Management of toxicities associated with high-dose interleukin-2 and biochemotherapy

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High-dose interleukin-2, administered as a single agent or in combination with antineoplastic agents, known as biochemotherapy, holds the promise of durable remissions for patients with metastatic renal cell carcinoma and metastatic melanoma. The toxicities arising from high-dose interleukin-2-based therapies affect every organ system, causing significant acute morbidity. Administration of high-dose interleukin-2-based therapies requires specialized care and knowledge because of the severity and uniqueness of toxicities compared with the toxicities encountered with other forms of anticancer therapy. However, the toxicities of high-dose interleukin-2-based therapies are predictable and manageable by vigilant monitoring and appropriate supportive care protocols. To maximize outcomes, both acute and delayed toxicities require vigilant monitoring and adroit symptom management. This review details the pathophysiology, monitoring parameters, and management strategies for patients receiving high-dose interleukin-2-based therapy, with a focus on new and important management principles. *Anti-Cancer Drugs* 24:1–13 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Upon cursory inspection, cutaneous metastatic melanoma (MM) and metastatic clear-cell renal cell carcinoma (MRCC) appear to have little in common. However, several unique characteristics exist between them that govern therapeutic modalities. These similarities include the relative insensitivity to chemotherapy and radiotherapy, the propensity for distant metastases early in the disease process, and antigenicity [1,2]. Numerous therapeutic modalities, including antiangiogenic and immunomodulatory agents, have induced impressive short-term responses that may lead to long-term clinical benefits in patients with MM and MRCC. Over the past 10 years, the therapeutic options for MM have changed considerably with the discovery of *BRAF* mutations and the subsequent introduction of vemurafenib and the cytotoxic T-lymphocyte antigen 4 antagonist ipilimumab. The options for the treatment of MRCC include the signal transduction inhibitors sunitinib, sorafenib, pazopanib, axitinib, everolimus, and temsirolimus, in addition to the antiangiogenic bevacizumab. A comprehensive discussion of these agents and their role in therapy for MM and MRCC is beyond the scope of this paper.

However, high-dose interleukin-2 (HD-IL2) remains a relevant therapeutic option as it uniquely possesses long-term data for MM and MRCC and has been shown to cure or, more accurately, induce a durable remission in select patients. Despite the therapeutic advances stemming from the introduction of targeted agents for MM and MRCC, HD-IL2 remains an important therapy against both malignancies. HD-IL2 may be administered concomitantly with traditional antineoplastic agents referred to as biochemotherapy, reserved strictly for MM, or as a single agent for both MM and MRCC.

Interleukin-2

Interleukin-2 is a primary cytokine released by CD4+ cells, the predominant T-helper 1 (Th1) cells, responsible for cell-mediated immunity. Interleukin-2 upregulates proinflammatory cytokines, expands CD4+ cells, and augments natural killer cell activity, the latter postulated as the primary antitumor mechanism [3]. This positive feedback loop is counterbalanced by CD8+ cells from the T-helper 2 (Th2) class. Under physiologic conditions, both Th1 and Th2 act to modulate the immune response selectively [4]. Although both MM and MRCC express antigens known to stimulate the Th1 response, for reasons that have not been completely elucidated, it is the rare patient who experiences spontaneous remission [5].

Exogenous administration of supraphysiologic doses of interleukin-2 stimulates Th1 considerably, theoretically leading to immune recognition of MM or MRCC lesions causing cell-mediated toxicity. Although there is a paucity of data describing the interplay among agents in biochemotherapy regimens, the benefit may be additive from both chemotherapy and immunotherapy. However, biochemotherapy includes antineoplastic agents, which have minimal single-agent efficacy for MM. In theory, the

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antineoplastic agents damage MM cells, allowing more efficient immune-mediated detection and destruction of tumor cells [6].

Clinical use of high-dose interleukin-2 and biochemotherapy

HD-IL2 was approved by the United States Food and Drug Administration in 1992 for the treatment of MRCC on the basis of initial response rates of 20–35% [7]. An objective response rate of 14% was observed in 255 patients with MRCC. Notably, of the 14% with observed responses, 12% experienced a complete response that was prolonged and durable for years [8]. Food and Drug Administration approval was based on the finding that HD-IL2 produced durable responses with prolonged disease-free survival in a small subset of patients. Trials examining the effects of combining interleukin-2 and interferon have shown the combination to be no better than HD-IL2 as a single agent, although the methodology and design of these studies cannot prove the superiority of single-agent HD-IL2 [9–11]. A variety of doses and schedules of interleukin-2 have been studied, all of which consistently show the benefit of HD-IL2 [11,12]. As an adjuvant therapy of RCC in the nonmetastatic setting, HD-IL2 did not affect the overall survival [13]. Although the introduction of targeted therapies, many of which are orally administered, has decreased the use of HD-IL2 for MRCC, HD-IL2 is still considered a treatment option.

HD-IL2 has overall response rates of 15–17%, with 6–8% of patients achieving a complete response that is durable for years in patients with MM [14,15]. In a large pooled analysis, 270 patients were assessed from eight clinical trials. The overall objective response rate was 16%, with 6% of these responders experiencing a complete and durable response. Responses occurred in all sites of disease and in patients with a large tumor burden. Patients who had visceral disease such as lung, liver, lymph nodes, and subcutaneous nodules were observed to have the best responses.

Dosing variations of both 720 000 and 600 000 IU/kg have been found to be effective in clinical trials. On the basis of these data, HD-IL2 600 000 IU/kg as a 15-min intravenous bolus every 8 h for a maximum of 14 doses beginning on days 1 and 15 of an 8–12-week cycle remains a treatment option for MRCC and MM.

The low response rate with chemotherapy in MM has led to research to improve the response rates and overall survival. Biochemotherapy involves a combination of antineoplastic agents (dacarbazine, platinum analog, and vinca alkaloids) and cytokines (interleukin-2 and interferon-α). Results from several large trials in patients with MM have consistently shown that biochemotherapy increases the overall response rates and has a rapid onset of clinical benefit when compared with chemotherapy alone [16–19]. Unfortunately, the increase in the response rate does not translate into a difference in overall survival because of the short duration of response [6,20]. Strategies to extend the duration of response, such as maintenance biotherapy sequentially following biochemotherapy induction, have shown limited success [21]. Despite the lack of survival data, biochemotherapy is still a treatment option in patients with rapidly progressing disease. Treatment with HD-IL2 may still be used after biochemotherapy, if needed. One small trial showed that sequential HD-IL2 following biochemotherapy produced equivalent outcomes as single-agent HD-IL2 first line [22].

