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Immunotherapy of Metastatic Melanoma with Interferon-α and Interleukin-2: Pattern of Progression in Responders and Patients with Stable Disease With or Without Resection of Residual Lesions

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This evaluation was performed in melanoma patients after successful immunotherapy to describe the pattern of relapse. 63 patients received interferon (IFN)-α and high-dose interleukin (IL)-2, resulting in three complete responses (CR), 13 partial responses (PR), three mixed responses (MR) and 17 stable diseases (SD). Median duration of response was 7 months (range 3–28) without surgery. Most relapses occurred at pre-existing sites. Duration of CR was 14–37+ months. In 11 patients, residual tumour lesions were resected. Interestingly, histology revealed almost complete tumour regression in 6 patients, including 2 of 4 with SD. 5 of these 11 patients have relapsed so far, 6 patients are still free of disease with a median of 17 months (range 8–34). Following relapse, 4 of 6 patients responded to retreatment with the identical IFNα/IL-2 protocol. The authors conclude that initial disease progression is mostly at previous sites of disease. Resection of residual lesions may offer a chance for extended disease-free survival similar to patients with CR to immunotherapy. Retreatment of relapsing patients is favourable.

Key words: melanoma, immunotherapy, interferon-α, interleukin-2, relapse pattern
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INTRODUCTION

IMMUNOTHERAPY USING high-dose interleukin (IL-2) is effective in a substantial proportion of patients with metastatic melanoma, although the duration of responses is limited [1–3]. The pattern of relapse in patients responding to immunotherapy has been reported to be equally distributed between disease at new and pre-existing sites. Following relapse, retreatment with IL-2-based immunotherapy was not successful [4].

Surgery in advanced metastatic melanoma is of limited value and not usually recommended [5–7]. A recent paper by Sherry and colleagues addressed the question of resection and metastases after response to immunotherapy in selected patients [8]. Surgery was performed during relapse after successful immunotherapy. Significant disease-free survival was only seen in patients with renal cell carcinoma, and not in patients with melanoma.

We evaluated the pattern of progression, the resection of residual lesions, and the value of retreatment in a cohort of 63 melanoma patients treated in our hospital with various protocols containing interferon (IFN)-α and high-dose IL-2.

PATIENTS AND METHODS

63 patients with metastatic melanoma had been enrolled in two subsequent immunotherapy trials using IFNα and high-dose IL-2 in our hospital from 1987 to 1992. These trials have been described in detail elsewhere [9]. Prior to immunotherapy, progressive disease was documented in all patients. In a selected group of patients responding to immunotherapy, residual lesions were resected.

The two treatment protocols are described below. The eligibility criteria were identical for both protocols: patients with histologically-proven metastatic malignant melanoma who had measurable progressive disease and a performance status of at least 60% (Karnofsky) were eligible for immunotherapy. Informed consent was obtained prior to initiation of treatment.

Treatment schedules

Schedule A consisted of IFNα (Intron A, Essex, U.K.), 10 million U/m²/day, subcutaneously (s.c.), for 5 days, followed by continuous intravenous (i.v.) infusion of IL-2 (Proleukin, Eurocetus), 1 mg/m²/24 h for 5 days. Schedule B consisted of the same dose and schedule of IFNα (Roferon, Roche), but a

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modified regimen of IL-2. The initial IL-2 dose was increased to 1 mg/m^2/6 h and then reduced in a stepwise fashion to 1 mg/m^2/12 h, 1 mg/m^2/24 h, and 0.25 mg/m^2/24 h for the final 3 days. The IL-2 infusion was initiated on day 3 instead of day 8 to shorten the period of hospitalisation. Both treatment regimens were repeated after 4 weeks. In the case of progression, mixed response (MR) or stable disease (SD) after three treatment cycles, treatment was discontinued. In the case of a partial response (PR), additional cycles were administered as long as antitumour responses were observed. Responses were defined as follows: complete response (CR) as the disappearance of all clinically evident disease for at least 4 weeks, PR as at least a 50% decrease of the sum of products of two perpendicular diameters of all lesions for at least 4 weeks, MR as a PR in certain lesions while others increased for more than 25%, and SD as changes in overall tumour size from less than 50% decrease to 25% increase for more than 3 months folowing immunotherapy, without development of new lesions. Patients rendered disease free by immunotherapy (CR) or surgery received one additional treatment cycle of immunotherapy as maintenance treatment, and were thereafter followed without further treatment. The trials had been approved by the University of Heidelberg Ethics Committee.

