and 1 patient each with tinea corporis, tinea vesicolor, common warts, and oral candidiasis.

Other mucocutaneous complications were found in less than 5 percent of the patients. These included 2 patients with mucositis, 3 with acneiform eruption (2 of these cases received corticosteroids and the other chemotherapeutic agents, and the other case received cisplatin and aminocamptothecin), and

Table 3. Correlation between chemotherapeutic agents and mucocutaneous complications

Chemotherapeutic agents	Prevalence of complications			
	Alopecia (%)	Hyper-Pigmentation (%)	Transverse white band of the nail (%)	Ichthyosis(%)
Aminocamptothecin	6/6 (100)	3/6 (50)	3/6 (50)	1/6 (16.7)
Amifostine	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)
Bleomycin	5/5 (100)	4/5 (80)*	2/5 (40)	1/5 (20)
Carboplatin	5/8 (63.5)	1/8 (12.5)	1/8 (12.5)	1/8 (12.5)
Chlorambucil	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)
Cisplatin	22/28 (78.6)	7/28 (25)	7/28 (25)	4/28 (14.3)
Cyclophosphamide	14/17 (82.4)	4/17 (23.5)	5/17 (29.4)	3/17 (17.6)
Cytarabine	17/20 (85)	8/20 (40)	6/20 (30)	10/20 (50)*
Dactinomycin	1/1 (100)	1/1 (100)	0/1 (0)	0/1 (0)
Docetaxel	9/11 (81.8)	2/11 (18.2)	4/11 (36.4)	1/11 (9.1)
Doxorubicin	30/38 (78.9)	14/38 (36.8)	9/38 (23.7)	11/38 (28.9)
Etoposide	12/14 (85.7)	3/14 (21.4)	4/14 (28.6)	3/14 (21.4)
Farmorubicin	3/3 (100)	1/3 (33.3)	0/3 (0)	0/3 (0)
Fluorouracil	3/5 (60)	2/5 (40)	1/5 (20)	0/5 (0)
Gemcitabine	5/11 (45.5)*	1/11 (9.1)	0/11 (0)	2/11 (18.2)
Hydroxyurea	1/2 (50)	2/2 (100)	0/2 (0)	2/2 (100)
Idarubicin	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Ifosfamide	5/6 (83.3)	2/6 (33.3)	0/6 (0)	0/6 (0)
Mechlorethamine	2/2 (100)	2/2 (100)	1/2 (50)	0/2 (0)
Melphalan	1/1 (100)	0/1 (0)	0/1 (0)	0/1 (0)
Methotrexate	4/5 (80)	2/5 (40)	2/5 (40)	0/5 (0)
Mitomycin	2/2 (100)	2/2 (100)	0/2 (0)	1/2 (50)
Mitoxanthrone	3/3 (100)	1/3 (33.3)	0/3 (0)	1/3 (33.3)
Vinblastine	4/4 (100)	2/4 (50)	1/4 (25)	1/4 (25)
Vincristine	15/19 (78.9)	6/19 (26.3)	3/19 (15.8)	3/19 (15.8)

* $P < 0.05$

Table 4. Correlation between groups of chemotherapeutic agents and mucocutaneous complications

Chemo. agents	Prevalence of complications			
	Alopecia (%)	Hyperpigmentation (%)	Transverse white band of the nail (%)	Ichthyosis (%)
Alkylating agents	21/25 (84)	7/25 (28)	6/25 (20)	3/25 (12)
Antibiotics	33/41 (80.5)	16/41 (36.6)	10/41 (24.4)	11/41 (26.8)
Antimetabolites	27/38 (71.1)	12/38 (31.6)	7/38 (18.4)	12/38 (31.6)*
Vinca alkaloids	25/31(80.6)	8/31 (25.8)	10/31 (32.3)*	4/31 (12.9)
Others	30/39 (76.9)	11/39 (28.2)	8/39 (20.5)	5/39 (12.8)

* $P < 0.05$

2 with dermatitis from extravasated chemotherapeutic agents (one caused by vinblastine (Fig. 6) and the other by docetaxel. Both of them had second degree dermatitis, which improved after supportive therapy).