Adjuvant and neoadjuvant approaches to treatment with biochemotherapy have been evaluated. One phase II study with neoadjuvant biochemotherapy reported increase response rates, relapse-free survival, and overall survival [23]. Currently, there are two phase III studies evaluating biochemotherapy compared with high-dose interferon as an adjuvant therapy in stage III disease (*http://www.clinicaltrials.gov*).

Overview of toxicities of high-dose interleukin-2 and biochemotherapy

Almost no organ system is spared from the toxicities of HD-IL2-based therapy (Table 1). The addition of interferon, alkylating, and microtubule-disrupting agents to HD-IL2 in biochemotherapy regimens increases toxicity. The mechanisms of action and toxicity are complex and, in the case of HD-IL2, not fully elucidated [24,31]. However, the toxicities encountered in patients receiving HD-IL2-based therapies are predictable, manageable, and resolve quickly following therapy (Table 2) [6,7]. The majority of patients receiving HD-IL2-based therapy will require treatment interruption or early treatment discontinuation because of toxicity [14,25].

The high incidence of toxicities and the low incidence of long-term response with HD-IL2 have led to interest in biomarkers predicting outcomes and guiding patient selection. Clinical factors, such as the timing of HD-IL2 within 6 months following nephrectomy, visceral disease, good performance status, and absence of bone metastases, correlate with favorable outcomes when present before HD-IL2-based therapy [10,32]. Favorable outcomes after initiation of therapy may be observed in those who develop thrombocytopenia and possibly thyroid dysfunction, among others [33,34]. In clinical practice, selection of patients on the basis of performance status is the most important consideration, as all clinical trials demonstrating benefit included only patients with a performance status of ECOG 0–2, with excellent organ function. A complete review of the prognostic factors associated with HD-IL2-based therapy is beyond the scope of this paper.

Administration of all planned doses of HD-IL2 per cycle is not required to achieve a favorable response in those

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Table 1 **Incidence and severity of toxicities reported in major trials**

	Rosenburg *et al.* [7]. Bolus IL-2 (all grades)	Atkins *et al.* [10]. Bolus IL-2 (grade 3 or 4)	Tarhini *et al.* [22]. Bolus IL-2 (all grades/grades 3 or 4)	Aldesleukin (Proleukin) (package insert) [24] Bolus IL-2 (all grades/grade 4)	Guleria *et al.* [25]. Bolus IL-2 (grades 3 or 4)	White *et al.* [26]. Bolus IL-2 (all grades)	Pockaj *et al.* [27]. Bolus IL-2 (all grades)	Macfarlane *et al.* [28]. Bolus IL-2 (all grades/grade 3 or 4)	Krouse *et al.* [29]. Bolus IL-2 (all grades)	Atkins *et al.* [30]. High-dose IL-2 + LAK cells (all grades)	Negrier *et al.* [11]. CIVI IL-2 (grades 3 or 4)	Atkins *et al.* [16]. BCT (grade 3 or 4)	McDermott *et al.* [17]. BCT (grade 3 or 4)
Neurologic toxicity (%)													
Fatigue, delirium	–	–	81/8	–	–	–	–	–	–	–	–	–	–
Somnolence	12	–	–	–	–	–	–	–	–	–	–	–	–
Dizziness	–	–	–	11/0	–	–	–	–	–	–	–	–	–
Anxiety	–	–	–	12/0	–	–	–	–	–	–	–	–	–
GI toxicity (%)													
Nausea or vomiting	69	25	–	19/0	–	–	–	–	–	–	47	–	27
Nausea	–	–	96/8	35/0	–	–	–	–	–	–	–	26	–
Vomiting	–	–	85/8	50/1	–	–	–	–	–	–	–	20	–
Diarrhea	61	21	77/4	67/2	–	–	–	–	–	–	38	–	–
Anorexia	–	–	–	20/0	–	–	–	–	–	–	–	–	–
Stomatitis	–	–	–	22/0	–	–	–	–	–	–	–	–	–
Renal toxicity (%)													
Oliguria	42	33	96/12	63/6	18				–	–	–	–	–
Elevated serum creatinine	74	31	27/0	33/1	–	–	–	–	–	–	5	–	2
Hypomagnesemia	–	–	–	12/0	–	–	–	–	–	–	–	–	–
Hypocalcemia	–	–	–	11/0	–	–	–	–	–	–	–	–	–
Hepatic toxicity (%)												15	
Hyperbilirubinemia	85	34	81/50	40/2	–	–	–	–	–	–	1	–	–
Transaminitis	–	–	–	–	–	–	–	–	–	–	15	–	–
Cardiac toxicity (%)													
Hypotension	50	69	96/15	71/3	53	53	–	–	–	–	–	15	25
Hypotension resistant to vasopressor agents	–	–	–	–	–	0	–	–	–	–	94	–	–
Tachycardia	–	–	88/19	23/0	–	–	–	–	–	–	–	–	–
Arrhythmias	6	11	–	10/0	–	6	–	–	–	–	–	–	–
Supraventricular tachycardia	–	–	–	12/1	–	5	–	–	–	–	–	–	–
Myocardial infarction	2	0	–	7/–	–	0	–	–	–	–	–	–	–
Pulmonary toxicity (%)													
Respiratory distress leading to intubation	6	1	–	–	–	1	–	–	–	–	–	–	–
Pleural effusion	2	–	–	–	–	1	–	–	–	–	–	–	–
Infectious complications (%)													
Bacteremia, catheter related	–	–	–	–	–	–	3.1	–	–	–	–	–	0.5
Urinary tract infection	–	–	–	–	–	–	46	–	–	–	–	–	–
Sepsis	5	–	–	0/1	–	–	–	–	–	–	–	–	–
Infection	–	8	8/8	13/1	–	–	13	5.2	–	–	11	10	9
Dermatologic toxicity (%)													
Pruritus	22	–	–	24/0	–	–	–	–	–	–	–	–	–
Stomatitis	3	–	–	–	–	–	–	–	–	–	–	–	–
Rash, dry skin	–	–	85/4	42/0	–	–	–	–	–	–	–	–	–
Exfoliative dermatitis	–	–	–	18/0	–	–	–	–	–	–	–	–	–
Endocrine and metabolic activity toxicity (%)													
Hypothyroidism	–	–	–	–	–	–	–	–	35	21	–	–	–
Hyperthyroidism	–	–	–	–	–	–	–	–	7	–	–	–	–

