

**Interleukin 2 Toxicity
&
Standard Procedures for Recording & Reporting Drug Toxicities**

By

Kendall A. Smith

December 24, 2000

- **Introduction**

There has been considerable confusion regarding the toxicity of interleukin 2 (IL2) administration, which has arisen in part, because of varying doses and treatment regimens that have been initiated in the last 5 years. However, in addition, it is difficult for the layperson to extrapolate the standard way of recording and reporting of drug toxicities, and to put the degree or severity of the toxicities into language understandable by the average person.

In 1977 and again in 1979, The World Health Organization (WHO) initiated meetings on the Standardization of Reporting Results of Cancer Treatment. These measures were necessary because these drugs were not only toxic to the cancerous tissue under treatment, but were also toxic to normal tissue as well. The result of these meetings was a consensus on the clinical and laboratory abnormalities produced as a consequence of the administration of drugs. A “graded toxicity scale” was initiated (*Cancer 47:207, 1981*), designed to group toxicities into none (Grade 0), mild (Grade I), moderate (Grade II), severe (Grade III), and intolerable (Grade IV). This type of graded toxicity scale has now become standard, not only for cancer therapies, but for all drugs. It serves to allow communication between physicians regarding the toxicities of different agents, or the same agent used in different doses and treatment regimens.

- **IL2 Causes Inflammation**

IL2 causes inflammation, which is the reason that it has been tried as a therapeutic to augment the function of the immune system. However, the IL2 effects are dose-dependent, and if the doses of IL2 are too high, toxicity will result. The toxic inflammatory side effects produced by IL2 are separable into local and systemic toxicities. However, the genesis of each of these reactions is identical. IL2 functions to recruit and activate white blood cells and cells of the blood vessels themselves that are involved in the generation of inflammation. Thus, if IL2 is injected or released locally, it activates Natural Killer (NK) cells to release pro-inflammatory cytokines, such as interferon- γ (IFN- γ), Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), and Tumor Necrosis Factor (TNF- α). These cytokines, in turn stimulate macrophages to release even more pro-inflammatory cytokines, which ultimately promote the cells lining

the blood vessels to leak both plasma and white blood cells into the tissues. When confined to a local site of injection, there is a recognizable focus of inflammation manifest by redness, swelling, firmness, and tenderness, which are the cardinal signs of inflammation. The magnitude of the local IL2 toxicity is dose-dependent, i.e. the larger the dose, the larger the area of inflammation at the injection site (*Biotech. 10:157, 1992*).

If IL2 is administered in high doses, especially if it is administered systemically (e.g. intravenously), the entire body undergoes exactly the same reaction, and systemic inflammation results. The constellation of symptoms has been termed the Systemic Inflammatory Response Syndrome (SIRS). The SIRS is manifest by a generalized leakage of blood plasma and cells from the vessels into all of the tissues, which results in low blood pressure (shock), fever, fatigue, muscle aches, and an overall bad feeling (malaise). The degree or magnitude of these symptoms, both local and systemic, is dependent on the dose of IL2 and the duration of IL2 administration. Moreover, these toxicities are quantifiable using the WHO Graded Toxicity Scale.

- **The WHO Graded Toxicity Scale**

The following WHO Graded Toxicity Scale has been abstracted to focus on the primary toxic symptoms attributable to IL2, i.e. fever, fatigue, & lethargy, and that can preclude normal daily activities on the part of the recipient.

Parameters	Grade				
	0 (None)	I (Minimal)	II (Moderate)	III (Severe)	IV (Intolerable)
Fever	None	101-103 °F	103-105 °F (< 6 hrs)	103-105 °F (Persistent)	> 105 °F (With shock)
Fatigue	None	Fatigue without change in daily activities	In bed <50% of day	In bed >50% of day	Unable to care for self
Lethargy	None	Transient	Somnolence <50% of day	Somnolence >50% of day	Coma

From this table, it is evident that even Grade I or Minimal toxicity would be difficult to sustain on a daily basis for prolonged periods of several weeks or months. Grade II or Moderate toxicity may be tolerable for a few days, but certainly no longer than a week. Grade III or Severe toxicity is incapacitating, and Grade IV toxicity is life threatening.

- **Intravenous High Dose Intermittent IL2: The Maximum Tolerated Dose**

In 1995, Kovacs and co-workers from the NIAID published results (*N. Eng. J. Med.* 332:567, 1995) from a preliminary dose escalation study, in which 23 subjects received a single 21-day or 5-day course of IL2 administered as a continuous intravenous infusion through an indwelling central venous catheter (i.e. in the heart) in doses ranging from 1.8 million U/day to 24 million U/day. “The *maximum tolerated dosage (MTD)* was found to be 12 million U/day when administered for 21 days, and 18 million units/day when administered for 5 days. The dose-limiting side effects included capillary leak (defined as a weight gain > 4.4 lbs; often associated with decreased urinary output, low blood pressure and edema), severe influenza-like symptoms, liver and kidney dysfunction, low blood platelets and low white blood cell counts”.

