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Maculopapular Skin Rashes Associated With High-Dose Chemotherapy: Prevalence and Risk Factors

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Purpose/Objectives: To determine the prevalence of and risk factors for maculopapular skin rashes associated with high-dose chemotherapy.

Design: Observational pilot study.

Setting: A bone marrow transplant hematology-oncology unit in a private city hospital.

Sample: Data were collected on 14 patients who developed maculopapular rashes out of 127 patients who received high-dose chemotherapy (purposive sampling).

Methods: Observation of the distribution and nature of skin rashes in relation to chemotherapy, disease, adjuvant medications, and white blood cell counts.

Main Research Variables: Diseases, chemotherapy protocols and doses, adjuvant medications, and blood counts.

Findings: Skin reactions ranged from mild, scattered macular or maculopapular rashes to severe rashes. Patients newly diagnosed with acute myelogenous leukemia (AML) who received induction protocols containing cytarabine had the most rashes, affecting 6 of 11 patients (55%). No rashes were observed on patients treated with the protocol that included high-dose corticosteroids. Patients rarely had recurrence of the rash with further courses of chemotherapy.

Conclusions: Cytarabine doses higher than 700 mg/m² may be a cause of maculopapular skin rashes. Patients most at risk were those newly diagnosed with AML who received induction therapy. Corticosteroids may prevent the development of skin rashes.

Implications for Nursing: No useful nursing strategy exists to prevent, lessen the intensity of, or shorten the course of a delayed hypersensitivity rash. Knowing which patients are most at risk is useful to enable close monitoring and patient and staff education.

During the course of treatment with high-dose chemotherapy, a substantial number of patients in a nine-bed bone marrow transplant hematology-oncology unit in a progressive inner-city hospital developed maculopapular skin rashes of varying intensity and subsequent complications that prolonged their courses of treatment and affected their physical and emotional well-being. The chemotherapy was given as induction therapy, consolidation therapy, or conditioning therapy prior to autologous peripheral blood stem cell transplantation (PBSCT).

This article describes an observational pilot study to monitor all skin rashes that occurred after certain high-dose chemotherapy protocols during a 12-month period. The aims of the study were to determine the prevalence of and risk factors leading to maculopapular skin rashes on the unit.

Key Points . . .

- A substantial number of patients developed maculopapular skin rashes after receiving high-dose chemotherapy for a range of hematologic diseases.
- When skin rashes occur, they have a severe effect on patients' physical and emotional well-being at a time when they are coping with a life-threatening disease and other debilitating side effects of treatment.
- Patients who are newly diagnosed with acute myelogenous leukemia and are treated with cytarabine-containing protocols are at greater risk for developing rashes.
- More research needs to be done to determine possible prophylaxis and to increase knowledge in this specialty area to enable nurse and patient education to decrease patient distress and length-of-stay issues.

Literature Review

A review of the current literature revealed a scarcity of research detailing the prevalence and causes of dermatologic problems. Much of the literature consisted of reviews rehashing current views on the management of toxicities (Armstrong, Rust, & Kohtz, 1997; Gallagher, 1995; McCarthy, 2002) or case studies focusing on rare skin reactions or chemotherapy not used in the current study (Gallagher, 2001; Haisfield-Wolfe & Rund, 2002; Hockett, 2004; Keung, Knovich, Powell, & Pettenati, 2004; Schaich, Schakel, Illmer, Ehninger, & Bornhauser, 2003; Tse, Lie, Ng, & Kwong, 2003). Pichler (2003) researched the pathophysiology of delayed drug hypersensitivity reactions in detail, but more research is needed in the context of high-dose chemotherapy. Only Pearson, Sirohi, Powles, Treleaven, and Mortimer (2004) reported data on

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the prevalence of dermatologic problems in a similar setting. The randomized prospective observational study looked at "snap shots" of the patient population and included hair loss, mucositis, and a variety of dermatologic pathologies. However, the study did not specify treatment protocols, individual drugs, or doses, and it did not correlate them with the rashes to determine risk factors.

Chemotherapy causes many dermatologic reactions, some of which are known to be linked to specific agents and have commonly expected outcomes. They include hyperpigmentation, photosensitivity, onycholysis (shedding of nails), and radiation recall and enhancement (McCarthy, 2002). However, the reactions rarely are seen in the setting of bone marrow transplant hematology-oncology because most chemotherapy protocols used on those units do not cause such skin reactions. The adverse skin reaction commonly observed in this setting and described in this study is a maculopapular rash, consistent with a delayed drug hypersensitivity reaction.

Skin reactions ranged from mild, scattered macular or maculopapular rashes (see Figure 1), with or without pruritus and fever, to severe rashes (see Figure 2), becoming confluent and including vesicles, purpura, pruritus, fever, and desquamation. The rashes usually appeared first on the trunk, then spread to the extremities (see Figure 3). Two of the patients had a rash only on their hands or fingers.

