Published in final edited form as:

J Immunother. 2002 ; 25(2): 185–187.

Response Rates of Patients With Metastatic Melanoma to High-Dose Intravenous Interleukin-2 After Prior Exposure to Alpha-Interferon or Low-Dose Interleukin-2

David M. Weinreich and Steven A. Rosenberg

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, U.S.A

Summary

We evaluated 567 patients with metastatic melanoma who were treated with high-dose intravenous interleukin-2 (IL-2) to determine whether prior treatment with either alpha-interferon or low-dose IL-2 altered the rates of response to subsequent high-dose IL-2. Of the 567 patients treated, 46 patients had received low-dose IL-2 before, and 78 had received alpha-interferon before. The response rate for patients who had received IL-2 before compared with IL-2 naïve patients was 15% versus 21% respectively ($p = 0.39$). The response rate for patients who had received alpha-interferon before compared with patients who had not was 13% versus 21% ($p = 0.084$). Therefore, prior low-dose IL-2 therapy does not appear to prevent a subsequent response to high-dose IL-2. There is a trend for patients who received alpha-interferon before to have a lower-response rate to subsequent high-dose IL-2, but the number of patients evaluated in this study is too small to definitively answer this question.

Keywords

Interleukin-2; Metastatic melanoma; Prior immunotherapy; Alpha; interferon

The median survival of patients with metastatic melanoma is 6–9 months with a 5-year survival rate of less than 4% (1). Two medications are approved by the United States Food and Drug Administration to treat patients with metastatic melanoma: dacarbazine and high-dose interleukin-2 (IL-2). Combination biochemotherapy using low-dose IL-2, alpha-interferon, and multiple chemotherapy agents, including dacarbazine, are in common use despite conflicting data on its usefulness (2–8). Even though some patients received alpha-interferon or low-dose IL-2 before, they were referred to the National Cancer Institute for treatment with high-dose IL-2. We questioned whether exposure to either alpha-interferon or low-dose IL-2 before impacted upon the response rate to treatment with high-dose IL-2.

MATERIALS AND METHODS

All patients with Stage IV cutaneous melanoma treated in the Surgery Branch of the National Cancer Institute from January 1, 1988 through December 31, 2000 with intravenous high-dose IL-2 (720,000 IU/kg/dose) were included in this study. All patients had lesions, which progressed after their last therapy, and were measurable by physical examination or diagnostic imaging. Patients received IL-2 at a dose of 720,000 IU/kg every 8 hours to tolerance not to exceed 12 or 14 doses, depending on the protocol (9). A cycle of treatment was repeated every

14–21 days depending on the particular protocol, and tumor-response rates were evaluated after two cycles of therapy. Patients with stable, mixed, or objective responses received at least one additional course of therapy. Patients who received IL-2 with adoptive-cell transfer, IL-2 bound to polyethylene glycol, or IL-2 with other cytokines were excluded. Patients were not excluded if they received a vaccination against a melanoma antigen in addition to high-dose IL-2 (10). Patients may have received alpha-interferon, IL-2, or both in an adjuvant or metastatic setting before referral, but none had received IL-2 at the high doses used in this study. Response assessments to these preceding therapies were not available.

Patients were evaluated after every course of therapy with complete physical exams and appropriate radiologic studies to evaluate sites of disease. Complete response was defined as complete regression of all lesions without the development of any new lesion. Partial response was defined as a 50% reduction in the sums of the products of perpendicular diameters of all lesions without growth of an existing lesion or development of a new lesion that lasted at least 1 month. All other patients were termed nonresponders. Patients who showed a mixed response with shrinkage or resolution of some lesions with growth of other lesions or development of new lesions were termed nonresponders.

RESULTS AND DISCUSSION

Five hundred sixty-seven patients were treated with high-dose IL-2 with or without vaccine during the study interval. Patient demographics are shown in Table 1. Of the 567 patients, 46 (8%) had received treatment before with low-dose IL-2 administered intravenously or subcutaneously. In these 46 patients, there were no complete responders and seven partial responders (15%). Of the 521 patients who never received IL-2 therapy before, there were 30 complete responders (6%) and 77 partial responders (15%). There was no significant difference in objective-response rates to high-dose IL-2 in patients who had either received or not received low-dose IL-2. Of the 521 patients who had never been exposed to IL-2 before, 256 were treated with a cancer vaccine, and 19% experienced an objective response compared with a response of 22% in the 265 patients that did not receive a vaccine (p_2 = not significant). Of the 46 patients who had received IL-2 before, there were seven responses (18%) in the 38 patients who received a concomitant vaccine and no responses in the eight patients not receiving a vaccine (p_2 = not significant). The role of the vaccine administered along with IL-2 may have played a role in these seven patients' responses although this cannot be determined in this study. A summary of the sites of disease in patients who received low-dose IL-2 before and responded to subsequent high-dose IL-2 is shown in Table 2 and Table 3.

Twenty-four of the 46 patients received low-dose IL-2 as part of their biochemotherapy. Six of the seven partial responders (87%) who received IL-2 before were part of this group who received biochemotherapy and, thus, received IL-2 and alpha-interferon. The median duration of response for patients who responded to high-dose IL-2 after receiving low-dose IL-2 before compared with patients who were IL-2 naïve was 13 ± 10 versus 23 ± 34 months (p_2 = not significant).

