Overview of IL-2 Treatment in Support of TIL Cell Therapy

November 2022

TIL CELL THERAPY WORKING GROUP

TIL Cell Therapy Working Group

- The TIL Cell Therapy Working Group is a team of internationally-recognized oncologists, cell therapists and researchers dedicated to helping healthcare practitioners better understand TIL cell therapy
- TIL cell therapy is a type of cell therapy in which tumor-infiltrating lymphocytes are harvested from a patient's tumor and grown in large numbers in vitro. These lymphocytes are then given back to the patient by infusion to help the immune system recognize and eliminate cancer cells
- To learn more about TIL cell therapy, visit

tilworkinggroup.com

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Role of IL-2 in TIL Cell Therapy

November 2022

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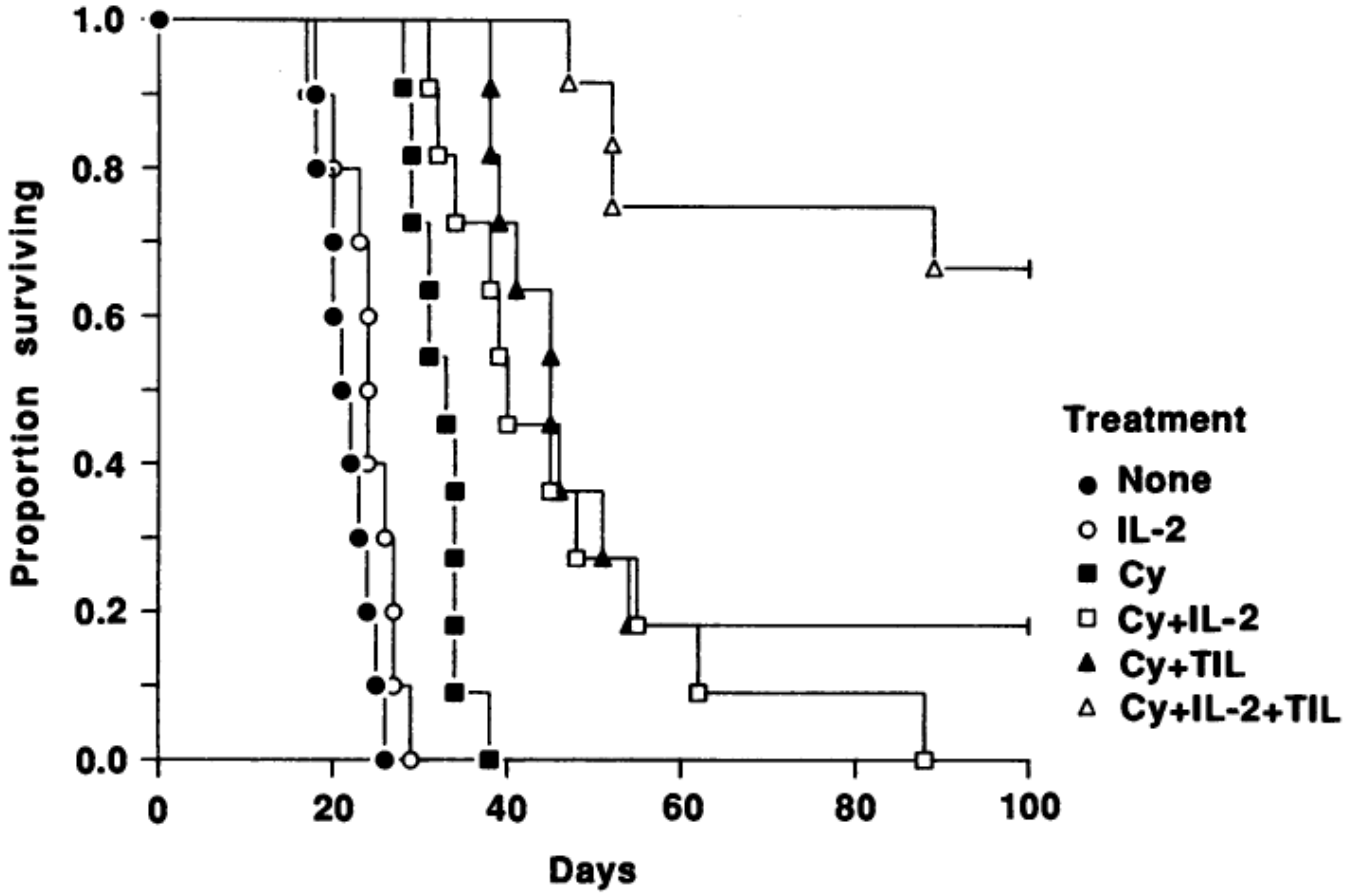
Preclinical Evidence of Rationale for IL-2 in TIL Cell Therapy