Fitzpatrick, Johnson, Wolff, Polano, and Suurmond (1997) described skin rashes as adverse cutaneous drug reactions or drug eruptions that are further classified into four hypersensitivity types. The rashes discussed in the present study are consistent with type IV, a cell-mediated immune reaction, and include the morbilliform or maculopapular (exanthematous) reactions. According to Fitzpatrick et al., drug eruption may occur at any time between day one and three weeks after beginning treatment, patients may have fevers, and rashes are usually pruritic. The skin lesions are macules and/or papules, and purpura may be present, particularly in the lower legs (see Figure 3). The lesions are erythematous and frequently become confluent. The distribution is symmetrical and almost always on the trunk and extremities. Acral erythema is characterized by erythematous patches on the palms or soles and on the digits (Kossard, 2000; McCarthy, 2002; Rest & Horn, 1992).

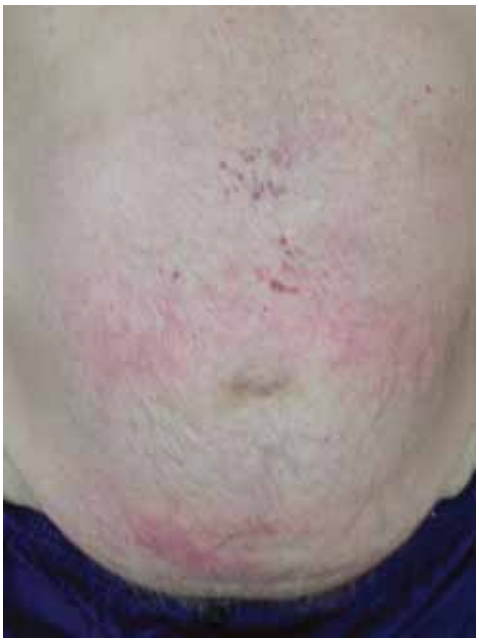

Figure 1. Mild Skin Rash

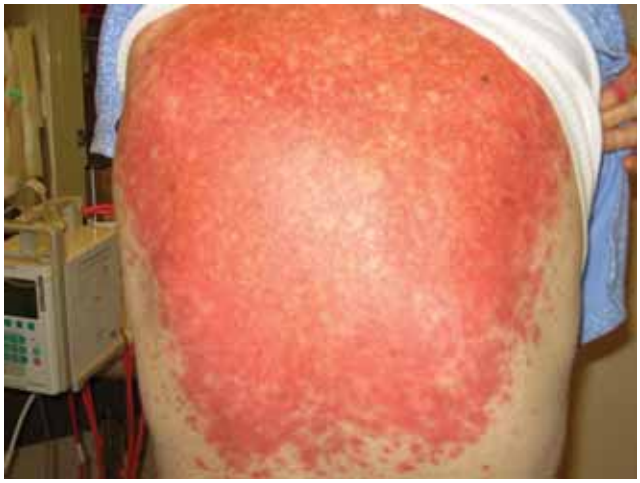

Figure 2. Severe Skin Rash

Methods

Design and Sample

This was an observational pilot study using purposive sampling. The sample consisted of 127 patients who received certain high-dose chemotherapy as induction therapy, consolidation therapy, or conditioning therapy prior to autologous PBSCT to treat acute myelogenous leukemia, non-Hodgkin lymphoma, amyloidosis, or multiple myeloma and who did not have preexisting skin conditions. The patients were chosen because the chemotherapy was considered high dose and the patients remained in the unit, which allowed for close monitoring throughout their treatment. The study was conducted during a 12-month period. Data were collected on all 14 patients who developed maculopapular rashes or acral erythema.

Instrument

An information sheet outlining the skin rash pilot study, the possibility of a patient developing a skin rash, and the possible course of action was given to each patient who fulfilled the study criteria. Consent was obtained from each patient. Nursing staff were tutored using a chart that contained terminology (see Figure 4), descriptions, and photos. Skin rash observation charts that included prompts, body forms, and descriptive terminology for consistency in data collection were included in patients' bedside charts. The observation charts were updated on a daily basis by qualified, specialist oncology RN staff members. The author collated all of the data. A digital camera was used to photograph some of the rashes with patient consent.

