Bolus High Dose Interleukin-2 for the Treatment of Malignant Melanoma

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Abstract

Background: High dose interleukin-2 therapy, administered in bolus, is considered to be a reasonable treatment option in a selected group of patients with metastatic malignant melanoma.

Objectives: To present our experience using this mode of therapy in 21 patients with metastatic melanoma.

Materials and Methods: The 21 patients in our study group comprised 13 men and 8 women with a mean age of 46 years (range 29–63). Their metastatic disease was present in all extracranial sites, dermal and sub-dermal metastases being the most common (15 patients had at least one site, in addition to other locations of metastases). Patients with intracranial disease were excluded due to the poor effectivity of IL-2 at this site. Treatment comprised a course of 2 weeks of therapy with a 1 week rest interval between. Radiological and physical evaluation was performed 6–8 weeks after the first course. If a response was achieved a second course of therapy was given. Patients received up to 14 planned doses of IL-2 in each week, 720,000 IU/kg of IL-2 per dose i.v. in 15 minutes. All treatments were given in the surgical ward, and only one patient was hospitalized in the intensive care unit.

Results: Of the 21 patients, one had a complete response that has lasted for 17 months and 5 patients had a partial response (range 3 months to 3 years). One patient died during treatment, and one patient who refused further treatment because of no response died a few days after completion of treatment. Prior to therapy three of the responders had received autologous vaccines with good immunological response ($P = 0.115$). Toxic side effects were significant, but they were treated successfully with no residual damage.

Conclusions: High dose IL-2 can be administered safely in a surgical department. The response rates achieved in this series justify the use of high dose IL-2 in a selected group of patients. To improve response rates, a combination of autologous vaccines prior to high dose IL-2 may be recommended.

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Interleukin 2 is a naturally occurring cytokine that was first identified in 1976 as a growth promotor of activated T lymphocytes [1]. Further studies revealed that IL-2 exerts a wide range of immunological functions. It was found that IL-2 is not only a proliferative factor of T cells but it also amplifies the activation of other types of cells, including cytotoxic T lymphocytes and B lymphocytes, as well as natural killer cells by promoting their killing activity [2]. Another important role attributed to IL-2 is its ability to induce non-major histocompatibility complex-restricted cytotoxicity against NK-resistant tumor cells. This type of cell is termed lymphokine-activated killer [3]. An important mechanism whereby IL-2 exerts part of its immunoregulatory functions is the induction of secondary secretion of other cytokines. Tumor necrosis factor, IL-1, IL-6, interferon-gamma and colony-stimulating factors were found to be secreted by responder cell populations [4].

In 1983, following the identification of the gene responsible for the coding of IL-2, it became possible to produce the recombinant IL-2. Recombinant IL-2, called proleukin, differs from the native protein by the deletion of the first amino acid, alanine, and the serine-replacing cystein in position 125. Unlike IL-2, proleukin molecule is not glycosylated [5]. These differences were not associated with any disturbances in the immunoregulatory functions but enabled the study of the functions of IL-2 in animals and humans [6].

Steven Rosenberg and colleagues from the surgical branch of the National Cancer Institute were the pioneers who demonstrated the significant anti-tumor effects of IL-2 in animals [7]. This cytokine was subsequently tested in human studies where it exerted an impressive anti-tumor effect. The first successful studies were conducted in patients with metastatic malignant melanoma and renal cell carcinoma, while the result achieved in other solid tumors was less significant [8–10]. In the initial investigations Rosenberg used the combination of IL-2 and LAK cells, which after multiplying *in vitro* were returned to the patient. IL-2 was administered in these studies in the highest possible doses and given intravenously as a bolus every 8 hours. Atkins et al. [11] recently reviewed the results achieved in treating 270 patients with metastatic melanoma in seven different medical centers [11]. They found a slightly lower overall response rate – 16% of patients with metastatic melanoma responded to IL-2.

The efficacy of IL-2 is severely compromised by the wide spectrum of side effects in patients treated with high doses of

IL = interleukin

NK = natural killer
LAK = lymphokine-activated killer

this cytokine. These toxic effects are dose and schedule related and resemble the clinical symptoms of gram-negative sepsis from bacterial sources. The clinical symptoms include hypotension, tachycardia, arrythmias, pulmonary edema, flu-like symptoms, vomiting and diarrhea, severe skin eczema, mucositis and significant peripheral edema. Most of these toxic effects are attributed to the vascular leak symptom, which results in increased permeability of peripheral capillaries to fluid and protein that are excreted to the extra-vascular space. Mechanisms of VLS include activation of released cytokines, mainly TNF, IL-1, and activation of endothelial cell antigen with release of nitrous antigen [12]. In order to reduce the toxicities of high dose IL-2, many groups modified the modes of administration of IL-2 by giving it continuously [13] or subcutaneously [14]. These modes of administering IL-2 to patients with metastatic melanoma may elicit slightly lower response rates and shorter duration of anti-tumor activity [15].