- The addition of cyclophosphamide and IL-2 to TILs potentiated the anti-tumor effect of TILs[1]
- The results from these murine studies formed the basis for the original and still most used TIL treatment protocol

Cy, cyclophosphamide; IL-2, interleukin-2; TIL, tumor-infiltrating lymphocyte.

1. Rosenberg SA, at al. *Science*. 1986;233:1318-1321.

Content prepared by Igor Puzanov, MD, MSCI, FACP; Roswell Park Comprehensive Cancer Center.

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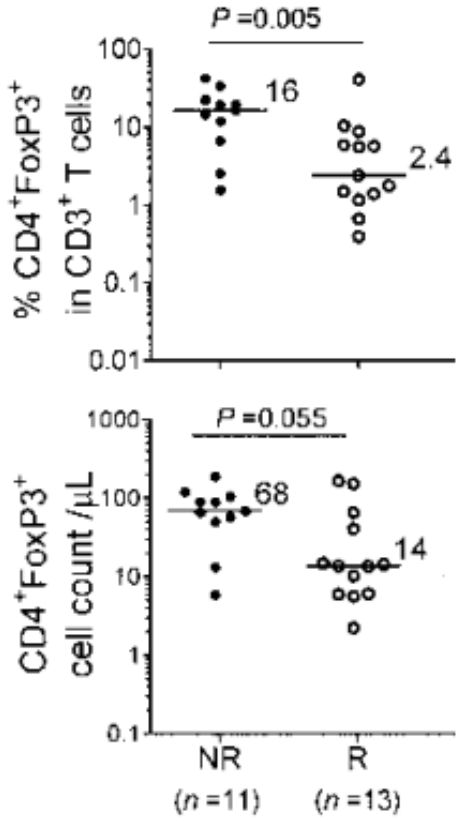
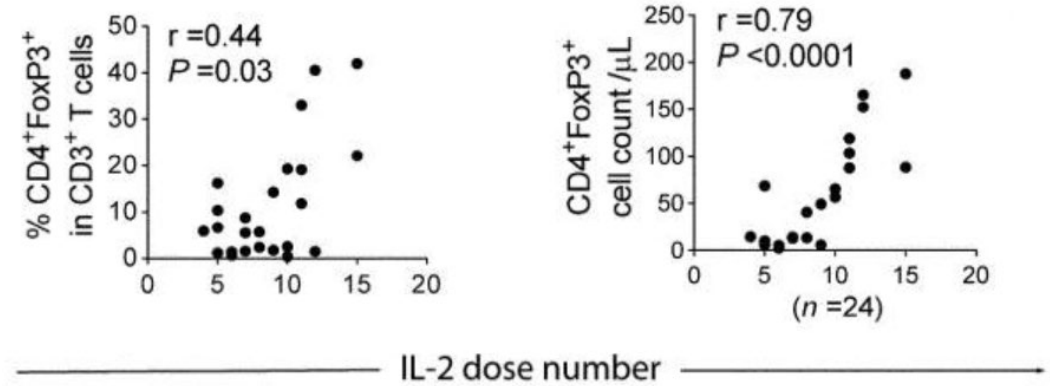
Clinical Evidence of Effect of Number of IL-2 Doses in TIL Cell Therapy



- Treg counts are higher on non responders versus responders to TIL cell therapy, indicating that Tregs may play an inhibitory role in TIL cell therapy[1]
- Treg counts were similar between responder and nonresponder groups prior to TIL cell therapy[1]



- Increasing doses of IL-2 lead to increased counts of Tregs in patients treated with TIL cell therapy, suggesting that IL-2 can selectively promote the growth of Tregs versus TILs[1]

IL-2, interleukin-2; NR, nonresponder; R, responder; TIL, tumor-infiltrating lymphocyte; Treg, regulatory T cell.