To examine the long-term effects of repeated courses of intravenous IL2, 10 subjects received a 5-day course of IL2 by continuous intravenous infusion, which was then repeated every 8 weeks for 4-13 cycles. The initial dose was 18 million U/day, but 6 of the 10 subjects required a reduction in the dose to 12 million U/day, while 2 subjects required reduction to 6 million U/day, “*primarily because of fever and severe influenza-like symptoms*”. Although the authors did not grade the toxicities encountered, they reported “the most common side effects were rash (79%), fatigue or malaise (76%), muscle/joint aches (61%), nausea (59%), capillary leak (57%) and fever > 102° F (57%)”.

To extend their experience with the high dose IL2 approach, the same group of investigators performed a randomized controlled study in which 60 subjects received nucleoside analogue antiretroviral therapy alone or in combination with intravenous IL2 at 18 million U/day for 5-days every 8 weeks. Although the authors (*N. Eng. J. Med.* 335:1350, 1996) did not report the toxicities experienced by the control group, nor the grade of the toxicities experienced by the group who received IL2, they reported Moderate (Grade II?) and Severe (Grade III?) fatigue/malaise in 90% of the IL2 recipients.

- **Subcutaneous High Dose Intermittent IL2: The Maximum Tolerated Dose**

According to Davey and co-workers (*J. Infect. Dis.* 175:781, 1997), among the “*major limitations to IL2 therapy by continuous IV infusion are the high degree of dose-limiting toxicities, including abnormal kidney and liver function tests, bone marrow dysfunction, central nervous system changes, a capillary leak syndrome with fluid imbalance, fever, and a variety of subjective symptoms*”. Therefore, they sought to try to decrease the toxicities of IV therapy by a dose escalation study administering IL2 by subcutaneous (SC) injections.

“*Each of the first 3 patients treated in this study with SC IL2 at 18 million U/day developed serious (greater than Grade III) toxicities, including significant hypotension (i.e. decreased blood pressure or shock) in 2 subjects, and mild congestive heart failure in 1 subject. Therefore, no additional patients were enrolled at this dose*”...and 15 million U/day was defined as the **Maximum Tolerable Dose (MTD)**.

At the **MTD** of 15 million U/day, “Mild to moderate (i.e. grade FII) constitutional side effects of fever (fatigue & muscle aches) in concert with low-grade blood, kidney and liver abnormalities were the most commonly seen toxicities; however, these were not generally treatment limiting”. Moreover, “switching patients from an initial single daily injection to a split-dosing schedule of 7.5 million U twice daily resulted in **increased** subjective symptomatic complaints, essentially prohibiting further dose escalation above 7.5 million U/injection on a twice daily dosing schedule”.

Accordingly, 15 million U/day, given either as a single dose or in 2 divided doses, is the **MTD** when given for 5 days. This means in lay terms that this dose, by definition, will produce toxic side effects that preclude going to higher doses. The toxic side effects of the **MTD** are described as being Grade FII (i.e. minimal-moderate). It is noteworthy that moderate (Grade II) toxicity is comprised of transient (< 6 hrs) fever of 103-105°F, fatigue requiring bed rest < 50% of the day, and somnolence (sleepiness) < 50% of the day. These symptoms essentially preclude working a full day, such that this dose will lead to the loss of work time during the treatment interval of 5 days.

- **Subcutaneous Intermediate Dose Intermittent IL2**

In an attempt to circumvent the toxic side effects of MTD SC IL2 therapy, another group of investigators reduced the IL2 dose to 9 million U/day in a single injection (which amounts to a 40% dose-reduction), and performed a randomized trial in 64 subjects, examining a 5-day dosing regimen that was repeated every 6 weeks, or alternatively a repetition when the CD4+ T cell count fell below 1.25-fold of baseline counts (**AIDS 12:F225, 1998**).

“The dose-limiting toxicity of 5-day cycles of SC injections of 9 million U of IL2 was similar to the side effect profile observed for intravenous IL2 therapy, with the overall intensity being substantially lower. The majority of side effects occurred on average 3-6 hours after SC injection. Fatigue, nasal/sinus congestion, fever, >100^o F and headache were the most common side effects of SC IL2. Severe side effects such as the capillary leak syndrome or significant hypotension were not observed.”

In this report, the side effects in the control group were also detailed, but the side effects were not graded, so that it is difficult to determine whether the side effects noted in the IL2-treated groups were similar or more severe than recorded for the control subjects.