We report here our experience with bolus high dose IL-2 to treat patients with metastatic malignant melanoma.

Patients and Methods

Patient population

Between January 1995 and June 1999 we treated 21 metastatic melanoma patients with high dose IL-2. The mean age of the patients, 13 males and 8 females, was 46 years (range 26–63 years). With regard to the organs involved in the metastatic disease, 11 patients had lung metastases, 11 had dermal and sub-dermal disease, 6 had peritoneal and pelvic disease, 4 had liver metastases, and one patient suffered from an aggressive scalp disease that recurred after repeated excisions and radiation therapy [Table 1].

Nineteen patients were treated by IL-2 following failure of other modes of oncological therapy, including radiation, chemotherapy and immunotherapy with or without lower doses of IL-2. Only in two patients was high dose IL-2 the first line of treatment for metastatic melanoma.

Patient eligibility

All participating patients had histologically confirmed metastatic malignant melanoma, were older than 18 years old and capable of giving informed consent. No prior therapy with any type of oncological therapy, including IL-2 in lower doses, was a reason to exclude a patient from therapy. All patients had a good performance status, a prospective survival of at least 3 months, and adequate organ function as follows:

- creatinine serum concentration < 2 mg/dl and creatinine clearance levels > 50 ml/24 hours
- no active ischemic heart disease, and a negative treadmill Thallium scan
- absence of any corticosteroid-dependent disease or condition
- no pulmonary disease or dysfunction according to pulmonary function tests
- no existing or past central nervous system metastases
- no infection with human immunodeficiency virus or hepatitis B or C.

VLS = vascular leak symptom
TNF = tumor necrosis factor

Table 1. Sites of metastases

	No. of patients (%)
Dermal and sub-dermal	11 (52%)
Lungs	11 (52%)
Peritoneal/pelvic disease	6 (28%)
Liver	4 (19%)
Local aggressive	1 (5%)

Treatment plan

IL-2 was administered by 15 minute i.v. infusion every 8 hours for up to 14 consecutive doses over 5 days as tolerated. Dose modification for toxicity was done by increasing or omitting the interval between doses. After a rest period of 1–2 weeks an additional 14 doses of IL-2 were scheduled over the next 5 days. A second course of therapy was given if the patient responded after an 8 week interval.

Dosing. IL-2 doses consisted of 720,000 IU/kg. Doses were omitted if life-threatening adverse effects occurred (such as hypotension that did not respond to maximal pressors, uncontrolled arryhthmias, or neurocortical toxicity manifested by mental confusion) or if the patient requested so due to unbearable toxicity.

Concomitant medications. A wide range of concomitant medications was introduced during IL-2 therapy to reduce toxicity. These drugs included paracetamol and indomethacin every 4 hours, cimetidine to reduce peptic complications, prophylactic antibiotics cloxacillin and dopamine in renal doses, anti-emetic drugs such as daily i.v. ondansetron and metoclopramide as requested, anti-diarrheal drugs, and sedatives. During therapy large amounts of fluids up to 7 L/day were given intravenously with replacement of absent electrolytes.

Response criteria. Prior to therapy, all patients were evaluated by a complete history taking and physical examination. Computed tomography of the head, chest and abdomen was performed to evaluate measurable disease. Six to eight weeks after the second week of the first course of therapy the response to treatment was evaluated by repeating detailed physical examination and whole-body CT. A partial response was defined as a reduction of at least 50% of the size of known tumors without the appearance of new lesions or a measurable increase in any pre-existing lesion. A complete response was defined as the total disappearance of identifiable disease. Response duration was measured from the beginning of IL-2 therapy.

Statistical analysis

A statistical study was performed to evaluate the significance of response among patients receiving autologous vaccine prior to IL-2 therapy. We used the Chi-square Fisher exact test and evaluated the *P* values for both groups of patients.

Results

Twenty-one patients were treated in our department between January 1995 and June 1999. The toxic adverse effects were similar to those reported in the past and included hypotension, tachycardia, arryhthmias, oliguria, peripheral edema, diarrhea and vomiting, skin changes and mucositis. Laboratory pathological changes included leukopenia, thrombocytopenia, hypokalemia, hypocalcemia, hypomagnesemia, and mild to moderate liver function abnormalities. The most significant side effects and their relative severity according to the World Health Organization scoring system are listed in Table 2.

One patient died as a direct result of treatment, most probably due to sepsis. Another female patient was admitted with aggressive and rapidly growing abdominal metastatic melanoma in the peritoneum. Four days after cessation of IL-2 treatment intestinal obstruction developed; the patient and her family refused any surgical help and she died 3 days later.