1. Yao X, et al. *Blood*. 2012;119:5688.

Content prepared by Igor Puzanov, MD, MSCI, FACP; Roswell Park Comprehensive Cancer Center.

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Determination of IL-2 Dose Used in Lifileucel TIL Cell Therapy

Short course of high-dose IL-2 used in lifileucel regimen:

- 600,000 IU/kg, every 8-12 hours, ≤6 doses

Number of IL-2 Doses Received[1]	N	Response			*P* Value	
		CR, n (%)	PR, n (%)	NR, n (%)	CR vs PR+NR	CR+PR vs NR
0-2[a]	11	0 (0)	3 (27)	8 (73)	0.46	0.53
3-5	39	12 (31)	13 (33)	14 (36)	-	-
6-8	41	10 (24)	11 (27)	20 (49)	-	-
>8	8	2 (25)	3 (38)	3 (37)	-	-
Median (25th-75th percentile)	-	5.5 (5.0-7.0)	5.0 (4.0-6.3)	6.0 (3.5-7.0)	0.34	0.55

- The decision for using ≤6 doses was based on an internal analysis performed by Iovance in mid-2016 of the mean number of IL-2 doses received from the 3 NCI studies
- Patient tolerance to IL-2 varies greatly (range, 0-10 doses) with no significant difference between responders and nonresponders[1]

[a]It was not possible to determine how many of the 11 patients received 0, 1 or 2 doses.
CR, complete response; IL-2, interleukin-2; NCI, National Cancer Institute; NR, no response; PR, partial response; TIL, tumor-infiltrating lymphocyte.
1. Goff SL, et al. *J Clin Oncol.* 2016;34:3006-3006.
Content prepared by Igor Puzanov, MD, MSCI, FACP; Roswell Park Comprehensive Cancer Center.

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Efficacy of TIL Cell Therapy Versus IL-2 Monotherapy in Melanoma

Response	Lifileucel (N=66)[1,2]	IL-2 Monotherapy (N=270)[3]
IL-2 dose	600,000 IU/kg Q8H or Q12H; ≤6 doses	600,000 IU/kg Q8H; ≤28 doses
Median number of IL-2 doses received	5	18
ORR, n (%)	24 (36)	43 (16)
CR, n (%)	3 (4)	17 (6)
PR, n (%)	21 (32)	26 (10)
DOR, months	NR	NA

- The cumulative IL-2 dose in TIL cell therapy is lower than the cumulative IL-2 dose in IL-2 monotherapy[4]
- Low-dose IL-2 monotherapy regimens do not result in consistent antitumor effects in patients with melanoma[5]

The response rates observed with lifileucel in patients with melanoma suggest that the activity is mediated by TIL infusion, with IL-2 supporting TIL activity

CR, complete response; DOR, duration of response; IL-2, interleukin-2; NA, not available; NR, not reached; ORR, objective response rate; PR, partial response; Q8H, every 8 hours; Q12H, every 12 hours; TIL, tumor-infiltrating lymphocyte.

1. Sarnaik AA, et al. *J Clin Oncol.* 2021;39:2656-2666. 2. Larkin JMG, et al. Presented at the 2021 American Society of Clinical Oncology Annual Meeting, June 4-8, 2021. 3. Aldesleukin [package insert]. Revised May 2019. 4. Chapman PB. *J Clin Oncol.* 2021;39:2640-2642. 5. Atkins MB. *Semin Oncol.* 2002;29:12-17.

Content prepared by Igor Puzanov, MD, MSCI, FACP; Roswell Park Comprehensive Cancer Center.

