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Review

Detailed protocol for administration of intralesional IL-2 for the treatment of Stage IIIc and IV M1a metastatic melanoma based on current NCCN guidelines

Forum Patel MD[1], Reason Wilken MD[1], Barbara Burrall MD[1], Steve Martinez MD[2], Victoria Wells BS[1], Brett King MD PhD[3], Emanual Maverakis MD[1,4]

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[1]University of California, Davis, Department of Dermatology

[2]University of California, Davis, Department of Surgery

[3]Yale University School of Medicine, Department of Dermatology, New Haven, CT

[4]Department of Veteran Affairs Northern California Health Care System

Correspondence:

Emanual Maverakis, MD
Department of Dermatology
University of California, Davis School of Medicine
3301 C Street, Suite 1400
Sacramento, CA 95816
Telephone (916) 843-7336
emaverakis@ucdavis.edu

Abstract

Melanoma claims approximately 9,000 lives in the United States annually [1]. Patients who present with satellite, in-transit, or distant cutaneous metastases have limited treatment options and the prognosis for patients with metastatic disease remains poor. Surgical excision remains the most common treatment modality for cutaneous metastases, but may not address concurrent subclinical in-transit metastases. Other palliative treatment options include Bacillus Calmette–Guérin (BCG) and isolated limb perfusion (ILP). Although intravenous IL-2 has been used for treatment of metastatic melanoma since 1998, intralesional IL-2 has only now been included in the most recent National Comprehensive Cancer Network (NCCN) guidelines after case series and phase I/II clinical trials have shown promising results against Stage IIIc and IV M1a melanoma. Intralesional IL-2 protocols have varied markedly from study to study and there are no consensus guidelines available to help direct treatment. Herein, we present a detailed protocol for the administration of intralesional IL-2 that has been successfully used at two different institutions for treatment of cutaneous melanoma metastases.

Keywords: Stage IIIc and IV M1a melanoma, Interleukin-2, Cutaneous metastatic melanoma

Introduction

IL-2 is a glycoprotein produced by T helper cells in response to antigenic or mitogenic stimulation. IL-2 promotes T cell and B cell proliferation and the development of lymphokine-activated killer (LAK) cells. LAK cells have the ability to directly lyse tumor cells [2]. IL-2 also functions through activation of monocytes, macrophages, and oligodendrocytes. Intravenous IL-2 was approved by the FDA in 1998 for the treatment of metastatic melanoma [3, 4]. Owing to the potential for adverse events including hypotension and cardiac arrythmias, its use is limited to otherwise healthy individuals. The anti-tumor effects of intravenous IL-2 are only seen in patients treated with high dose regimens. Interestingly, mice are able to tolerate high doses of

exogenous IL-2, which is likely why IL-2 has been very successful in the treatment of a variety of malignancies in murine models [5]. At lower doses, IL-2 has the potential to expand regulatory T cells, which would theoretically diminish the desired anti-cancer response [6]. Thus, drastically reducing the administered dose of IL-2 in the hopes of making the therapy more tolerable for the patient is not recommended. In order to achieve local therapeutic doses of IL-2 while avoiding the IL-2-associated systemic toxicities, several groups have adopted an intralesional approach for administration. The resulting high *local* concentration of IL-2 is likely the reason for the excellent response rates observed in patients treated with intralesional IL-2 [7-11]. Several case series and phase I/II clinical trials have demonstrated the efficacy of intralesional IL-2 for the treatment of Stage IIIc and IV M1a melanoma with response rates ranging from 62.5 to 100% [7-11].