A gastric cancer patient developed acral erythema after receiving the third cycle of fluorouracil, doxorubicin and mitomycin. The symptom developed in the first and also second cycle. It spontaneously disappeared within 1 week. A lung cancer patient developed onycholysis (Fig. 7) after the third cycle of docetaxel and carboplatin. The fungus culture of the nail was negative. A non-Hodgkin lymphoma patient developed severe itching after receiving every cycle of cyclophosphamide, doxorubicin, and vincristine. Severe excoriation throughout his body was found. One patient with metastatic squamous cell

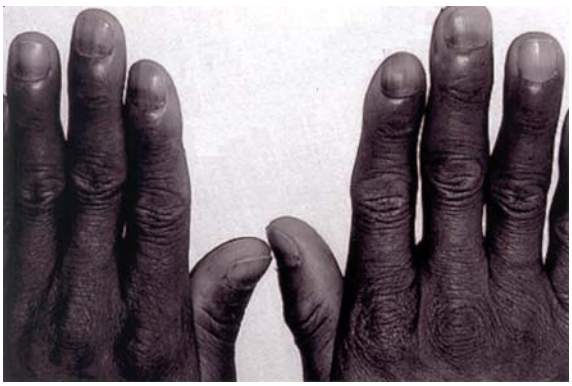

Fig. 1 Nail hyperpigmentation in a patient who received cytarabine, doxorubicin and mitoxanthrone

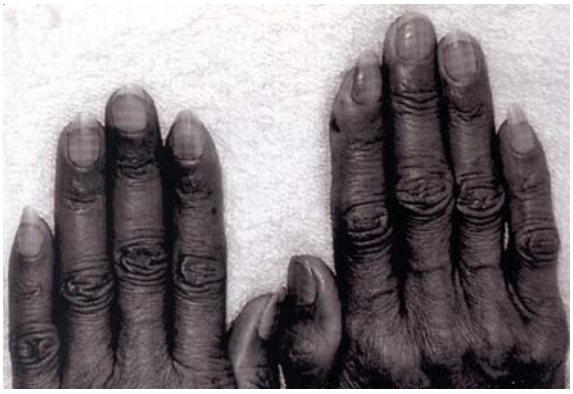

Fig. 4 Transverse white bands of the nails in a gastric cancer patient who received 6 cycles of fluorouracil, doxorubicin and methotrexate

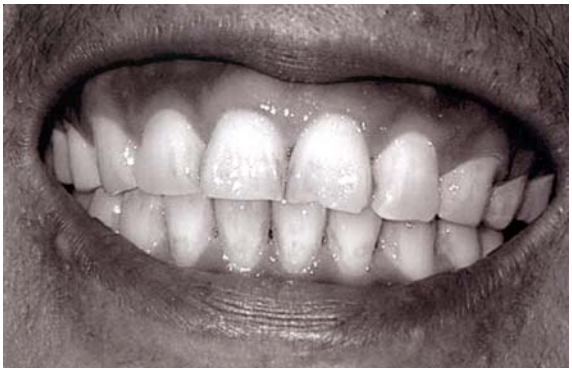

Fig. 2 Gum hyperpigmentation in a patient who received cyclophosphamide, doxorubicin and vincristine

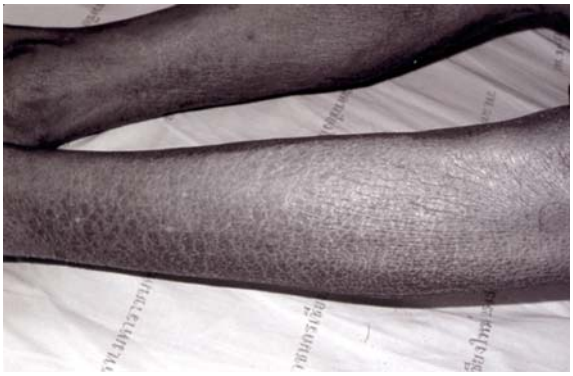

Fig. 5 Acquired ichthyosis in a patient with lung cancer who received cisplatin and etoposide

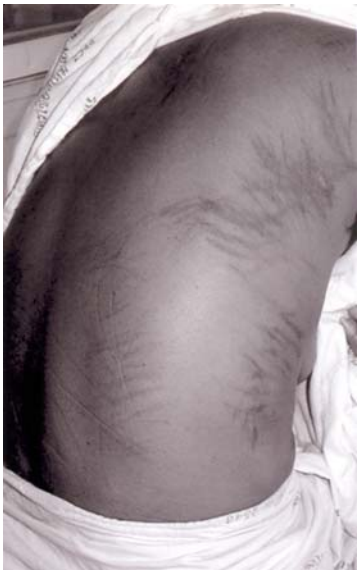

Fig. 3 Hyperpigmentation along scratching area in a patient who received cisplatin, etoposide and bleomycin