Among those who responded, one patient with subcutaneous and lymphatic spread of the disease had a complete response that has lasted for 17 months after initiation of IL-2 therapy. Six patients had a partial response. In two of them it lasted for 3 months; in another two it lasted for 4 and 6 months, but both had subcutaneous metastases and the disease reappeared. In the remaining two patients the response is durable – 12 months in the patient with pelvic and subcutaneous metastases [Figure 1], and 3 years in the patient with liver disease. Among the responding patients, five received IL-2 following autologous vaccination against melanoma. Four of them had a good delayed-type hypersensitivity response and three responded to treatment (one complete and two partial response). One patient with locally aggressive disease in the scalp did not have positive DTH and did not respond to IL-2 either.

Three of the 21 patients had ECOG performance status of 2 and did not respond to therapy, while all responders had a performance status of 0.

Table 2. Toxic effects of high dose bolus IL-2

	Mean severity WHO scoring 1–4
Hematological (thrombocytopenia, leukopenia anemia)	2.5
Gastrointestinal (diarrhea, vomiting)	2.4
Hemodynamic (hypotension, arrhythmia)	2.2
Peripheral edema	2.2
Skin changes, mucositis	2.2
Urinary (oliguria, creatinine elevation)	1.6
Electrolyte changes (hypokalemia, hypomagmesemia, hypocalcemia)	1.2

DTH = delayed-type hypersensitivity

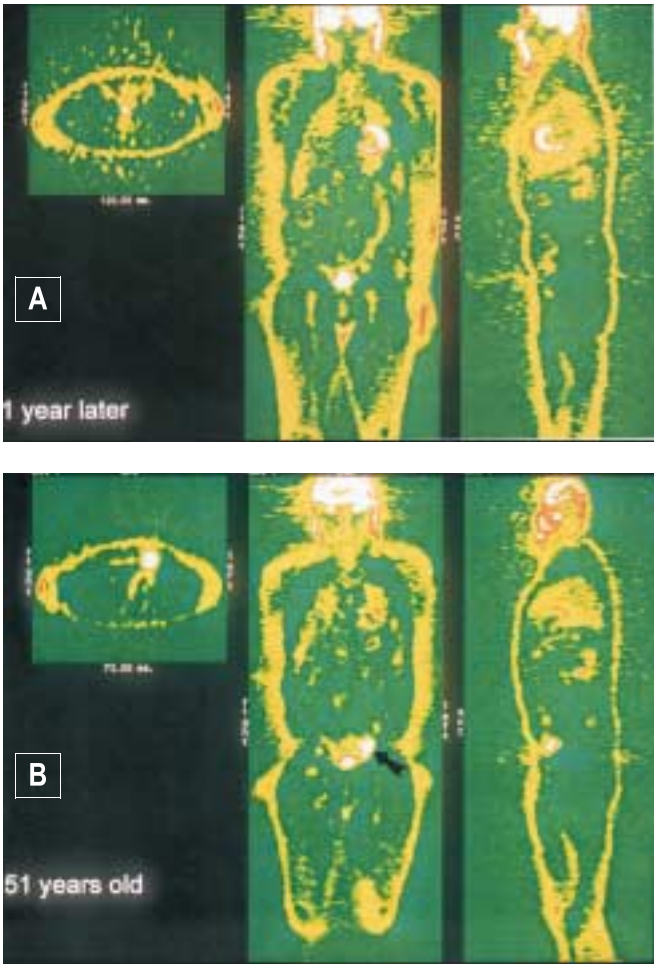

Figure 1. A patient with metastatic melanoma and a left pelvic metastatic deposit. Positron emission tomography images with ^{18}FDG before IL-2 therapy [**A, arrow**] and a year after terminating treatment **[B].**

Statistical evaluation was performed to evaluate the likelihood of response among patients who received autologous vaccination. The response rate among all patients receiving vaccinations and only in those who responded positively to DTH testing was not statistically significant ($P = 0.115$ and 0.4 respectively).

Discussion

Early-stage melanoma is a disease that can be successfully treated by surgery with or without adjuvant therapy in most cases. However, in a patient with malignant melanoma and distant metastases the median survival ranges between 6 and 9 months and 5 year survival is less than 4% [16]. Existing conventional modes of treatment including combined chemotherapy were demonstrated to achieve a 5 year survival of 1–2% [17]. Clinical and laboratory observations suggest that immunological responses may occasionally influence the course

of metastatic melanoma. The fact that metastatic melanoma was demonstrated to regress spontaneously in a few instances, and the efficacy of specific T cell lymphocytes to recognize unique antigens of melanoma [18,19], led researchers to develop biological response modifiers in this disease. Since the discovery of recombinant IL-2, this agent became an important immunotherapeutical modality for malignant melanoma.

