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Review

Guidelines for the Safe Administration of High-Dose Interleukin-2

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Summary: High-dose interleukin-2 (IL-2) results in objective clinical regression of metastatic cancer in 15% to 17% of patients with melanoma and renal cell carcinoma. Durable complete regression of all metastases is seen in 6% to 8% of patients. Based on these findings, the U.S. Food and Drug Administration has approved the use of high-dose IL-2 for the treatment of patients with metastatic melanoma and renal cell carcinoma. Interleukin-2 administration is associated with many different side effects, and after many years of use, clinicians have learned how to safely administer high-dose IL-2. This article details practical guidelines for the safe administration of high-dose IL-2. Key Words: High-dose IL-2—Toxicity—Melanoma—Renal cell carcinoma.

High-dose interleukin-2 (IL-2) has resulted in objective clinical regression of disease in 15% to 17% of patients with metastatic melanoma and renal cell carcinoma, with 6% to 8% of patients experiencing durable complete regression of all metastases (1–3). In these studies, IL-2 was administered at 600,000 or 720,000 IU/kg per dose intravenously every 8 h until maximally tolerated (generally 8–12 doses in the first cycle of treatment). Based on these findings, the U.S. Food and Drug Administration approved the dose of 600,000 IU/kg ("high-dose" IL-2) for the treatment of patients with metastatic melanoma and renal cell carcinoma.

High-dose IL-2 administration is associated with many different side effects; as such, it may have an impact on every organ system in the body (4). After many years of use, clinicians have learned how to safely administer high-dose IL-2; indeed, the intensity of many of the side effects has diminished from that reported in early studies (5). This article details practical guidelines for the safe administration of high-dose IL-2. Patients receiving high-dose IL-2 require close observation and frequent decisions that cannot be preplanned but must be individualized in a rapidly changing clinical setting.

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DISCUSSION

Overview

It should be emphasized that there is great variation in the toxicities experienced by patients receiving high-dose IL-2 and that some patients experience few side effects. The typical clinical course of patients receiving high-dose IL-2 begins with fever and chills 2 to 3 h after the first or second dose of IL-2 (4). Mild to moderate hypotension develops soon after starting IL-2, and a new state of relative hypotension and tachycardia is generally maintained for the majority of the treatment. Oliguria frequently manifests in the first 24 h and requires additional fluids to restore urine output. As the end of the cycle of treatment approaches, hypotension and oliguria may worsen and require pharmacologic intervention. Nausea, vomiting, and diarrhea become more prominent toward the end of therapy. Manifestations of capillary leak such as edema, weight gain, and pulmonary congestion are progressive. The most prominent and clinically consequential laboratory abnormalities noted during treatment are a rise in serum creatinine and a fall in platelet count. The majority of the side effects quickly

reverse on termination of IL-2, and most patients are ready for discharge from the hospital 2 to 3 days after the last dose of IL-2. Patients typically receive 8 to 12 doses of IL-2 in their first cycle of therapy and progressively less in subsequent treatments.

The toxicities of IL-2 therapy are thought to result primarily from a capillary leak syndrome (CLS) as well as from lymphoid infiltration, which has been observed histologically in many organs (4). The earliest clinical manifestations of CLS are hypotension and tachycardia, which can be seen 2 h after the first dose of high-dose IL-2. Decreased systemic vascular resistance has been measured at this time and contributes to the early drop in blood pressure. Because of these changes, antihypertensive medications should be discontinued before initiating high-dose IL-2.

Intravenous fluids are the initial therapy for hypotension, and the goal is to maintain systolic blood pressure greater than 80–90 mm Hg. It is common to require additional fluid in the first 24 h of therapy in response to hypotension and oliguria. After initial resuscitation, most patients reach a steady state of relative hypotension and tachycardia that is maintained until the final doses of IL-2. No intervention is generally needed for these parameters unless they exceed predetermined guidelines or oliguria ensues.