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IL-2 Management in Support of TIL Cell Therapy

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High-Dose IL-2 Overview

Dosing *(see package insert for more details)*

Dose: 600,000 IU/kg (0.037 mg/kg) dose Q8H or Q12H by a 15-minute IV infusion for a maximum of 6 doses. Dosing may start as soon as 3-6 hours after TIL infusion and should begin within 24 hours of TIL infusion

Pharmacokinetics

- Distribution half-life: 13 minutes
- Elimination half-life: 85 minutes after 5-minute IV infusion
- Biological effects peak several hours after initial exposure
- Short half-life and rapid clearance contribute to manageability and reversibility of toxicity when drug is discontinued

Most Common AEs: hypotension, nausea and vomiting, diarrhea, confusion, SOB, pulmonary edema, abnormal LFTs, renal failure, pancytopenia, rash, fevers, chills, rigors, malaise, infections

To help mitigate these issues:

1. Counsel patients on likelihood of these AEs and most AE will occur
2. Ensure proper fluid status, vitals and utilize pressor support as needed
   - Minimize IV fluids when tolerating diet and not clinically vasodilated
3. Monitor cognitive function
4. Discontinue use if a patient safety concern arises

Careful Monitoring and Early Management of AEs Is Critical

Monitor at baseline and during treatment as clinically indicated:

1. Hematologic panel (CBC w/diff & platelets), CMP, blood chemistries before each dose; monitor for rising serum creatinine
2. Vitals every 4 hours, unless on pressors then every 2 hours
3. Pulse oximetry Q8H or Q4H on pressors (start O_2 if oximeter is <90%), and check chest x-ray
4. Neuro-assessment/mental status every 8 hours
5. Strict intake and output every 8 hours and daily weights
6. Telemetry monitoring during therapy
7. EKG if persistent tachycardia for over 2 hours

AE, adverse event; CBC, complete blood count; CMP, comprehensive metabolic panel; EKG, electrocardiogram; IL-2, interleukin-2; IV, intravenous; LFT, liver function tests; Q4H, every 4 hours; Q8H, every 8 hours; Q12H, every 12 hours; SOB, shortness of breath; TIL, tumor infiltrating lymphocyte.

Aldesleukin [package insert]. Revised September 2019.

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IL-2 Management

- Institutional-based guidelines are necessary for therapy management
- Pretherapy interventions:
  - Discontinue antihypertensive medications 24 hours prior to IL-2 administration
  - Start scheduled acetaminophen, indomethacin/naproxen*, antiemetics, and H2 blocker before administering IL-2
  - Minimize unnecessary IV fluids before beginning IL-2
- General principles of IL-2 administration:
  - Blood pressure target assigned based on baseline blood pressure and assessed prior to each dose
  - Urine output assessed prior to each dose (150 mL/8 hours)
  - Chills/rigors typically occur within 1-2 hours of each dose, fever occurs 1-2 hours after chills/rigors
  - **Note: IL-2 management should not be confused with CAR-T adverse event management with tocilizumab and steroids.** Steroids should be avoided unless adrenal insufficiency is suspected; for pts with known adrenal insufficiency/hypophysitis, keep on their physiologic replacement steroids and boost if there is clinical sign of adrenal insufficiency

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

*Avoid naproxen/indomethacin if any baseline renal dysfunction.
H2, histamine 2; IL-2, interleukin-1; IV, intravenous.
Schwartzentruber DJ. *J Immunotherapy*. 2001;24:287-293.

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General IL-2 Management Guidelines for TIL Cell Therapy