Procedure

Ethical approval was granted by the Wesley Hospital Multidisciplinary Ethics Committee. Baseline data were collected,

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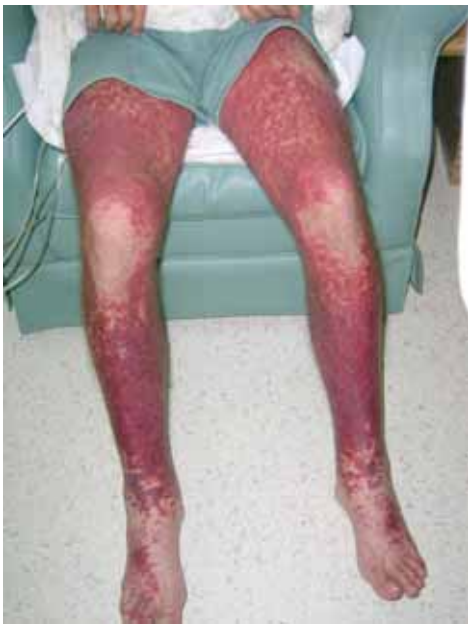

Figure 3. Purpural Rash on the Legs

including patients' diseases, types of chemotherapy protocol, adjuvant medications, and allergies. On the manifestation of a skin rash, further data were collected regarding the distribution and description of each rash, any newly introduced drugs (e.g., antibiotics), and blood counts. These data were collected on all 14 patients while they exhibited a rash.

Nursing interventions to maintain skin integrity and relieve discomfort included cool washes or cold compresses and the application of aqueous cream with 1% menthol or clear calamine lotion. IV antihistamines were prescribed for intractable pruritus, which was the most distressing symptom associated with rashes (Goldsmith, Lazarus, & Tharp, 1997; Marks, 1993). Skin rashes were monitored closely for signs of infection or other complications, and patients were educated about skin care and self-acceptance and were reassured about the transient nature of the rashes.

The following IV chemotherapy protocols were used to treat the 127 patients: dexamethasone, cyclophosphamide, doxorubicin, cisplatin, etoposide, and oral thalidomide (DT PACE); methylprednisone, methotrexate, cyclophosphamide, etoposide, and cytarabine (MADEC); dexamethasone, cyclophosphamide, doxorubicin, vincristine, and intrathecal methotrexate or cytarabine (HYPER C-VAD Cycle A); IV and intrathecal methotrexate and cytarabine (HYPER C-VAD Cycle B); idarubicin, etoposide, and cytarabine (7-3-7, 5-2-5, and HIDAC, representing the differing lengths of the protocol and differing strengths of the drugs); carmustine, etoposide, cytarabine, and melphalan (BEAM) prior to autologous PBSCT; and melphalan prior to autologous PBSCT.

Data Analysis

The prevalence of maculopapular rashes associated with each chemotherapy protocol was recorded. The collected data regarding the distribution and nature of the rash, the disease, chemotherapy, concomitant drugs, and blood counts were tabled, but statistical analysis was not done because of the many variables. The researchers were, however, able to look at trends and make observations regarding chemotherapy, disease state, and the perceived risk associated with the different protocols.

Results

Prevalence

During the duration of the study, a total of 127 patients were treated with a variety of chemotherapy regimens, and 14 patients (11%) developed a rash. The chemotherapy protocols that caused the most rashes were 7-3-7 and the HIDAC protocols, with a total of 6 out of 11 (55%) affected patients in those groups. Three of 25 patients (12%) who had BEAM conditioning and 3 of 31 patients (10%) who had melphalan conditioning developed a rash. Of 13 patients who had DT PACE, only one (8%) developed a rash. Of seven patients who received HYPER C-VAD Cycle A, none had a rash, but of 10 patients who were given HYPER C-VAD Cycle B, one developed a rash. Twenty-three patients received MADEC, but none of them developed a rash. The seven patients who received consolidation therapy with 5-2-5 did not develop a rash (see Table 1).

The rashes observed during the study first developed from days 2–24, after the commencement of chemotherapy (see Figure 5), and were transient, lasting as many as 17 days. The duration and intensity of the rashes varied, with the rashes resulting from melphalan being less intense, less to not at all pruritic, and of short duration (one to three days). Rashes in the BEAM group were of 5–17 days' duration and of moderate intensity. The rash following HYPER C-VAD Cycle B lasted seven days, and the rashes in the 7-3-7 and HIDAC groups were 6–14 days in duration and more intense, with pruritus, purpura, vesicles, desquamation, and moderate to intense erythema.

Symptoms consistent with acral erythema were observed in two patients—one had a localized macular rash on the fingers, and the other had a maculopapular rash with edema on the

Confluent: flow together, as in the macules and papules joining

Desquamation: peeling of the skin

Erythematous: red or inflamed

Exanthematous: measles-like. Synonyms are maculopapular and morbilliform.

Macule: circumscribed area of change in normal skin color, with no skin elevation or depression (nonpalpable)

Maculopapular: characterized by a combination of macules and papules. Synonyms are exanthematous and morbilliform.

Morbilliform: measles-like. Synonyms are maculopapular and exanthematous.

Papule: solid, raised lesion as large as 0.5 cm in diameter

Pruritus: itching

Purpura: blood leaking from the vessels into the skin. Pressure does not blanch the lesion. Lesions smaller than 3 mm are called petechiae.

