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Managing Toxicities of High-Dose Interleukin-2

ABSTRACT

Although high-dose interleukin-2 (IL-2, Proleukin), a highly toxic agent used in the treatment of renal cell carcinoma and melanoma, was initially associated with treatment-related mortality, it can, in the appropriate setting, be administered safely. High-dose IL-2 is associated with significant morbidity; however, the incidence and severity of toxicities have decreased as clinicians have gained experience with this agent and implemented toxicity prevention and management strategies. IL-2 toxicity can manifest in multiple organ systems, most significantly the heart, lungs, kidneys, and central nervous system. The most common manifestation of IL-2 toxicity is capillary leak syndrome, resulting in a hypovolemic state and fluid accumulation in the extravascular space. Capillary leak syndrome can contribute significantly to development of oliguria, ischemia, and confusion. Safe and effective administration of high-dose IL-2 consists of five key components: (1) administration by an experienced and knowledgeable health-care team, (2) adherence to strict patient-eligibility criteria, (3) implementation of standardized administration and patient assessment guidelines, (4) adherence to administration criteria, and (5) compliance with retreatment contraindications. This article reviews high-dose IL-2 toxicities and symptom management strategies and provides practical guidelines to facilitate the safe and effective administration of high-dose IL-2.

Interleukin-2 (IL-2) is a cytokine produced endogenously by activated T cells and is commercially available as aldesleukin (Proleukin), a human recombinant product.[1] IL-2 is effective in the treatment of a variety of malignancies, including renal cell carcinoma and melanoma, because it has both immune-modulating and antitumor properties.[2] A variety of IL-2 doses and schedules have been studied; however, high-dose IL-2 administered as a single agent has proven to be one of the most effective regimens for metastatic renal cell carcinoma and melanoma to date.

Initially, administration of high-dose IL-2 was associated with mortality rates of up to 4%.[2-4] Although

mortality rates have decreased substantially, IL-2 therapy still causes significant dose-related morbidity.[5] Manifestations of IL-2 toxicity occur in most organ systems, including the heart, lungs, kidneys, and central nervous system. Lower doses, prolonged infusions, and subcutaneous administration have been evaluated as strategies for improving IL-2 tolerability, but these regimens have produced

response rates lower than those produced with high-dose regimens.[6]

Based on the results of clinical trials and practical experiences, a two-cycle course of high-dose IL-2 administered intravenously (IV) is standard. Each course consists of two 5-day cycles (600,000 IU/kg/dose administered IV over 15 minutes q8h) separated by a minimum of 9 days. If tolerated, IL-2 is given for a maxi-

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Table 1

Management of Interleukin-2–Associated Toxicity

Toxicity	Symptom Management
Hypotension	<ol style="list-style-type: none"> (1) Expect drop in blood pressure of at least 20–30 mm Hg. Establish new baseline blood pressure. Base treatment on drop in blood pressure below new baseline. (2) Minimize fluid resuscitation to avoid fluid overload. (3) Limit use of crystalloid solutions (eg, saline) to 1–1.5 L/d. (4) Administer colloidal solutions (eg, albumin, hetastarch) if systolic blood pressure is lower than new baseline blood pressure, patient is symptomatic, or urine output declines. (5) Administer phenylephrine 0.1–2.0 µg/kg/min to stabilize blood pressure. (6) Expect routine weight gain of 10 lb.
Sinus tachycardia	<ol style="list-style-type: none"> (1) Common, may reflect fever, hypotension, hypoxia, anemia, infection, or dopamine administration; correct underlying problem.
Supraventricular tachycardia	<ol style="list-style-type: none"> (1) Consider treatment with rate-controlling agent (eg, verapamil, digoxin) if sustained heart rate > 150 bpm. (2) Withhold interleukin-2 therapy until rate is controlled.
Atrial fibrillation	<ol style="list-style-type: none"> (1) Withhold interleukin-2 therapy. (2) Convert to normal sinus rhythm and resume therapy when patient is hemodynamically stable.
Other significant ventricular arrhythmia	<ol style="list-style-type: none"> (1) Withhold interleukin-2 therapy. (2) Evaluate for cardiac damage (eg, ischemia or infarction).
Metabolic acidosis	<ol style="list-style-type: none"> (1) Administer sodium bicarbonate to maintain serum bicarbonate level at > 18 mEq/L. (2) If low serum bicarbonate level persists, withhold interleukin-2 therapy.
Fever/chills	<ol style="list-style-type: none"> (1) Premedicate with acetaminophen 650 mg, with or without a nonsteroidal anti-inflammatory (eg, indomethacin 25 mg po) and continue every 6 h until 24 h after discontinuation of interleukin-2. (2) Give meperidine 25–50 mg IV to treat chills/rigors.
Gastrointestinal toxicity	<ol style="list-style-type: none"> (1) Premedicate with dopamine antagonist if moderate to severe nausea and/or vomiting occurs; provide alternative antiemetic for breakthrough nausea and/or vomiting; do not use corticosteroids as antiemetics. (2) Use H₂-receptor antagonist prophylactically to minimize epigastric pain. (3) Treat diarrhea with ant motility agents (eg, loperamide). (4) Encourage patient to eat small, frequent meals.
Dyspnea	<ol style="list-style-type: none"> (1) Check oxygen saturation and monitor frequently. (2) Withhold interleukin-2 therapy until oxygen saturation is > 90%. (3) Use diuretics for fluid overload as clinically tolerated. (4) Clarify that serum bicarbonate level is > 18 mEq/L.
Peripheral edema	<ol style="list-style-type: none"> (1) During interleukin-2 therapy, expect edema that does not fully resolve until completion of therapy. (2) Use diuretics as clinically indicated and tolerated.
Oliguria, rising serum creatinine level	<ol style="list-style-type: none"> (1) Use fluids judiciously to increase urine output (eg, 1–1.5 L/d). (2) Use dopamine 2–5 µg/kg/min if patient is unresponsive to or unable to tolerate fluids. (3) Withhold or delay interleukin-2 therapy for urine output < 10 mL/h for 16–24 h with rising SCr level, SCr level ≥ 4.0 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia, or SCr level > 4.5 mg/dL.
Transaminase level elevations	<ol style="list-style-type: none"> (1) Usually not clinically significant; reverses with interleukin-2 discontinuation.
Neurotoxicity	<ol style="list-style-type: none"> (1) Withhold interleukin-2 for persistent confusion, disorientation, hallucinations, progressive agitation, or somnolence unrelated to concomitant medication. (2) May resume therapy when symptoms resolve, if no grade 4 toxicity occurred. If symptoms recur, discontinue interleukin therapy.
Skin rash, pruritus	<ol style="list-style-type: none"> (1) Treat symptomatically with emollients (non-steroid-containing) and antihistamines.