Imiquimod is an immune modulator that is FDA approved for the treatment of actinic keratosis, superficial basal cell carcinoma, and external genital warts, but has also been used off-label for squamous cell carcinoma, extramammary Paget's disease, lymphoma, and melanoma [8, 12-20]. Imiquimod activates the immune system via the toll-like receptor 7 (TLR7)-MyD88–dependent signaling pathway resulting in the production of a variety of pro-inflammatory cytokines including IFN-α, TNF, and IL-12 [21, 22] and the recruitment of plasmacytoid dendritic cells to the skin [23]. Deep dermal and subcutaneous metastases are often resistant to treatment with imiquimod, likely because of due to the absence of imiquimod-responsive dendritic cells in subcutaneous tissue [8, 24-26]. It has also been well documented that melanoma can *develop* resistance to the death receptor-independent apoptotic pathways induced by imiquimod [27]. Thus, we do not recommend imiquimod as monotherapy.

Supplementing imiquimod therapy with a topical retinoid such as tazarotene is not uncommon in the treatment of warts and precancerous lesions. The addition of a retinoid may increase imiquimod's effectiveness by increasing keratinocyte differentiation and drug penetration [28]. Although strong clinical evidence is lacking, one group reported a trend towards significance when imiquimod was combined with tazarotene gel compared to imiquimod alone for the treatment of melanoma *in situ* [29].

Taking the above observations into account, a protocol combining intralesional IL-2, imiquimod, and topical retinoid for the treatment of Stage IIIc and IV M1a melanoma was developed and is presented below.

Baseline Evaluation

The work-up of a patient with metastatic melanoma is described elsewhere [NCCN 2014]. In brief, before beginning intralesional IL-2 therapy, a baseline evaluation (Table 1) consisting of a complete physical examination, including lymph node exam, vital signs, complete blood count, complete metabolic panel, lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) assessment, whole body PET/CT, and a brain MRI (preferably T1 MRI with contrast) should be performed. Imaging is necessary to screen for visceral and CNS metastases, which would lessen the enthusiasm for therapy with intralesional IL-2. Current medications should be reviewed, in particular, antihypertensives. The lesions to be treated should be photographed prior to starting therapy.

Administration of IL-2 combination therapy

A detailed protocol is provided in Figure 1. On the first day of treatment, a "test" dose of 7 million IU of IL-2 is distributed between the cutaneous melanoma metastases. For comparison, a 70 kg patient treated with *intravenous* IL-2 would receive 42 million IU every 8 hours. Unlike intravenous IL-2, it is important to realize that intralesional IL-2 often does not produce adverse reactions immediately. When present, these usually take 2-6 hours to develop. However, if the patient is relatively healthy, they can be discharged home following their test dose with instructions to self-monitor their temperature and blood pressure for the next 6 hours. Patients should be advised to go to the emergency room if they experience a significant drop in their blood pressure (Table 2).

Common adverse events include fever, chills, myalgias, nausea, and vomiting (Table 3). These can usually be managed with warm blankets, acetaminophen (325-1000 mg every 4-6 hours as needed), and ondansetron (4-8 mg one hour prior to treatment and every 8 hours after as needed). Hypotension is not uncommon and, if clinically significant, antihypertensives may be held on future treatment days (Table 3). However, if the antihypertensive agent is prescribed for its antiarrhythmic properties, a cardiology consultation should be obtained to ensure that the medication may be safely discontinued, mainly because atrial fibrillation is known to be triggered by IL-2.

If the patient is able to tolerate the test dose, a biweekly regimen of intralesional IL-2 injections may be continued for the next 4 weeks. At each visit, the dose of IL-2 can be incrementally increased to a maximum of 22 million units, taking into consideration that a "stacking" effect may occur, i.e. 10 million units successfully administered during the first week of therapy may be

intolerable during the second week of therapy. Thus the 22 million-unit dose should be reserved for patients with few co-morbidities and even then, only administered cautiously.