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Table 1 (*continued*)

	Rosenburg *et al.* [7]. Bolus IL-2 (all grades)	Atkins *et al.* [10]. Bolus IL-2 (grade 3 or 4)	Tarhini *et al.* [22]. Bolus IL-2 (all grades/grades 3 or 4)	Aldesleukin (Proleukin) (package insert) [24] Bolus IL-2 (all grades/grade 4)	Guleria *et al.* [25]. Bolus IL-2 (grades 3 or 4)	White *et al.* [26]. Bolus IL-2 (all grades)	Pockaj *et al.* [27]. Bolus IL-2 (all grades)	Macfarlane *et al.* [28]. Bolus IL-2 (all grades/grade 3 or 4)	Krouse *et al.* [29]. Bolus IL-2 (all grades)	Atkins *et al.* [30]. High-dose IL-2 + LAK cells (all grades)	Negrier *et al.* [11]. CIVI IL-2 (grades 3 or 4)	Atkins *et al.* [16]. BCT (grade 3 or 4)	McDermott *et al.* [17]. BCT (grade 3 or 4)
Hematologic toxicity (%)													
Leukopenia	–	0	77/12	16/0	–	–	–	–/2/–	–	–	1	78	71/22
Anemia	44	–	100/15	29/0	–	–	–	17/–/–	–	–	24	24	–
Thrombocytopenia	69	13	96/27	37/1	–	–	–	–/12/1	–	–	5	57	43
Hemostasis toxicity (%)													
Partial thromboplastin time elevation	–	–	–	–	–	–	–	70/–/–	–	–	–	–	–
Prothrombin time elevation	–	–	–	–	–	–	–	25/–/–	–	–	–	–	–
Hemorrhage	–	–	–	–	–	–	–	–/1/1	–	–	–	–	–
Miscellaneous (%)													
Fever	–	–	100/0	29/1	–	–	–	–	–	–	59	–	–
Chills	32	–	96/0	52/0	–	–	–	–	–	–	–	–	–
Weight gain	100	–	81/0	16/0	–	–	–	–	–	–	–	–	–
Malaise	–	–	–	27/0	–	–	–	–	–	–	–	13	–

BCT, biochemotherapy; CIVI, continuous intravenous infusion; GI, gastrointestinal; IL-2, interleukin-2.

who are responders [35]. For this reason, providing maximal supportive care with the sole intent of administering every planned dose of HD-IL*2* is not recommended. Although a threshold number of HD-IL*2* boluses that a patient should receive per cycle has not been investigated rigorously, it appears that 7–9 boluses out of 14 planned doses represent the median in those who respond [7,10,14,33,35]. Supportive care guidelines should be established at each institution to ensure consistency.

Neurologic toxicity

Neurologic toxicity, primarily delirium, visual, or auditory hallucinations, depression, somnolence, dizziness, and anxiety are common in patients receiving HD-IL*2*-based therapy (Table 1) [7,10,14,22,24]. Neurologic toxicity may be multifactorial, as HD-IL*2* and interferon, concomitant medications, and the hospital environment may cause or exacerbate neurologic toxicities. Less than 2% of patients experience Common Toxicity Criteria Adverse Events grade 4 neurologic toxicity [24]. Other reported neurologic toxicities include cerebral vasculitis, neuropsychiatric changes, and emotional lability [14,36,37]. The exact cause of neurologic toxicity from HD-IL*2* is elusive, but may be because of an increase in cerebral water content [38]. However, other theories for HD-IL*2*-associated neurotoxicity exist, such as activation of endothelial cells or lymphocyte-mediated myelin damage [39,40]. The use of cisplatin, vinblastine, and dacarbazine in biochemotherapy regimens increases the incidence of peripheral neuropathy. Peripheral neuropathy occurs in patients who have received more than three cycles of biochemotherapy and may be severe (grades 3 or 4) in 20% of patients [41]. Dose modification of cisplatin and vinblastine may be warranted. Symptoms of peripheral neuropathy rarely peak until 1–3 months following the end of therapy, necessitating close attention to early signs of peripheral neuropathy and a close follow-up after the end of therapy.

Prevention is crucial to the management of neurologic and psychiatric adverse events. Care should be exercised when choosing medications to combat nausea, vomiting, insomnia, and anxiety as the choice of pharmacotherapy may exacerbate neurologic or other toxicities. The use of medications that have minimal neurologic adverse effects should be given priority, whenever possible (Table 2). Severe or prolonged neurologic deficits require treatment interruption or early treatment discontinuation in rare cases. Confusion or delirium, placing the patient at risk of harm, is an absolute criterion to hold HD-IL*2*-based therapy. Mental status usually returns to normal within 24 h of discontinuation of therapy. Of note, the incidence of acute neurologic toxicity is less with biochemotherapy, possibly because of the difference in peak HD-IL*2* serum concentrations observed with different infusion schedules [11,17].

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Table 2 Supportive care therapies for a high-dose interleukin-2-based regimen

