At a Glance

✦ Metastatic melanoma and metastatic renal cell carcinoma present challenging treatment dilemmas.

✦ Continuous-infusion plus pulse interleukin-2 dosing with famotidine can provide good treatment outcomes for patients with metastatic melanoma or renal cell carcinoma.

✦ Nursing care of patients receiving continuous-infusion followed by pulse interleukin-2 is unique, requiring a different approach than care of patients receiving chemotherapy or the traditional high-dose bolus regimen.

High-dose, continuous-infusion interleukin-2 (IL-2) followed by pulse dose and concurrent administration of famotidine has demonstrated response rates of 64% and 33% in patients with metastatic melanoma and metastatic renal cell carcinoma, respectively. Currently, no information is available concerning the nursing care of patients receiving that IL-2 regimen. Given the high response rates of patients on the treatment, attention by the nursing profession is warranted. Effective nursing care of patients receiving IL-2 is essential to the regimen’s success. Recognition and prompt treatment of common side effects lead to better patient outcomes. This article provides nurses with an overview of the treatment regimen, expected side effects, psychosocial considerations, and discharge instructions for patients receiving continuous-infusion plus pulse IL-2 and famotidine.

Metastatic melanoma and metastatic renal cell carcinoma present challenging and somewhat dismal treatment dilemmas. Traditional chemotherapy, namely cytotoxic drugs, has yielded marginal response and has not been proven to extend life expectancy significantly (Brown & Kirkwood, 2003; Li & McClay, 2002; Mitchell, 2004). Immunologic treatment modalities have proven much more effective but are offered at relatively few treatment centers across the United States because of the specialized training required by all staff involved with treatment.

Treatment with interleukin-2 (IL-2) has provided better outcomes for patients with these cancers. IL-2 is a lymphokine or protein produced primarily by activated T-helper cells. Natural killer cells are stimulated by IL-2 to become lymphokine-activated-killer (LAK) cells. LAK cells act as supercharged cancer killer cells. When given as high-dose bolus (600,000 IU/kg IV piggyback every eight hours), which is perhaps the most familiar dosing, IL-2 has a number of dose-limiting side effects. Because of the toxicity of the regimen, many patients are not eligible for the treatment (Dillman, Wiemann, Bury, Church, & DePriest, 1997; Dillman, Wiemann, VanderMolen, et al., 1997).

Recently, researchers (Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004; Quan, Ramirez, Taylor, Vinogradov, et al., 2005; Quan, Ramirez, Taylor, Quan, et al., 2005) found that a combination of IL-2 given as a continuous infusion for 72 hours (18 million IU/m² every 24 hours) with famotidine 20 mg IV every 12 hours, followed by a 24-hour rest period, then IL-2 18 million IU/m² over 15–30 minutes (“pulse” dose) produced promising results in patients with Eastern Cooperative Oncology Group performance status of 0 or 1 with metastatic melanoma or renal cell carcinoma. The cycle generally is repeated...
every three to four weeks. Patients may remain on treatment for as long as it is physically tolerated or until disease progression occurs. Response rates were 33% in patients with metastatic renal cancer and 64% in patients with metastatic melanoma; a median of four cycles are received prior to noting a major clinical response (Quan, Ramirez, et al., 2004; Quan, Ramirez, Taylor, Vinogradov, et al., 2005).

Although research has studied the side effects and response rates of IL-2 given as a high-dose bolus (600,000 IU/kg), a much smaller research base is emerging related to side effects and response seen with IL-2 given as continuous infusion followed by pulse dose IL-2 (Hank, Weil-Hillman, Surfus, Sosman, & Sondel, 1990; Quan, Ramirez, et al., 2004; Quan, Ramirez, Taylor, Quan, et al., 2005; Quan, Ramirez, Taylor, Vinogradov, et al., 2005). Given in this manner, IL-2 may become an even more effective tool against stage IV renal cell carcinoma or metastatic melanoma.

Nursing care of patients receiving continuous-infusion IL-2 followed by pulse is unique, requiring a different approach than care of patients receiving chemotherapy or the traditional high-dose bolus regimen (see Figure 1). Unlike the high-dose bolus regimen, the decision to continue or stop therapy is not based on a prescribed set of criteria but rather is individual from patient to patient. Each cycle of the continuous infusion followed by pulse regimen must be tailored to patients’ needs and tolerance. For example, patients with baseline elevations in creatinine or liver function tests will be given individual consideration with respect to continuing therapy during the cycle rather than uniformly having their treatment discontinued prematurely. In light of this, close supervision by an experienced healthcare team is paramount. The side effects of IL-2 are relatively predictable but vary in severity among patients. Nursing care should take into account the known side effects of treatment as well as anticipate adverse effects that may stem from treatment. Optimally, patient care should take place on a monitored, intermediate care unit by nurses who are knowledgeable about patients with cancer. Staffing ratios on such units usually are more amenable to dynamic patients; the use of dopamine for control of blood pressure is possible, and cardiac monitoring is available if needed. Intensive care should not be the standard of care for these patients, and such care has not been required to date (Quan, Ramirez, et al., 2004).