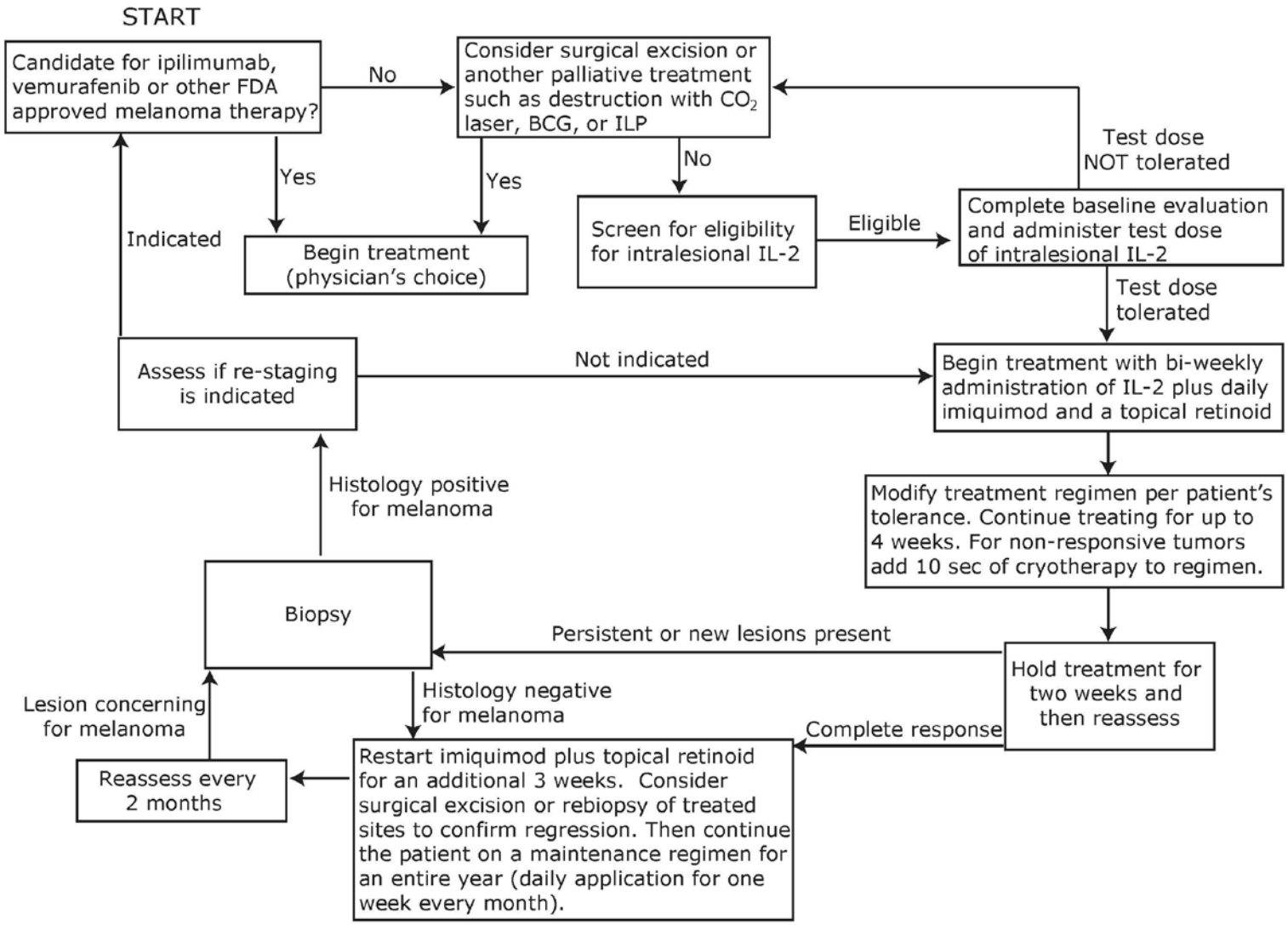

Figure 1. A detailed algorithm to guide treatment of patients with Stage IIIc or IV M1a melanoma