Symptoms	Supportive therapy
Anemia	Red blood cell transfusion; goal hematocrit >28%
Acidosis (serum bicarbonate <20 mmol/l)	Give 50–100 mEq sodium bicarbonate intravenously
Bleeding/guaiac-positive stool	Discontinue HD-IL2 therapy; phytonadione 5 mg orally daily × 3 days
Coagulopathy/elevated prothrombin time	Phytonadione 5 mg orally daily × 3 days
Creatinine kinase elevation	Measure troponin; ECG; discontinue therapy if evidence of myocarditis
Delirium	Discontinue sedating medications; ensure normal sleep cycle; encourage physical activity during daytime; open window coverings during day; provide a clock to the patient. Consider haloperidol if necessary. Discontinue therapy in severe cases
Dependent edema	Elevate symptomatic extremity; judiciously use furosemide
Depression/emotional lability	Encourage and reassure patient; antidepressant medications (note: take several weeks to onset); counseling services
Dermatitis	Oatmeal baths; mineral oil/petrolatum/lanolin cream; silver sulfadiazine if open sore/wound; strictly avoid steroids
Diarrhea	Loperamide 2–4 mg orally every 4 h scheduled; if inadequate response, consider adding lomotil two tablets orally every 4 h alternating with loperamide; if inadequate response, add tincture of opium 10% 1 ml orally q6 h; if inadequate response, add octreotide 100–500 mcg subcutaneously every 8 h to loperamide/tincture of opium
Dyspnea	Obtain chest radiograph; consider work-up for pulmonary embolism; supplemental oxygen by nasal cannula or mask to maintain oxygen saturation >95%; judiciously use furosemide if rales or pleural effusions are present; interrupt or discontinue HD-IL2 for inadequate oxygenation
Epigastric pain	Differentiate cardiac vs. gastric source; discontinue NSAID; as needed cation-based antacid; change histamine-2 antagonist to proton pump inhibitor
Fever breakthrough	Increase NSAID frequency; consider septic work-up if occurs on or after the fourth dose of HD-IL2
Hypocalcemia	Assess corrected calcium, given hypoalbuminemia. Calcium carbonate 500 mg orally three times daily with meals or intravenous replacement
Hypokalemia	Intravenous bolus or oral potassium replacement; goal > 3.6 mmol/l
Hypomagnesemia	Intravenous bolus replacement; goal > 1.6 mg/dl (0.8 mmol/l)
Hypophosphatemia	Intravenous bolus replacement; goal > 3.5 mg/dl
Hypotension	Discontinue antihypertensives, irrespective of dose or indication; normal saline 500 ml bolus, may repeat twice if ineffective; if fluid bolus alone ineffective or patient cannot tolerate, initiate dopamine to titrate to 10 mg/kg/min or phenylepherine to titrate to 2 mcg/kg/min. If still hypotensive on maximal dopamine or phenylepherine, add pseudoephedrine 60 mg orally every 6 h; continued hypotension requires interruption or discontinuation of HD-IL2
Hypothyroidism	Thyroid replacement therapy
Infection	Positive blood culture requires discontinuation of HD-IL2 and appropriate antimicrobial therapy
Liver function test elevations	Interrupt or discontinue HD-IL2 therapy; consider discontinuing dacarbazine or temozolomide
Mucositis/stomatitis	Normal saline mouth rinses/salt and soda mouth rinses every 4 h while awake; mucositis mouthwash every 1–2 h as needed or viscous lidocaine 2% solution 15 ml every hour as needed; systemic opioids [note: use opioids cautiously if serum creatinine >2 mg/dl (176.8 μmol/l)]
Myocarditis/myocardial infarction	Discontinue HD-IL2; prompt cardiology supportive care
Oliguria	Discontinue NSAID; normal saline 500 ml bolus, may repeat twice if ineffective; if fluid bolus ineffective or patient cannot tolerate, initiate dopamine to titrate to 10mg/kg/min. If oliguria <20 ml/h remains, interrupt or discontinue HD-IL2
Nausea/vomiting	Maximize antiemetics based on institutional formulary; combine 5-HT3 and dopamine antagonists; add benzodiazepines; use aprepitant for cisplatin-containing regimens; strictly avoid all glucocorticoids; judiciously use sedating antiemetics
Nasal congestion	Room humidifier; normal saline nasal spray; pseudoephedrine 30–60 mg orally every 6 h as needed; topical nasal decongestants, such as oxymetazoline; strictly avoid nasal glucocorticoid administration
Peripheral neuropathy	Reduce doses of antineoplastic agents; use tricyclic antidepressant, antiepileptic, or topical capsaicin to affected area (note: may take days to weeks for effect)
Pruritus	Oatmeal bath; topical mineral oil-based cream; maximize histamine-1 antagonists; gabapentin 2400 mg/day orally in divided doses; judicious use of sedating antipruritics; strictly avoid topical and systemic glucocorticoids
Pulmonary effusion/orthopnea	Judiciously use furosemide and additional fluid boluses; interrupt or discontinue HD-IL2 therapy if unable to maintain oxygen saturation >95%
Rigors	Warm blanket; meperidine or hydromorphone [note: avoid meperidine if serum creatinine >2 mg/dl (176.8 μmol/l)]. Consider premedication with meperidine 12.5–25 mg 30 min before each interleukin or interferon dose
Sinus tachycardia	Correct hypotension with fluid bolus and/or vasopressor (see above); maximize antipyretics if fever present; correct hypoxia (goal oxygen saturation >95%); correct anemia with red blood cell transfusion (goal hematocrit >28%); if receiving dopamine, change vasopressor to phenylephrine; discontinue pseudoephedrine
Tachyarrhythmia	Correct electrolyte abnormalities; correct anemia with red blood cell transfusion (goal hematocrit >28%); correct hypoxia (goal oxygen saturation >95%); if corrective measures inadequate, interrupt or discontinue HD-IL2
Thrombocytopenia	Transfuse platelets to maintain >20 000/mm^3
Troponin elevation	Discontinue HD-IL2

HD-IL2, high-dose interleukin-2; 5-HT3, 5-hydroxytryptamine-3.

Gastrointestinal toxicity

Nausea, vomiting, and diarrhea are the most common gastrointestinal adverse events encountered with HD-IL2-based therapy, occurring in 30–60% of patients receiving HD-IL2 alone (Table 1) [7,11,14,24]. The onset of nausea and vomiting with both HD-IL2 and biochemotherapy occurs within the first day and resolves spontaneously within 3–4 days following each cycle. The administration of 5-hydroxytryptamine-3 (5-HT3) or dopamine antagonists is effective for nausea and vomiting in both the prophylactic and the treatment setting (Table 2) [42]. For prophylactic use, 5-HT3 antagonists are preferred because of efficacy and tolerability. For breakthrough nausea or vomiting, the use of either a benzodiazepine or a phenothiazine dopamine antagonist is preferred, although neurologic status should be considered, as both drug classes may exacerbate neurologic status. Butyrophenone dopamine antagonists, such

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as droperidol, should be used with caution, owing to cardiac adverse effects. It is critical that systemic glucocorticoids be avoided before, during, and immediately after each cycle because of diminution of cytokine effect. As an antiemetic, neurokinin-1 antagonists have not been investigated for HD-IL2 alone.

The incidence and severity of gastrointestinal toxicities with biochemotherapy are greater than HD-IL2 alone because of the addition of antineoplastic agents [16,43,44]. Patients receiving biochemotherapy should receive maximal antiemetic prophylaxis, including 5-HT3, dopamine, and neurokinin-1 antagonists, along with prophylactic benzodiazepines. Again, glucocorticoids must be strictly avoided. Breakthrough antiemetics should be made available from multiple drug classes, with neurologic status governing drug choice and schedule of administration. Delayed nausea and vomiting is common with biochemotherapy, but not with single-agent HD-IL2, necessitating patient education and oral antiemetics for 5–7 days following each cycle.