In a separate study, Davey and co-workers, who originated the IV and SC MTD intermittent treatment regimens, conducted a study to “search for a better-tolerated, more practical means of IL2 administration without compromising efficacy” (**J. Infect. Dis. 179:849, 1999**).

Forty-nine subjects were randomized to receive either “low dose” (1.5 million U twice daily) or high dose (7.5 million U twice daily) IL2 SC, either every 4 weeks or every 8 weeks. There was a strong dose-dependency to the toxicities observed. “For example, among 24 patients who received 7.5 million U either every 4 or 8 weeks, 18 episodes of

fatigue and malaise of grade III (resting in bed > 50% of day) severity were reported. In contrast, of 25 patients who received 1.5 million U either every 4 or 8 weeks, only 5 episodes of fatigue and malaise of comparable severity were reported”.

In a separate study, another group compared SC and IV IL2 intermittent therapy in a randomized, controlled trial (*The Lancet 353:1, 1999*). Ninety-four subjects were randomized to receive either nucleoside antiretroviral therapy alone or in combination with IV IL2 (12 million U/day for 5 days), SC IL2 (3 million U twice daily for 5 days), or polyethylene glycol-modified IL2 (2 million U/m² IV) every 2 months for 1 year. The severity of the side effects experienced on these different treatment regimens was not graded, and the side effects of the control group, which did not receive IL2, were not mentioned. However, there were fevers > 103°F (39.5° C) in 42% of those individuals who received SC IL2 vs. 59% of those who received IV IL2.

- **Summary: Systemic Toxicity of Intermittent Dose IL2**

From all of these studies and reports, it is clear that the intermittent dosing regimen of IL2 in doses ranging from 3 million U/day to 18 million U/day, results in systemic symptoms consisting of fever, fatigue, malaise, and lethargy. The severity of these side effects is dose-dependent, with the least severe resulting from the lowest doses, and the most severe resulting from the highest doses. In addition, despite the number of trials that have been undertaken, few if any of these trials have graded the toxicities according to the criteria published by the WHO or other agencies. Moreover, none of the controlled trials reported the details of the toxicities experienced by the control groups, in which no IL2 was administered. Consequently, it is very difficult to come to a consensus as to the extent or severity of the intermittent administration of high or intermediate dose IL2. Suffice it to conclude that intermediate dose IL2 therapy will probably yield minimal (Grade I) to moderate (Grade II) systemic toxicity, and the high dose intermittent therapy (i.e. 18 million U/day IV, and 15 million U/day SC), will yield moderate (Grade II) to severe (Grade III) toxicity.

- **Low Dose Daily IL2 Therapy**

In 1989, we initiated studies with Jerome Ritz at the Dana Farber cancer Institute in Boston, to determine whether it was possible to administer IL2 in doses low enough that would not lead to toxicity, but high enough to result in augmentation of immune reactivity. Using IL2 supplied first by the Roche Corporation and then by the Amgen Corporation, we found that IL2 administered daily for 3 months in the range of 300,000 U/day to 600,000 U/day IV as a 24 hour continuous infusion only led to mild (Grade I) toxicity (*J. Clin. Onc. 9:2110, 1991*)

Based on these results, we initiated a phase I dose finding/safety study of daily SC Amgen IL2 injections in 16 HIV+ individuals in 1994. We found that the **Maximum Nontoxic Dose (MND)** given for 6 months was 250,000 U/m² body surface area (BSA). Since the average BSA of a normal adult is ~ 1.7 m², this calculates to ~ 425,000 U/day. It is noteworthy that we are the only investigators who have calculated the dose of IL2

based upon the BSA of each individual, which is standard pharmacological procedure to ensure that each individual receives an equivalent dose of the drug. If this dose was doubled, toxicity occurred, manifest by fatigue, fever ($< 101^{\circ}\text{F}$) & malaise. We published these results in 1996 (*Proc. Natl. Acad. Sci. USA* **93:10,405, 1996**), and then extended our observations to 40 additional subjects in an uncontrolled phase I/II study (*AIDS Reader* **9:563,1999**). At this maximum nontoxic dose, we found no systemic toxicities using the Amgen IL2 preparation, even when SC IL2 therapy was administered for 1 year.

Subsequently, the Amgen Corporation discontinued the production of IL2. Consequently, we switched to the use of Chiron IL2, which is manufactured and marketed under the trade name of ProleukinTM. In a series of assays both in the laboratory and in the clinic we found that Proleukin is ~ 5 -6-fold less potent than the Amgen preparation. Accordingly, $250,000 \text{ U/m}^2 \text{ Amgen IL2} = 1.25 \text{ million U/m}^2 \text{ Proleukin}$, and the equivalent maximum nontoxic dose of Proleukin for a normal adult was calculated to be $\sim 2 \text{ million U/day}$.

