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# A PHASE II STUDY OF RECOMBINANT INTERLEUKIN-2 (IL-2) PLUS INTERFERON-ALFA-2A (IFN-ALFA) GIVEN SUBCUTANEOUSLY IN PATIENTS WITH METASTATIC MALIGNANT MELANOMA (MMM)

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*O objetivo deste estudo foi avaliar o perfil de toxicidade, índices de respostas objetivas e sobrevida de pacientes portadores de melanoma maligno metastático tratados com a combinação de Interleucina-2 (IL-2) e Interferon-alfa (IFN-alfa) administrados por via subcutânea (SC). Vinte e cinco pacientes com dignóstico histopatológico de melanoma maligno metastático e doença mensurável foram tratados com IL-2 na dose de 18 milhões de unidades/m2 e IFN-alfa na dose de 3 milhões de unidades/m2 por via SC diariamente nos dias 1-5 e 8-12 de ciclos com 21 dias. Os pacientes foram todos avaliáveis quanto a toxicidade de acordo com o Common Toxicity Criteria do Instituto Nacional do Câncer dos EUA (CTC-NCI), enquanto que as respostas foram codificadas segundo os critérios da OMS. Os pacientes não haviam recebido tratamento químio, rádio ou imunoterápico prévio. Uma mediana de 3 (2-4) ciclos foram administrados. A toxicidade consistiu sobretudo de fadiga, artralgia, mialgias, febre e calafrios e retenção líquida. Não foram observadas toxicidades com risco severo de óbito. Quatro dos 25 pacientes (17%) apresentaram respostas objetivas. Em 2 destes casos foi possível a ressecção completa de massas residuais pós-tratamento imunoterápico, com remissões mantidas por 6 e 24+ meses, respectivamente. Nos outros 2 casos com resposta parcial, progressão clínica foi observada após 7 e 8 meses, respectivamente. Os pacientes que não responderam inicialmente ou apresentaram progressão posterior foram ao óbito após um seguimento mediano de 3 (1-7) meses. Em conclusão, a combinação de IL-2 e IFN-alfa por via SC produziu respostas limitadas em pacientes com melanoma maligno metastático. Ainda que a toxicidade tenha sido manejável, os resultados acima descritos não recomendam esta abordagem para uso clínico de rotina.*

***Unitermos***: *Melanoma maligno metastático - Interleucina. Melanoma maligno metastático - Interferon-alfa.*
***Keywords***: *Metastatic malignant melanoma - Interleukin-2. Metastatic malignant melanoma - Interferon-alpha-2A.*

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## Introduction

Metastatic malignant melanoma (MMM) remains incurable with the currently available therapeutic strategies (24, 25). Dacarbazine is the single approved agent for melanoma chemotherapy, producing objective responses in about 15-20% of patients, usually partial and of short duration (17). Although combination chemotherapy including dacarbazine, cisplatin, nitrosoureas and/or fotemustine can induce a high percentage of objective responses in patients with MMM in some trials, the estimated range of true response rates for these studies have not significantly exceeded the response rates observed with dacarbazine alone (4, 14, 17, 25, 27).

Phase II studies with recombinant IFN-alfa have shown objective responses in about 10-20% of cases, wich seems comparable to that of single agent dacarbazine in unselected patient populations (5, 15, 16, 20, 21). Regarding the use of interleukin-2 (IL-2) alone or combined with lymphokine-activated killer cells (LAK), tumor-infiltrating lymphocytes

(TIL) and/or cytotoxic agents, objective response rates have ranged from 0-50% of patients with MMM (1, 6, 7, 11, 22, 29). Notably, long-lasting responses have been documented in some patients achieving complete remission with IL-2 alone or in combination, or in those achieving a partial response but rendered disease-free following surgical ressection (20, 24, 25, 30).