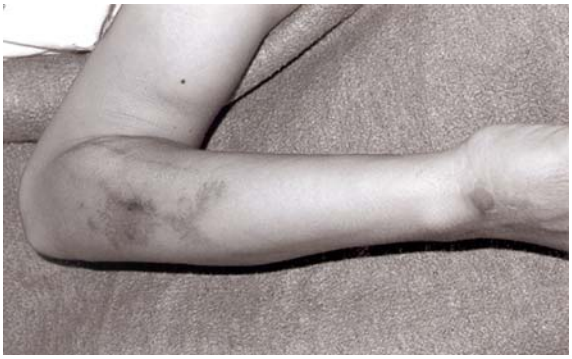

Fig. 6 Dermatitis from extravasated vinblastine

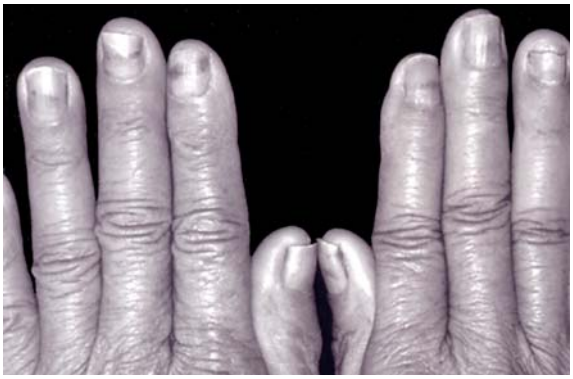

Fig. 7 Onycholysis in a patient who received docetaxel and carboplatin for 3 cycles

carcinoma of the lymph nodes developed erythematous patches on his arms and legs after receiving gemcitabine for 11 days. The skin biopsy showed mononuclear inflammatory vasculitis. Facial flushing appeared in a lung cancer patient six hours after receiving docetaxel and carboplatin, but resolved spontaneously within 2 hours. One patient with cholangiocarcinoma developed urticaria two hours after the first cycle of gemcitabine and cisplatin. Hydroxyzine was prescribed and the rash persisted for 10 days.

Discussion

The present study is the first report of mucocutaneous complications of chemotherapy in Thai patients. Alopecia was the most common mucocutaneous complication (75.7%), as in other reports from western countries[1]. The time between the first cycle of chemotherapy and onset of alopecia is difficult to determine because of recall bias. This is the disadvantage of the cross sectional examination designed in this study. In fact, patients who develop alopecia from chemotherapy should preserve about 10 percent of their scalp hair follicles[3], but most of the presented patients had their heads shaved. Hairs falling out of other parts of the body and changing their texture or color were also found, as reported[3]. Although most chemotherapeutic agents can cause alopecia, the authors found that only gemcitabine had a significant correlation with alopecia in the present study, and this has not been reported as a cause of alopecia in many other reviews[1,2].

Both localized and generalized hyperpigmentation are the second most common complications, found in 31.1 % of patients. In some patients, hyperpigmentation was found in irritating areas, nails, tongue, and oral mucosa. In the present study, the authors found that bleomycin had a significant correlation with hyperpigmentation, but other reports[4-6] found a relationship to cisplatin and ifosfamide. Transverse white bands of the nails could be found in 23.0 % of patients. Victoroff et al reported one patient with fluorouracil, who developed transverse white bands of the nails[7]. In the present study, it was found that the number of transverse white bands correlated with that of chemotherapeutic cycles, and Beau's line might be found in the same nail. Vinca alkaloids had a significant correlation with transverse white bands of the nail. Chapman was unable to identify a significant correlation between chemotherapeutic agents and transverse white bands, but it could be found frequently in patients who received cyclophosphamide, doxorubicin, and vincristine[8]. Acquired ichthyosis was found in 20.3 % of the patients and there was a significant correlation with cytarabine and antimetabolites. To the best of our knowledge, there is no report of acquired ichthyosis from chemotherapeutic agents. Viral and fungal infections were found in the presented patients, and they could be from the indirect effect of decreasing immunity caused by chemotherapeutic agents.

Other complications are not uncommon. Oral mucositis was found in only 2 patients, although it was found in 40 percent of patients in other reports[9]. Dermatitis from extravasated chemotherapy was found in 1 patient (2.6%), with an incidence reported elsewhere of about 0.1-6 percent[10]. The difference might be caused by the duration of the study, as oral mucositis was found in two phases, 4-7 days and 12-14 days after chemotherapy[1]. However, the length of stay in hospital for the presented patients was about 1-3 days.