Based upon our findings at Weill Cornell, the Chiron Corporation sponsored a phase II randomized, multicenter, controlled trial testing low dose daily IL2 (i.e. $1.2 \text{ million U/m}^2/\text{day}$) for 6 months (*HIV Clinical trials 1:1, 2000, please see a PDF version of this report in the "Investigate" section of this web site*). A total of 115 patients were enrolled in the trial. Fifty-six subjects received HAART + daily low dose IL2, while 59 subjects received HAART alone (control group). For those individuals who received IL2, after receiving $1.2 \text{ million U/m}^2$ daily for at least 2 weeks, if there was no grade II toxicity (i.e. moderate toxicity), the dose could be escalated by $0.3 \text{ million U/m}^2$ every 2 weeks, until grade II toxicity was experienced. By comparison, in the event that a patient experienced a grade II or greater toxicity, IL2 treatment was withheld until the toxic symptoms resolved, and the IL2 treatment was resumed at a dosage reduced by $0.3 \text{ million U/m}^2$, to $0.9 \text{ million U/m}^2$ ($\sim 1.5 \text{ million U/day}$ for a normal adult with $1.7 \text{ m}^2 \text{ BSA}$). In other words, it was attempted to arrive at a maximum dose for each individual that still allowed normal daily activities with minimal side effects, grade 0-I.

This is the only controlled study in the literature that reports and grades the toxicities encountered by both the control group as well as the group that received IL2. All of those studies mentioned above only report the toxicities of the IL2-treated group. Therefore, even though a control group participated in some of the other studies, it remains obscure as to how much of the toxicity encountered was actually due to the IL2 therapy.

"The adverse events reported for the majority of patients in the IL2 and control groups were generally characterized as mild or moderate (i.e. grade I or grade II, see table 3 in the report). In general, the number and frequency of patients with adverse events of any grade were similar in the IL2-treated group and control patients. The most common systemic adverse events for patients in the IL2 group that were found infrequently in the control group were fatigue (53%), flu syndrome (46%), nausea (36%), and diarrhea (27%). Less than 13% of patients in the control group experienced each of these adverse events. Severe (grade III) and life-threatening (grade IV) adverse events were infrequent

in both treatment groups (table 3). Therefore, by comparison with the higher doses of IL2 used intermittently, the low dose daily regimen was tolerated considerably better.”

- **Local Toxicity of SC IL2 Injections**

As mentioned at the beginning of this essay, IL2 causes local inflammation at the site of the SC injection. The size and duration of this inflammatory reaction is IL2 dose-dependent. We conducted a series of examinations of IL2 injection sites, and established that the underlying basis for the appearance of the cardinal signs of inflammation at the injection sites is a classic cell-mediated immune reaction, manifest by dilation of the blood vessels, leakage of plasma and white blood cells from the blood vessels into the tissues, and accumulation of white blood cells, mostly lymphocytes and macrophages, at the site (*Biotech. 10:157, 1992*).

To minimize the discomfort of the local reactions, the sites of injection are rotated daily, usually from the lower abdominal wall, to the anterior, then posterior thighs. If these procedures are followed, we have had no one discontinue SC IL2 administration because of the local reactions to daily low dose IL2 administration. At 2 million U/injection, the diameter of the local reaction is ~ 2 inches. However, because the size of the local reactions is dose-dependent, it should be expected that the intermediate and high doses of IL2 would produce a proportionally greater local inflammatory response. Thus, intermediate dose IL2 at 4.5 million U SC twice daily will lead to an inflammatory response with a diameter of ~ 4.5 inches, while the high dose of 7.5 million U injected SC twice daily will lead to a response with a diameter of ~ 7.5 inches.

- **Summary: The Dose-Dependency of IL2 Toxicity**

From this review of the literature of the various clinical trials of the use of IL2 in HIV infection, we now have a great deal of data that allow a clear prediction of toxicities, both systemic and local, to be expected by the differing doses and treatment regimens that are currently being tested. These data are summarized as follows:

IL2 Dose	Regimen	Grade/ Systemic Toxicity	Diameter/Local Toxicity
18 mU	CIV/5 days	III	-----
15 mU	7.5 2x SC/5 days	II-III	7.5 inches
9 mU	4.5 2x SC/5 days	I-II	4.5 inches
6 mU	3.0 2x SC/5 days	I	3.0 inches
3 mU	1.5 2x SC/5 days	I	1.5 inches
2 mU	SC/ daily	0-I	2.0 inches

1.5 mU

SC/ daily

0

1.5 inches