Fluid replacement of 1–1.5 L/d above maintenance requirements should not be exceeded, because it extravasates and compounds the progressive generalized edema and pulmonary congestion. The use of additional fluids late in the cycle of treatment should be restricted, because the transient benefit achieved may be overshadowed by the unwanted consequences of fluid leak (special caution must be exercised if body weight is >10% above baseline). Crystalloid is favored over colloid for the treatment of hypotension based on a randomized study that showed both were equally effective (6). If hypotension persists despite judicious fluid resuscitation, vasopressor support with an α agonist such as phenylephrine is indicated. The hypotensive effects of each IL-2 dose are cyclic and generally peak 4 to 6 h after infusion, requiring vasopressors to be titrated accordingly. When phenylephrine can be weaned to 0.5 μg/kg/min or less, it is generally safe to proceed with additional IL-2 dosing. As IL-2 therapy nears completion, phenylephrine requirements increase; doses approaching 1.5–2 μg/kg/min and inability to wean 8 h after an IL-2 dose suggest that IL-2 infusions should be discontinued. Blood pressure measurements generally return to baseline within 24 to 48 h of discontinuation of IL-2.

Within the first 8 h of starting IL-2, decreased urine output is frequent and is a consequence of hypotension and decreased intravascular volume. Renal dysfunction during IL-2 has been described as prerenal in nature, transient, and without evidence of intrinsic renal damage (7). Oliguria is first treated with fluid boluses; if 1–1.5 L crystalloid does not restore urine flow, an indwelling urinary catheter is inserted and dopamine at renal perfusion doses (2 μg/kg/min) is initiated. Urine output greater than 10–20 mL/h must be established before additional IL-2 dosing can be considered. Serum creatinine levels are measured at least daily, and the results are considered when making decisions about IL-2 dosing.

Patients receiving high-dose IL-2 may experience progressive shortness of breath during therapy, which infrequently requires endotracheal intubation or drainage of a pleural effusion. The mechanism of pulmonary congestion has been attributed to increased vascular permeability. Careful pretherapy screening of patients who smoke heavily or have a large tumor burden in the lungs (forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC] should be greater than 65% of predicted value and PaO_2 should be >75 on room air) and advising smokers to quit 2 weeks before therapy as well as judicious fluid replacement during therapy have resulted in a low incidence of severe toxicity. The selective monitoring of transcutaneous O_2 saturation has been helpful in patients experiencing pulmonary symptoms. O_2 saturation should be maintained above 95%, and if this level cannot be met by 4 L O_2 by nasal cannula or 40% O_2 by mask, IL-2 dosing should be discontinued. The auscultation of rales in the lung bases is not infrequent during therapy, but progression to the midlung fields coupled with marginal O_2 saturation is a reason to discontinue IL-2 dosing. Chest radiographs revealing interstitial edema and pleural effusions provide complementary information to the clinical assessment and are performed selectively. After discontinuation of IL-2, symptoms of pulmonary congestion resolve promptly, and recovery is aided by rapid diuresis.

One of the more visible sequelae of CLS is the generalized total body edema and consequent weight gain demonstrated during high-dose IL-2. Neurovascular compression from edema is rare and is best treated with elevation of the involved extremity and use of compression garments. Cautious use of fluids to correct hypotension and oliguria is important in minimizing edema. Diuresis is not always possible during therapy, because patients may be hypotensive and are frequently unresponsive to diuretics. After stopping IL-2 and when the blood pressure is returning to baseline (and not requiring vasopressors), diuresis should be vigorously initiated by pharmacologic means. Frequent increasing doses of di-

