Interleukin-2

Background:

Interleukin-2 (IL-2) was initially investigated by a number of labs as a T-cell growth factor and subsequently developed as a medical therapy for kidney cancer and melanoma in the early 1980s by Steven Rosenberg at the National Institutes of Health. It won Food and Drug Administration (FDA) approval in 1992 and has been marketed since then under the name Proleukin by the Chiron Corporation based in Emeryville, California. In 2006, Chiron merged with Novartis Pharmaceuticals. Novartis has subsequently sold the American distribution rights to Prometheus Labs.

Interleukin-2 is a cytokine, which is a protein that acts as a regulator of the body's immune system, similar to interferon. By giving the patient large doses of this protein, it is hoped that the body's own immune system will destroy the cancer cells. Interleukin-2 is administered via intravenous (IV) injection as high dose (HD) (usually defined as 600,000 – 720,000 units/kg). Lower dosage IV and subcutaneous IL-2 are also prescribed for kidney cancer, but HD IL-2 is the only regimen that has FDA approval. The other uses are off-label.

HD IL-2 is highly toxic, and although it is administered for a brief cycle, usually one week, it must be given in a hospital setting where the patient can be closely monitored by physicians and staff who have significant experience in its use. The prospective candidate must be in fairly good health to qualify for this drug. For example, he or she must have a creatinine level < 1.5, have no uncontrolled heart arrhythmia, and have good pulmonary and liver function.

Side Effects of HD IL-2:

The patient often experiences flu-like symptoms during treatment, i.e. chills, fever, malaise, nausea, and diarrhea. More of a problem can be hypotension and renal issues (renal toxicity, oliguria,[1] and increased creatinine). The side effects usually disappear shortly upon completion of treatment. For the management of side effects of HD IL-2 treatment, see Janice Dutcher's article in the *Kidney Cancer Journal* .[2]

When HD IL-2 treatment was in its early days, there were treatment related mortalities. Since that time, practitioners have gained sufficient experience to improve the safety of the drug. The National Cancer Institute conducted a study[3] investigating the safety of HD IL-2 administered to metastatic patients (a total of 1241 renal cell carcinoma and melanoma patients) over a 12-year period. They found a "progressive reduction in morbidity and mortality" due to the ability to better screen patients, to control the therapeutic conditions, and to terminate dosing when faced with toxicities. At the same time, there was no significant reduction in complete response rates for renal cell and melanoma patients over this period.

Efficacy Studies:

Since Interleukin-2 was approved for use in kidney cancer by the FDA, several studies have been conducted to qualify its effectiveness including two seminal studies comparing high dose (HD) versus low dose (LD) IL-2.

David McDermott of the Beth Israel Deaconess Medical Center in Boston was the principal investigator[4] on a Cytokine Working Group[5] sponsored, randomized Phase III trial of 192 patients (165 of them clear cell) testing high-dose IL-2 (HD IL-2) versus a combination of subcutaneous IL-2 and Interferon-alpha (INF). The trial, which ran from April 1997 to July 2000, showed the following:

Summary of Tumor Response Data:

	LD IL-2 & IFN	HD IL-2
	91 patients	95 patients
	Patients (%)	Patients (%)
Overall Response Rate (ORR)	9 (9.9%)	22 (23.2%)
Complete Response (CR)	3 (3.3%)	8 (8.4%)
Partial Response (PR)	6 (6.6%)	14 (14.7%)
Durable 3-yr CR	0%	7 (7.4%)

As can be seen, only HD IL-2 had a durable, 3-year complete response (CR) rate (7.4%) for metastatic RCC (mRCC). For HD IL-2 therapy, the overall response rate for patients with liver or bone metastases was comparable to that of patients with other metastatic sites. However, for the patients taking the combination of subcutaneous IL-2 and Interferon-alpha, the story was quite different.

	LD IL-2 & IFN		HD IL-2	
	Other Sites	Liver/Bone Metastases	Other Sites	Liver/Bone Metastases
Overall Response (ORR)	15.4%	2.6%	23.5%	22.7%

	Other Sites	Liver/Bone Metastases	Other Sites	Liver/Bone Metastases
Overall Response (ORR)	15.4%	2.6%	23.5%	22.7%

The median response duration was 24 months for HD IL-2 therapy compared with 15 months for LD IL-2 and INF, but the difference was not statistically significant. The difference in the overall median survival, although favoring HD IL-2, 17.1 months to 13.0 months, was also not statistically significant.