Urticaria: hive; a pruritic skin eruption characterized by edematous wheals with an erythematous halo

Vesicle: circumscribed, elevated, fluid-containing lesion less than 0.5 cm in diameter

White cell nadir: the lowest white cell count

Figure 4. Descriptive Terminology

Note. Based on information from Fitzpatrick et al., 1997.

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Table 1. Incidence of Skin Rashes Detailed According to Chemotherapy Protocols

Chemotherapy Protocol	Drugs	Dose[a] and Days of Treatment	N	Incidence of Skin Rash	
				n	%
(R)BEAM[b] Conditioning	Carmustine Cytarabine Etoposide Melphalan	300 mg/m² day 1 400 mg/m² days 2–5 200 mg/m² days 2–5 140 mg/m² day 6	25	3	12
Melphalan Conditioning	Melphalan	100–200 mg/m² day 1 (or split days 1 and 2)	31	3	10
DT PACE Induction and consolidation	Cisplatin Cyclophosphamide Etoposide Doxorubicin Thalidomide Dexamethasone	10 mg/m² days 1–4 400 mg/m² days 1–4 40 mg/m² days 1–4 10 mg/m² days 1–4 100 mg days 1–6 40 mg days 1–4	13	1	8
HYPER C-VAD Cycle A induction and consolidation	Dexamethasone Cyclophosphamide Doxorubicin Vincristine Methotrexate I/T or cytarabine I/T	40 mg days 1–4 and days 11–14 600 mg/m² days 1–3 50 mg/m² day 4 2 mg days 4 and 11 12.5 mg day 2 100 mg day 7	7	–	–
HYPER C-VAD Cycle B induction and consolidation	Methotrexate Cytarabine Methotrexate I/T Cytarabine I/T	1,000 mg/m² day 1 6,000 mg/m² days 2–3 12.5 mg day 2 100 mg day 7	10	1	10
7-3-7 (Little ICE) Induction	Cytarabine Idarubicin Etoposide	100 mg/m² days 1–7 12 mg/m² days 1–3 75 mg/m² days 1–7	8	4	50
5-2-5 Consolidation	Cytarabine Idarubicin Etoposide	100 mg/m² days 1–5 12 mg/m² days 1–2 75 mg/m² days 1–5	7	–	–
HIDAC-3-7 (Big ICE) Induction	Cytarabine Idarubicin Etoposide	6,000 mg/m² days 1, 3, 5, and 7 12 mg/m² days 1–3 75 mg/m² days 1–7	2	1	50
HIDAC-2-5 (Big ICE) Consolidation (modified)	Cytarabine Idarubicin Etoposide	2,000 mg/m² days 1, 3, and 5 9 mg/m² days 1–2 75 mg/m² days 1–5	1	1	100
(R)MADEC[b] Induction and consolidation	Methylprednisone Methotrexate Cyclophosphamide Etoposide Cytarabine	400 mg days 1–5 400 mg/m² day 1 750 mg/m² day 1 75 mg/m² days 1–5 75 mg/m² days 1–5	23	–	–
Total			**127**	**14**	**11**

[a] Some patients had a modified dose.

[b] "R" denotes the addition of rituximab 375 mg/m². However, rituximab is not always added.

hands. None of the patients had urticaria, which normally is an indication of a type I or II hypersensitivity reaction (Fitzpatrick et al., 1997).

White Blood Cell Counts

When a rash was present, the patients' total white blood cell counts ranged from 0–21,300 cells/mcl, the lymphocyte counts ranged from 0–23,100 cells/mcl, and the eosinophil counts for 9 of 14 patients was zero, with the range for the other five being 0–200 cells/mcl (see Table 2). The white cell nadir occurred from days 9–17, reflecting the differing lengths of protocols, and sometimes preceded and sometimes coincided with the rashes (see Figure 5). No consistent relationship existed between the white cell nadir and the timing of the rashes.

Discussion

Skin and Hypersensitivity Reactions

Healthy, intact skin is essential to total well-being. The skin is the body's first line of defense against assault, pathogens, and ultraviolet radiation. It also regulates body temperature, helps maintain fluid and electrolyte balance, synthesizes