Unfortunately, IL-2 therapy can be associated with significant side-effects, such as fluid retention, pulmonary edema, renal failure and a flu-like syndrome. The latter adverse effects are mainly observed in patients receiving high-dose IL-2 as a short-term intravenous infusion (24). In order to reduce the risk of severe toxicity, IL-2 has been also tested as a continuous intravenous or subcutaneous administration (25). Preliminary results of those studied have suggested that the toxicity profile can be modified when IL-2 is administered by the above mentioned routes (24, 25).

Considering that preclinical studies have documented synergistic immunomodulatory effects of IL-2 and IFN-alpha and that each of these agents exhibits antitumor activity against MMM (15, 17,), we have initiated a phase II study whereby the percentage of objective responses and clinical toxicity of the IL-2/IFN-alpha combination was evaluated in patients with MMM by the subcutaneous route.

## *Patients and methods*

### a) Patient selection

Patients with histologically proven MMM were eligible for study entry. They were required to have a life expectancy of at least 3 months and a Zubrod'performance status scale of 0-2. Patients who had been exposed to chemotherapy and/or immunotherapy were ineligible. Patients with single metastatic lesions for which tumor ressection could make them disease-free were not included in the study. Patients who had received prior radiotherapy were acceptable if at least 3 weeks had elapsed since they completed therapy and all acute toxic effects of treatment had resolved. Patients with brain metastases were excluded. The study required bidimentionally measurable lesions in non-previously irradiated areas and, if in a previously irradiated area, the marker lesion had to show progressive new measurable disease (2, 23).

Patients had to have adequate bone marrow (WBC count equal or above 3500 cells/uL, absolute granulocyte count equal or above 2000 cells/uL and a platelet count equal or above 100.000/uL), hepatic (serum bilirubin level equal or less than 1.5mg/dL) and kidney (serum creatinine level equal or less than 2.0mg/dL) funtion. Patients with active infections, severe concurrent medical conditions and brain metastases were excluded.

### b) Pretreatment and follow-up evaluation

All patients underwent a history and physical examination, complete blood cell count, biochemistry (renal and liver tests, and serum electrolites), urinalysis, chest X-ray, ECG. During drug treatment, patients were re-examined and had laboratory tests repeated on a weekly basis.

Tumor measurements and toxicity assessment were performed before each course of therapy. Additional imaging studies, such as CT scan or NMR were repeated in specific cases. Objective tumor responses were reviewed by an outside radiologist and the study chairman (31).

### c) Treatment plan

Interleukin-2 (IL-2) was supplied by Eurocetus Inc., while IFN-alpha (interferon-alpha-2a) was supplied by Roche Labs., Brazil. IL-2 was administered at the dose of a 18 million units/sqm and IFN-alpha at the dose of 3 million IU/sqm both as a subcutaneous injection on days 1-5 and 8-12 of each 21-day course. Treatment was then repeated if patients had sufficiently recovered from drug-related side effects (3).

In the case of severe toxicity, treatment was postponed for an additional week and then reintroduced at the same dose and schedule. Patients necessitating treatment interruption for further than this period were removed from the study due to unnacceptable toxicity and reported accordingly. No dose-reductions were applied in the study. Treatment was continued for a total of 4 courses in patients showing stable disease or tumor regression. Surgical ressection of residual masses was considered in responding patients. Otherwise, treatment was discontinued due to disease progression or unacceptable toxicity. Antiemetics and hematopoietic growth factors were administered on the basis of clinical judgement.

### d) Response and toxicity evaluation

Objective responses were based on the standardized response definitions established by te World Health Organization (WHO)(31). Duration of response was calculated as the time from first documentation of objective major response (complete or partial) to first documentation of disease progression. Time to progression was calculated as the time from the first treatment administration to the first objective evidence of tumor progression. Toxicity evaluation was based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (2).