Secretory diarrhea occurs in up to 70% of patients receiving HD-IL2-based therapy [7,11,14,24]. HD-IL2 and biochemotherapy have a similar incidence and severity of diarrhea, although this incidence increases linearly with subsequent cycles [11,16,44]. Treatment with antimotility agents should be started upon first signs of diarrhea and continued until formed stools return (Table 2).

Other gastrointestinal adverse effects, such as gastritis, anorexia, and stomatitis, have also been reported with HD-IL2-based therapy [7,24,43]. All patients require a prophylactic histamine-2 antagonist or a proton pump inhibitor while actively receiving therapy. Breakthrough gastritis or gastroesophageal reflux symptoms may still occur and calcium-based or magnesium-based antacids should be used as required. Anorexia is difficult to treat, but resolves spontaneously within 5–7 days following each cycle. Stomatitis is uncommon and generally mild in severity. Symptomatic treatment with topical anesthetics, such as viscous lidocaine 2%, or systemic opioids may be required.

Renal toxicity

Along with cardiovascular toxicities, renal toxicity is the most common reason to truncate or interrupt HD-IL2-based therapy, principally, prerenal because of capillary leak syndrome and decreased renal perfusion; oliguria occurs in over 60% of patients (all grades) and grade 4 oliguria/anuria occurs in ~10% (Table 1). Serum creatinine levels peak during the second cycle [24,25]. Intrarenal defects occur because of vasoconstriction stemming from abnormal renal prostaglandin synthesis, potentially causing acute tubular necrosis [25,45,46]. Additional findings include azotemia and decreased fractional excretion of sodium, all of which reverse within 7–14 days following therapy. Electrolyte wasting, particularly magnesium, potassium, and phosphorus, in addition to hemodilution necessitate prophylactic administration of magnesium and phosphorus. Supplementary electrolyte replacement is frequently required (Table 2). Despite the addition of cisplatin, biochemotherapy regimens have a similar incidence of renal toxicity as HD-IL2 alone, which may be explained by the relatively low daily doses administered [16,24,41]. The avoidance of concurrent nephrotoxic medications is critical, with a drug holiday started several days before each cycle of HD-IL2-based therapy. NSAIDs, commonly administered concurrently with HD-IL2-based therapies, may exacerbate renal dysfunction and should be discontinued upon signs of decreased urine output or an increase in serum creatinine.

A rapid increase in serum creatinine or absolute serum creatinine more than 1.6 mg/dl (141 μmol/l) requires prompt attention. Renal adjustment of concomitant medications is warranted and, in the case of biochemotherapy, withholding the administration of cisplatin may be considered. Cisplatin administration in the setting of reduced renal perfusion may lead to permanent damage to the proximal tubules [41].

Maintaining renal perfusion is imperative during HD-IL2-based therapy to avoid permanent renal dysfunction. Continuous administration of crystalloid fluids must be maintained concurrently with HD-IL2-based therapy irrespective of oral fluid intake. Although both crystalloid and colloid fluids were found to be equivalent in a randomized trial, crystalloid is preferred because of the costs and ease of administration [47]. A decrease in urine output generally coincides with increased serum creatinine, necessitating strict accounting of fluid balance. Periodic intravenous administration of normal saline boluses of 500–1000 ml over 1–2 h in addition to maintenance normal saline can temporarily ameliorate renal hypoperfusion. However, the cumulative effect of HD-IL2-associated hypoperfusion and capillary leak syndrome encountered within a treatment cycle may mitigate the usefulness of additional crystalloid fluids. Vasopressors should be initiated if crystalloid fluids do not produce the desired effect or additional crystalloid fluids are contraindicated. Dopamine, administered up to 10 mcg/kg/min, is the most widely used agent and has been shown to reverse the nephrotoxicity of HD-IL2 [48]. The prophylactic use of low-dose dopamine to maintain renal perfusion is not recommended [49]. Temporarily discontinuing the administration of continuous infusion interleukin-2 or skipping a dose of HD-IL2 is an effective remedy for nephrotoxicity (Table 2). Progressive nephrotoxicity despite corrective measures warrants discontinuation of the current cycle of HD-IL2-based therapy. The renal toxicity from HD-IL2 alone is reversible as the acute effects wear off, generally within 72 h following the final dose. Rarely, permanent renal impairment may occur in patients who experience profound hypoperfusion. Although the addition

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of cisplatin in biochemotherapy marginally affects acute nephrotoxicity, the cumulative administration of cisplatin over multiple cycles increases the incidence of chronic renal impairment [6].

Hepatic toxicity

Hepatic toxicity with HD-IL2-based therapies is because of the direct effect of HD-IL2 and chemotherapeutic agents, as well as indirectly because of hypoperfusion and volume changes, but is rarely clinically significant. Increases in serum total bilirubin occur in up to 40% of all patients receiving HD-IL2 alone, but only 2% of patients experience grade 4 hyperbilirubinemia. Similarly, increases in transaminases are found in up to 25% of patients, but grade 4 toxicity is rare (Table 1) [11,24]. Elevations in liver function tests may be exaggerated in patients with liver metastases. The purported mechanism for hepatic toxicity is hepatic edema or an infiltrative process [50]. The addition of chemotherapy, especially dacarbazine or temozolomide, increases the incidence and severity of hyperbilirubinemia or transaminitis [6,16,43]. Discontinuation or dose reductions of these agents and vinblastine should be considered for patients experiencing rapid or extreme increases in liver function tests. Synthetic function is also altered by HD-IL2-based therapies, including decreased albumin production, decreased production of clotting factors, and dyslipidemia [50–53]. Decreases in serum albumin are exacerbated by the dilutional effect of crystalloid fluids, capillary leakage, and acute physiologic stress [50,54].

Few therapies exist to correct the hepatic effects caused by HD-IL2-based therapies, such as hyperbilirubinemia or transaminitis. Avoidance of concurrent hepatotoxic agents and frequent assessment of liver function tests should be universally applied. Exogenous administration of albumin to correct hypoalbuminemia is not recommended on the basis of a head-to-head comparison with crystalloid administration [47]. Increases in prothrombin time may be reversed with exogenous phytonadione (Table 2) [52]. However, overt gastrointestinal tract bleeding warrants treatment interruption or discontinuation.

Reduced hepatic metabolic and synthetic capacity confers the potential to alter drug disposition. There is a paucity of data examining the extent of altered drug disposition and the appropriate corrective action that may be taken in patients receiving HD-IL2-based therapies. As a general rule, hepatically eliminated medications are preferred during HD-IL2-based therapies because of the significant and rapid changes in renal function. However, when hepatic aberrations occur simultaneously with renal dysfunction, caution should be exercised when administering medications with significant hepatic clearance. Recovery of hepatic metabolic and synthetic function following each course of HD-IL2-based therapy occurs within in 3–6 days [14,50].