Of the 567 patients treated with high-dose IL-2, 78 (14%) had received alpha-interferon before for the treatment of their melanoma (Table 4). Of these 78 patients, there were two complete responders (3%) and eight partial responders (11%). Of the 489 patients who did not receive alpha-interferon before, there were 28 complete responders (6%) and 76 partial responders (15%). (p_2 = 0.084 comparing responses in patients who had or had not received alpha-interferon before)

We conclude that prior IL-2 given in a low-dose form does not alter response rates to subsequent high-dose IL-2. There is a slight trend for patients who received alpha-interferon before to have

a lower response to high-dose IL-2, but a larger study is needed to confirm this observation. Thus, patients with metastatic melanoma should be considered for treatment with high-dose IL-2 even if they have previously received lower-dose IL-2 or alpha-interferon.

References

1. Lee ML, Tomsu K, Von Eschen KB. Duration of survival for disseminated malignant melanoma: results of a meta-analysis. *Melanoma Res* 2000;10:81–92. [PubMed: 10711644]
2. McDermott DF, Mier JW, Lawrence DP, et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin 2, and interferon alpha-2B in patients with metastatic melanoma. *Clin Cancer Res* 2000;6:2201–8. [PubMed: 10873069]
3. Margolin KA, Liu PY, Unger JM, et al. Phase II trial of biochemotherapy with interferon alpha, dacarbazine, cisplatin, and tamoxifen in metastatic melanoma: a Southwest Oncology Group trial. *J Cancer Res Clin Oncol* 1999;125:292–6. [PubMed: 10359134]
4. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alpha-2b. *J Clin Oncol* 1999;17:968–75. [PubMed: 10071291]
5. Legha SS. Durable complete responses in metastatic melanoma treated with interleukin-2 in combination with interferon-alpha and chemotherapy. *Semin Oncol* 1997;24:S39–43. [PubMed: 9122733]
6. Hauschild A, Garbe C, Stolz W, et al. Dacarbazine and interferon alpha with or without interleukin 2 in metastatic melanoma: a randomized phase III multicenter trial of the Dermatologic Cooperative Oncology Group (DeCOG). *Br J Cancer* 2001;84:1036–42. [PubMed: 11308250]
7. Hauschild A, Garbe C, Stolz W, et al. Dacarbazine and interferon-alpha with or without interleukin 2 in metastatic melanoma: a randomized phase III multicenter trial of the Dermatologic Cooperative Oncology Group (DeCOG). *Br J Cancer* 2001;84:1036–42. [PubMed: 11308250]
8. Johnston SR, Constenla DO, Moore J, et al. Randomized phase II trial of BCDT carmustine (BCNU), cisplatin, dacarbazine and tamoxifen] with or without interferon-alpha (IFN-alpha) and interleukin (IL-2) in patients with metastatic melanoma. *Br J Cancer* 1998;77:1280–6. [PubMed: 9579834]
9. Rosenberg SA, Yang JC, White DE, et al. Durability of complete responses in patients with metastatic cancer treated with high-dose interleukin-2: identification of the antigens mediating response. *Ann Surg* 1998;228:307–19. [PubMed: 9742914]
10. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma. *Nat Med* 1998;4:321–7. [PubMed: 9500606]

TABLE 1
Demographics of study patients

	All patients	Prior IL-2	Prior interferon- α
		Number of patients (%)	
Sex			
Male	355 (63)	26 (57)	47 (60)
Female	212 (37)	20 (43)	31 (40)
Age			
11–20	5 (1)	0	1 (1)
21–30	61 (11)	5 (11)	9 (12)
31–40	155 (27)	11 (24)	16 (21)
41–50	176 (31)	12 (26)	25 (32)
51–60	123 (22)	11 (24)	20 (26)
61–70	46 (8)	7 (15)	7 (9)
Over 70	1 (0)	0	0
ECOG			
0	468 (83)	39 (86)	69 (88)
1	84 (15)	5 (11)	9 (12)
2	11 (2)	1 (3)	0
Prior treatment			
None	6 (1%)	0	0
Surgery	558 (98)	45 (98)	78 (100)
Chemotherapy	164 (29)	35 (76)	28 (36)
Radiotherapy	88 (16)	14 (30)	19 (24)
Hormonal	47 (8)	13 (28)	12 (15)
Immunotherapy	325 (57)	46 (100)	78 (100)
Any 2 or more	377 (66)	44 (96)	78 (100)
Any 3 or more	175 (31)	36 (78)	40 (51)

ECOG, Eastern Cooperative Oncology Group.

TABLE 2

Response to high-dose interleukin-2 (IL-2) with or without prior lower-dose interleukin-2 therapy

	Prior IL-2	No prior IL-2	All patients
NR	39 (85%)	414 (79%)	453 (80%)
PR	7 (15%)	77 (15%)	84 (15%)
CR	0	30 (6%)	30 (5%)
Total	7 (15%)	107 (21%)	114 (20%)
p = 0.39 (PR + CR)			

NR, nonresponders; PR, partial responders; CR, complete responders.

TABLE 3

Sites of disease of responders to high-dose interleukin-2 who received low-dose interleukin-2

Patient #	Site(s) of disease
1	Lung, lymph nodes
2	Lung, mediastinum, lymph nodes
3	Lung
4	Lung, skin
5	Skin, lymph nodes
6	Skin, lymph nodes, abdominal viscera, lung
7	Skin, lymph nodes

TABLE 4

Response to high-dose interleukin-2 with or without prior alpha interferon therapy

	Prior alpha	No prior alpha	All patients
NR	68 (87%)	385 (79%)	453 (80%)
PR	8 (10%)	76 (15%)	84 (15%)
CR	2 (3%)	28 (6%)	30 (5%)
Total	10 (13%)	104 (21%)	114 (20%)
p = 0.084 (PR + CR)			

NR, nonresponders; PR, partial responders; CR, complete responders.