High-Dose Interleukin-2

Evaluation of a standardized order set for biotherapy in an intensive care unit

Rusticio Portillas, DNP, MSN, RN, Barbara Turner, PhD, FAAN, RN, Audrey Jeffers, PharmD, Lee-Lynn Chen, MD, and Mary Champagne, PhD, FAAN, RN

BACKGROUND: Life-threatening toxicity may result from administration of high-dose (HD) interleukin-2 (IL-2). Patients receiving HD IL-2 treatment often experience severe adverse side effects, which result in the interruption of treatment.

OBJECTIVES: A standardized order set (SOS) was developed for patients with melanoma or renal cell carcinoma receiving HD IL-2. The aims of the study were to determine compliance of clinicians to the SOS, report the completed doses and major side effects of HD IL-2, and document the satisfaction level of clinicians.

METHODS: A retrospective chart review of 40 health records of patients with melanoma or renal cell carcinoma who were treated with HD IL-2 was conducted to determine compliance to the SOS. Staff satisfaction with the SOS was surveyed.

FINDINGS: The SOS was successfully implemented with a provider compliance rate of 90%. Cardiovascular side effects were the most common. Clinicians found the SOS very satisfactory or superior in guiding care and treatment of side effects.

KEYWORDS

high-dose interleukin-2; metastatic melanoma; renal cell carcinoma; toxicity

HIGH-DOSE (HD) INTERLEUKIN-2 (IL-2) RESULTS IN objective clinical regression of metastatic cancer in 15%–17% of patients with melanoma and renal cell carcinoma (Fisher, Rosenberg, & Fyfe, 2000). Durable complete regression of all metastases is seen in 6%–8% of patients (Atkins, Kunkel, Sznol, & Rosenberg, 2000; Fisher et al., 2000; Rosenberg, Yang, White, & Steinberg, 1998). Based on these findings, the U.S. Food and Drug Administration approved the use of HD IL-2 for the treatment of patients with metastatic melanoma and renal cell carcinoma. However, HD IL-2 induces severe and sometimes life-threatening side effects, including vascular leak syndrome (Gallagher et al., 2007), cardiac arrhythmias (Margolin et al., 1989; Singla & Denmeade, 2008), fever, and end organ damage (Schwartzentruber, 2000).

Despite the use of HD IL-2 biotherapy for more than 20 years, its administration and management of potential side effects remain unstandardized in many hospital settings. Acquavella et al. (2008) conducted a retrospective chart review of 41 consecutive patients with metastatic melanoma (n = 33) or renal cell carcinoma (n = 8) who were treated with a modified HD IL-2 regimen and admitted to monitored hospital beds. They found that about 10% of patients required vasopressors for severe hypotension, and 24% were transferred electively or emergently to the intensive care unit (ICU) because of decline in status. Quan et al. (2005) studied 15 patients aged 70 years or older who were treated with HD IL-2 in an oncology inpatient unit or intermediate unit. Twenty percent required the use of dopamine infusion for blood pressure support. A study by Allard et al. (2015) suggested that patients receiving HD IL-2 were increasingly being treated in teaching hospitals and concluded that centralization of care is needed.

The HD IL-2 program was initiated at University of California, San Francisco (UCSF) Medical Center for patients with metastatic renal cancer and melanoma because of the complexity of care and severity of adverse events. The collaborative team developed a standardized order set (SOS) based on the best evidence so that patients receiving HD IL-2 could be closely monitored for any life-threatening complications to be detected and treated expeditiously.

Following the implementation of the SOS, a quality-improvement project was implemented with four aims: (a) determine compliance to the SOS,
(b) describe the percentage of patients who fully complete the first (14 doses) and second (14 doses) cycles of HD IL-2, (c) document the major side effects of HD IL-2, and (d) describe the satisfaction level of clinicians using the SOS.

**Methods**

This was a descriptive, retrospective database review of clinical and treatment information of patients treated with HD IL-2 for metastatic melanoma or renal cell carcinoma in an oncology ICU at UCSF Medical Center from January 2010 to August 2013. Satisfaction of healthcare providers with the SOS was gathered by an anonymous Internet survey.