**Side Effects**

Nursing care of patients receiving continuous-infusion IL-2 plus pulse is focused on recognition and management of common side effects (see Table 1). To maintain patients on the therapy, nurses must recognize side effects and adverse effects quickly and administer treatment properly. Standing orders for commonly experienced side effects written by a physician familiar with the IL-2 regimen are helpful to expedite treatment (see Figure 2). Improper management of side effects may lead to premature cessation of therapy, which jeopardizes patient outcomes.

**Flu-Like Symptoms**

Flu-like syndrome is commonly experienced and includes fever, chills, myalgias, arthralgias, nausea, anorexia, abdominal discomfort, headache, nasal stuffiness or sinus congestion, and malaise. Patients may begin to experience such symptoms within two to four hours of initiation of the IL-2 infusion. Effective management of the symptoms includes regular prophylactic dosing of acetaminophen, ondansetron, meperidine, and dronabinol beginning 30 minutes prior to the start of therapy and is augmented by as-needed dosing of ibuprofen, metoclopramide, and meperidine (Dillman et al., 1991; Quan, Bindus,
Casal, Davis, & Rosenfeld, 1997; Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004; Schwartzentzuber, 2001). Symptoms usually begin to dissipate within a few hours of completion of continuous-infusion IL-2.

Proper nursing management of symptoms can greatly increase patient comfort and increase treatment tolerance. Timely administration of medications, such as antiemetics at the onset of nausea, meperidine at the onset of rigor, and ibuprofen when temperature first reaches 101°F, can greatly reduce the severity of side effects. As such, patients must be monitored carefully. Vital signs should be taken every four hours but may be taken more often at nurses’ discretion if fever, hypotension, tachycardia, or respiratory symptoms are noted.

Gastrointestinal Effects

Nausea is a common side effect of IL-2 treatment (Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004). Prophylactic dosing of ondansetron and dronabinol are effective in combating nausea. Metoclopramide also can be used as needed. Patients with persistent nausea may be given prochlorperazine. If the medications fail to relieve nausea adequately, low doses of lorazepam may be used. Care must be taken with administration of prochlorperazine and lorazepam, however, because drug metabolism is significantly impaired during IL-2 treatment and the drugs may cause excessive drowsiness or mental status changes (Micromedex Healthcare Series, n.d.). Promethazine is not used for nausea control for patients receiving this IL-2 regimen because it may be oversedating and not as effective as other antiemetic medications at controlling nausea in this population. Antiemetic regimens may be tailored to each patient’s need. When an effective regimen is formulated for a patient, the regimen should be continued during subsequent treatment cycles. Appetite is frequently poor during hospitalization, and taste alterations may be present. Patients may not feel like eating at all; however, patients who attempt oral intake should be encouraged to try frequent small meals including cold, salty, or dry foods. Fluids should be consumed between meals as opposed to with meals. Patients should avoid spicy, fried, and sweet foods because they may increase nausea. Patients and families should be reassured that anorexia is a common side effect and that patients’ appetites should return shortly after discharge.

Some patients may experience constipation caused by medications given to reduce side effects, including antiemetics and meperidine (Micromedex Healthcare Series, n.d.). Patients who experience constipation should receive dietary instructions and be encouraged to increase fluid intake. They also can be given a stool softener or laxative such as lactulose daily to alleviate the problem. Patients who experience constipation and/or abdominal pain and bloating with one or more cycles of therapy may experience relief if placed on lactulose daily for subsequent cycles.