bpm = beats per minute; SCr = serum creatinine.

Adapted with permission from Dutcher.[1,8,10-12]

mum of 14 doses per cycle and 28 doses per course.[1] Higher dosages have not been associated with improved response rates or survival times.[7] Courses of therapy are separated by at least 7 weeks after hospital discharge and should only be repeated if the results of restaging studies demonstrate tumor responsiveness or stabilization.[1,8]

Because of intolerable side effects, most patients do not receive 100% of the planned dosing in a full cycle or course of high-dose IL-2. Furthermore, most IL-2 administration and toxicity management guidelines recommend withholding therapy, not reducing the dose, in patients who experience various toxicities. Other strategies for safe administration include appropriate patient selection, administration by an experienced health-care team, and adherence to standardized treatment guidelines. This article reviews high-dose IL-2 toxicities and symptom-management strategies and provides practical guidelines to facilitate the safe and effective administration of high-dose IL-2.

Toxicities and Symptom Management

High-dose IL-2 efficacy and toxicity are dose- and schedule-dependent.[8] High-dose IL-2 administered as an IV bolus is more toxic than low-dose IL-2 administered as either an IV bolus or subcutaneously.[9] Continuous IV infusion of high-dose IL-2 is more toxic than bolus administration of the same doses.[8] IL-2-related toxicities are generally reversible after therapy discontinuation, resolving within 2 to 3 days of therapy completion.[8] Long-term sequelae due to IL-2 toxicity are rare, but may occur, especially in patients whose toxicities are not managed appropriately.

IL-2 toxicity is mediated through lymphoid infiltration, a well-described capillary leak syndrome, and the local effects of secondary cytokines.[8] The complex mechanism of action whereby IL-2 induces capillary leak syndrome is postulated to involve a series of steps, including

induction of circulating cytokines, such as tumor necrosis factor- α (TNF- α) and other interleukins; generation of complement-activation products; neutrophil activation; and activation of endothelial-cell antigens.[8] After IL-2 administration, induced cytokines are released, leading to increased capillary permeability and decreased vascular resistance, which results in a shift of fluid from the bloodstream into the extravascular space. This fluid shift ultimately leads to a hypovolemic state and excessive fluid in the extravascular space. Capillary leak syndrome-associated fluid accumulation in the extravascular spaces may manifest as generalized edema, weight gain, pulmonary congestion, pleural effusions, and ascites.[8] Capillary leak syndrome-associated hypovolemia may cause decreased blood flow to the kidneys, gut, heart, and brain, resulting in oliguria, ischemia, and confusion. Usually, capillary leak syndrome affects more than one organ system simultaneously, contributing to the toxicity often observed in patients receiving high-dose IL-2. The release of cytokines after IL-2 administration has also been implicated as the cause of flu-like symptoms, such as fever, chills, myalgias, and arthralgias.