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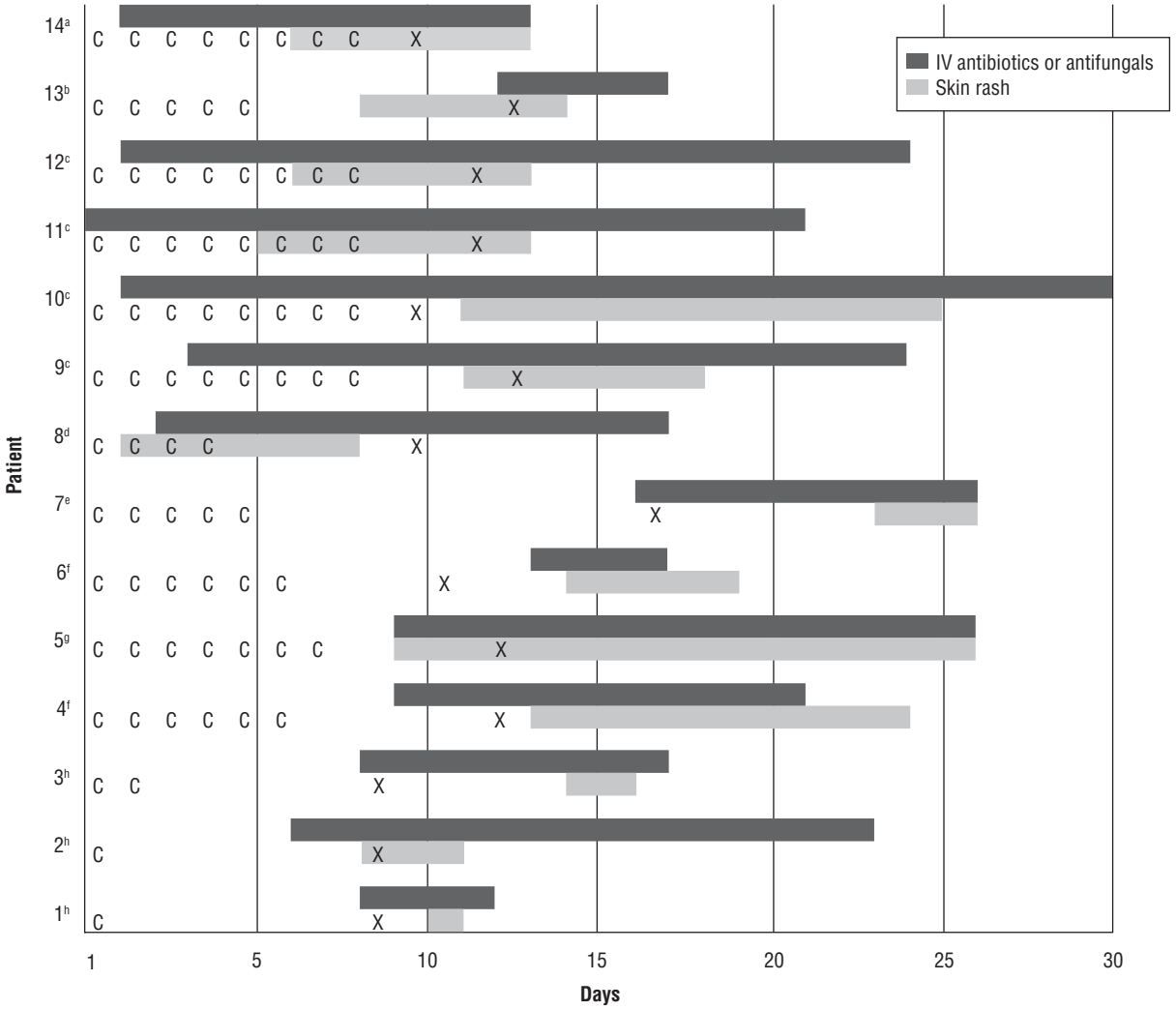

Figure 5. Time Frame of Skin Rashes in Relation to the Administration of Chemotherapy, IV Antibiotics or Antifungals, and the White Cell Nadir

[a] HIDAC-3-7 (idarubicin, etoposide, and cytarabine)

[b] HIDAC-2-5 (idarubicin, etoposide, and cytarabine)

[c] 7-3-7 (idarubicin, etoposide, and cytarabine)

[d] HYPER C-VAD Cycle B (IV and intrathecal methotrexate plus cytarabine)

[e] DT PACE (dexamethasone, cyclophosphamide, doxorubicin, cisplatin, etoposide, and oral thalidomide)

[f] BEAM (carmustine, etoposide, cytarabine, and melphalan)

[g] (R)BEAM (BEAM plus rituximab)

[h] Melphalan

C—chemotherapy; X—white cell nadir

Note. Day 1 is the commencement of chemotherapy.

vitamin D, receives stimuli, and is essential for healthy self-concept and communication (Gallagher, 1995). When skin's integrity is altered, it no longer can protect the body against fluid loss, pathogens, and damage to underlying structures; temperature regulation is compromised; pain and touch sensations are altered; and body image is disturbed (Armstrong et al., 1997).

The rashes in the present study were transient because the skin is rapidly renewing tissue and the epidermal layer completely regenerates approximately every 30 days. Hence, tissue can renew prior to total regeneration (Armstrong et al., 1997). However, when rashes occur, they can have a severe effect on patients' physical and emotional well-being at a time when they are already coping with a life-threatening disease and other debilitating side effects of treatment.