Acral erythema was found in one patient, who received fluorouracil, doxorubicin and mitomycin. However, in other literature, it was most commonly found in fluorouracil, doxorubicin, cytarabine and docetaxel[1,11-13]. The role of steroids in the prevention of this complication is controversial. Dose reduction and pyridoxine may prevent this complication[1]. One patient, who received carboplatin and docetaxel, developed onycholysis, and one with gemcitabine developed vasculitis, as previously reported[14-18]. However, vasculitis can be found in cancer patients who have had no treatment. In this study, the authors did not find radiation recall[19-21], although 17 patients had received radiation therapy. Neither anaphylactoid reaction, sunburn from methotrexate, neutrophilic

eccrine hydradenitis nor cutaneous eruptions of lymphocytic recovery was found[22-26].

In conclusion, the present study is the first preliminary one on chemotherapy-induced mucocutaneous complications in Thai patients. However, patients from other departments of internal medicine were not included and the duration of the study was very short. Since most of a small number of patients received more than one chemotherapeutic agent, it was difficult to conclude the exact causative agent. The complications found in the present study were similar to those shown in previous reports. The high prevalence of mucocutaneous hyperpigmentation from chemotherapy may be a result of Thai skin phototypes and the climate. The data in the present study were collected by the cross sectional approach, so there might be some complications that develop later. A study with a larger number of patients, longer follow up time, and prospective approach will be valuable in the future.

References

1. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. J Am Acad Dermatol 1999; 40: 367-97.
2. Fitzpatrick JE, Yokel BE, Hood AF. Mucocutaneous complications of antineoplatic therapy. In: Freedber IM, Eisen AZ, Wolff K, editors. Fitzpatrick's Dermatology in general medicine 5th edition. McGraw-Hill companies, Inc; 1999, 1642-53.
3. Pillans PI, Woods DJ. Drug-associated alopecia. Int J Dermatol 1995; 4: 149-56.
4. Yule SM, Pearson AD, Craft AW. Ifosfamide-induced hyperpigmentation. Cancer 1994; 73: 240-1.
5. Teresi ME, Murry DJ, Cornelius AS. Ifosfamide-induced hyperpigmentation. Cancer 1993; 71: 2873-5.
6. Lamki ZA, Pearson P, Jaffe N. Localized cisplatin hyperpigmentation induced by pressure. Cancer 1996; 77: 1578-81.
7. Victoroff VM. Transverse white lines in the fingernails induced by combination chemotherapy. Arch Dermatol 1993; 129: 1217-8.
8. Chapman S, Cohen PR. Transverse leukonychia in patients receiving cancer chemotherapy. South Med J 1997; 90: 395-8.
9. Sonis S. Oral complications of cancer chemotherapy. In: Devita V, Hellman S, Rosenberg S, editors. Cancer: principle and practice of oncology. Philadelphia: Lippincott; 1993, 2385-94.
10. Heckler F. Current thoughts on extravasation injuries. Clin Plast Surg 1989; 16: 557-67.
11. Curran CF, Luce JK. Fluorouracil and palmar-plantar erythrodysesthesia. Ann Intern Med 1989; 111: 858.
12. Jucgla A, Sais G. Hand-foot syndrome. J Clin Oncol 1997; 15: 3164.
13. Zimmerman MGC, Keeling JH, Burris MHA, et al. Acute cutaneous reactions to docetaxel, a new chemotherapeutic agent. Arch Dermatol 1995; 131: 202-6.
14. laninio J, Papaldalou M, Panogos G, et al. Sequential chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer. Am J Clin Oncol 2001; 24: 227-31.
15. Georgoulios V, Scagliotti G, Miller V, Eckaratt J, Douillard JY, Manegild C. Challenging the platinum combination: docetaxel (taxotere) combined with gemcitabine or vinorelbine in non-small cell lung cancer. Semin Oncol 2001; 281: 5-21.
16. Miller VA, Krug LM, NG KK, et al. Phase II trial of docetaxel and vinorelbine in patients with advanced non-small cell lung cancer. J Clin Oncol 2000; 18: 1346-50.
17. Ornstein DL, Rigas JR. Taxotere: clinical trial in non-small cell lung cancer. Oncologist 1998; 3: 86-93.
18. Banach MJ, William GA. Purtscher retinopathy and necrotizing vasculitis with gemcitabine. Arch Ophthal 2000; 118: 726-7.
19. Burdon J, Bell R, Sullivan J, Henderson M. Adriamycin-induced recall phenomenon 15 years after radiotherapy. JAMA 1978; 239: 93.
20. Kelllie SJ, Plowman PN, Malpas JS. Radiation recall and radiosensitisation with alkylating agents. Lancet 1987; 8542: 1149-50.
21. Raghavan VT, Bloomer WD, Merkel DE. Taxol and radiation recall dermatitis. Lancet 1993; 8856: 1354.
22. Alkins SA, Byrd JC, Morgan SK, Ward FT, Weiss RB. Anaphylactoid reactions to methotrexate. Cancer 1996; 77: 2123-6.
23. Korossy KS, Hood AF. Methotrexate reactivation of sunburn reaction. Arch Dermatol 1981; 117: 310-1.
24. Shear NH, Knowles SR, Shapiro BL, Poldre P. Dapsone in prevention of recurrent neutrophilic eccrine hidradenitis. J Am Acad Dermatol 1996; 35: 819-22.
25. Beutner KR, Packman CH, Markowitch W. Neutrophilic eccrine hidradenitis associated with Hodgkin's disease and chemotherapy. Arch Dermatol 1986; 122: 809-11.
26. Horn TD, Redd JV, Karp JE, et al. Cutaneous eruptions of lymphocyte recovery. Arch Dermatol 1989; 125: 1512-7.