Early murine studies using IL-2, followed by clinical studies performed by Ettinghausen and Rosenberg at the National Cancer Institute [20], resulted in significant anti-tumor responses, mainly in melanoma and renal cell carcinoma. They found a direct correlation between the dose of IL-2 and the response rate. They also demonstrated that the same total dose when administered in three daily doses was more effective than one daily dose.

The main obstacle in treating patients with high dose IL-2 is its high toxicity. In our study we preferred to use bolus high dose IL-2 in spite of its high rate of adverse effects, because of the long-term response attributed to this therapy. The toxicity that we observed in our patients was significant, and all experienced significant hemodynamic changes as well as many other adverse effects. However, most of the side effects disappeared a few days after cessation of treatment. We used symptomatic medication only, as described previously by other groups using high doses of IL-2 [5]. In an attempt to reduce renal insufficiency we gave dopamine in low renal doses beginning with the first dose of IL-2 administration, before the appearance of oliguria. We also administered daily intravenous ondansetron, which significantly reduced vomiting events. Only one patient received vasopressors in cardiac doses. At the end of treatment all patients received loop diuretics for several days in order to excrete the excessive fluid overload.

Most of our patients experienced significant weakness 7 to 10 days after terminating treatment, a phenomenon not reported in other series. We attributed it to hypothyroidism, which was frequently described as the result of autoimmune thyroiditis [21]. In all our patients in whom thyroid level was measured the results were normal.

The mortality induced by this treatment in our series was 4% (1/21), most probably due to sepsis, although all patients received prophylactic antibiotics. The two most common explanations given in previous studies were line sepsis and cardiac events. The incidence of both causes was greatly reduced following the routine use of prophylactic antibiotics and pre-treatment cardiac screening treadmill tests.

Most side effects of IL-2 therapy were attributed to the VLS phenomenon as well as to lymphoid infiltration observed in many organs [22]. While the exact mechanism of VLS is not entirely clear, a few explications have been proposed including activation of cell antigens [23] and the effect of secondary secreted cytokines [24]. Two cytokines were reported responsible for VLS, and some investigations employed the co-administration of IL-2 and inhibitors to them. Several of these inhibitors were promising in animal studies but failed to reduce toxicity of high dose IL-2 therapy [25]. Organ edema, which is the most significant adverse effect, is caused by the combination of VLS and the large amount of fluids administered to patients to ameliorate these side effects. Most patients in this series experienced a 10–20% weight gain above their baseline, but since the fluid shift reverses rapidly the majority of our patients as well as those in other studies reached their baseline weight or below it within 3–5 days after treatment [26].

An interesting observation in the present series was the relatively high number of patients who received IL-2 following the administration of autologous vaccination against melanoma in the Department of Oncology of the Hadassah Medical Center, Jerusalem [27]. This auto-vaccination method was based on the harvesting of melanoma tumors from the patient, and releasing the melanoma cells from the specimen by mechanical dissociation and enzymatic digestion. Prior to immunization the cells were prepared by irradiation and haptenization with DNP mixed with Bacille Calmette-Guerin and introduced into the patient subcutaneously. Delayed-type hypersensitivity was elicited by subcutaneous injection of irradiated autologous melanoma cells. As mentioned before, three of five patients who received the combined approach responded to treatment and all had a good DTH response. However, due to the small number of patients these results could not reach significance.

The relatively good results in this small group of patients raise the hope that combining high doses of IL-2 and vaccination against melanoma might be a better solution for metastatic melanoma than the available modes of treatment. Following recent identifications of effective cytotoxic thymus lymphocytes against melanoma, Rosenberg and colleagues from the NCI [28] recently reported a similar favorable response rate in treating metastatic melanoma patients with the co-administration of anti-melanoma vaccines and high dose bolus IL-2. They used a combination of synthetic peptides taken from antigens of melanoma and followed this treatment with IL-2. The rate of responders to this combination was 41%, which was significantly higher than the known response rate to high doses of IL-2 alone.

In summary, high dose bolus IL-2 remains an important tool in the available armamentarium against metastatic melanoma. It can be given safely in a dedicated surgical department with trained medical and nursing personnel who have the appropriate expertise. It is clear both from this series and previous research that it is crucial to select patients with good performance status in order to enable the study, despite the significant toxicity of high doses of IL-2, and to improve the chances of response. At the present time it is difficult to predict precisely which patients will respond to therapy, and further studies should address this question. The co-administration of anti-melanoma vaccine and high doses of IL-2 is promising, however further study is necessary to examine the beneficial effect of the combined therapy and to improve the efficacy of present vaccinations. Larger numbers of patients and further research may address the question whether combining high doses of IL-2 and melanoma vaccines is superior to each therapy administered separately.

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We don't pay taxes. Only the little people pay taxes

Liona Helmsley (1920–), self-styled American hotelier