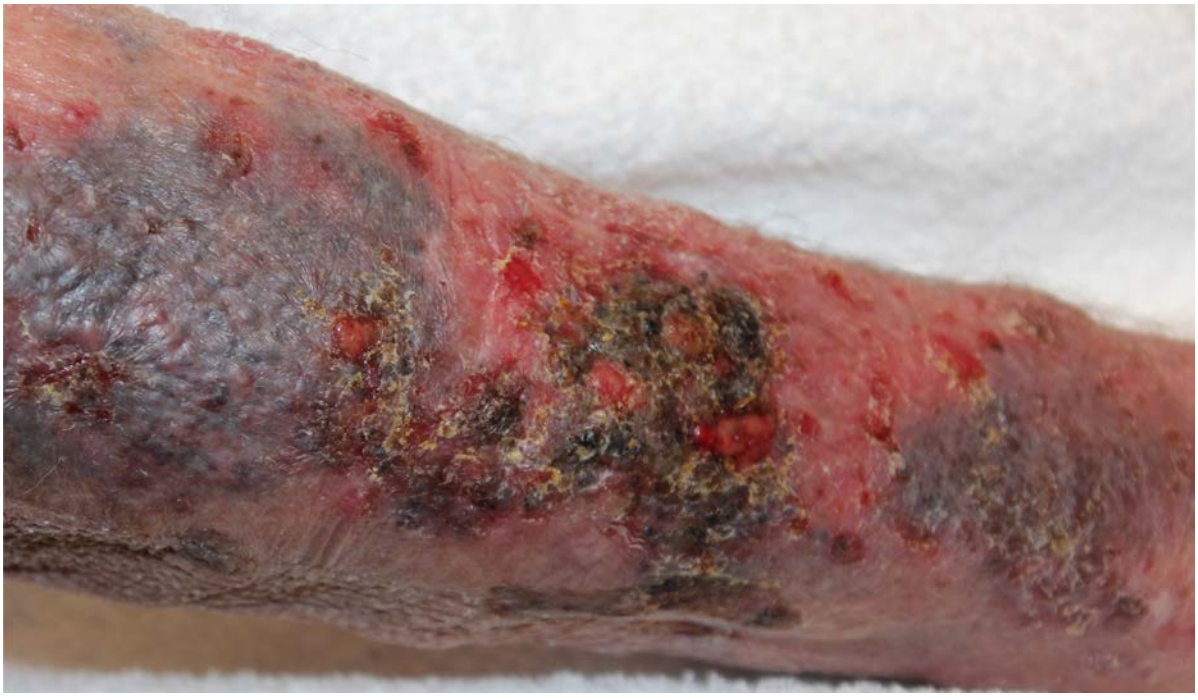

Figure 2. Expected level of cutaneous inflammation during treatment with intralesional IL-2, imiquimod, and tazarotene

Topical therapy with imiquimod and a retinoid (tazarotene 0.1%) should be applied nightly, with the goal of keeping the treated sites clinically inflamed (Figure 2). If the inflammatory response is not intense, the topical regimen can be applied under telfa bandage occlusion. The topicals should be applied directly to the melanoma lesions including a 10 cm margin of normal appearing skin. By the end of therapy, erosions and ulcerations will likely occur (Figure 3). If these become unacceptably large or intolerable, the frequency of the topical regimen may be reduced. As much as possible, however, treatment per the protocol should be maintained. If concern of infection arises, empiric antibiotic therapy can be started with doxycycline or double strength trimethoprim-sulfamethoxazole (Table 1). Topical therapy should be continued for an additional three weeks after completion of intralesional IL-2, and then for one week every month for one additional year, as described in Figure 1. Patients may be restarted on intralesional IL-2 therapy for persistent, recurrent, or new metastatic cutaneous lesions. Patients should also be aware that treatment with intralesional IL-2 usually causes vitiligo, which may be permanent (Figure 3).