Toxicity	Management
Cardiovascular	Sinus tachycardia >120 beats per minute sustained for 1 hour ▪ Assess fluid status and may administer NS or LR 500 mL IV fluid bolus ▪ Assess telemetry/EKG for arrhythmias ▪ Replace electrolytes ▪ If arrhythmia or sustained tachycardia despite correction of reversible factors (hypotension, fever, dopamine) then may need to hold dose or stop IL-2 therapy
Gastrointestinal	▪ Nausea/vomiting scheduled ondansetron 8 mg IV Q8H 30 min prior to each dose ▪ Prochlorperazine 10 mg IV Q6H PRN nausea/vomiting or lorazepam 0.5 mg IV Q6H PRN nausea/vomiting ▪ Diarrhea PRN loperamide 2mg every 2 hours as needed for diarrhea & diphenoxylate/atropine 2 tabs po Q6H PRN diarrhea refractory to loperamide ▪ Gastrointestinal prophylaxis pantoprazole 40 mg PO/IV daily/Famotidine 20mg POI/IV BID ▪ Transient cholestasis is reversible after discontinuation of IL-2 therapy
Dermatologic	▪ Macular erythema, pruritus, desquamation ▪ Diphenhydramine 25 mg PO Q6H PRN itching OR hydroxyzine 10 mg PO Q6H PRN itching ▪ Aveeno and Lubriderm lotion TID
Endocrine	▪ Hypothyroidism may need supplementation with levothyroxine if it persists after therapy completed ▪ Keep pts on their physiologic replacement steroids and boost if there is clinical sign of adrenal insufficiency; consider treating at 2X or 3X baseline during IL-2-induced hypotension
Hematologic	▪ Anemia transfusion if Hgb <7 g/dL ▪ Thrombocytopenia transfusion if <10,000 if no prior history of CNS metastasis or <20,000 if history of CNS metastasis ▪ Transient lymphopenia, rebound lymphocytosis, eosinophilia, and transient granulocytopenia ▪ Neutropenia filgrastim; can be stopped when ANC is >1000 for 2-3 consecutive days
Infectious	▪ 10-30% incidence of staphylococcus bacterial infections ▪ Antibiotic treatment per institutional standards

BID, twice a day; EKG, electrocardiogram; Hgb, hemoglobin; IL-2, interleukin-2; IV, intravenous; LR, lactated Ringer's; NS, normal saline; PO, by mouth; PRN, take as needed; Q6H, every 6 hours; Q8H, every 8 hours; sCR, serum creatinine; TID, 3 times a day.

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General IL-2 Management Guidelines for TIL Cell Therapy

Toxicity	Management
Fevers/chills/rigors	Fever above 100.5°C ▪ Acetaminophen 650 mg PO Q4H scheduled ▪ Indomethacin/naproxen* PO BID scheduled (stop if sCr >2, decreased UOP, or platelets <50K) ▪ Hydromorphone 0.5 mg IV every 15 min as needed for rigors, may repeat x 3 total doses ▪ Meperidine 25 mg IV once as needed for rigors refractory to hydromorphone (if sCr <1.7)
Blood pressure	Target blood pressure set on admission and assessed prior to each dose – Assess about 2 hours prior to dose ▪ If not meeting target administer NS or LR 250-500 mL IV bolus over 30 min ▪ Repeat blood pressure 30 min post IV bolus; if not meeting target then may repeat additional 250-500 mL IV bolus ▪ If a patient is not on oxygen, more fluid can typically be given and pressors/stopping IL-2 are typically not needed
Urine output	sCR monitored daily Urine 150 mL/8 hours – Assess 2X daily, including about 2 hours prior to dose ▪ If not meeting target administer NS or LR 250-500 mL IV bolus over 30 min ▪ Check urine output 1 hour post IV bolus, if <150 mL/8 hours then may repeat another 250-500 mL IV bolus ▪ Persistent low urine output despite IV fluid bolus then initiate dopamine at renal perfusion doses 2 µg/kg/min, urine output of 150 mL/8 hours must be established before additional IL-2 doses may be given
Pulmonary	▪ O_2 saturation should be maintained above ≥92%, initiate oxygen therapy if O_2 <95% (study 90-92%) ▪ Physical exam with auscultation of rales in lung bases ▪ Chest X-ray should be obtained to assess for pleural effusions or pulmonary edema

*Avoid naproxen/indomethacin if any baseline renal dysfunction.
BID, twice a day; IL-2, interleukin-2; IV, intravenous; LR, lactated Ringer's; NS, normal saline; PO, by mouth; Q4H, every 4 hours; sCR, serum creatinine; UOP, urinary output.