Guidelines for surgery

In all patients who have been treated since 1991 (43 patients) and had a PR, MR or SD following immunotherapy, surgery was considered. Resection of limited residual tumour lesions was performed if considered technically possible and the patient agreed to the surgical procedure.

In all patients undergoing surgery, an attempt was made to resect all lesions noted on physical examination and/or with imaging techniques. The resected lesions were examined for presence of vital tumour cells by routine histological examination.

Patient follow-up

The patients were re-evaluated by physical examination, ultrasound of abdomen and peripheral lymph nodes, chest radiograph, and imaging procedures relevant for the assessment of involved sites at 4–6-weekly intervals following immunotherapy. After 1 year, patients were followed at 3-monthly intervals.

RESULTS

Of 63 patients treated with immunotherapy with IFNα and IL-2, 3 had a CR, 13 PR, 3 MR and 17 SD for more than 3 months. 12 patients underwent subsequent resection of residual lesions while in continuing response, 5 patients with SD and 2 with MR received chemotherapy, while 17 patients were observed without further therapy.

Results in patients without surgery

A prolonged relapse-free interval was seen in the 3 patients achieving a CR (14, 24+, 37+ months). All patients with PR or SD not undergoing surgery progressed with a median time to progression of 7 months from the commencement of immunotherapy (PR range 4–28, SD range 4–17 months). All but one initial progress occurred at pre-existing sites of disease or in draining lymph nodes. 2 additional patients developed brain metastases (Table 1).

Results in patients with surgery

6 patients with continuing response, 5 patients with SD, and 1 patient with MR underwent surgery. Table 2 shows the characteristics of the patients who underwent surgery. Most patients had lesions at cutaneous/s.c. sites and/or lymph nodes. 3 patients had visceral metastases. Surgical procedures included laparotomy in 6 cases, thoracotomy in a patient with mediastinal lymph nodes, and mastectomy in a patient with severe involvement of one breast. The number of lesions removed ranged from one to over 20. No surgery-related complication was observed in any patient.

Table 1. Results in patients with response to immunotherapy without surgery

Patient no.	Site of metastases	Response to immunotherapy	Time to progression* (months)	Site of initial progression
1	s.c., LN, visceral	CR	37+	
2	s.c., LN	CR	14	Draining LN
3	LN, soft tissue	CR	27+	
4	s.c.	PR	7	Draining LN
5	LN	PR	13	p.s.o.d.
6	lung	PR	10	p.s.o.d.
7	s.c., LN, lung	PR	5	p.s.o.d.
8	lung, liver	PR	5	CNS
9	lung	PR	4	CNS
10	skin, LN, pancreas	PR	28	p.s.o.d.
11	nodal	SD	17	p.s.o.d.
12	lung, s.c.	SD	4	p.s.o.d.
13	LN	SD	7	p.s.o.d.
14	s.c., gut	SD	5	Draining LN
15	LN	SD	7	p.s.o.d.
16	LN	SD	3	p.s.o.d.
17	LN, liver	SD	8	Distant

*From the commencement of immunotherapy. LN, lymph nodes; p.s.o.d., previous sites of disease; s.c., subcutaneous; CR, complete response; PR, partial response; SD, stable disease.

Table 2. Results in patients with response to immunotherapy, who subsequently underwent surgery

Patient no.	Response to immunotherapy	Site of metastases and resection (no. of lesions)	Time to progression* (months)	DFS (months) since surgery	Site of relapse
18	PR	Skin (8)	34+	29+	
19	PR	Axillary and mediastinal LN (3)	14/27+†	9/22+†	CNS
20	PR	Supraclavicular LN (2)	24+	15+	
21	PR	Axillary LN (3)	7	5	p.s.o.d.
22	PR	Gallbladder, palate (1), skin (ca. 10)	11+	7+	
23	PR	Skin (multiple) (mastectomy) Supraclavicular LN (2)	10+	4+	
24	MR	Bone lesion (PD) Adrenal gland (PR)	9	2	Bone marrow
25	SD	Retroperitoneum LN (1)	26+	21+	
26	SD	Skin, s.c. (> 20)	10	8	p.s.o.d. and liver
27	SD	Ileum (1)	6	3	p.s.o.d.
28	SD	Retroperitoneum LN (1)	Resection not possible		
29	SD	Retroperitoneum LN (1)	8+	4+	

*From commencement of immunotherapy. †A single CNS metastasis developed 9 months later and could be resected. DFS, disease-free survival from date of surgery; LN, lymph node; p.s.o.d., previous sites of disease; PR, partial response; MR, mixed response; SD, stable disease; PD, progressive disease; s.c., subcutaneous.