The UCSF Medical Center is a licensed 650-bed not-for-profit acute care hospital that provides all levels of care: primary, secondary, tertiary, and quaternary. It has three inpatient campuses with about 30,000 admissions annually. The unit where the project was implemented is a small adult medical-surgical and oncology ICU in a community campus hospital that has an average daily census of three patients per day. The nurse-to-patient ratio is 1:2. The unit nursing staff is varied in age, years of nursing experience, and background. About 80% of the 20 staff nurses have a BSN, and 20% have an MSN. All ICU nurses completed a course from the Oncology Nursing Society on chemotherapy and biotherapy administration in handling proper chemotherapy and biotherapy agents.

**Sample**

Records of all patients (N = 40) who met admission criteria for HD IL-2 treatment from January 2010 to August 2013 were reviewed. Patients were screened by a hematologist-oncologist for major cardiopulmonary disease prior to beginning HD IL-2 treatments and were admitted electively to the ICU. Before each cycle of HD IL-2 therapy, patients underwent placement of a temporary peripherally inserted central catheter line, which was removed at the end of each cycle. All patients received a two-cycle regimen. For cycle 1, HD IL-2 was administered at a dose of 600,000 IU/kg every eight hours by a 15-minute IV infusion for a maximum of 14 doses. After 10–14 days of rest, cycle 2 repeated the cycle for another 14 doses for a maximum of 28 doses per course. During each cycle of treatment, patients were monitored for grade 3 or 4 adverse events during each treatment series (Gitlitz, Hoffman, Moldawer, Beldegrun, & Figlin, 2001). In the event of reversible grade 3 toxicity, IL-2 treatments were withheld until toxicity level decreased to grade 0 or 1 (Gitlitz et al., 2001). HD IL-2 treatments were discontinued after the occurrence of nonhematologic grade 4 adverse events. Prior to selection for HD IL-2 therapy, patients had stress echocardiograms and complete pulmonary function tests with diffusion capacity. In addition, patients had a magnetic resonance imaging scan with gadolinium and a comprehensive set of serum chemistry tests. Those with an impaired ejection fraction, abnormal diffusion capacity, and/or a history of restrictive or obstructive pulmonary disease were excluded from the treatment and were referred to the appropriate specialist for evaluation and appropriate treatment.

**Intervention**

The ICU formed an interdisciplinary task force of critical care nurses, physicians, pharmacists, and an oncology clinical nurse specialist (CNS) to design an SOS to provide guidance for safe administration of HD IL-2. The orders were based on the principles and standard guidelines for safe administration of HD IL-2 (Margolin et al., 1989; Poust, Woolery, & Green, 2013; Schwartzentruber, 2000).

The interdisciplinary team developed and implemented a revised five-page SOS in December 2010. The first page of the first section contained the patient’s preparations (items such as allergies, height, weight, diagnosis, and treatment cycle), routine and scheduled laboratory tests, and frequency of hemodynamic monitoring and diet. The second page included the immunotherapy order calculated by the hematologist-oncologist and verified by a pharmacist based on the patient’s current weight, antipyretic of choice, and gastrointestinal prophylaxis. The third page provided orders for antibiotic prophylaxis, skin care, bowel regimen, and guideline management of rigors. The fourth page contained orders for fluid and electrolyte replacement, management of tachycardia, and management of oliguria. The fifth page provided guidelines for the management of hypotension.

The SOS form was presented at several forums within the hospital for feedback from a multidisciplinary group. Suggestions were incorporated into the SOS form, and the ethics committee and the critical care advisory committee from UCSF Medical Center reviewed and approved the final form. Once the SOS was approved, an oncology CNS conducted in-service training regarding its use to all shifts in the ICU to reach as many staff nurses as possible. The training consisted of reviewing the SOS and understanding the rationale for each order. The institutional review
boards at UCSF Medical Center and Duke University Medical Center approved this quality-improvement project.

Data Collection Plan and Outcome Measures
Basic patient demographic characteristics were gathered from the health record and included age, gender, race, allergies, height, weight, and length of stay. Compliance of the provider in completing the SOS was recorded as “yes” if all required items were completed and “no” if some items were missing. The numbers of completed treatment of HD IL-2 were recorded from the clinical data set. Adverse events were classified according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events, version 3.0 (Bukowski et al., 1990; Fyfe et al., 1995; Rosenberg et al., 1994).