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Guidelines for IL-2 Dose Skipping or Discontinuation

System	Relative Criteria	Absolute Criteria
Cardiac	Sinus tachycardia (>120 beats per min)	Sustained sinus tachycardia >2 hr while afebrile after correcting hypotension, fever, and tachycardia and stopping dopamine Atrial fibrillation, supraventricular tachycardia, or ventricular arrhythmias Elevated CK, troponin (cardiac/renal source), or EKG changes of ischemia
Gastrointestinal	Diarrhea 1000 mL/shift	Diarrhea 1000 mL/shift x 2 AST/ALT LFTs>500 U/L, or bilirubin >8 mg/dl
Hemodynamic	Any requirement for pressors	Fluid requirement results in pulmonary edema requiring supplemental O_2 that cannot be weaned off before next dose is due Maximum phenylephrine 1.5-2 µg/kg/min
Hemorrhagic	Guaiac + sputum, emesis, stool Platelets 30,000 to 50,000	Frank blood sputum, emesis, stool
Musculoskeletal	Extremity tightness	Extremity paresthesias
Neurologic	Vivid dreams Emotional lability	Hallucination, disorientation, or mental status changes not reversible Persistent crying
Pulmonary	Resting shortness of breath Rales 1/3 up chest	> 2L O_2 by nasal cannula for saturation ≥ 95% or 40% O_2 mask Endotracheal intubation Moist rales 1/2 up chest Pleural effusion requiring tap or chest tube
Renal	Urine <150 mL/8 hours sCR increase of 2-3X baseline Bicarbonate <18 mEq/L	Urine < 80 mL/8 hours sCR ≥ 3 mg/dL Persistent acidosis despite replacement

CK, creatinine kinase; EKG, electrocardiogram; IL-2, interleukin-2; sCR, serum creatinine.

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TIL Cell Therapy: When to Skip a Dose or Discontinue IL-2

- Assess IL-2 criteria prior to each dose of IL-2 to determine if dosing is appropriate

Observation Category	Action
≤ 3 relative criteria	Initiate corrective measure ± skip IL-2
≥ 3 relative criteria	Initiate corrective measures, skip IL-2 Stop IL-2 if not reversible
Any absolute criteria	Initiate corrective measures, skip IL-2 Stop IL-2 if not reversible

- Allow dosing delay of up to 2 hours if pt can get within parameters, but do not delay the next dosing
- Administer IL-2 doses at least 6 hours apart
- If dosing skipped for >24 hours → Stop IL-2
- If two consecutive doses are skipped → Stop IL-2

IL-2, interleukin-2

Schwartzentruber DJ. *J Immunotherapy.* 2001;24:287-293.

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Example IL-2 Pre-Dose Assessment Checklist

Aldesleukin Pre-Dose Assessment for TIL Cell Therapy

OK To Give IL-2 dose?

❑ Yes (give dose)
❑ No (skip dose)
❑ No (permanently discontinue IL-2)

Dose Date: DD-Month-YYYY Dose Time: HH:mm

Parameter Reviewed:

❑ General (fatigue, fever, rigor-chills)
❑ Pulmonary (cough, dyspnea)
❑ Cardiac (arrythmia, edema, hypotension)
❑ Dermatology (dry skin, erythema, pruritus, rash)
❑ Gastrointestinal (anorexia, diarrhea, mouth dryness, nausea, vomiting)
❑ Neuro-assessment (brief mental status exam)
❑ Laboratory (chemistry, hematology)
❑ Vital Signs (T, P, R, BP)
❑ I/O Totals (prior 8 hours)

Aldesleukin Pre-Dose Assessment for TIL Cell Therapy (continued)

Reasons to Skip IL-2 Dose

❑ Cardiovascular criteria
❑ Gastrointestinal or liver function criteria
❑ Hemodynamic/hypotension refractory to fluid resuscitation
❑ Hemorrhagic criteria
❑ Musculoskeletal criteria
❑ Neurological changes
❑ Pulmonary criteria/hypoxia
❑ Renal injury/dysfunction
❑ Any other serious toxicities that are not controlled at time of next dose

Reasons to Permanently Discontinue IL-2 Dosing

❑ Cardiovascular criteria
❑ Gastrointestinal or liver function criteria
❑ Hemodynamic/hypotension refractory to fluid resuscitation
❑ Hemorrhagic criteria
❑ Musculoskeletal criteria
❑ Neurological changes
❑ Renal injury/dysfunction
❑ Pulmonary criteria/hypoxia
❑ Documented systemic infection
❑ Any other serious toxicities that are not controlled at time of next dose

Additional details (optional)

IL-2, interleukin-2.

