Biotherapy Skin Reaction

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Case Study

M.B. is a 71-year-old male who presented in January 2001 with renal cell carcinoma metastatic to paraesophageal, peri-aortic, hilar, and mediastinal lymph nodes. He was started on interleukin-2 (IL-2, aldesleukin) 18 million units, interferon alpha 10 million units, and 5-fluorouracil 1 g, all administered by IV continuous infusion for 96 hours every three weeks. No significant complications occurred after his first cycle of combined chemotherapy/biotherapy, except for a rise in his serum creatinine level from 1.3–1.5 mg/dL. However, during the second treatment, his creatinine level rose from 1.8–3.1 mg/dL (normal range is 0.6–1.5 mg/dL), and he was placed on a renal dose (5 mcg/kg/hr) of dopamine. He developed grade II diarrhea and grade II stomatitis and subsequently was placed on octreotide acetate and an oral rinse of equal parts of diphenhydramine, nystatin, and viscous lidocaine. The IL-2 infusion was stopped after day three. The interferon and 5-fluorouracil were continued for the full 96 hours.

Twelve days after receiving the second course of chemotherapy/biotherapy, M.B. called the office and complained that his legs were swelling; it was so severe that he was having trouble standing. He also described the presence of a red, flat rash and red streaks that he said looked like a “roadmap going up my legs.” The rash had been present for three or four days. A bilateral doppler ultrasound was ordered to rule out deep vein thrombosis, and the test result was negative. The advanced practice nurse in the physician’s office then examined M.B. The examination revealed 3+ edema in both legs. His skin was dry and flaky, and a bright red, lacy-looking rash covered his upper and lower legs. Examination supported the patient’s description of this phenomenon. M.B. reported that the rash was accompanied by the sensation of a severe sunburn. M.B. was placed on furosemide 20 mg by mouth twice a day for two weeks and given Eucerin® cream (Beiersdorf, Inc., Wilton, CT), which he was instructed to apply to the dry areas of his extremities twice a day. He was instructed to stay out of the sun, avoid hot baths or showers that may increase moisture loss, and gently towel dry after bathing.

Ten days later, M.B.’s physician examined him. Assessment revealed that his rash had resolved. His lungs were clear, his heart rate was regular, and no organomegaly was present. However, he still had 2+ edema in his lower extremities.

Discussion Questions

Given M.B.’s clinical picture, of which of the drugs he received has the highest incidence of causing this type of skin rash? Are the clinical signs and symptoms consistent with the clinical course usually observed with biologic therapy for renal cell carcinoma?

Discussion

Biologic therapy often is used to treat renal cell carcinoma because it stimulates the host’s immune system to attack and kill foreign cells. The process of stimulating the immune system involves the use of cytokines, which function as messengers in the immune system response by communicating between macrophages and lymphocytes. IL-2 and interferon alpha belong to the class of cytokines termed lymphokines and monokines. The lymphokines and monokines are produced by the lymphocytes, monocytes, and macrophages and control the immune system function and inflammatory response (Corwin, 2000). IL-2 is a cytokine that causes T cell proliferation in response to an antigen. The body stimulates further production of T cells through a positive feedback mechanism. In addition, IL-2 mediates the secretion of other cytokines through immunomodulation. IL-2 activates natural killer (NK) cells, monocytes, and cytotoxic T cells to produce a host defense mechanism against infection and in response to injury (Corwin, 2000).

IL-2 activation of T cells, B cells, and NK cells stimulates the pro-inflammatory cytokine production of interferon gamma, granulocyte macrophage colony-stimulating factor, tumor necrosis factor, and C-reactive protein. The activation of these pro-inflammatory cytokines initiates the events that cause IL-2 dose-dependent side effects. Adverse reactions from IL-2 are dose dependent, self-limiting, and usually reversible within two to three days of therapy completion (Sundin & Wolin, 1998).

Interferon alpha is a cytokine that targets uninfected host cells and is capable of inhibiting viral replication (Corwin, 2000). Interferon alpha comes from T- and B-lymphocytes and macrophages and belongs in the lymphokine/monokine classification of

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In addition to providing protection against viruses, interferon alpha decreases B cell proliferation and tumor growth and increases NK cells (Rote, 1998).

Interferon alpha enhances the production of the NK cell, a pro-inflammatory cytokine. Stimulation of NK cell production by interferon alpha causes side effects, such as fever, arthralgia, myalgia, and fatigue (Sundin & Wolin, 1998). Interferon alpha also may cause pruritis and exacerbate dermatologic and autoimmune disorders (Koppel & Boh, 2001).

Side effects from combining these two agents are a result of the pro-inflammatory response to the cytokines. The stimulation of the pro-inflammatory cytokines, such as IL-6, interferon gamma, granulocyte macrophage colony-stimulating factor, and tumor necrosis factor, causes the common side effects of biological therapy. Some of the common side effects from biological therapy are flu-like symptoms, fever, arthralgia, myalgia, fatigue, rigors, capillary leak syndrome, hypotension, and skin rashes.