### e) Statistical analysis

This phase II open-label trial was designed to detect a true objective response rate of at least 20%. For that purpose, a two stage Gehan's approach was used, which called for an initial accrual of 14 evaluable patients and the additional en-

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**Table 1 - Patients characteristics**

| Age (median years, range) | 43 (26-65) |
|---|---|
| Performance status* | Nº pts |
| 0 | 5 |
| 1 | 14 |
| 2 | 6 |
| 3 | 0 |
| Prior therapy | Nº pts |
| Surgery | 25 |
| Radiotherapy | 2 |
| Immunotherapy | 0 |
| Hormonal therapy | 0 |
| Chemoterapy | 0 |
| Site of disease | Nº pts |
| Skin/soft-tissue | 11 |
| Visceral | 9 |
| Both | 5 |

* WHO; Nº pts = number of patients.

try of patients depending upon the observed number of responders in the first part of the study (12).

## Results

### a) Patient characteristics

Between May 1992 and July 1994, 25 patients were accrued in this study. The main characteristics of this group of patients are listed in table 1. All patients had visceral only or visceral plus soft-tissue stage IV disease. The median performance status (WHO) was 1. All patients were initially treated by tumor ressection and none had undergone prior hormonal, immunologic or cytotoxic therapy.

### b) Tumor response

Objective tumor responses were evaluated in all 25 patients using bidimentional tumor measurements and carefully reviewed by an independent and well-trained physician not directly involved in the study. Patients received a median of 3 courses (range 2-4).

Four out of 25 patients responded (17%). All four cases achieved a partial response. Of the 21 remaining patients, minor responses (defined as tumor regressions between 25-50%) were observed in two cases, which lasted for 2 and 3 months, respectively. The other 19 patients exhibited tumor progression while on study. In two patients showing a partial response, surgical excision of remaining tumor was successfully attempted, converting the patients into complete responders (table 2).

**Table 2 - Objective tumor responses to IL-2/IFN-alpha**

| | Number | % |
|---|---|---|
| Number of patients | 25 | 100 |
| CR | - | - |
| PR* | 4 | 17 |
| NR | 21 | 83 |

Abbreviations: CR, complete response; PR, partial response; *two patients entered complete remission with surgery.

Median time to partial response was 5 (range, 4-9) weeks. Duration of partial responses (measured from first documentation of a partial response to documented progression) was 7 and 8 weeks, respectively; and in the other two patients rendered completely disease-free with surgery, one is still in complete remission after 24 months+, while the second progressed after being in complete remission for 6 months.

### c) Toxicity

All patients were evaluable for toxicity. The main toxic effects observed in the trial were fatigue, arthralgia/myalgia, fever an fluid retention. These results are summarized in table 3.

**Table 3 - Toxic effects of IL-2/IFN-alpha**

| Type of toxicity | NCI-CTC grade* | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| fatigue | - | 15 | 6 | 4 |
| arthralgia/myalgia | 5 | 8 | 3 | - |
| fever/chills | 7 | 5 | 6 | 1 |
| weight gain | 13 | 12 | - | - |
| perypheral edema | 8 | 17 | - | - |
| dispnea/lung dysfunction | 6 | 2 | 1 | 1 |
| abnormal serum creatinine | 10 | 3 | - | - |
| transient hypotension | 6 | 6 | 4 | - |
| skin reaction | 3 | 2 | - | - |
| congestive heart failure | - | - | - | - |
| cardiac arritmia | - | - | - | - |
| angina | - | - | - | - |

* National Cancer Institute Common Toxicity Criteria.

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## Discussion

IL-2 has shown objective antitumor activity against MMM in several clinical trials (24, 28). The percentage of objective responses to IL-2 therapy remains modest, being in the range of 10-30% in most studies. However, long-term remissions have been reported in a small percentage of patients receiving IL-2-containing regimens, who achieve a complete remission.

*Rosemberg and cols.* (22) compared the effects of high-dose IL-2 alone versus high-dose IL-2 combined with lymphokine-activated killer (LAK) cells in a group of patients with metastatic malignant melanoma. The authors were not able to shown any advantage of the combination in terms of response rates and overall survival. However, all long-term survivors had received the adoptive cellular therapy.