TABLE 1. *Patient monitoring guidelines*

	Not requiring vasopressors	Requiring intensive care unit/vasopressors
Vitals signs	Every 4 h	Every 1 h
Intake and output	Every 4 h	Every 1 h
Weight	Daily	Daily
Mental status	Every 8 h	Every 8 h
Intravenous site	Every 8 h (change arm intravenous line every 3 days)	Every 8 h
Laboratory tests		
Complete blood cell count	Daily	Twice daily
Electrolytes, blood urea nitrogen, creatinine, glucose	Daily	Twice daily
Alanine aminotransferase, aspartate aminotransferase, total bilirubin	Daily	Daily
Ca^{++}, Mg^{++}, phosphorus	Daily	Daily
Prothrombin time, partial thromboplastin time	Daily after day 2	Daily
Creatine kinase, total	Daily	Daily
Thyroid stimulating hormone, free T4	Each cycle	Each cycle
Urinalysis	Each cycle	Each cycle
Electrocardiogram	Each cycle	Each cycle
Chest Xray or chest radiograph	Each cycle	Each cycle

uretics should be administered until a brisk diuresis is achieved (i.e., 200 mL/h). Fluid balance is rapidly restored, and the majority of patients are discharged at or below admission weight about 3 days after stopping IL-2.

Many of the side effects of high-dose IL-2 relate to the gastrointestinal tract. Individualized treatment of nausea, vomiting, and diarrhea may be required, because no uniform regimen has been observed to be always effective. Ondansetron and droperidol have been found to be equally effective in controlling nausea (8).

Infections during therapy (9) have been primarily bacterial in origin and associated with an IL-2–induced neutrophil dysfunction. Prevention of infection by using prophylactic antibiotics in patients with central lines and prompt use of antibiotics in suspected or documented infection have resulted in a decreased incidence and severity of this complication.

The neuropsychiatric side effects of IL-2 (10) may begin with subtle confusion, and patients must be assessed frequently for orientation and cognitive ability. True neuropsychiatric alterations require discontinuation of IL-2 dosing for that cycle of treatment.

A variety of laboratory abnormalities develop during IL-2 treatment and may require intervention. Electrolytes and minerals frequently require correction. Anemia and thrombocytopenia may require transfusion (11). Transient cholestasis is reversible on discontinuation of IL-2 and rarely clinically consequential (12). Asymptomatic elevations in cardiac isoenzymes (occasionally noted at the end of treatment or after stopping IL-2) may represent myocarditis and should be further evaluated before the next cycle of treatment (13). Hypothyroidism, occurring in up to one third of patients, is a long-term consequence of IL-2 administration, and when detected on routine screening, it may require hormone replacement (14).

TABLE 2. *Target blood pressure during therapy*

Normal blood pressure for patient	Target blood pressure on therapy
<100 mm Hg	>80 mm Hg
100–120 mm Hg	>85 mm Hg
>120 mm Hg	>90 mm Hg

Pretherapy Assessment

- Perform careful history and physical examination. Patients should not have major cardiac, pulmonary, or renal disease.
- Obtain complete radiographic assessment at baseline and after every two cycles of IL-2 to evaluate response to therapy.
- Verify no recent use of steroids (systemic, topical, or inhalational). Delay IL-2 therapy 1 to 2 weeks if the patient has received steroids.
- Confirm no recent (<7 days) history of infections (respiratory, renal, intravenous site, other). If present, delay IL-2 1 week and treat as appropriate.
- Check laboratory test results (i.e., normal or returned to baseline if patient previously received IL-2).
- Serum creatinine 1.6 mg/dL or lower
- Serum bilirubin 2 mg/dL or lower
- Check electrocardiogram (i.e., normal or unchanged if patient received previous IL-2).

- Check stress cardiac test if patient is 50 years of age or older (or has family history of heart disease).
- Check chest Xray (i.e., no infectious infiltrates and no effusion if received previous IL-2).
- Check pulmonary function tests if patient is a heavy smoker or has a heavy tumor burden (should have FEV_1 and FVC >65% of predicted).
- Advise patient to quit smoking 2 weeks before IL-2 if pertinent.

Pretherapy Intervention

- Discontinue antihypertensive medications.
- Start acetaminophen, indomethacin, and H_2 blocker 8–12 h before IL-2.
- Start maintenance intravenous fluids (i.e., lactated Ringer's) at 50–100 mL/h immediately before IL-2 is started.
- Premedicate patient for nausea (before IL-2 dose).

Intervention During Therapy

Patient monitoring guidelines are provided in Table 1. Target blood pressure during therapy is provided in Table 2.