The clinical symptoms of the rashes in the present study are consistent with type IVb and IVc delayed drug hypersensitivity reactions as described by Pichler (2003), who investigated

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Table 2. Range of Blood Counts During Time of Skin Rash

Patient	White Blood Cells	Neutrophils	Eosinophils	Lymphocytes	Platelets
1	400	240	0	90	37,000
2	100–300	30–210	30–50	30–60	19,000–46,000
3	3,200–9,100	3,000–7,550	0	100–1,270	30,000–43,000
4	0–8,900	0–8,190	0	0–160	13,000–73,000
5	100–21,300	0–17,040	0–200	90–2,340	7,000–71,000
6	200–6,700	160–5,960	0	40–200	7,000–42,000
7	4,100–5,900	3,240–5,250	0–80	410–530	31,000–47,000
8	1,500–14,200	1,400–14,000	0	100–350	33,000–151,000
9	200–600	0–40	0	160–580	11,000–19,000
10	100–16,700	0–11,390	0	100–1,170	15,000–83,000
11	300–500	0–80	0	300–500	15,000–27,000
12	100–3,500	0–3,300	0–10	100–200	20,000–116,000
13	100–200	0–120	0	40–200	< 5,000–16,000
14	300–500	0–20	0–10	300–500	16,000–37,000

Note. All blood counts were measured in cells/mcl.

the underlying mechanisms of immune-mediated idiosyncratic and unpredictable delayed drug hypersensitivity reactions. Drug hypersensitivity and other immune reactions can be classified into four categories (Coombs & Gell, 1968).

1. Type I, resulting from immunoglobulin E, mainly causes anaphylactic reactions.
2. Type II are immunoglobulin-mediated cytotoxic reactions.
3. Type III are immune complex mediated (e.g., vasculitis).
4. Type IV reactions are mediated by T cells, which cause delayed hypersensitivity reactions.

Furthermore, different types of T-cell reactions can elicit clinically distinct forms of drug reactions, hence the addition of subclassification type IVa, in which T-helper 1 cells activate monocytes; type IVb, in which T-helper 2 cells activate eosinophils; type IVc, in which CD4+ and CD8+ cells assume cytotoxic functions; and type IVd, which recruits neutrophils (Pichler). "Small drugs" can act as antigens for T cells (Pichler). Primary sensitization requires at least a three- to four-day sensitization phase, frequently longer, and the innate immune system needs to be activated. Pichler debated whether the drug-specific immune response is activated by the drug or if it occurs in an immune system already stimulated by an existing assault on the body because those patients have a higher frequency of drug allergies.

According to Marks (1993), pruritus is the most distressing of symptoms associated with a skin rash, a phenomenon that the current study also found to be true. Treatment focused on symptom relief. To maintain skin integrity and relieve discomfort, aqueous with menthol cream or clear calamine lotion was used to moisturize and soothe patients' irritated, itchy skin with good effect, and an antihistamine was prescribed for intractable pruritus. Cool washes or cold compresses were used when the rash radiated heat.

McCarthy (2002) suggested that preemptive nursing strategies appear to be useful to lessen the cutaneous side effects of chemotherapy and that preventive skin care regimens should be established prior to appearance of a rash. Preventive skin care regimens may be helpful with photosensitivity, radiation recall, or onycholysis. However, because of the pathophysiology associated with the development of rashes in the study population, no useful nursing strategy was found to prevent, lessen the intensity of, or shorten the course of the delayed drug hypersensitivity rash during this study. This observation was supported by Gravett (2001), who conducted a study comparing standard treatment and aromatherapy treatment for skin problems resulting from high-dose chemotherapy. He concluded that no differences existed between the aromatherapy and control groups.

Eleven percent of the patients in the present study developed a rash, which contradicts Gallagher's (1995) finding that cutaneous hypersensitivity reactions associated with antineoplastic agents are uncommon. The rate of adverse skin reactions to drugs among all hospitalized patients is reported to be 2%–3% (Fitzpatrick et al., 1997; Pichler, 2003; Sauer & Hall, 1996; Zurcher & Krebs, 1992). Pearson et al. (2004) found that the incidence of maculopapular rash consistent with drug allergy was as high as 7%. The authors concluded that the patients received more antibiotics than the control group; therefore, the rashes were significantly associated with the antibiotics, which failed to consider other variables such as chemotherapy.

In patients receiving chemotherapy, few direct causes of cutaneous toxicities have been identified (Armstrong et al., 1997). Armstrong et al. noted that rashes usually occur two to nine days postchemotherapy (they did not state whether rashes followed the commencement or completion of chemotherapy). The chemotherapeutic agents implicated were etoposide, cyclophosphamide, methotrexate, and cytarabine. The present study found that 9 of 14 patients developed a rash two to nine days after the completion of chemotherapy, not the commencement. Pearson et al. (2004) reported that the maculopapular eruptions documented in their study appeared more often at the nadir of the white blood cell count postchemotherapy. The present study found that the nadir occurred during days 9–17, but the rashes first appeared from days 2–24, with seven patients developing a rash prior to the nadir (see Figure 5).