Successful administration of IL-2 is facilitated by anticipating and proactively managing toxicities (Table 1).[1,8,10-12] Before each dose, patients should be reassessed to ensure they meet the criteria for continuing therapy. Various guidelines provide parameters for withholding or discontinuing IL-2 therapy (Tables 2 and 3).[1,13,14] One set of guidelines developed by the National Cancer Institute (NCI) and modified by the University of Pittsburgh Cancer Institute (UPCI) categorizes toxicities according to relative or absolute criteria and bases treatment delays or discontinuation of therapy on the number of criteria present and the patient's responsiveness to interventions (Table 3).[13,14]

Constitutional Symptoms

Chills, fever, and malaise are among the most common and pre-

dictable adverse events associated with high-dose IL-2. Typically, chills develop within 1 to 2 hours of the first or second dose and are treated with repeated doses of meperidine and warm blankets.[8]

Fever, which usually develops within 2 to 4 hours of administration of the first or second dose and may reach 40.5°C, is likely caused by activation of secondary cytokines, such as TNF- α . Although steroids can block the induction of TNF- α , their use is contraindicated during IL-2 therapy because steroids block immune system activation and IL-2 antitumor activity.[10] Further, as fever is commonly observed in patients receiving high-dose IL-2, it is most effectively prevented and managed with antipyretics before and during therapy. Administering acetaminophen before the first IL-2 dose and every 4 hours until 24 hours after the last IL-2 dose within a cycle is universally advocated.[8,10] The addition of a nonsteroidal anti-inflammatory drug (NSAID), such as indomethacin, to this antipyretic regimen has also been advocated.[8,10] Other clinicians believe that NSAIDs should be used with caution because of their potential to exacerbate gastritis and further impair renal blood flow in patients with renal manifestations of capillary leak syndrome.[15] Malignant hyperthermia related to IL-2 therapy has been associated with one death.[8]

Generalized fatigue, often accompanied by rapidly reversible myalgias and arthralgias, is dose-dependent, and may persist between cycles (Chiron Corporation, data on file, August 2002).[1]

Infectious Toxicity

Most IL-2-related infections occur in the urinary tract or at the site of venous catheter placement, with *Staphylococcus aureus* and *S epidermidis* being the most commonly isolated pathogens.[8,16] Patients receiving IL-2 therapy are also at risk of infection, because IL-2 causes a reversible and profound defect in neutrophil chemotaxis.[16] Patients with persistent fevers despite routine administration of antipyretics and

Table 2

Guidelines for Withholding Interleukin-2 Therapy

Body System	Conditions Requiring Withholding	Resumption of Interleukin-2 Administration
Cardiovascular	Atrial fibrillation, supraventricular tachycardia, or bradycardia that requires treatment or is recurrent or persistent Systolic blood pressure < 90 mm Hg, with increasing requirements for vasopressors Any electrocardiogram changes consistent with myocardial infarction, ischemia, or myocarditis with or without chest pain; clinical suspicion of cardiac ischemia	Patient asymptomatic, with full recovery to normal sinus rhythm Systolic blood pressure \geq 90 mm Hg and patient stable or requirement for vasopressors decreased Patient asymptomatic, myocardial infarction, and myocarditis ruled out, clinical suspicion of angina low; no evidence of hypokinesia
Respiratory	Oxygen saturation < 90%	Oxygen saturation > 90%
Nervous	Mental status changed (eg, moderate confusion or agitation)	Mental status changes completely resolved
Body as a whole	Sepsis syndrome, patient clinically unstable	Sepsis syndrome resolved, patient clinically stable, infection under control
Urogenital	SCr level > 4.5 mg/dL or SCr level \geq 4 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia Persistent oliguria, urine output of < 10 mL/h for 16–24 h with rising SCr level	SCr level < 4 mg/dL and fluid and electrolyte status stable Urine output > 10 mL/h with a decrease of SCr level > 1.5 mg/dL or normalization of SCr level
Digestive	Signs of hepatic failure (eg, encephalopathy, increasing ascites, liver pain, hypoglycemia) Stool guaiac repeatedly > 3–4+	Resolution of all signs of hepatic failure ^a Stool guaiac negative
Skin	Bullous dermatitis or marked worsening of preexisting skin condition	Resolution of all signs of bullous dermatitis

^a Initiate a new course of treatment, if warranted, no sooner than 7 weeks after cessation of hepatic failure and hospital discharge.

SCr = serum creatinine.

Adapted with permission from Chiron Corporation.[1]

those with signs and symptoms of infection should be promptly assessed, undergo testing to identify the causative organism, receive empiric antibiotic therapy, and, if appropriate, have the indwelling catheter removed. IL-2 therapy should be withheld until the symptoms of infection resolve and culture results are negative.

Use of prophylactic antibiotics may be appropriate for patients receiving IL-2 through a central venous catheter. The results of a small, non-randomized trial comparing antibiotic prophylaxis with no prophylaxis in patients receiving high-dose IL-2 through a central IV catheter show that antibiotic prophylaxis significantly reduced the incidence of infection.[17] The results of early studies report IL-2-related infection rates of up to 38%, but results of more recent

studies, indicate an infection rate of only 13%.[1,16] Kammula et al[5] reported that the incidence of catheter-related sepsis decreased from 18% to between 1% and 4% over several years of high-dose IL-2 administration; they attributed the decrease to vigilant monitoring for infection and liberal use of empiric and prophylactic antibiotics.