Interleukin-2 Dosing

No dose reductions of IL-2 are performed. IL-2 doses are delayed according to symptomatic recovery from the previous dose. A delay longer than 24 h should result in discontinuation of that cycle of IL-2.

Guidelines for delay or discontinuation of IL-2 are given in Table 3 and Table 4. The presence of relative criteria implies that a patient is nearing the completion of a cycle of therapy and that with appropriate corrective measures or with a time delay to allow for recovery, it may be safe to administer another IL-2 dose. Several relative criteria that are not easily reversible or correctable are usually an indication to discontinue dosing. The

TABLE 3. *Guidelines for delay or discontinuation of interleukin-2*

System	Relative criteria	Absolute criteria
Cardiac	Sinus tachycardia (120–130 beats per min)	Sustained sinus tachycardia (>130 beats per min persists after correcting hypotension, fever and tachycardia and stopping dopamine)
		Atrial fibrillation
		Supraventricular tachycardia
		Ventricular arrhythmias (frequent premature ventricular contractions, bigeminy, tachycardia)
		Elevated creatine kinase isoenzymes or troponin
		Electrocardiogram changes of ischemia
Dermatologic		Moist desquamation
Gastrointestinal	Diarrhea, 1,000 mL/shift	Diarrhea, 1,000 mL/shift ×2
		Vomiting not responsive to medication
	Ileus/abdominal distention	Severe abdominal distention affecting breathing
	Bilirubin >7 mg/dL	Severe abdominal pain, unrelenting
Hemodynamic	Maximum neosynephrine 1–1.5 μg/kg/min	Maximum neosynephrine 1.5–2 μg/kg/min
	Minimum neosynephrine >0.5 μg/kg/min	Minimum neosynephrine >0.8 μg/kg/min
Hemorrhagic	Guiac + sputum, emesis, stool	Frank blood sputum, emesis, stool
	Platelets 30,000–50,000/mm^3	Platelets <30,000/mm^3
Infectious		Strong clinical suspicion or documented
Musculoskeletal	Weight gain >15%	
	Extremity tightness	Extremity paresthesias
Neurologic	Vivid dreams	Hallucination
	Emotional lability	Persistent crying
		Mental status changes not reversible in 2 h
		Inability to subtract serial 7s or spell "WORLD" backward (DLROW)
		Disorientation
Pulmonary	Resting shortness of breath	>4 L O_2 by NC for saturation ≥95% or 40% O_2 mask for saturation ≥95%
	3–4 L O_2 by nasal cannula (NC) for saturation ≥95%	
		Endotracheal intubation
	Rales ⅓ up chest	Moist rales ½ up chest
		Pleural effusion requiring tap or chest tube while on therapy
Renal	Urine 80–160 mL/shift	Urine <80 mL/shift
	Urine 10–20 mL/h	Urine <10 mL/h
	Creatinine 2.5–2.9 mg/dL	Creatinine ≥3 mg/dL

TABLE 4. *When to delay or discontinue interleukin-2*

Observation category	Action
Any relative criteria	Initiate corrective measure ± delay IL-2
≥3 relative criteria	Initiate corrective measures, delay IL-2 Stop IL-2 if not easily reversible
Any absolute criteria	Initiate corrective measure, delay IL-2 Stop IL-2 if not easily reversible

IL-2, interleukin-2.

presence of an absolute criterion that is not easily reversible is generally considered an indication to stop dosing IL-2. Corrective measures are listed in Table 5, and concomitant medications used during IL-2 therapy are listed in Table 6.

Posttherapy Assessment

- Continue monitoring vital signs until patient is stable.
- Continue measuring intake and output until patient is discharged.
- Measure laboratory tests daily. Before discharge, a plateau in abnormalities, with values beginning to return to normal, should be observed.