Cardiac toxicity

Hypotension occurs in 50–70% of patients because of the release of nitric oxide from the endothelial cells, producing vasodilatation and an increase in vascular permeability, leading to a decrease in systemic vascular resistance (Table 1) [24,26,55]. Hypotension with reflexive tachycardia may be observed within 2 h following the first dose and is cyclic, with a peak occurring 4–6 h after each dose [55]. Upon discontinuation of HD-IL2, hypotension resolves within 24–48 h.

Patients considered for HD-IL2 must undergo a baseline ECG and thallium stress test to assure adequate cardiac function. All patients receiving antihypertensive agents must discontinue these medications 24–48 h before HD-IL2-based therapy. Caution should be exercised in patients who are on β-blockers as abrupt discontinuation may lead to rebound tachycardia and hypertension; tapering may be necessary. Patients on β-blockers for cardiac tachyarrhythmia may require tapering to a lesser dose that is continued during treatment. Antihypertensive medication may be resumed 24–48 h after blood pressure has stabilized following each cycle.

Frequent routine monitoring of blood pressure every 2–4 h is necessary. A goal systolic blood pressure greater than 80–90 mmHg is desired depending on the patient's baseline blood pressure and risk factors. Mild hypotension can be managed with saline boluses, similar to the management of oliguria. Again, saline fluids are preferred over colloid because of the efficacy, cost, and ease of use. Fluid resuscitation should be limited to 1.5 l/day to limit exacerbation of capillary leak syndrome. On occasion, hypotension may persist despite fluid challenges and may require a vasopressor with dopamine or phenylephrine [26]. Dopamine is the preferred vasopressor because of potential renal benefits, but phenylephrine should be used if patients have tachyarrhythmias (Table 2). Pseudoephedrine may be used adjunctively with other vasopressors, if required. When vasopressor support is maximized and the patient remains below goal diastolic blood pressure, discontinuation of HD-IL2 is recommended.

Hypotension with HD-IL2 can be severe, whereas hypotension from biochemotherapy is usually mild to moderate. Persistent hypotension despite fluid boluses requiring vasopressor support occurs in 10–40% of patients [56]. Most patients receiving biochemotherapy can be managed effectively with renal-dose dopamine at 3–5 mcg/kg/min.

Tachyarrhythmias, particularly atrial fibrillation, may occur in 24% of patients undergoing treatment with HD-IL2 [24,26]. Supraventricular tachycardia may occur in up to 12% of patients [24]. Atrial fibrillation is more common in patients with a history of atrial fibrillation or those who are receiving dopamine for vasopressor support.

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Electrolyte replacement is necessary to minimize propagation of arrhythmias. Tachyarrhythmias are generally brief and abrogated by interruption of HD-IL2-based therapy. Rarely, discontinuation is required because of recalcitrant tachyarrhythmias.

Myocarditis and myocardial infarction has been reported in 7% of patients in the original clinical trials (Table 1) [24]. However, stringent screening criteria before treatment may help to decrease the incidence of this toxicity.

Pulmonary toxicity

Dyspnea and pulmonary congestion because of increased vascular permeability from capillary leak syndrome occur in over 40% of patients receiving single-agent HD-IL2 (Table 1) [24,26,55]. Pulmonary congestion can lead to severe respiratory distress requiring intubation in less than 4% of patients [26]. Careful screening and patient selection is critical, especially in patients with a history of tobacco smoking or pulmonary metastases. All patients require continuous monitoring of pulse oxygen throughout therapy with a goal oxygen saturation of more than 95%. Daily weights should be followed closely. Dyspnea and pulmonary congestion increase in severity with continued treatment. Rales, pleural effusions, and orthopnea can develop during treatment and may resolve spontaneously following therapy. Although extensive fluid resuscitation is necessary to treat hypotension and prevent nephrotoxicity from cisplatin for biochemotherapy, careful balance is necessary to prevent exacerbation of pulmonary congestion (Table 2). Diuretics should be used with caution because of the effect on blood pressure and relative intravascular dehydration while actively receiving HD-IL2. If pharmacologic diuresis is desired, loop diuretics are recommended because of efficacy. Severe dyspnea, heart failure, and noncardiogenic pulmonary edema are less frequent with biochemotherapy [56]. Once IL-2 therapy is discontinued, autodiuresis occurs rapidly.

Infectious complications

Symptomatic bacteremia or bacteriuria developing during or immediately after receiving HD-IL2 occurs in 10–40% in published experience (Table 1) [27,57]. Although HD-IL2 acts to stimulate Th1 cells, HD-IL2 induces a paradoxical and transient defect in neutrophil chemotaxis [57]. Additional risk factors include central venous catheters, excoriation from pruritus, and indwelling urinary catheters. Gram-positive flora translocating from skin are the most prevalent cause of bacteremia, whereas Gram-negative bacteria, particularly *Escherichia coli*, are a common cause of urinary tract infections [27,57]. Atypical bacterial, fungal, and viral infections are rare.

Initial protocols for HD-IL2 did not include antibacterial prophylaxis, contributing toward the reported high incidence of infectious complications. A greater understanding of infectious risks, judicious monitoring for infection, and the use of antibacterial prophylaxis have considerably reduced the incidence and severity of bacterial infections [57]. There is a general consensus that all HD-IL2 patients should receive prophylactic Gram-positive antibacterials, such as first-generation cephalosporins [27,58,59].

Fever and hypotension are both hallmarks of infection and common HD-IL2 side effects confounding or delaying appropriate antibacterial therapy. Clinicians are urged to be aware of infectious causes of fevers in patients receiving HD-IL2. Potential signs of infection include persistent fevers despite scheduled antipyretics, fevers not temporally associated with the administration of HD-IL2, and signs of focal infection, such as catheter site induration or dysuria. In patients suspected of having an infection, cultures should be obtained and empiric antibacterial therapy should be promptly initiated, accounting for local bacterial sensitivity patterns. Antibacterial therapy should be tailored once an organism is identified and used for 10–14 days following the last positive culture result. A strong suspicion of infection or identification of an infectious pathogen warrants discontinuation of HD-IL2 therapy.