Cardiopulmonary Toxicity

IL-2 administration causes a broad range of cardiopulmonary toxicities, with hypotension, tachycardia, and dyspnea being the most common.[1] Hypotension and tachycardia often develop within 2 hours of the first dose, progressing in severity as therapy continues.[8] Hypotension usually reverses within 48 hours after IL-2 discontinuation.[8] The results of early clinical trials show that high-

dose IL-2 produced grade 3/4 hypotension requiring vasopressor support in up to 81% of patients.[5] A more recent study shows that only 31% of patients required vasopressor support.

Because hypotension is an expected complication of therapy, antihypertensive agents should be discontinued 24 hours before initiating IL-2. They may be resumed after IL-2 therapy is completed and blood pressure has stabilized. Patients receiving beta-blockers, require a stepwise taper of doses before initiation of high-dose IL-2 to avoid reflex tachycardia.

Blood pressure should be measured at baseline and every 2 to 4 hours in patients receiving high-dose IL-2. Patients who experience a drop in blood pressure and associated hemodynamic instability (eg, heart rate > 130 beats

per minute [bpm]) should have IL-2 doses withheld and appropriate treatment initiated (Tables 1–3). The two-step treatment approach toward managing IL-2-induced hypotension includes fluid replacement and pharmacologic vasopressor support (Table 1). Fluid resuscitation should be limited to 1.5 L/d above maintenance needs to minimize the risk of exacerbating capillary leak syndrome-associated pulmonary edema.[8]

The results of one trial suggested that crystalloid and colloidal solutions are equally effective for replac-

ing intravascular volume, but the lower cost of crystalloid solutions made it the fluid of choice.[18] Colloidal solutions, however, are still advocated by some clinicians to maximize intravascular volume.[10] Vasopressor support with phenylephrine is a very effective treatment for IL-2–induced hypotension, but generally requires administration in an intensive care unit. Doses of phenylephrine greater than 2.5 µg/kg/min are rarely needed.[11] Vasopressor support with dopamine is not recommended because this agent may

precipitate arrhythmias if doses greater than 5 µg/kg/min are used; however, low-dose dopamine, 2 to 5 µg/kg/min, is often given before or concomitantly with phenylephrine to improve renal perfusion and urine output.[8,10,11]

IL-2 should not be resumed unless the patient is hemodynamically stable (Tables 2 and 3). If blood pressure stabilizes after minimal intervention, IL-2 therapy may be resumed. Vigilant monitoring of blood pressure is recommended, with prompt discontinuation of therapy if

Table 3

Relative and Absolute Criteria Used to Determine University of Pittsburgh Cancer Institute Guidelines for High-Dose Interleukin-2 Administration^a

Toxicity	Relative Criteria	Absolute Criteria
Cardiac	Sinus tachycardia = 120–130 bpm	Sinus tachycardia > 130 bpm (persists after correcting for hypotension, fever, and stopping vasopressor support) Electrocardiogram changes indicating ischemia Atrial fibrillation Supraventricular tachycardia Ventricular arrhythmia (eg, frequent premature ventricular contractions, bigeminy) Elevated creatinine phosphokinase—myocardial band isoenzyme
Dermatologic		Moist desquamation
Gastrointestinal	Diarrhea ≥ 1,000 mL/8-h shift Ileal/abdominal distention	Diarrhea ≥ 1,000 mL/h-8 shift × 2 Severe abdominal distention affecting breathing Vomiting unresponsive to medication
Hemodynamic	Maximum phenylephrine dose = 1.0–1.5 µg/kg/min Minimum phenylephrine dose > 0.5 µg/kg/min	Maximum phenylephrine dose = 1.5–2.0 µg/kg/min Minimum phenylephrine dose > 0.8 µg/kg/min
Hemorrhagic	Guaiac-positive sputum, emesis, or stool Platelet count = 30,000–50,000 µL	Overt blood in sputum, emesis, stool Platelet count < 30,000/µL
Infectious		Strong clinical suspicion of or documented infection
Neurologic	Vivid dreams Emotional lability	Mental-status changes not reversible in 2 h Disorientation, hallucinations
Pulmonary	Shortness of breath during rest 3–4 L O ₂ using NC to maintain O ₂ saturation > 95% Rales one-third up chest	> 4 L O ₂ using NC to maintain O ₂ saturation > 95% ≥ 40% O ₂ mask to maintain O ₂ saturation > 95% Rales one-half up chest Pleural effusion requiring tap or chest tube Endotracheal intubation
Renal	Urine output = 80–160 mL/8h Urine output = 10–20 mL/h SCr level = 2.5–2.9 mg/dL	Urine output < 80 mL/8h Urine output < 10 mL/h SCr level ≥ 3.0 mg/dL
Weight gain	≥ 15% weight gain over baseline weight	

^a Administration, delay, or discontinuation of interleukin-2 based on the following: If no relative or absolute criteria, administer interleukin-2 as scheduled, stop interleukin-2 for that cycle. If 1–3 relative criteria and no absolute criteria, withhold dose and apply corrective measures; If > 3 relative criteria or any absolute criteria, stop interleukin-2 for that cycle.

bpm = beats per minute; NC = nasal cannula; SCr = serum creatinine.