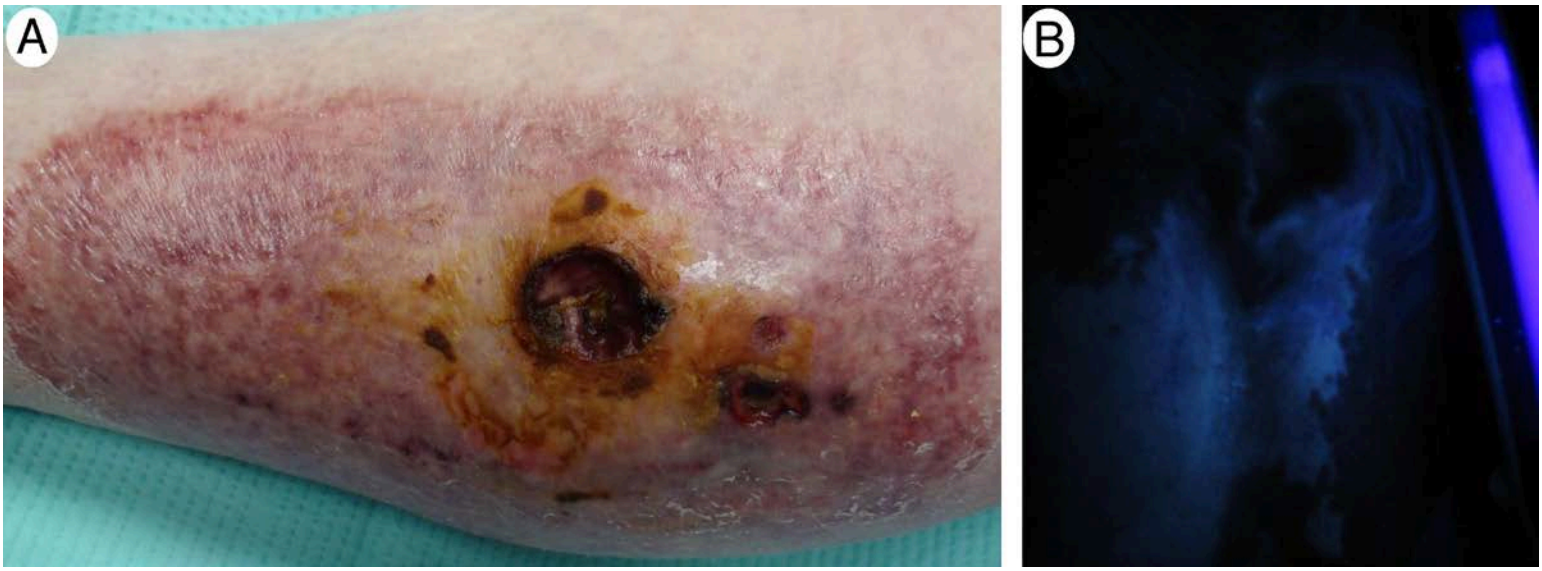

Figure 3. A) A deep cutaneous ulcer in a patient after 4 weeks of treatment with intralesional IL-2 and nightly application of imiquimod and tazarotene 0.1% is shown. Note that surrounding tissue has an appropriate inflammatory response. B) White patches under Wood's lamp indicates the presence of vitiligo in a patient after 4 weeks of treatment. Vitiligo is a common adverse event of intralesional IL-2 and may be permanent.

Management of severe IL-2 toxicities

Although severe adverse events in patients receiving intralesional IL-2 have not been reported, it is reasonable to request additional support from an oncologist or primary care physician to help co-manage patients that are medically more complicated prior to starting IL-2 therapy. Nevertheless IL-2-related, adverse events such as capillary leak syndrome (CLS) are well described in patients receiving *intravenous* IL-2 and published management strategies can help guide treatment if similar adverse events are encountered with intralesional administration (Table 3) [30]. In CLS, cytokine release following IL-2 administration leads to increased capillary permeability, which results in fluid shift from the vascular space to extravascular space and a decrease in systemic vascular resistance. This may create a relatively hypovolemic state with possible decreased blood perfusion to end organ systems such as the kidneys and intestines [30]. This can lead to hypotension, tachycardia, and decreased urine output, which are the earliest manifestations of CLS.