ภาวะแทรกซ้อนทางผิวหนัง และเยื่อเมือกจากยาเคมีบำบัดในผู้ป่วย 74 ราย จากโรงพยาบาลมหาราชนครเชียงใหม่

สิริ เชี่ยวชาญวิทย์, ขจรศักดิ์ นพคุณ, กิตติกา กาญจนรัตนากร

ความเป็นมา *: มีรายงานการศึกษาหลายรายงานถึงภาวะแทรกซ้อนทางผิวหนัง และเยื่อเมือกจากยาเคมีบำบัด โดยรายงานเหล่านี้เป็นรายงานผู้ป่วยจำนวนน้อยและมาจากประเทศทางตะวันตก และยังไม่มีรายงานลักษณะเช่นนี้ในประเทศไทย*

วัตถุประสงค์ *: เพื่อศึกษาภาวะแทรกซ้อนทางผิวหนังและเยื่อเมือกในผู้ป่วยที่ได้รับยาเคมีบำบัด*

วิธีการศึกษา *: ทำการศึกษาผู้ป่วย 74 ราย ที่เข้ารับการรักษาเพื่อรับยาเคมีบำบัดในภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ระหว่างเดือนตุลาคม พ.ศ. 2544 ถึง เดือนมกราคม พ.ศ. 2545*

ผลการศึกษา *: จากการศึกษาผู้ป่วย 74 ราย (เพศชาย 53 ราย และเพศหญิง 21 ราย) พบความสัมพันธ์ระหว่างการได้รับยา gemcitabine กับผมร่วง ($p = .020$), ยา bleomycin กับการมีสีผิวคล้ำ ($p = .030$), และยา cytarabine กับการเกิดผิวหนังแห้ง ($< .001$) ภาวะแทรกซ้อนที่พบได้บ่อยคือผมร่วง (ร้อยละ 76.7), ผิวหนัง และเยื่อเมือกมีสีคล้ำ (ร้อยละ 31.1), รอยขาวตามแนวขวางของเล็บ (ร้อยละ 23.0), และผิวหนังแห้ง (ร้อยละ 20.3) ภาวะแทรกซ้อนอื่นที่พบคือ ปากอักเสบ, ฝ่ามือฝ่าเท้าแดง, อาการหน้าแดง, เล็บถอด, สิว, ลมพิษ, อาการคัน, หลอดเลือดอักเสบ, หลอดเลือดดำอักเสบ, และการติดเชื้อที่ผิวหนัง ได้แก่ กลากลำตัว, กลากที่เล็บ, และหูด*

สรุป *: ภาวะแทรกซ้อนทางผิวหนัง และเยื่อเมือกพบได้บ่อยในผู้ป่วยที่ได้รับยาเคมีบำบัด อย่างไรก็ตามยังต้องมีการศึกษาผู้ป่วยจำนวนมากกว่านี้ และศึกษายาเคมีบำบัดเฉพาะชนิดเพื่อหาความสัมพันธ์กับการเกิดภาวะแทรกซ้อนทางผิวหนัง และเยื่อเมือกต่อไป*