Posttherapy Intervention

- Discontinue maintenance intravenous fluids early, generally 8 h after the last IL-2 dose (even though the patient is not taking fluids well orally). Intravenous fluids should not need to be reinstated unless the patient has severe gastrointestinal toxicity and his or her weight drops to below admission weight.
- Continue acetaminophen, indomethacin, and H_2 blocker for 16–24 h (if stopped too soon, patient may develop fever).
- Start diuresis when blood pressure has stabilized (patient off vasopressors). Monitor for response to diuretic, and aggressively repeat doses until the desired effect is achieved (i.e., urine output of 200 mL/h).

TABLE 5. *Corrective measures*

Symptom	Corrective measure
Arrhythmia (other than sinus tachycardia)	Stop IL-2 (most arrhythmias); correct electrolytes, minerals, anemia, hypoxia; use medications as indicated
Anemia	Transfuse packed red blood cells to achieve hematocrit >28% during IL-2 dosing
Acidosis	
CO_2 <20 mmol/L	Give 50 mEq sodium bicarbonate intravenously
CO_2 <18 mmol/L	Give 100 mEq sodium bicarbonate intravenously
Chills (generally after first or second IL-2 dose)	Warm blankets as first measure; intravenous meperidine if chills persist
Creatine kinase elevation	Measure isoenzymes or troponin, electrocardiogram; if have evidence of myocarditis, must stop IL-2; will need exercise ECHO before next cycle of IL-2 to rule out myocardial dysfunction; future IL-2 may be considered if the ECHO is normal
Dermatitis	Oatmeal baths, lotions (No steroid- or alcohol-containing lotions)
Diarrhea	Antidiarrheals (alternate medications); avoid overuse because of complicating ileus and distention
Edema	Elevate symptomatic extremity; use fluids judiciously
Epigastric pain	Evaluate cause; give indomethacin rectally; consider antacids
Fever breakthrough	Increase frequency of indomethacin to every 6 h; Consider septic workup if happens after first 24 h of therapy (i.e., high spike above rising baseline during therapy)
Hypoalbuminemia	Observe
Hypocalcemia	Maintain above lowest normal value
Hypokalemia	Maintain potassium above 3.6 mmol/L
Hypomagnesemia	Maintain above lowest normal value
Hypotension	Initially fluids; add neosynephrine after 1–1.5 L of fluid boluses (see overview)
Infection	Stop IL-2 and treat infection as indicated
Mucositis/stomatitis	Frequent oral care, mouthwashes, topical anesthetics, room humidifier
Oliguria	Initially fluids; add dopamine after 1–1.5 L of fluid boluses (see overview)
Nausea/vomiting	Antiemetics (alternate medications and routes if any one not effective)
Nasal congestion	Room humidifier, decongestant (no inhalational steroids)
Poor venous access	Insert PIC or central line; antibiotic prophylaxis started when PIC or central line inserted and continued until line out (remove line as soon as not needed for fluids, vasopressors, replacements, diuretics)
Pruritis	Oatmeal baths, lotions, antipruritics
Shortness of breath	Check transcutaneous O_2 saturation; if <95%, use O_2; use fluids judiciously; do not use inhalational steroids
Tachycardia (sinus)	Correct fever, hypotension, hypoxia, anemia; consider discontinuation of dopamine if used
Thrombocytopenia	Consider transfusion if count <20,000/mm^3
Troponin elevation	Must stop IL-2; will need exercise ECHO before next cycle of IL-2 to rule out myocardial dysfunction; future IL-2 may be considered if the ECHO is normal

IL-2, interleukin-2; ECHO, echocardiogram; PIC, peripherally inserted central catheter.