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hypotension recurs. In rare cases and under the strict supervision of experienced clinicians using an intensive care setting, IL-2 therapy can be resumed in patients whose blood pressure is meticulously maintained with low doses of vasopressors. In these cases, hypotension that persists despite the use of maximal vasopressor support warrants discontinuation of IL-2.[1]

Although the incidence of myocardial infarction and myocarditis with high-dose IL-2 therapy are rare, significant morbidity and mortality related to cardiotoxicity can occur. Early trial results showed that myocardial infarction, which occurred in 2% to 4% of patients receiving high-dose IL-2, has been associated with treatment-related deaths.[10] More recent studies reported no myocardial infarctions, most likely because underlying cardiac dysfunction is now considered a contraindication to IL-2 therapy.[5] However, despite appropriate pretreatment screening, myocarditis occurs in 2.5% to 5% of patients; it is commonly asymptomatic and associated with temporary left-ventricular dysfunction.[10,11] The results of a study by White et al[11] of 199 patients receiving high-dose IL-2 suggested that diminished ventricular function is associated with a global myocardial process, most likely inflammatory, rather than a specific vascular ischemic event.

Before IL-2 therapy is initiated, baseline electrocardiograms (ECG) and thallium stress tests are recommended to assess cardiac function; patients with abnormal left-ventricular ejection fraction or significant wall motion abnormalities should not receive high-dose IL-2 therapy. Cardiac function (eg, heart rate, blood oxygen saturation levels) should be assessed before each IL-2 dose or

more frequently, if indicated, during therapy. Patients who develop abnormal heart rates or hypoxia should have creatine phosphokinase and myocardial band (CPK-MB) isoenzyme levels assessed at least daily. Elevations in creatine phosphokinase and CPK-MB isoenzyme levels, which may occur during therapy or up to 3 days after IL-2 discontinuation, warrants stopping IL-2 therapy.[10,11] Cardiac enzyme and ECG monitoring for 48 hours after normalization of enzyme levels are recommended.[11] Because myocarditis may resolve completely, subsequent therapy is not automatically excluded; instead, continuation is based on ECG and/or thallium stress tests.[11]

Arrhythmias, generally supraventricular, may develop during high-dose IL-2 therapy, but they are often short-lived and rarely compromise therapy.[8] Electrolyte abnormalities caused by fluid shifts may also contribute to the occurrence of arrhythmias. If arrhythmias occur, IL-2 therapy should be withheld until after cardiac evaluation and normal sinus rhythm is regained. Interventions to manage arrhythmias may include supplemental oxygen, diuretic therapy, electrolyte supplementation, and temporary use of heart rate controlling agents, such as digoxin or verapamil.[8,11] Ventricular arrhythmias are uncommon, but if they occur, IL-2 therapy should be stopped.[8]

Pulmonary complications occurring during high-dose IL-2 therapy are directly related to the development of capillary leak syndrome and may be more severe in patients with coexisting cardiac toxicities. Of these, progressive pulmonary edema is most problematic and may lead to severe respiratory distress requiring intubation. Early experiences with high-dose IL-2 showed that 12% of patients required intubation. However, judicious use of replacement fluids and appropriate patient selection has decreased the need for intubation to less than 3%.[4,11] Further, pulmonary toxicities are rapidly reversed with IL-2 discontinuation.[8,11]

Pulmonary function tests should be performed before initiating IL-2 therapy, and patients with abnormal

results should not receive high-dose IL-2. In patients with normal baseline pulmonary function tests, vigilant monitoring of body weight and blood oxygen saturation levels before each IL-2 dose can help identify those at risk for developing progressive pulmonary symptoms.

Pulmonary edema is usually preceded or accompanied by clinical symptoms of edema and weight gain, often greater than or equal to 5% of baseline body weight.[10] A correlative analysis of radiographic and clinical findings suggest that the etiology of the pulmonary edema is more likely related to increased pulmonary capillary permeability than renal insufficiency, fluid overload, or hypotension.[19] Pleural effusions commonly develop during high-dose IL-2 therapy, but rarely require drainage.[8,11] Fluid intake and output should also be monitored and cautiously managed with IV fluids and diuretics. Aggressive use of IV fluids and diuretics can adversely affect blood pressure. Consequently, IL-2 therapy should be withheld in patients who develop clinically significant shortness of breath, significant decreases in blood oxygen saturation levels, progressive edema, symptomatic pleural effusions, or fluid imbalances that are not easily controlled with fluid replacement and diuretics (Tables 1–3).