Descriptive statistics were performed for baseline patient characteristics, rate of provider’s compliance, number of treatments completed, most common major adverse events, and clinician satisfaction with the SOS. Two-tailed independent t tests were used to compare age and diagnosis, two-tailed t tests with 95% confidence intervals were run. No significant difference was found between groups for age (p = 0.07).

Compliance of the Provider
To assess compliance, charts were reviewed within 24 hours of patient admission to evaluate if the SOS had been completed. Compliance was defined as the oncologist checking all sections of the SOS that were specific for a patient’s admission. A checklist to document compliance was used by the admitting staff nurses to assess the completion of the SOS. An oncology-admitting nurse who was trained to review the checklist retrospectively collected data from each patient chart to determine provider compliance with the SOS. All participants recruited received training, worked in the unit, and cared for patients using the SOS.

Average Dose Completed
Cycles 1 and 2 had maximum numbers of 14 HD IL-2 doses. For each patient in the study, the number of doses completed in each cycle was recorded until treatment was stopped because of side effects. Historically, in other settings, the average number of doses completed was 10 doses per cycle (Acquavella et al., 2008; Gitlitz et al., 2001), and the maximum number of doses completed was 14 doses each cycle (Poust et al., 2013).

Side Effects and Toxicity
Individual adverse responses to the HD IL-2 regimen were assessed by chart review. The number of adverse effects were collected and classified by body system. Major adverse events were categorized by ranking each occurrence and reporting as percentage of patients who experienced these major adverse events.

Clinician Satisfaction
To assess clinician (physician and nurse) satisfaction with the use of the SOS, an online survey was conducted after implementation of the SOS using a Likert-type scale. The survey questions consisted of five items: health professional designation, phone consultation, provider callback time, provider guidance for effective care, and provider guidance to manage side effects.

Results
The SOS was successfully implemented, with a compliance rate of 90%. The patient sample (N = 40) consisted of 17 men and 23 women (see Table 1). The age frequency was normally distributed, ranging from 40–78 years, with a median age of 58. To compare age and diagnosis, two-tailed t tests with 95% confidence intervals were run. No significant difference was found between groups for age (p = 0.07). All 40 patients received the HD IL-2 treatment protocol. The treatment goal was 14 doses; throughout cycle 1, 16 patients received the goal number of doses. Twenty-four patients had skipped, delayed, or discontinued doses because of side effects from previous doses. The mean number of patients who completed cycle 1 was 10.9 (SD = 3, range = 3–14). The mean doses completed in cycle 2 was 8.7 (SD = 2.3, range = 3–13). In cycle 2, 10 participants received 10 doses; no patients completed 14 doses in cycle 2.

The comparison of diagnosis on number of treatment cycles 1 and 2 is tabulated in Table 2. A significant difference was found between cycle 1 and 2 for patients with melanoma. For patients with melanoma, the two-sample t-test value was 2.98 in cycle 1 and 1.58 in cycle 2; therefore, significantly more treatments were completed for patients with melanoma in cycle 1 compared to cycle 2.

<table>
<thead>
<tr>
<th>TABLE 1. SAMPLE CHARACTERISTICS (N = 40)</th>
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<tr>
<td>CHARACTERISTIC</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Melanoma</td>
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<tr>
<td>Renal cell carcinoma</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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<td>Male</td>
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<td>Race</td>
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<td>White</td>
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<td>Latino</td>
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<td>Black or African American</td>
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<td>Asian</td>
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No treatment-related deaths occurred. Cardiovascular symptoms were the most common major side effects (21 patients in cycle 1 and 22 patients in cycle 2) and included hypotension, hypertension, cardiac arrhythmias, and tachycardia. One of 40 patients required vasopressor infusion for severe hypotension. In cycle 1, the other most common major side effects were increased total bilirubin (greater than 3 mg/dl) (n = 9), pulmonary symptoms (n = 4), and renal failure (n = 3). In cycle 2, the other major side effects were impaired renal function (n = 5) (serum creatinine level greater than 2 mg/dl) and pulmonary symptoms (n = 4).