As stated, the clinical symptoms are consistent with type IVb and IVc hypersensitivity reactions; however, because the eosinophil count of most patients with a rash was nil, the researchers believed that the rashes were unlikely to be type IVb. Therefore, through a process of elimination, the researchers determined that the rashes most likely were the result of a type IVc hypersensitivity reaction, mediated by CD4+ and CD8+ T cells.

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Furthermore, 10 patients in the present study had a peripheral blood lymphocyte count of 100 or less on the day their rashes appeared. The patients with more severe rashes, however, had as many as 23,400 lymphocytes during the duration of the rash (see Table 2). Armstrong et al. (1997) and Rest and Horn (1992) wrote of cutaneous eruptions that appeared to be related to delayed hypersensitivity reactions and that occurred at the time of earliest recovery of lymphocytes, 6–21 days postchemotherapy; however, Kossard (2000) and Apisarnthanarax and Duvic (2000) discussed those occurrences as two separate phenomena, despite the fact that both are T-cell mediated. That patients can still develop rashes with so few peripheral blood lymphocytes may be explained by the presence of Langerhan cells—dendritic cells that lodge in the skin. The cells take up antigen and present it to CD4+ T cells in the lymph nodes, spleen, and thymus (Sewell, 2000).

High-Dose Cytarabine

Patients who received high-dose cytarabine (≥ 700 mg/m²) tended to develop more rashes, as in 7-3-7 and HIDAC protocols, which had the highest percentage of rashes (55%). Six patients received 700–24,000 mg/m^2 of cytarabine in total. One patient given HYPER C-VAD Cycle B, who developed a rash, received 12,000 mg/m^2 of cytarabine. BEAM patients received 1,600 mg/m^2 of cytarabine, and 12% of those patients had rashes. The protocols that did not include cytarabine (melphalan and DT PACE) or that included only a low dose (MADEC and HYPER C-VAD Cycle A) had the fewest number of rashes.

Etoposide

Etoposide was used in all of the protocols except HYPER C-VAD and melphalan. The HIDAC and 7-3-7 groups had a higher incidence of rashes but received a lower dose of etoposide than the BEAM group, and two of the patients who developed a rash after receiving 7-3-7 actually received modified protocols with no etoposide. Of the two patients who had localized rashes on their hands, one had received DT PACE and one received HIDAC-2-5, both of which included etoposide. In those cases, patients appeared to have acral erythema, which is documented to occur with cytarabine, doxorubicin, methotrexate, cyclophosphamide, and etoposide (Apisarnthanarax & Duvic, 2000; Armstrong et al., 1997; Kossard, 2000; Rest & Horn, 1992).

Other Potential Causative Agents

IV antibiotics and IV antifungals were used extensively after patients spiked high temperatures (> 100.4°F) and continued to be given while patients were febrile or had positive blood cultures. The most common antibiotics used were ticarcillin and potassium clavulanate, vancomycin, cefepime, meropenem, and gentamicin. Commonly used IV antifungals were amphotericin and voriconazole. The appearance of a rash usually was accompanied by fever. However, in two patients, rash developed prior to the commencement of IV antibiotics or antifungals, and in nine patients, rash resolved prior to the time the IV antibiotics or antifungals were discontinued. In these instances, the antibiotics unlikely were the cause of the rash. Healthcare providers must not to be too hasty to attribute a rash to an antibiotics allergy because if patients are declared to be allergic to a drug, it will not be administered in the future, which is unfortunate if the drug was not at fault and may be beneficial during future infections.

Another drug of interest is allopurinol, which can cause adverse cutaneous reactions (Fitzpatrick et al., 1997). A typical allopurinol rash begins on the face, and the onset is two to three weeks after the initiation of therapy. In most cases in the present study, allopurinol was given only for a brief period, four to nine days after the commencement of treatment, and usually was discontinued at the completion of chemotherapy. One patient did receive allopurinol for an extended period, until day 18 postchemotherapy, but his rash resolved on day eight. Patients who received the melphalan protocol were not given allopurinol.

All patients in the study were administered granulocyte colony-stimulating factor (G-CSF) on the day following their chemotherapy or PBSCT. This drug has been documented to cause maculopapular rashes (Armstrong et al., 1997; Gallagher, 1995; Kossard, 2000). Gallagher (1995) reported that G-CSF reactions occur on approximately the 10th day of therapy as a result of the upregulation of neutrophils. Armstrong et al. believed the rashes were related to lymphocyte recovery 6–21 days after chemotherapy. A direct relationship does not appear to exist between the administration of G-CSF and the appearance of a rash in the present study.