Fluid status in these patients may be tenuous and efforts must be made to avoid excessive fluid administration. Capillary leak and subsequent fluid retention associated with drug administration can result in edema, weight gain, and pulmonary congestion. Crystalloid or colloid fluid administration should be limited to 1-1.5 liters to decrease the risk of exacerbating capillary leak-associated pulmonary edema. Fluid administration should be used in combination with vasopressor support if needed, with the goal of maintaining systolic blood pressures greater than pre-treatment goals (Table 2) [30].

Conclusion

Intralesional IL-2 therapy should be considered for Stage IIIc and IV M1a melanoma. Although intralesional IL-2 has the potential for the same severe adverse events as intravenous IL-2 administration, these events have yet to be reported with local injection directly into metastatic lesions. Recently revised 2014 NCCN guidelines have validated intralesional IL-2 as a treatment

for Stage III in-transit melanoma metastases. Combining intralesional IL-2 with imiquimod and a topical retinoid is a novel approach for treatment of cutaneous metastatic melanoma and may improve the chances of successful treatment in this often lethal disease.

Tables 1-3.

Table 1: Treatment Protocol	
Screening for Eligibility of IL-2	• Histologically confirmed cutaneous metastatic melanoma • ECOG performance status of 0 - 3 • Life expectancy of greater than 6 months • Absence of uncontrolled cardiac arrhythmias
Baseline Evaluation	• Complete physical examination, including full body skin exam and thorough lymph node examination • Vital Signs, including blood pressure • Lab Tests: complete blood count, comprehensive metabolic panel, lactate dehydrogenase • Complete medical history and medication list, with particular attention to prescribed antihypertensives • Photographic documentation of all cutaneous melanoma lesions • Imaging studies (brain MRI preferably T1 with contrast, whole-body computed tomography, or positron emission tomography) to evaluate for internal metastases
Test Dose	• Vital signs, modified physical exam, including lymph node and skin exam, ECOG assessment, and review of current medication list • A total of 7 million IU of IL-2 is distributed amongst all melanoma lesions . • If test dose is tolerated and severe adverse events are absent, patient returns in 3-4 days to start the "Treatment Cycle."
Treatment Cycle	• Vital signs, modified physical exam, including lymph node and skin exam, ECOG assessment, review of current medication list, and assessment of any possible adverse events is completed at every visit • Administer 7 - 21 million IU total of IL-2 distributed amongst melanoma lesions every 3-4 days. The dose given at each visit will depend on the number of melanoma lesions being treated, the patient's ability to both maintain baseline blood pressure and tolerate systemic toxicities. • For lesions that become intolerably inflamed and ulcerated, the frequency of injections should be reduced to once weekly. • For lesions that have not completely regressed after 3 weeks of treatment, additional therapy with 10 seconds of cryotherapy to further induce inflammation should be considered. • If concern for infection arises, empiric antibiotics with either doxycycline 100 mg or double strength Bactrim (160 mg trimethoprim and 800 mg sulfamethoxazole) twice daily should be started. Antibiotic regimen can be adjusted according to culture results and bacteriological sensitivities. • Both imiquimod and topical retinoid (tazarotene 0.1% or tretinoin 0.1% cream) should be applied nightly to all sites, including a 10 cm margin of normal-appearing skin. Keeping in mind the goal of continued clinical inflammation in the treated areas, the frequency of topical imiquimod and the retinoid may be reduced to five-times weekly or less depending on the degree of intolerable pain and ulceration of the lesions. • After 4 weeks of treatment, IL-2 (a total of eight treatments, including test dose), imiquimod and topical retinoid are held for 2 weeks to permit the treated sites to heal.
Reassessment	• Treated sites are re-evaluated and full body skin exam is performed to assess for unresolved or new lesions. Lesions suggestive of melanoma should be photographed and biopsied. • If complete response is achieved, topical therapy with imiquimod plus topical retinoid should be restarted for an additional 3 weeks, and then continued on a maintenance regimen (daily application for one week every month).