Of 45 clinicians, 30 participated in an electronic survey to assess their satisfaction with the SOS. Participants were RNs (n = 26), physicians (n = 3), and pharmacists (n = 1). Fifty-three percent of participants found that telephone consultation was very satisfactory to superior, and 25 physicians responded to telephone consultations within an hour. Overall, 24 respondents found that the SOS provided guidance to clinicians and rated the SOS component on managing side effects as very satisfactory to superior. In response to the question assessing if the SOS provided guidance for clinicians in giving effective and safe care, 24 participants replied that it was very satisfactory to superior.

**Discussion**

In this study, hypotension was the most common toxicity and occurred in 55% (n = 22) of patients during cycle 1 and 53% (n = 21) of patients in cycle 2, compared to 96% of patients in other studies (Acquavella et al., 2008). In addition, only 1 of 40 participants required vasopressors; in similar studies, Quan et al. (2005) found that 20% of participants required vasopressors, and Acquavella et al. (2008) found that 10% required them. Treatment-induced hypotension was treated with normal saline boluses instead of vasopressors. Sixteen patients had skipped, delayed, or discontinued doses because they were recovering from side effects caused by previous doses.

**TABLE 2.**

<table>
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<tr>
<th>DIAGNOSIS</th>
<th>n</th>
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<th>SD</th>
<th>SE X</th>
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<tbody>
<tr>
<td>Cycle 1</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Melanoma</td>
<td>30</td>
<td>11.7</td>
<td>2.6</td>
<td>0.48</td>
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<tr>
<td>RCC</td>
<td>10</td>
<td>8.7</td>
<td>3</td>
<td>0.94</td>
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<tr>
<td>Cycle 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>30</td>
<td>8.9</td>
<td>2.3</td>
<td>0.41</td>
</tr>
<tr>
<td>RCC</td>
<td>10</td>
<td>7.6</td>
<td>2.2</td>
<td>0.69</td>
</tr>
</tbody>
</table>

RCC—renal cell carcinoma; SE—standard error

**Limitations**

The current study has a number of limitations. The single-site oncology ICU resulted in less generalizability (Polit & Beck, 2008). Because of the descriptive retrospective study design, baseline comparability is not possible. Another limitation was the relatively small sample size of 40 participants, including the small number of patients with renal cell carcinoma (n = 10). A larger sample would have permitted a subset analysis of comparison of mean adverse symptoms of patients with renal cell carcinoma receiving HD IL-2. This study had a homogeneous sample, with 87% of the population identifying as Caucasian. Therefore, the generalizability of this study is limited.

**Implications for Practice**

Overall, clinicians found the SOS evaluated in this study to be very satisfactory or superior in guiding care and providing guidance on the treatment of side effects. Other organizations should consider the implementation of an SOS for HD IL-2 treatment.

**Conclusion**

The standard HD IL-2 regimen is 600,000 IU/kg every eight hours via IV infusion for as many as 14 doses during cycle 1 (one to five days) and separated by 10–14 days before repeat dosing during cycle 2. This regimen is associated with acute dose-related toxicities that affect multiple organs. The safe administration of an HD IL-2 regimen requires admission of patients to the ICU and frequent evaluation of patients during treatment. Developing practical management guidelines has increased the overall safety of HD IL-2 and markedly reduced treatment-related mortality (Dutcher et al., 2001; Kammula, White, & Rosenberg, 1998; Schwartzentruber, 2000). Further exploration is warranted to determine if the SOS increases the number of doses completed by patients during the two cycles.

Quality of care in all settings is vital. A collaborative management occurs when patients, families, and healthcare providers have shared goals, a mutual understanding of responsibilities, a sustained working relationship, and skills in carrying out individualized cancer care. These findings suggest that the role of nurses as adopters is crucial. Healthcare organizations, facing the challenges of taking care of a growing and diverse population, need administrative support and leadership that recognizes this important role of nursing staff who have received specialized training to take care of patients with cancer. When barriers to innovation are present, active collaboration among all clinicians helps
to improve the system. An effective process for implementing change helps healthcare organizations improve quality care and patient outcomes.

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REFERENCES