Patients occasionally may experience diarrhea, which in some cases may be extreme—as many as 16 bowel movements per day. Initiation of antidiarrheal therapy at the first signs of diarrhea has been shown to reduce the incidence of severe

Table 1. Potential Side Effects of Continuous-Infusion Plus Pulse Dose Interleukin-2 and the Likelihood of Complication

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
<th>LIKELIHOOD OF COMPLICATION (%)</th>
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<tbody>
<tr>
<td>Fever, chills, or flu-like symptoms</td>
<td>85</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>75</td>
</tr>
<tr>
<td>Muscle or joint pain</td>
<td>50</td>
</tr>
<tr>
<td>Shortness of breath or pulmonary edema</td>
<td>10–30</td>
</tr>
<tr>
<td>Hypotension</td>
<td>40</td>
</tr>
<tr>
<td>Abnormal liver or kidney function</td>
<td>50</td>
</tr>
<tr>
<td>Irregular heart rhythm</td>
<td>1–5</td>
</tr>
<tr>
<td>Decrease in platelet count</td>
<td>10–20</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>80</td>
</tr>
<tr>
<td>Nervous system symptoms</td>
<td>1–2</td>
</tr>
</tbody>
</table>

*Note.* Based on information from Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004; Quan, Ramirez, Taylor, Vinogradov, et al., 2005; W. Quan, personal communication, June 15, 2005.

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Dermatologic Effects

Skin-related side effects from IL-2 include generalized flushing, erythematous rash, dry skin with flaking and peeling, and varying degrees of pruritus. Patients may appear as though they have sunburn. Oatmeal lotion preparations often are helpful and should be applied liberally. Patients may use mild soaps, oatmeal-based body washes, and/or oatmeal baths. Patients should avoid hot showers as well as overly chlorinated water because they are very drying to the skin. Diphenhydramine cream also may be used to alleviate pruritus. Itching that persists despite liberal application of creams and lotions may be helped by hydroxyzine. IV diphenhydramine should be avoided and oral diphenhydramine should be used with care because of possible hypotensive and sedating effects (Micromedex Healthcare Series, n.d.).

Mucosal side effects may include stomatitis, glossitis, mucositis, and/or pharyngitis (Mavroukakis, Muehlbauer, White, & Schwartzentruber, 2001; Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004). Frequent mouth care using a sodium chloride and sodium bicarbonate (“salt and soda,” or approximately 2 tablespoons of baking soda to 1 L normal saline) mouth rinse throughout treatment is encouraged. Sucralfate may be helpful with pain relief and healing of oral and esophageal mucosa.

Capillary Leak Syndrome

IL-2 significantly increases vascular permeability, resulting in capillary leak syndrome (Margolin et al., 1989; Siegel & Puri, 1991). The increased permeability of the vascular membrane causes a shift of fluid from the intravascular space to the interstitial space. The phenomenon can result in significant weight gain during treatment. Patients should be weighed every morning during hospitalization and monitored by medical and nursing staff. Patients will develop symptoms that resemble dehydration associated with the fluid shift, including oliguria, tachycardia, and possibly hypotension. The degree of hypotension varies among patients. Healthcare providers may notice a drop in systolic blood pressure from baseline that does not represent a problem. However, when systolic blood pressure drops below 90 mmHg, the kidneys are hypoperfused, worsening already impaired filtration and oliguria. Oliguria and hypotension are associated with elevated creatinine but may be prevented or treated through therapeutic intervention (Guleria et al., 1994; Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004; Quan, Ramirez, Taylor, Vinogradov, et al., 2005; Schwartzentruber, 2001). These treatment-related factors do reverse rapidly after treatment is completed (White et al., 1994). Quan, Brick, et al. noted elevations in serum creatinine in 50% of patients treated; however, the elevations were transient, and creatinine quickly returned to baseline after completion of each cycle.

Capillary leak syndrome also may affect patients’ respiratory status because fluid can be deposited interstitially to the lungs (Schwartzentruber, 2001). Auscultation of the lungs should be performed with vital signs to monitor patients for pulmonary congestion and pulmonary edema. Nursing staff should make physicians aware of respiratory changes immediately because they may indicate the need for diuretics. Diuretics are avoided unless specifically warranted by findings of symptomatic pulmonary edema because of their hypotensive effects and should be used with caution. In the event of pulmonary edema, oxygen by nasal cannula or face mask may be required to maintain saturation greater than 90%.

Patients who develop oliguria with urine output less than 250 cc in 12 hours or have elevations in creatinine greater than 2.1 mg/dl with low but adequate urine output should be placed on a renal dose of dopamine at 1 mcg/kg per minute (Quan, Brick, et al., 2004). Patients who experience hypotension with systolic blood pressure less than 90 mmHg should be placed on dopamine starting at 5 mcg/kg per minute and titrated as needed to maintain systolic blood pressure greater than 90 mmHg. Fluid bolus generally is not helpful because it produces only transient elevations in blood pressure, likely will not substantially increase urine output because the vascular membrane remains compromised, and actually may increase the risk of pulmonary edema (Dillman, 1994; Schwartzentruber, 2001). Cardiac monitoring should be initiated for dopamine doses required to maintain blood pressure, and patients should be monitored carefully for tachycardia, which may be worsened by administration of dopamine. Diltiazem, a calcium channel blocker, may be used if tachycardia becomes extreme or problematic but should be used with care because of its hypotensive effects (Micromedex Healthcare Series, n.d.).