Musculoskeletal toxicity

Myalgias and arthralgias may occur with HD-IL2-based therapies and often present in a symptom cluster with fever and chills. These so-called flu-like symptoms may occur at any time during a course of HD-IL2-based therapy. Rarely do these symptoms merit withholding or discontinuing the administration of HD-IL2. Routine administration of antipyretics or NSAIDs minimizes the severity and incidence to less than 10% of patients (Table 1) [60]. In rare cases, myositis, including severe rhabdomyolysis, has been reported with HD-IL2-based therapies [61]. However, it is unclear whether this is caused by HD-IL2 or interferon-α as rhabdomyolysis has not been reported with HD-IL2 alone [62,63].

Upon discontinuation of HD-IL2-based therapies, musculoskeletal toxicities abate quickly. Persistence of such complaints may indicate infection, particularly of viral origin.

Dermatologic toxicity

Dermatologic toxicities of HD-IL2 can be both acute and delayed. Acutely, HD-IL2 leads to pruritus in the majority of patients, occurring initially in the face and the neck area, but may spread over the entire body. Although generally manageable with oral H_1-histamine antagonists, pruritus may be severe and recalcitrant to H_1-histamine blockade alone. Unrelenting pruritus may lead to sleep deprivation or neuropsychiatric adverse effects. In rare instances, treatment interruption or discontinuation is required for pruritus and is typically at the request of

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the patient. All patients should be counseled to expect pruritus and provided scheduled H_1-histamine antagonists and topical anti-itch lotions, such as diphenhydramine cream or colloidal oatmeal lotion, to ease pruritus symptoms and minimize excoriation (Table 2). Gabapentin, by blocking sodium channels and decreasing afferent nerve transmissions, has been shown to decrease pruritus in a manner that is independent of and even complementary to H_1-histamine blockade [64]. The administration of gabapentin three times daily (i.e. before each scheduled dose of HD-IL2 when administered as a bolus) in a dose ranging from 300 to 3600 mg/day has been shown to reduce pruritus by 75%. This study evaluated 33 patients receiving bolus HD-IL2 with a mean dose $\sim$1400 mg/day and a mean onset time of $\sim$1 h, making it an ideal premedication for each dose of bolus HD-IL2 or provided as a scheduled medication for patients receiving a continuous infusion of IL2. The primary toxicity was sedation, which was perceived as favorable by study patients, many of whom experienced sleeplessness because of pruritus. Although no data for the treatment of HD-IL2-related pruritus currently exist, aprepitant may be a promising and novel treatment for recalcitrant pruritus. Serendipitously found to have antipruritic activity, the neurokinin-1 pathway may be involved in HD-IL2-related pruritus [65–67]. Currently, it may be premature and cost-prohibitive to administer aprepitant routinely. However, for patients with severe recalcitrant pruritus, particularly in patients contemplating early treatment discontinuation, aprepitant may be a consideration.

Other acute dermatologic toxicities associated with HD-IL2 include stomatitis, erythroderma, bullous dermatitis, acute flare of dermatologic conditions, and wet desquamation [68]. Daily thorough skin examinations are required during the administration of HD-IL2-based therapy. Severe skin breakdown merits treatment discontinuation and lesions should be treated with topical antibacterials such as silver sulfadiazine (Table 2). Skin breakdown because of HD-IL2 has been linked to *Staphylococcus aureus* bacteremia [69,70].

Delayed dermatologic manifestations of HD-IL2 therapy include immune-mediated phenomena, such as vitiligo, hair depigmentation, or depigmentation surrounding cutaneous nevi. Symptomatic flare of dermatologic conditions, such as psoriasis, may occur over time.

Patients should be counseled that pruritus may persist for weeks following HD-IL2 and topical or systemic glucocorticoid treatment must be strictly avoided. Patients should also be counseled to avoid sun exposure because of increased skin sensitivity and to wear sunscreen with sun protection factor 15 when in direct sunlight on exposed skin.

Endocrine and metabolic toxicity

Autoimmune thyroiditis leading to thyroid dysfunction may result from HD-IL2, leading to hypothyroidism in 35% of patients and hyperthyroidism in 7% of patients (Table 1) [29,30]. This reflects the natural history of effects on the thyroid because of HD-IL2, where initially destructive thyrotoxicosis gives way to cell-mediated autoimmune destruction [71]. However, thyroid dysfunction may be subclinical, with a small percentage of hypothyroid patients requiring thyroid replacement therapy. Hypothyroidism appears to be related to the duration of therapy and is not permanent, often resolving within 1 year [29]. All patients receiving HD-IL2-based therapy should have scheduled thyroid function panel monitoring with the initiation of thyroid replacement therapy (Table 2). Early investigations have found correlation of thyroid dysfunction with the clinical outcome of HD-IL2 [29,30]. However, subsequent investigations have found a correlation with response, but not overall survival improvement. Rather, thyroid dysfunction occurs in patients who are responding to HD-IL2 and, therefore, receiving numerous courses of therapy [72].

Aberrations in the hypothalamic–pituitary–adrenal axis have been observed in patients receiving HD-IL2-based therapy, particularly in patients with MRCC [73,74]. Transient effects on serum lipids are also noted with HD-IL2 [75,76]. Total cholesterol, low-density, and high-density lipoprotein levels decrease by up to 60% from the baseline, whereas triglycerides increase modestly. The effects of HD-IL2 on hepatic function may be the cause [76]. Electrolyte replacement is commonly required in patients receiving HD-IL2, particularly potassium, phosphorus, calcium, and magnesium [77]. Because of fluid shifts during therapy, evaluation of the corrected or ionized calcium is recommended. Rarely, a syndrome of inappropriate antidiuretic hormone secretion may lead to hyponatremia [78].

Hematologic toxicity

Single-agent HD-IL2 causes transient decreases in one, two, or all three hematologic lineages (Table 1). Severe cytopenias from HD-IL2 alone requiring dose delay or treatment discontinuation occur rarely [28]. Changes in white blood cells (WBCs) manifest as leukopenia and altered functional activity. The alterations in WBC activity and chemotaxis predispose to a risk of an infection, discussed elsewhere in this paper [57]. Transient lymphopenia from sequestration of lymphocytes occurs and resolves rapidly, often rebounding above the baseline [28]. Eosinophilia occurring with pruritus and rash also occurs rapidly as patients actively receive HD-IL2.

Anemia is multifactorial during HD-IL2-based therapy. Hemodilution and the direct effects of HD-IL2 lead to anemia and may require red blood cell transfusions [28]. Hematocrit must be maintained above 28% to minimize cardiac toxicities (Table 2). Erythrocyte-stimulating agents play no role in the management of anemia in this setting.