Renal Toxicity

Renal toxicity associated with high-dose IL-2 is typical of prerenal azotemia and is commonly a result of hypotension, decreased intravascular volume, and/or impaired cardiac function.[8] An intrarenal defect may also contribute to nephrotoxicity during IL-2 therapy.[20] Oliguria is reported in up to 63% of patients and can be severe in up to 26%.[6,21] Elevations in serum creatinine levels are common; in one large study, patients receiving high-dose IL-2 demonstrated a mean peak serum creatinine level of 2.7 mg/dL after the second IL-2 cycle.[22] Elevations in serum creatinine levels were dose limiting in 13% of courses. Hemodialysis is rarely needed during IL-2 therapy, and renal dysfunction typi-

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cally returns to a normal or baseline value within 7 to 14 days of therapy discontinuation.[8] The results of urinalyses performed during IL-2 therapy indicate the presence of protein, bilirubin, red blood cells, white blood cells, and granular casts, but after therapy discontinuation, results of urinalyses are normal.[22] Factors associated with a greater risk of nephrotoxicity include a diagnosis of renal cell carcinoma, older age, male gender, prior nephrectomy, preexisting hypertension, and sepsis.[22,23] Although permanent renal damage is rare, it has been observed in patients who become septic during IL-2 therapy.[23]

Renal function studies should be assessed at baseline and daily during IL-2 therapy. Significant increases in serum creatinine levels warrant withholding IL-2 therapy until levels return to normal or baseline levels. Renal toxicity is most effectively managed by administering fluid boluses at the onset of oliguria, with a relative limit on the total volume of 1 to 1.5 L/d above maintenance needs (Table 1).[8]

If patients do not respond to fluids or experience fluid overload, administration of low-dose dopamine effectively increases urine output. Prophylactic use of low-dose dopamine is not recommended.[24] Use of diuretics is ineffective during the peak of nephrotoxicity, but aggressive use after therapy completion and discontinuation of vasopressor support establishes a normal fluid balance.[8] The progression of nephrotoxicity despite corrective efforts warrants IL-2 discontinuation (Tables 2 and 3).

Hepatic Toxicity

Hepatic dysfunction related to IL-2 therapy usually manifests as reversible hyperbilirubinemia but can also develop as transient elevations in serum hepatic transaminase levels.[10] Mild elevations in prothrombin time and decreases in albumin levels may also occur.[8] Liver function tests, including prothrombin times and albumin levels, should be assessed at baseline and periodically during IL-2 therapy. Significant increases in

bilirubin or hepatic transaminases, decreased albumin levels, or prolonged prothrombin times warrant withholding IL-2 therapy. Hepatic toxicity is rarely a cause for the discontinuation of IL-2 therapy, but, if discontinuation is necessary, liver function test results typically normalize within 5 to 6 days. Because of transient hepatic dysfunction experienced during IL-2 administration, medications metabolized by the liver should be used with caution.

Hematologic Toxicity

Hematologic abnormalities, including anemia, leukopenia, and thrombocytopenia, are common during IL-2 therapy, but are rarely severe or dose limiting. Baseline and routine (at least daily) assessment of complete blood counts are used to identify changes in hematologic parameters that would require treatment. The results of one large study showed that 14% of patients receiving high-dose IL-2 developed anemia requiring red blood cell transfusions.[25] Severe leukopenia occurred in only 1.5% of patients and was not associated with an increased risk of infection; however, alterations in neutrophil function caused by a profound chemotactic defect are common and associated with the development of infection.[16]

Profound lymphopenia due to lymphocyte sequestration occurs rapidly and persists during therapy.[25] Upon IL-2 discontinuation, lymphocyte levels rebound to almost twice those of baseline, then decrease to normal levels.[25] Eosinophilia also commonly develops and is often associated with pruritus and a skin rash, particularly at the end of IL-2 therapy.[10,25]

Severe thrombocytopenia is uncommon and rarely requires transfusion. In one study, platelet counts decreased to less than 50,000/ μ L and 25,000/ μ L in 12% and 1% of treatment courses, respectively; only 3% of patients received platelet transfusions.[25] Thrombocytopenia may be progressive; with IL-2 discontinuation, platelet counts drop within 1 to 2 days and return promptly to baseline.[8]

Coagulopathies are also common-

ly observed in patients receiving high-dose IL-2, with elevations in partial thromboplastin time occurring more frequently than elevations in prothrombin time. IL-2-induced coagulopathies are, however, rarely associated with bleeding complications prompting the need for fresh frozen plasma or blood products.[25]

Neurologic Toxicity

One of the most common toxicities associated with high-dose IL-2 therapy is neurologic changes; these toxicities can be caused by IL-2, an "ICU psychosis," or medications used to manage other IL-2-related adverse effects. Common neurologic adverse events associated with IL-2 are confusion, somnolence, disorientation, anxiety, and dizziness.[1,21] Patients receiving IL-2 may also experience altered sleep patterns; behavioral changes, such as agitation and combativeness; vivid dreams; paranoia; or emotional lability.[8] Many of these symptoms may be caused by medications used to treat other IL-2-induced symptoms (eg, meperidine for chills in an opiate-naïve patient, phenothiazine for nausea).