Table 2: Blood Pressure Goals After IL-2 Administration

Baseline Systolic Blood Pressure	Target Systolic Blood Pressure on Days of Treatment*
<100 mm Hg	>80 mm Hg
100-120 mm Hg	>85 mm Hg
>120 mm Hg	>90 mm Hg

* Blood pressure goals do not apply if patient is either symptomatic, e.g. lightheadedness, altered mental status, decreased urine output, elevated cardiac enzymes, and should be treated with fluid resuscitation and/or vasopressors.

Adopted from (Schwartzentruber, 2001)

Table 3: Management of IL-2 Associated Adverse Events

Adverse Event	Management*
Hypotension	• Hold antihypertensives on day of IL-2 administration. Confirm with cardiology if also being used as an antiarrhythmic. • Fluid resuscitation (limit to 1-1.5L) to meet blood pressure goals (Table 2). Colloid solutions are preferred to crystalloid. • Administer phenylephrine 0.1-2.0 mcg/kg/min if fluid administration is insufficient to increase blood pressure.
Sinus tachycardia	• Evaluate for underlying etiology (i.e. fever, hypovolemia, pulmonary embolism, ischemia, pain, hypoxia, infection, anemia, medication induced) and treat accordingly. • If sustained (>130 beats per minute despite correction of possible underlying etiologies), discontinue IL-2
Supraventricular tachycardia (including atrial fibrillation)	• Discontinue IL-2 therapy • If heart rate is sustained > 150 beats per minute, consider valsalva maneuver or carotid massage or pharmacologic therapy depending on rhythm and per cardiology consult
Fever/ chills	• Administer acetaminophen 325 mg- 650 mg orally every 4-6 hours with warm blankets
Nausea	• Administer antiemetics, such a ondansetron 4 mg-8 mg orally every 8 hours as needed (avoid steroids) • Administer histamine 2-blockers, such as ranitidine 150 mg orally nightly
Diarrhea	• Administer antimotility agents, such as loperamide 2 mg- 4 mg (do not exceed 16mg/day) after each episode
Dyspnea	• Monitor oxygen saturation and administer supplemental oxygen if sat <90% • Attain chest-x-ray to evaluate for pulmonary edema. If pulmonary edema is present without hypotension, administer diuretics (i.e. furosemide 80 mg intravenously every hour), morphine sulfate 1-3 mg intravenously every 5 minutes, nitroglycerin 5-200 mcg intravenously every minute, supplemental oxygen, and place patient in upright position
Peripheral edema	• Recommend compression stockings on days of treatment. • If edema is severe, administer diuretics as clinically indicated, while monitoring for hypotension.
Acute Kidney Injury or Oliguria	• Administer fluid boluses (limit to 1-1.5L) • If urine output does not resume after fluid resuscitation, place indwelling urinary catheter and consider intravenous dopamine at 2 mcg/kg/min. • If urine output is sustained at < 10 mL/h or creatinine > 3 mg/dl, discontinue IL-2 therapy.
Anemia	• Transfuse as medically indicated for hematocrit < 28%
Thrombocytopenia	• Consider platelet transfusion if count <20,000/mm^3 • Discontinue IL-2 therapy if platelet count sustained at <30,000 mm^3
Infection or Cutaneous Ulcerations	• Administer antibiotics empirically with doxycycline 100 mg or double strength Bactrim (800 mg sulfamethoxazole and 160 mg trimethoprim) twice daily • Consider culturing wound and adjust antibiotic therapy according to organism and susceptibility panel
Transient Cholestasis	• Most often reversible upon discontinuation of IL-2 therapy and rarely clinically consequential
Elevated Cardiac Enzymes	• Attain electrocardiogram and trend cardiac enzymes every 8 hours • Consider cardiology consult for evaluation of myocarditis • Discontinue IL-2 therapy until echocardiogram has ruled out myocardial dysfunction
Neurotoxicity (i.e. confusion, delirium)	• Discontinue IL-2 therapy.
Rash or Pruritus	• Treat symptomatically with emollients and antihistamines • Avoid steroid or alcohol based medications and lotions.

* Managing adverse events may require inpatient hospitalization and/or involvement of the primary care physician, based on the treating physician's comfort level and accessibility to medications.

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