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Thrombocytopenia, often cumulative with bolus HD-IL2 as a single agent, rarely requires transfusions or treatment interruptions, with platelet counts less than 50 000 and 25 000 cell/μl found in 12 and 1% of treatment cycles, respectively [28]. The mechanism is poorly elucidated, but involves peripheral platelet destruction [79,80].

The use of growth factors for the prophylaxis or the treatment of any cytopenia is not recommended for single-agent HD-IL2. Transfusions should be utilized for rapid correction in symptomatic individuals. Patients who do not experience the recovery of all three hematologic lineages should be evaluated for causes other than HD-IL2, such as concomitant medications or autoimmune processes.

Whereas single-agent HD-IL2 induces relatively mild and rapidly reversible cytopenias, the addition of antineoplastic agents to HD-IL2 in biochemotherapy severely exaggerates hematologic toxicities. All patients experience cumulative cytopenias to varying degrees [28]. The onset of cytopenias varies, however, with a bimodal decrease in hematologic parameters. The initial decrease is because of HD-IL2, followed by antineoplastic-induced cytopenias. These cytopenias from antineoplastic agents nadir 10–14 days following the end of therapy [41,56]. Prophylaxis with WBC colony-stimulating factor is essential to minimize the sequelae of neutropenia and augment the immunologic response [41,43]. The WBC colony-stimulating factor should be started 24–48 h following cessation of therapy and continued until neutrophil recovery. Anemia is guaranteed following biochemotherapy, with subsequent cycles causing progressive anemia because of cumulative bone marrow suppression [81]. The use of erythrocyte-stimulating agents is controversial and not recommended in this setting. Transfusion of red blood cells should be used to maintain hematocrit more than 28% (Table 2). Thrombocytopenia is also augmented in biochemotherapy. Platelet transfusions should be used because stimulating agents, such as oprelvekin and thrombopoietin mimetics, are not recommended. The occurrence of Common Toxicity Criteria Adverse Events grade 4 neutropenia (WBC nadir <500 cells/ml) or thrombocytopenia (platelets $< 25\,000$/ml) requires dose reduction of both dacarbazine and vinblastine by 25% in subsequent cycles [41].

Hemostatic toxicity

Besides transient thrombocytopenia, HD-IL2 is associated with changes in hemostatic parameters (Table 1). Early studies of HD-IL2 have reported thrombotic complications with HD-IL2-based therapy [82–84]. However, the more prevalent hemostatic effect of HD-IL2-based therapies is elevation in thromboplastin time and, to a lesser extent, prothrombin time [83]. Bleeding is uncommon with HD-IL2 and correlates with changes in coagulation parameters rather than thrombocytopenia [28,80,85]. Rapid decreases in vitamin K-dependent coagulation factors occur rapidly following HD-IL2, largely because of acute effects on hepatic synthesis of clotting factors [86]. In rare cases where bleeding is detected, administration of fresh-frozen plasma is recommended.

Miscellaneous toxicity

Constitutional symptoms, such as fevers, chills, rigors, and malaise, are common with HD-IL2 (Table 1). These constitutional symptoms peak ~ 4 h after each dose of bolus HD-IL2 and increase in intensity as therapy continues. Acetaminophen or NSAID premedication minimizes symptom severity. Intravenous meperidine or hydromorphone should be promptly administered for rigors and the addition of this agent as a premedication for subsequent HD-IL2 should be considered. Nasal congestion may also occur with greater frequency as patients receive more cycles of HD-IL2-based therapy. Topical or systemic sympathomimetic administration is recommended for symptomatic relief.

Guidelines for monitoring patients

Patients undergoing treatment with either HD-IL2 or biochemotherapy require a careful evaluation before therapy, including baseline cardiac and lung function, and therapy should be reserved for patients with good performance status (ECOG score 0–1). Prior to administering the initial dose of HD-IL2, all patients require comprehensive laboratory panel including complete metabolic panel, magnesium, phosphorus and complete blood count (CBC) with differential. Once therapy commences, these laboratory values should be assessed repeatedly1–3 times daily, often immediately before the next scheduled dose of HD-IL2. Daily routine laboratory monitoring should continue until laboratory values return to or trend toward normal. In addition, following biochemotherapy, patients require nadir laboratory values obtained after treatment to assess the hematologic effects of traditional chemotherapy.

Guidelines for symptom management

Patients treated with HD-IL2 or biochemotherapy should be weaned off any systemic corticosteroids 2 weeks before the initiation of treatment. Asthmatics who are strictly controlled on their inhaled corticosteroids may continue, if absolutely necessary, as the minimal systemic absorption is unlikely to abrogate the antitumor effect of HD-IL2. Treatment of adrenal insufficiency with physiologic doses of corticosteroids may be continued. Antihypertensives should be discontinued the day before starting HD-IL2-based therapy; however, caution should be exercised with β-blockers and α-agonists to prevent reflexive tachycardia. If necessary, continuation of β-blocker or α-agonist therapy with 10–25% of the usual daily dose may be required to prevent reflex tachycardia. Therapeutic dosing of antihypertensives may resume 24–48 h

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following the end of HD-IL2-based therapy once blood pressure has stabilized. Overlapping of sedatives, such as antiemetics, antihistamines, sleep aids, and opioids should be avoided. Concurrent nephrotoxic medications should be strictly avoided, including discontinuing scheduled NSAIDs with as-needed dosing used during treatment.

Upon discharge, appropriate diuretic, antiemetic, antipruritic, and antidiarrheal agents should be prescribed for 2–4 days. Biochemotherapy patients should receive marrow support with WBC colony-stimulating factors, which acts to minimize the neutropenic period and enhance the antitumor effect, in theory.

Conclusion

HD-IL2, either as a single-agent bolus or as a continuous infusion or in combination with antineoplastic agents and interferon-α in biochemotherapy, remains a valuable tool in our limited arsenal against MM and MRCC. Although recent years have witnessed treatment advances of both diseases through elucidation of new therapeutic targets and introduction of signal transduction inhibitors or immune modulators, HD-IL2 remains one of the only therapies to induce durable remissions. Although a therapeutic benefit may be encountered in a small subset of patients, substantial toxicity may be encountered in all patients receiving this therapy. Clinicians must establish supportive care treatment protocols for the optimal administration of HD-IL2-based regimens by relying on predictable toxicities and decades of experience. Strict reliance on eligibility criteria, vigilant monitoring for acute and delayed toxicities, and prompt intervention are the cornerstones of the successful management of toxicities associated with HD-IL2 and biochemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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