IL-2 can cause cutaneous skin reactions that produce pruritis and flushing, and exacerbate psoriasis. Skin reactions from IL-2 begins a few days after therapy has started and can cause an erythematous rash that starts out locally, typically on the back, and may spread to the legs, arms, and abdomen. The rash may be pruritic and has been described as dusky red. These symptoms may last 7–10 days after the last dose.

Skin peeling or sloughing has occurred during treatment with IL-2. During subsequent cycles, this peeling and sloughing may be seen sooner if they occurred in the first cycle. A study of six patients, three males and three females, conducted by Blessing, Park, Heys, King, and Eremin (1992) involved skin biopsy samples of patients receiving therapy with IL-2 continuous infusion for the first five days followed by 5-fluorouracil bolus on days 7, 14, and 21. Biopsies were performed prior to initiation of therapy and on the day the rash appeared. The rash typically appeared two to four days after the IL-2 infusion was started. Baseline skin biopsies were unremarkable. The biopsy results after the rash appeared showed an increase in the expression of HLA-DR and ICAM-1 on perivascular cells, endothelium, and keratinocytes. HLA-DR and ICAM-1 are antibodies; the expression of these immunohistological features are related to the pro-inflammatory cytokine activities caused by IL-2’s increased production of interferon gamma and tumor necrosis factor. If the skin rash was caused by a hypersensitivity reaction, eosinophils would have been present in the biopsies taken after the rash appeared. The biopsies were negative for eosinophils (Blessing et al.).

### Nursing Implications

If a patient does have a skin rash, thorough assessment and documentation are critical. Pretreatment nursing assessment must include documentation of a history of skin disorders (e.g., psoriasis) and pre-existing skin lesions or rashes and, if known, the cause of these skin lesions and rashes. Note the patient’s symptoms associated with the rash if present (e.g., pruritus, burning), characteristics of the rash, dimensions, and location, and document these findings in the patient record. When patients are undergoing therapy, healthcare professionals must assess constantly for any new lesions or rashes.

When skin rashes appear in patients on therapy, documentation must include a description of the rash, its location and dimensions, and presence of symptoms, such as itching or pain associated with the rash. The patient also will need to be assessed for other causes of skin rash. The possibility of herpes zoster or infection in patients receiving biological therapy must be ruled out when skin changes are being assessed.

What can nurses do to support the patient in caring for a biotherapy-induced skin rash? Patient education is the key. Patients should be advised to use a moisturizer on dry skin. The moisturizer should be alcohol-free, perfume-free, and water-based. Skin should be cleansed with a gentle, nontoxic soap. Oatmeal baths and oral diphenhydramine hydrochloride or oral hydroxyzine hydrochloride may help to alleviate symptoms of pruritis. Patients should wear loose-fitting cotton clothing. When outside, sun exposure should be avoided and sunscreen should be worn and reapplied throughout the day. Remind patients to avoid hot showers and baths (Sandstrom, 1996). Viele and Moran (1993) suggested that patients with skin rashes should avoid excessive swimming in salt or chlorinated water. Because of the suppression of the immune system by steroids, topical steroids should be avoided so that the antitumor effects of the biological therapy are not affected (Viele & Moran).

### Case Study Follow-Up

M.B. continued with his chemotherapy/biotherapy as scheduled; however, doses were reduced as a result of the severe skin rash that occurred after each treatment. In April, his disease progressed and all therapy was discontinued. M.B. and his wife chose to pursue other possibilities for treatment, and they were referred to a comprehensive cancer center. Because of the prior therapy that he received, he was ineligible for any of the trials that were open at that time. In July, he presented to the office with neurologic changes and was found to have brain metastasis. At the time this article was written, M.B. had not decided between pursuing further treatment or hospice care.

On examination of all of the evidence in treating this patient and the cutaneous changes, it was highly suggestive of an IL-2 skin reaction. The descriptions in the literature of IL-2 skin reactions and what has been seen in other patients at Medical Oncology Hematology Associates, Inc., are similar. Secondly, the rash tended to last the characteristic 7–10 days, as stated in the literature. Finally, M.B. did experience skin sloughing (he stated it was “just like a snake loses his”) that often is associated with IL-2 infusions.

### Summary

Although skin reactions from biotherapy are relatively rare, patients must be assessed regularly for these symptoms. Patient and family education and support are critical. Understanding the underlying pathophysiology of a skin rash in response to the administration of IL-2 or other cytokine-mediated therapies assists nurses in determining the implications for care. With accurate assessment, documentation, and patient education, care of patients undergoing biological therapy can be improved.

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### References