Electrolyte imbalances, including decreased serum bicarbonate, hypophosphatemia, hypomagnesemia, and hypokalemia, are common and necessitate daily monitoring and possible replacement (Guleria et al., 1994; Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004). Electrolytes should be replaced via IV because patients often are nauseated and may not tolerate oral replacement. Based on the primary author’s personal experience, standing orders that include replacement thresholds for magnesium levels less than 2 mg/dl, phosphorus levels less than 2.9 mg/dl, and potassium levels less than 3.8 mEq/L are a good method to ensure adequate electrolyte replacement.

Patients should be informed that they may become edematous and should be encouraged to remove all jewelry from fingers and toes prior to admission. They also should be encouraged to bring loose-fitting clothing and elastic-waist pants for the day of discharge because generalized edema may render their usual clothes too tight. Patients should be prescribed...
oral furosemide to take after discharge to help with diuresis. A dose of 40 mg orally taken every other day should provide adequate diuresis without negative effects on serum electrolyte concentrations.

Neurologic Effects

IL-2 may have some direct effect on the central nervous system; however, just as IL-2 enhances vascular permeability leading to capillary leak syndrome, it also may increase the permeability of the blood-brain barrier, which exposes the central nervous system to other behaviorally activating factors (Denicoff et al., 1987). Neurologic side effects are rare with high-dose continuous-infusion plus pulse IL-2; however, patients may experience side effects such as sleep disturbances, altered concentration, lethargy, anxiety, and vivid dreams. Very rare side effects include delirium, confusion, mood swings, combative ness, hallucinations, depression, and coma (Denicoff et al.; Lerner, Stoudemire, & Rosenstein, 1999). Neurologic side effects generally begin to clear within hours to days after the continuous infusion has completed. Patients who experience any neurologic side effects should be monitored closely by nursing staff for deterioration of mental status or progressive neurologic symptoms. Occurrence of such side effects must be reported to a physician promptly and medication regimens reviewed for possible causes. Patients experiencing more serious side effects may require treatment interruption. Medical management of sleep disturbances and other neurologic effects may be difficult because drug metabolism is impaired and use of drugs such as benzodiazepines and some anticholinergics can exacerbate delirium (Lerner et al., 1999). Nonmedical management of neurologic symptoms is preferred and frequently very effective. Pretreatment patient teaching should include a discussion of possible side effects, and patients should be reassured that the side effects should resolve completely after each treatment cycle. Patients who report symptoms of depression during the initial assessment should be considered for treatment with antidepressants because the symptoms may be persistent throughout the course of therapy.

Nursing management of neurologic side effects for patients receiving continuous-infusion IL-2 plus pulse IL-2 therapy should focus on nondrug modalities. Frequent interpersonal contact, reality orientation, and use of environmental stimulation may be helpful. Perhaps the most effective treatment strategy is inclusion of an immediate family member or close friend who is supportive of the treatment and who realizes that the side effects are temporary. Denicoff et al. (1987) found that patients who were cared for by a supportive family member or spouse were less likely to have neurologic management problems than those who had no supportive companion.

Hematologic Effects

Patients receiving IL-2 may experience hematologic effects. Thrombocytopenia has been noted infrequently and rarely is dose limiting (Quan, Ramirez, et al., 2004). Effects on coagulation pathways are common, with elevations in prothrombin time noted (MacFarlane et al., 1995). For that reason, anticoagulant regimens may require adjustment during hospitalization; daily coagulation values (prothrombin time/international normalized ratio [INR]) should be monitored in patients who receive anticoagulant therapy. Additionally, neutrophil function may be impaired during treatment. Inspection of obvious sites of potential infection, including indwelling catheter or port sites and peripheral IV sites, should be performed every shift by nursing staff; however, infection in patients receiving this IL-2 regimen is rare, so prophylactic dosing of antibiotics is not warranted (Quan, Brick, et al., 2004). Elevated liver enzymes and creatinine levels are seen more commonly. The elevations normally are transient in nature and quickly reverse after treatment is completed; however, patients’ medication regimens should be reviewed carefully and amended as necessary any time elevation from baseline is noted. Elevated creatinine may necessitate reduced doses of ibuprofen and famotidine, and elevated liver enzymes necessitate adjustment of acetaminophen and narcotic analgesic dosages.