Initial clinical trials with high-dose IL-2 reported coma, often requiring intubation for airway protection, in 2% of patients. Today, clinicians experienced in identifying and managing early neurologic symptoms rarely observe coma.[8,21] Neurologic toxicity symptoms usually appear near the end of therapy, with symptoms often worsening, then resolving completely several hours or days after therapy discontinuation.[8] However, it is important that patients receiving IL-2 are routinely monitored for altered mental status and changes in behavior or sleep patterns. Management of neurotoxicity includes prompt discontinuation of IL-2 at the onset of neuropsychiatric toxicity, evaluation of concomitant medications, informing patients and family that neurotoxicity is transient, and providing a monitored environment for recovery (Tables 1-3).[1,8,10] Haloperidol is the recommended agent for control of agitation that progresses rapidly to combativeness.[8]

Table 4

Contraindications to High-Dose Interleukin-2 Treatment

Reason to Avoid Initial Treatment	Reason to Avoid Interleukin-2 Retreatment
Abnormal pulmonary function test results (ie, FEV ₁ < 2 L or < 75% of predicted value)	Sustained ventricular tachycardia (≥ 5 beats)
Inadequate cardiac function, measured by a thallium stress test (ie, abnormal LVEF or significant wall motion abnormality)	Cardiac tamponade
SCr level > 1.5 mg/dL	Cardiac rhythm disturbances not controlled or unresponsive to management
Evidence of active infection	Chest pain with ECG changes, consistent with angina or myocardial infarction
Poor performance status (ECOG > 1)	Intubation for > 72 h
History of organ allograft	Renal failure requiring dialysis > 72 h
	Coma or toxic psychosis lasting > 48 h
	Repetitive or difficult-to-control seizures
	Bowel ischemia/perforation
	Gastrointestinal bleeding requiring surgery

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FEV₁ = forced expiratory volume in one minute; LVEF = left-ventricular ejection fraction; SCr = serum creatinine.

Adapted with permission from Chiron Corporation.[1]

A baseline magnetic resonance imaging (MRI) or computed tomography (CT) scan to assess for the presence of brain metastases should be performed. Patients with brain metastases have generally been excluded from receiving high-dose IL-2 therapy because IL-2-induced edema may cause increased intracranial pressure and increase the risk of hemorrhage into brain lesions.[8] Yet, recent data suggest that patients with effectively controlled brain lesions, a limited number of small metastases, and/or limited to no intracranial edema may safely receive high-dose IL-2.[26]

Peripheral nervous system toxicity in the form of carpal tunnel syndrome is also reported with IL-2.[27] Severe pain and tingling in upper extremities, caused by a peripheral nerve entrapment syndrome, is associated with significant peripheral edema and weight gain.[27] Preventive management, consisting of limited fluid replacement and early initiation of vasopressor support for hypotension, is used in subsequent cycles.[27] Additionally, some patients report increased pain at the tumor site.

Gastrointestinal Toxicity

Transient nausea, vomiting, diarrhea, and anorexia occur frequently with high-dose IL-2 therapy.[1,21] Early study results show that up to

92% of patients experienced severe diarrhea, although the incidence has since decreased substantially, and diarrhea is now manageable.[5] Anorexia remains a common complication of IL-2 therapy. Although less common, abdominal pain, gastritis, mucositis, and xerostomia may also be associated with IL-2 therapy.[8] Abdominal pain during IL-2 therapy has rarely been caused by pancreatitis.[8] Most GI toxicities resolve within 2 to 3 days of IL-2 discontinuation, although the patient's appetite may not return to that at baseline for a week or longer.

Prophylactic antiemetics given before the first dose of IL-2 and throughout therapy minimize nausea and vomiting. The dopamine antagonist antiemetics are generally preferred because they are as effective as and less expensive than the serotonin antagonists and do not increase the risk of hypotension.[12] Serotonin antagonists can be used in patients unable or unlikely to tolerate dopamine antagonists. Steroids should not be used as part of the antiemetic regimen. Prophylactic use of H₂-receptor antagonists, such as ranitidine or famotidine, is recommended to manage gastritis.[8] Antidiarrheals should be initiated at the onset of loose stools; because the use of antimotility agents may exacerbate abdominal distention related to

ileus, patients should be monitored closely while receiving antidiarrheals.[8] IL-2 should be discontinued with evidence of gastrointestinal hemorrhage, specifically repeatedly positive results of stool guaiac testing (see Table 2).

Endocrine and Metabolic Toxicity

Thyroid dysfunction may result from high-dose IL-2 therapy, but is often undetected because of its subclinical presentation.[28] Hypothyroidism occurs in 35% of patients and hyperthyroidism in 7% of patients.[28] Hypothyroidism, which is related to the duration of therapy, requires treatment in 9% of patients.[28] Routine monitoring of serum free thyroxine and thyroid-stimulating hormone with each course of therapy is recommended.[28] Moderate to severe IL-2-induced hypothyroidism requires thyroid hormone replacement therapy.[8] If hypothyroidism is detected before administration, thyroid hormone replacement therapy should be initiated and IL-2 therapy should be delayed for at least 2 weeks.[8,28] Replacement therapy should be continued for approximately 1 year after IL-2 therapy has been completed or until thyroid function has normalized.[8,28]

Potassium, calcium, magnesium, and phosphorus levels commonly decrease during IL-2 therapy and require electrolyte replacement.[1] Other rarely reported endocrine or metabolic disturbances include low cholesterol levels and adrenal insufficiency and alteration in numerous stress-related hormones, such as cortisol and C-reactive protein.[8]

Dermatologic Toxicity

Dermatologic toxicity caused by IL-2 generally manifests as erythema; pruritus develops on the face and neck and progresses to the trunk and extremities within 3 days of IL-2 initiation.[8] Pruritus generally resolves as mild desquamation occurs within 3 days of IL-2 discontinuation, but both pruritus and desquamation may persist for up to 6 weeks after therapy.[8] Topical steroid treatment should be avoided. Severe desquamation or bullae should be

treated with silver sulfadiazine and antibiotic prophylaxis.[8] Patients should avoid sun exposure because it increases photosensitivity.