Post IL-2 Completion

- Stop IL-2 related medications after completion of therapy (ie, hydromorphone, ondansetron, acetaminophen, naproxen)
- Frequent need for transfusions, blood and platelets
- Minimize IV fluid when recovered from IL-2 and strongly consider diuresis with furosemide 40 mg IV for 3-5 days
- Electrolyte monitoring and replacement
- Stop filgrastim if ANC >500 or 1000 and afebrile for 24 hours or as specified in protocol

ANC, absolute neutrophil count; IL-2, interleukin-2; IV, intravenous.

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Discharge Considerations

- Patient may be discharged once ANC >500 and afebrile x 24 hours after stopping IV antibiotics and fluconazole (~7-10 days post TIL infusion)
- If patient is to maintain IV access set up line care
- Antibiotics per institutional standard as CD4 count recovers ≥200

ANC, absolute neutrophil count; IV, intravenous; TIL, tumor-infiltrating lymphocyte.

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Considerations for IL-2 in Support of TIL Cell Therapy

- Patients who receive IL-2 as part of TIL cell therapy differ from patients who receive IL-2 monotherapy, as they have:
  - Received lymphodepletion therapy prior to IL-2
  - Are neutropenic
  - Experienced considerable fluid weight gain before receiving IL-2
- Special considerations for patients who receive IL-2 therapy as part of TIL cell therapy:
  - IL-2 administration starts the day following TIL infusion and is administered on a standard schedule, either Q12H or Q8H (may be helpful to schedule around standard vital times for institution)
  - Check vital signs and UOP 2 hours prior to first IL-2 dose so abnormalities can be addressed
  - If the patient experiences fever with IL-2 administration, start neutropenic fever protocol and stop prophylactic anti-infective
  - No IV contrast or corticosteroids should be administered without physician approval
  - IL-2 can be held/discontinued at the discretion of treating clinician at any point in time
  - There is no clear correlation between total number of IL-2 doses given and TIL cell therapy response

IL-2, interleukin-2; IV, intravenous; Q8H, every 8 hours; Q12H, every 12 hours; TIL tumor-infiltrating lymphocyte; UOP, urinary output.

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Patient Case Studies

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Patient Case #1

47-year-old male receiving high-dose IL-2 therapy following TIL infusion. Target SBP is 90 mmHg. Patient has received 3 doses of IL-2 and BP prior to dose #4 is 85/63 mm Hg. Patient has 450 mL UOP since his last dose.

1. What is the most appropriate decision for the patient's IL-2 therapy?

Administer NS bolus 500 mL over 30 minutes and recheck BP30 minutes after bolus is completed

2. BP 30 minutes later is 95/55 mm Hg. What decision should be made on the patient's next IL-2 dose

Proceed with dose #4 of IL-2, patient is meeting BP & UOP criteria

BP, blood pressure; IL-2, interleukin-2; NS, normal saline; TIL tumor-infiltrating lymphocyte; SBP, systolic blood pressure; UOP, urinary output.

Content prepared by Jen Swank, PharmD, BCOP; Clinical Pharmacy Specialist – Medical Oncology, Moffitt Cancer Center.

Patient Case #2

Patient received his 4th dose of high-dose IL-2 after the IV fluid bolus. His maintenance fluids were maintained at 50 mL/hr. Prior to the 5th dose the patient parameters are as follows.

BP: 83/55 HR: 105 O_2 Saturation: 95% on RA UOP: 250mL/8hr WBC: 6.54 Hgb: 9.5 Platelets: 95 sCr: 2.1

Pulmonary exam clear no rales or crackles

What is the most appropriate intervention at this time?