Corticosteroids

Patients on protocols that included corticosteroids did not develop rashes. This finding is consistent with documentary evidence that corticosteroids can prevent or minimize hypersensitivity reactions. Edwards (2003) reported that dexamethasone has been used as a premedication for patients receiving chemotherapy to prevent or minimize such reactions.

Corticosteroids affect circulating white blood cells by increasing polymorphonuclear leukocytes but inducing apoptosis in T cell lymphocytes (McKay & Cidlowski, 2000; Sewell, 2000). According to McKay and Cidlowski, corticosteroids inhibit lymphocyte participation in delayed hypersensitivity reactions. Corticosteroids are used in combination therapy for cancers of lymphoid origin, including acute lymphoblastic leukemia, chronic lymphoid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma, but not in the treatment of acute myeloid leukemia (AML) (McKay & Cidlowski). Fitzpatrick et al. (1997) suggested the administration of IV corticosteroids as treatment of cutaneous drug reactions if the drugs could not be discontinued and to induce more rapid remission of the rash. Apisarnthanarax and Duvic (2000) found that corticosteroids had shown variable success in the treatment of acral erythema.

Therefore, the absence of rashes in patients who received MADEC may be explained by the large doses of methylprednisone, which inhibits the T-cell–mediated delayed hypersensitivity reactions, administered to them as part of the protocol. The seven patients who received HYPER C-VAD Cycle A also did not develop any rashes. This protocol included dexamethasone. Another feature associated with the MADEC group was that IV antibiotic use was reduced and in some instances not needed at all. This phenomenon may be linked to another side effect of steroid use, the masking of fevers.

Recurrence of Rash

Another trend seen during the present study was that patients who developed rashes with the induction chemotherapy

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protocol often did not develop them with subsequent doses of chemotherapy, even though they were given the same drugs. One patient who had a severe rash following 7-3-7 induction therapy had 2,000 mg/m² of cytarabine for five days with her next chemotherapy protocol, a much higher dose of cytarabine than she originally received (700 mg/m²), yet she had no further rashes. The phenomenon is common and was observed with all but two of the patients in the study. One of the patients had a much paler rash of shorter duration with follow-up therapy; the other had a similar rash during the same consolidation therapy previously administered. According to Fitzpatrick et al. (1997), an exanthematous drug eruption may not recur if the drug is given again. The literature also documents that acral erythema may or may not recur with readministration of chemotherapy (Apisarnthanarax & Duvic, 2000).

Patients at Risk

The most severe rashes are those seen with induction therapy, in patients newly diagnosed with AML, which indicates that disease-related complicating issues may exist such as a high white cell count on diagnosis at the commencement of chemotherapy. This finding substantiates Pichler's (2003) theory of a T-cell–mediated type IVc delayed hypersensitivity reaction. A retrospective review of data from the researchers' unit found that from June 2003–June 2005, one patient each year developed a severe cutaneous reaction. Each of the patients had been newly diagnosed with AML and given 7-3-7 chemotherapy as induction therapy. None of the patients had a recurrence of rash with further treatment.

Conclusion

As stated by McCarthy (2002) and Armstrong et al. (1997), causative agents of skin reactions in patients undergoing chemotherapy are difficult to isolate because patients receive so many possible causative agents and so many variables exist. The drugs that are administered are essential to patients' treatment and, therefore, cannot be withdrawn because of a skin rash. The present study was observational; therefore, determining particular offending drugs, except to recognize trends, is beyond its scope. Many of the chemotherapy drugs given during the study have been documented to cause rashes, but not all publications are consistent, and some drugs have not been implicated (Armstrong et al.; Gallagher, 1995; Kossard, 2000; McCarthy). As an example, Barton-Burke, Wilkes, and Ingwerson (2001), editors of a nursing oncology text book, did not document that cytarabine can cause a rash.

In conclusion, high-dose cytarabine is implicated as being a possible cause of many of the rashes, and the patients most at risk are newly diagnosed with AML receiving induction therapy. This might be because they present with a high white cell count. Another finding of interest was the possibility that corticosteroids may be of use in preventing hypersensitivity rashes and, therefore, must be considered an option for future prophylactic treatment. Further research is needed to confirm these findings.

Nursing Implications

Contrary to McCarthy's (2002) suggestion that preemptive nursing strategies appear to be useful, the results of the present review indicate that in the study population, nursing strategies are best aimed at maintaining skin integrity, relieving discomfort, increasing self-acceptance, educating patients about skin care, and monitoring and managing complications, such as infection.

Nurses need to be aware of the risk factors that make their patients susceptible to hypersensitivity skin reactions and which patients are at highest risk so they can provide quality care. Oncology nurses should understand the role of steroids and their effect on patients. More research needs to be done in this specialty area, focusing on prophylactic measures and treatment options. Most importantly, nursing staff can give patients emotional and spiritual support and encouragement with education and reassurance that their skin reactions are transient.

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