IL-2 therapy may cause hair loss or thinning, but this is typically mild.[8] Vitiligo manifesting as depigmented skin, white patches of hair, or halo depigmentation around nevi or cutaneous tumors is reported in up to 45% of metastatic melanoma patients.[8]

Reductions in IL-2 Toxicities

A recent review of more than 1,200 metastatic cancer patients treated with high-dose IL-2 therapy at the NCI reported significant decreases in toxicity. Over the 12-year study period, the incidences of grade 3 and/or 4 toxicities, including sepsis, diarrhea, neuropsychiatric toxicity, hypotension, and cardiac ischemia decreased sharply.[5] Additionally, no treatment-related deaths were reported in the last 809 patients treated with high-dose IL-2. This study suggests that with appropriate management skills and patient selection, high-dose IL-2 therapy can now be safely administered.

Practical Guidelines for High-Dose IL-2 Administration

The safe and effective administration of high-dose IL-2 consists of five key components: (1) administration by an experienced and knowledgeable health-care team, (2) adherence to strict patient eligibility criteria, (3) implementation of standardized administration and patient assessment guidelines, (4) adherence to administration and toxicity management criteria, and (5) compliance with retreatment contraindications.

NCI's 12-year data show that the toxicity of IL-2 decreased because of more strict patient selection criteria and toxicity management guidelines.[5] Since high-dose IL-2 may cause severe and acute toxicity, it should be administered in an inpatient medical oncology unit proximate to, or in, an intensive care unit.[29]

Ensuring that patients have normal cardiac, pulmonary, renal, and neurologic function before initiation of IL-2 is crucial.[5] If organ function is even slightly reduced at base-

line, a risk-benefit analysis must be performed. Recommended screening tests include pulmonary function studies, a thallium stress test, an MRI or CT scan of the brain, and baseline hematologic and chemistry profiles.[1] A review of current medications will assist in identifying potential drug interactions or contraindications to IL-2 therapy. Table 4 lists contraindications to IL-2 treatment.

The mechanisms of action that result in IL-2 toxicity are complex, but the manifestations of toxicity are often predictable; therefore, standardized order sets and/or critical pathways are practical tools to facilitate effective high-dose IL-2 administration.[13,30] These tools should include guidelines for patient monitoring, laboratory assessments, administration of ancillary medications, patient education, and discharge planning. Routine monitoring should include, at a minimum, daily weights; a pulse oximetry reading at admission and thereafter as needed; and evaluation of vital signs at least every 2 to 8 hours. Neurologic evaluation, physical examination, and strict measurement of fluid intake and output, including emesis, diarrhea, and urine volumes at regular intervals, are essential when monitoring patients receiving IL-2.

Baseline and daily laboratory assessments should include a complete blood count and comprehensive metabolic profile. A CPK level and coagulation profile should be obtained at baseline. At the time IL-2 is prescribed, medication orders should specify ancillary medications, such as antipyretics, H₂-antagonists, antiemetics, antidiarrheals, and opiates, and institutional protocols for mouth and skin care. If used, antibiotic prophylaxis orders should be based on institutional susceptibility patterns. Strategies for managing tachycardia, fever, and decreases in blood pressure, urine output, and blood oxygen saturation levels should also be prescribed at the time IL-2 is ordered. Finally, nursing clinical pathways should anticipate and address the need for administration of IV fluid boluses, renal-dose dopamine, and vasopressors.[30]

Toxicity of many chemotherapeutic agents is managed by dose attenuation, whereas IL-2 toxicity is managed by skipping or withholding therapy for a specified time (Tables 2 and 3).[1] Examples of conditions that require withholding therapy include persistent hypotension, prolonged oliguria, neurologic toxicity, and dyspnea with low oxygen saturation detected by pulse oximetry.[6] IL-2 therapy may be resumed if toxicity resolves (Tables 2 and 3). IL-2-related toxicity often results in the receipt of less than the prescribed regimen.[1] Before proceeding with subsequent cycles of therapy, patients should be assessed for any contraindication that prohibits retreatment (Table 4).[1] Disease responsiveness should be assessed before proceeding with another course of therapy.[1]

Conclusions

Despite the high mortality and severe morbidity rates initially produced by IL-2, experienced and knowledgeable personnel can now safely and effectively administer high-dose IL-2. Implementation of and adherence to standard dosing and patient assessment criteria during IL-2 administration are crucial to minimize symptoms and manage toxicities. The ability to administer high-dose IL-2 effectively to renal cell carcinoma and melanoma patients may allow for the investigation and expanded use of IL-2 in other diseases.

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