Administer a NS 500 mL IV fluid bolus over 30 min and recheck blood pressure 30 min after bolus completed

BP is 88/60 mm Hg after the IV fluid bolus, what should be done at this time?

May administer a second NS 500 mL IV fluid bolus over 30 min since they may receive 1.0-1.5 L of additional fluid bolus in 24 hours if pulmonary status is stable

If patient's respiratory status is compromised or the patient has rales, then may opt to initiate phenylephrine 0.1 µg/kg/min and may be titrated up to obtain target blood pressure, do not administer IL-2 if phenylephrine dose is 0.5 µg/kg/min or above

BP, blood pressure; Hgb, hemoglobin; HR, heart rate; IL-2, interleukin-2; IV, intravenous; NS, normal saline; RA, radial artery; sCR, serum creatinine; UOP, urinary output; WBC, white blood cell.

Content prepared by Jen Swank, PharmD, BCOP; Clinical Pharmacy Specialist – Medical Oncology, Moffitt Cancer Center.

Patient Case #3

55-year-old female receiving high-dose IL-2 therapy following TIL infusion. Target SBP is 90 mmHg. Patient has received 3 doses of IL-2 and labs prior to the 4th dose her labs show a sCr of 2.5. Patient's blood pressure is 96/54 and patient has had 140 mL of UOP in the last 8 hours.

What is the appropriate intervention for this patient prior to their next dose?

Administer NS bolus 500 mL over 30 minutes and recheck urine output after bolus is completed. Discontinue naproxen due to decreased UOP and sCr of 2.5

Patient had urine output of 200 mL after the bolus, therefore IL-2 dose #4 was given. Prior to dose #5 patient did not meet their urine output criteria again and lungs were clear. What should be done at this time?

May administer a NS 500 mL IV fluid bolus over 30 min since they may receive 1.0-1.5 L of additional fluid bolus in 24 hours if pulmonary status is stable

Patient's urine output responded to a second bolus and received dose #5 of IL-2. Repeat sCr was ordered prior to dose #6 and was 3.1 What should be done at this time?

sCr of >3 is a criteria for stopping IL-2 therapy. Physician should discontinue the IL-2 orders and all supportive care medications

IL-2, interleukin-2; IV, intravenous; NS, normal saline; SBP, systolic blood pressure; sCR, serum creatinine; TIL, tumor-infiltrating lymphocyte; UOP, urinary output.

Content prepared by Jen Swank, PharmD, BCOP; Clinical Pharmacy Specialist – Medical Oncology, Moffitt Cancer Center.

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Patient Case #4

51-year-old female receiving high-dose IL-2 therapy with TIL. Patient's target blood pressure is 85. Patient received 3 doses of high-dose IL-2 and morning labs prior to dose #4 were as follows.

BP: 92/63 HR: 105 O2 Saturation: 95% on RA UOP: 300 mL/8 hr WBC: 8.94 Hgb: 9.3 Platelets: 155 sCr: 1.7

I/O 24 hours: 3350 mL/950 mL weight: 3 kg gain since admission Pulmonary exam: mild rales in bottom fourth of b/l lungs

What should be done at this time for the patient?

Patient has rales, weight gain, and decreased UOP recommend Lasix 40 mg IV x 1, but may proceed with IL-2 dose

Prior to the next dose (#5) the patient has been tachycardic at 130-140 for the last 2 hours and BP is 88/52. What would you recommend at this time?

Contact the provider and perform an EKG. If sinus tachycardia, then administer a NS 500 mL bolus over 30 minutes. If HR responds may proceed with next dose, if persists may hold IL-2 dose.

Patient skips dose #5 of high-dose IL-2 due to persistent tachycardia. BP, UOP, and HR are all acceptable prior to dose #6 so may proceed with dose.

b/l, bilateral lower; BP, blood pressure; EKG, electrocardiogram; Hgb, hemoglobin; HR, heart rate; IL-2, interleukin-2; I/O, input/output; NS, normal saline; RA, radial artery; sCR, serum creatinine; TIL, tumor-infiltrating lymphocyte; UOP, urinary output; WBC, white blood cell.

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