IL-2 was also evaluated in patients with MMM as part of various combinations, including cytotoxic agents, tamoxifen and/or alpha-interferon (6, 27, 28, 30). Although increased overall response rates have been shown in some trials, no superiority for the chemoimmunotherapy regimens has been confirmed in prospective randomized trials (22).

IL-2 plus alpha-interferon was reported to produce higher response rates over alpha-interferon alone in previous studies (30). However, there results were not confirmed by others (25, 28). In our study, we evaluated the antitumor effects and toxicity of a combination of IL-2 plus IFN-alpha given subcutaneously. Unfortunately, the percentage of objective responses was only 17% (4 out of 25 patients achieving a partial response). These results are not superior in terms of objective responses and overall survival rates when compared to those obtained with any of the two agents alone. Therefore, the combination of IL-2 plus IFN-alpha cannot be considered as standard therapy for patients with MMM.

Notably, two of the responding patients in our study could be rendered disease-free following surgical ressection of residual disease. One of them relapsed 6 months later, while the other is still in complete remission after 24 months. This observation confirms previous reports of long-lasting remissions in patients with metastatic malignant melanoma following IL-2-based regimens (22, 24).

The administration of IL-2 plus IFN-alpha by the subcutaneous route can be theorectically atractive, as it may produce more sustained levels of these agents in plasma, without producing peak-related toxic concentrations. Indeed, in our trial the above mentioned regimen could be administered in an outpatient basis, producing only moderate side-effects and being also advantageous in terms of treatment costs. However, its marginal antitumor effects precludes the routine use in patients with MMM.

Unfortunately, the initial enthusiasm with IL-2 plus interferons and IL-2-containing chemoimmunotherapy in MMM in diminishing, and the role of this agent is not yet defined. Novel approaches aiming at the selective delivery of cytotoxic molecules and/or cytokines, making use of tumor-infiltrating lymphocytes or monoclonal antibodies are being developed (8, 9, 10, 13, 14, 18, 25). Furthermore, preclinical studies are beginning to elucidate the molecular basis of tumor promotion, growth-factor dependence, metastatic behavior and tumor immunology in malignant melanoma (1, 17, 19). The latter information will probably lead to the identification of novel and more effective strategies for the management of patients with this disease.


## Summary

*The purpose of this study was to evaluate the toxicity profile, response and survival rate of the combination of IL-2 plus IFN-alpha given subcutaneously to patients with metastatic malignant melanoma. Twenty-five patients with histopathologically-proven metastatic malignant melanoma and measurable disease were treated with IL-2 at a dose of 18 million units/m2 plus IFN-alpha at a dose of 3 million units/m2 subcutaneously daily on days 1-5 and 8-12 of a 21-day cycle. All patients were evaluated for toxicity according to the National Cancer Institute Common Toxicity Criteria, while responses were coded according to the WHO criteria. Patients had no prior chemo, immune and/or radiotherapy. They received a median of 3 (2-4) courses. Toxicity consisted mainly of fatigue, arthralgia/myalgia, fever/chills, and fluid retention. No life-threatening toxicity was documented. Four out of 25 (17%) patients achieved a partial response with the IL-2 plus IFN-alpha combination. In 2 cases, surgical removal of residual disease rendered the patients completely disease-free for 6 and 24+ months, respectively. In the other 2 cases, tumor progression was observed after 7 and 8 weeks, respectively. All non-responders and those progressing after an initial response (3 patients) died after a median follow-up of 3 (range, 1-7) months. In conclusion, IL-2 plus IFN-alpha given subcutaneously to patients with metastatic malignant melanoma showns only marginal antitumor activity. Although it has acceptable toxicity, the level of objective responses observed in this study does not recommend its use in routine medical practice.*

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