TABLE 6. *Concomitant medications used during interleukin-2 therapy*[a]

Side effect treated	Medication	Dose/frequency/route
Scheduled		
Fever/myalgia	Acetaminophen	650 mg q 4 h, PO/PR
	Indomethacin	50–75 mg q 8 h, PO/PR
Gastritis	Ranitidine HCL	50 mg q 8 h, IV
Nausea	Granisetron HCL	0.01 mg/kg daily
Prevent line sepsis (central line)	Cefazolin	1–2 g q 6 h, IV, or 900 mg q 8 h, IV
	Clindamycin	
As needed (PRN)		
Agitation/combativeness	Haloperidol	1–5 mg q 1 h, IV/IM
Anxiety	Lorazepam	0.5–1 mg q 6 h, PO/IV
Chills	Meperedine HCL	25–50 mg q 1 h, IV
Diarrhea	Loperamide	2 mg q 3 h, PO
	Diphenoxylate HCL (2.5 mg) Atropine sulfate (25 μg)	q 3 h, PO
	Codeine sulfate	30–60 mg q 4 h, PO
Gastric upset	Aluminum hydroxide (200 mg) Magnesium hydroxide (200 mg) Simethicone (20 mg)	30 mL q 3 h, PO
Hypocalcemia	Calcium gluconate, 10%	1 g (over 1 h), IV
Hypokalemia	Potassium chloride	10 mEq (over 1 h), IV
Hypomagnesemia	Magnesium sulfate	1 g (over 1 h), IV
Hypophosphatemia	Potassium phosphate	10–15 mmol (over 6 h), IV
Hypotension	Normal saline	250–500 mL IV
	Phenylephrine	40 mg/100 mL, titrate IV (0.1–2 μg/kg/min)
Insomnia	Temazepan	15–30 mg qhs, PO
	Zolpidem	5–10 mg qhs, PO
Mucositis	Sodium bicarbonate 6 tsp per 1,500 mL	Swish and swallow
	Lidobenalox oral	5 ml q 3 h, PO
Nausea	Droperidol	1 mg 1 4–6 h, IV
	Prochlorperazine	25 mg q 4 h, PR, or 10 mg q 6 h, IV
	Ondansetron HCL	10 mg q 8 h, IV
	Lorazepam	0.5–1 mg q 6 h, PO/IV
Oliguria	Normal saline	250–500 mL IV
	Dopamine HCL	100 mg/250 mL, IV (2 μg/kg/min)
Perianal discomfort	Tucks	Apply locally
Pruritis	Hydroxyzine HCL	10–20 mg q 6 h, PO
	Diphenhydramine HCL	25–50 mg q 4 h, PO/IV
	Oatmeal powder/baths	Apply locally
	Lubriderm (8 oz) with 0.25% camphor and 0.25% menthol	Apply locally
Sinus congestion	Pseudoephedrine HCL	30 mg q 6 h, PO

[a] Adapted from Schwartzentruber DJ. In: De Vita, VT, Jr, Hellman S, Rosenberg SA, ed. *Principles and Practice of the Biologic Therapy of Cancer,* 3rd ed. Philadelphia: Lippincott, Williams and Wilkins, 2000, pp 32–50; with permission.

HCL, hydrochloride; q, every; PO, orally; PR, rectally; IV, intravenously; IM, intramuscularly; PRN, as needed.

CONCLUSIONS

Treatment with high-dose IL-2 is extremely safe when patients are carefully selected for this therapy and when it is administered by trained physicians and nurses. In the Surgery Branch, National Cancer Institute, a decrease in the incidence and severity of most side effects was observed during the first decade of IL-2 use (5). Over 800 consecutive patients with metastatic cancer were treated with high-dose bolus IL-2 without any treatment-related mortality. The improved safety paralleled a decrease (13 $\rightarrow$ 8) in the median number of doses of IL-2 administered in the first cycle of treatment and seemed to maintain clinical efficacy (5).

The safe administration of high-dose IL-2 requires careful attention to the many physiologic changes occurring in patients during treatment and making frequent decisions about management of the side effects. The decision to administer IL-2 is generally made on a dose-by-dose basis and requires frequent input by the team caring for the patient. Treatment algorithms are useful tools in managing these patients but cannot replace the careful judgment and individualized decision making that is needed. The health care team should be familiar with the scope of possible side effects that may be encountered (4), because they must be prepared for the common as well as unusual events that occur when treating patients with high-dose IL-2. Printed clinical pathways (15) and the guidelines in this article were designed to create a safe environment for high-dose IL-2 administration.

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