A desirable lymphocytosis may be seen within 48 hours after administration of the IL-2 pulse dose. In vitro, LAK cells generated by continuous infusion of IL-2 followed by pulse or bolus dose IL-2 had significantly higher lytic activity, suggesting that the IL-2 combination may enhance tumor-cell killing (Hank et al., 1990; Quan, Ramirez, et al., 2004).

Drug Contraindications and Dose Adjustments

Impaired renal and hepatic function may warrant dose adjustments or revision of home medication regimens while patients still are hospitalized. Patients taking hypoglycemics, benzodiazepines, warfarin, narcotic analgesics, or some antipsychotics may need to have their regimens altered during hospitalization. Additionally, patients receiving angiotensin-converting enzyme inhibitors should likely be taken off the medications while they are hospitalized for treatment because of their potential to exacerbate renal hypoperfusion (Micromedex Healthcare Series, n.d.). Extended-release cardiovascular medications should be converted to immediate-release forms if possible because clearance of long-acting medications is inhibited. Diabetics taking oral hypoglycemics may need to have the medications held during hospitalization and may require subcutaneous sliding-scale or supplemental-dose insulin to maintain blood glucose levels within desired limits because of poor oral intake and altered metabolism.

Psychological Considerations

The detrimental effects of stress on the immune system have been documented (Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994). Increased levels of stress have a proven association with lower levels of natural killer cell activity. Given the importance of natural killer cell activity in fighting cancer, the ability to increase the numbers of those cells using noninvasive methods can have great clinical significance (Bennett, Zeller, Rosenberg, & McCan, 2005). As such, the importance of minimizing stress levels in patients receiving IL-2 is clear. Ensuring that patients have a good understanding of the IL-2 treatment process, possible side effects and their treatment, and what patients are expected to do will assist greatly in decreasing treatment anxiety.
Caregivers who are well-trained and knowledgeable about the therapy they are providing can alleviate many fears experienced by patients and their families.

Many nonpharmacologic interventions can decrease anxiety during hospitalization when patients are receiving IL-2. Some may be facilitated by nursing staff or family members. As previously discussed, the presence and involvement of family members or close friends can be very therapeutic. Audio tapes that coach progressive relaxation or visualization techniques are helpful for some patients. Others may find interventions such as massage calming and relaxing. The key is individualizing treatment to each patient; whatever works best at the time is the right therapy. Most patients, however, appreciate a quiet, uncluttered environment.

Discharge instructions should include teaching related to at-home stress prevention, relief, and coping. Patients also should be encouraged to begin an exercise program as tolerated because exercise has been shown to lower stress levels and improve stress management (Brown, 1991; Willfrey & Kunce, 1986). Patients who enjoy the benefits of exercise should continue to do so as tolerated.

Discharge Teaching

Discharge teaching for this patient population is important but may become redundant as patients are admitted for multiple treatment cycles. A standardized discharge information sheet designed for patients who receive IL-2 therapy can be helpful. Patients should be encouraged to report a temperature greater than 100.8°F; swelling, redness, or pain at the site of implanted port; persistent edema after taking prescribed furosemide; shortness of breath; or confusion. Patients should have a prescription for furosemide to take every other day, starting the day after discharge. Normally, a prescription for three pills is sufficient for adequate diuresis. Progressive activity also should be encouraged, such as a progressive walking program. Patients should be instructed to continue their daily routines as tolerated after discharge and that activity generally is not restricted. Patients who are employed should be able to continue working if desired. Patients may have laboratory tests drawn within 48–72 hours after discharge, including complete blood count with differential and chemistry panels. Follow-up and pretreatment laboratory appointments may be scheduled for the week prior to admission for the next cycle of IL-2 therapy.

Summary

High-dose, continuous-infusion IL-2 followed by pulse IL-2 for metastatic melanoma or metastatic renal cell carcinoma has produced high response rates, especially considering the refractory nature of the cancers (Quan, Brick, et al., 2004; Quan, Ramirez, et al., 2004). Nursing care plays a significant role in the outcomes of patients on this IL-2 regimen. IL-2 therapy generally is considered an extremely safe treatment option when managed by physicians and nurses who are knowledgeable about the treatment (Schwartzentruber, 2001). Nurses who care for this patient population should become familiar with the treatment regimen, side effects, and care of patients receiving continuous 72-hour infusion with pulse IL-2.

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References


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