In 8 patients, complete resection of all visible residual tumour lesions was possible converting them into CR. 6 of these patients are still free of disease with a median of 17 months (range 8–34). Of the 2 patients who have relapsed, patient no. 24 had a MR with a > 50% regression in an adrenal tumour, but showed progression in a single osteolytic metastasis of the lumbar spine. Although both tumour lesions could be resected, this patient had relapsed 2 months later with extensive diffuse infiltration of the bone marrow. Eight months after resection of axillary and mediastinal lymph nodes, patient no. 19 developed a solitary brain metastasis which was removed. This patient is at present still in remission after 27+ months.

In 3 patients, complete resection of tumour lesions was not possible. Patient no. 26 had diffuse subcutaneous metastases in addition to cutaneous nodules. In patient no. 21, the axilla had previously been irradiated and complete resection of all residual involved lymph nodes was not possible. Patient no. 27 developed his relapse from a small second intraabdominal mass that was retrospectively already visible on computed tomography scan prior to immunotherapy. All of these 3 patients had an initial progression at the site of pre-existing disease. In patient no. 28, with a large parailiac lymph node and SD for 3 months, laparoscopy revealed unresectable tumour lesions.

Interestingly, histology revealed almost complete tumour regression in 6/11 patients, including 2/4 patients with SD. In patient no. 25, a rapidly growing parailiac metastasis infiltrating adjacent tissues, including large vessels and bladder, showed only minor shrinkage after three cycles of treatment. The tumour was successfully removed, and on macroscopic examination, it was a cyst-like lesion containing black fluid with a wall of fibrous tissue approximately 5 mm thick. Histology revealed almost total necrosis of the tumour tissue, and only at the rim could vital tumour cells be detected. Patient no. 27 had SD of a large intra-abdominal mass originating from the ileum following three treatment cycles. Histologically, the tumour was completely fibrotic and again was encapsulated by a firm fibrous wall.

Patients retreated with IFNα/IL-2

Patients who relapsed after initial response to immunotherapy were eligible for retreatment with the identical regimen in the absence of brain lesions. 6 patients were retreated, and all of the 4 patients with an initial CR or PR had a second PR, while the 2 patients with initial SD and MR did not respond to retreatment (Table 3). The other patients who in principle were eligible for retreatment choose other standard treatment modalities, such as DTIC/tamoxifen or no treatment. We are not aware of an obvious selection bias for retreating patients with our protocol.

Table 3. Response in patients who relapsed, retreated with IFNα/IL-2

Patient no.	Response to first therapy	Duration of first remission (months)	Response to second therapy	Duration of second remission (months)
5	PR	13	PR	5
10	PR	28	PR	3+
21	PR	7	PR	12+
26	SD	10	PD	—
2	CR	14	PR	NE*
24	MR/surgergy	9	PD	—

*NE, not evaluable: patient received chemotherapy while in second partial response (PR). SD, stable disease; CR, complete response; MR, mixed response.

DISCUSSION

We analysed a cohort of 63 patients with metastatic melanoma, who were treated with IFNα and IL-2, for response duration and relapse pattern. A limited number of responding patients had received subsequent resection of residual lesions, converting them into CR. The following may be concluded from our data: (a) the median time to progression in patients with PR or SD is rather brief, while the 3 patients showing a CR have an extended disease-free survival, (b) most of our patients had initial disease progression at preexisting sites of disease, (c) in a selected group of patients with PR or SD, resection of residual lesions is technically possible and may offer a chance for extended disease-free survival, as in patients with a CR following immunotherapy, (d) histology of resected specimens also revealed almost complete tumour regression in 2 patients with clinically SD, (e) further therapy resulted in a second remission in 4 of 6 relapsing patients.

The median response duration of patients responding to immunotherapy with IL-2 has been reported to range from 5 to 9 months [2, 3, 4, 10] in accordance with our data. Only a few patients with PR have been reported to show extended progression-free survival. Considering treatment options aimed at control of residual lesions following immunotherapy, the pattern of disease progression after response to immunotherapy is of special importance. Most of our patients had progression at pre-existing sites of disease. The initial progression in most of the remaining patients was noted in lymph nodes draining pre-existing sites before new distant metastases occurred. 3 patients developed brain metastases, while they were still in remission elsewhere. Relapses in the brain following successful immunotherapy with IL-2 have also been observed by others [11], suggesting that the accessibility of the central nervous system for immunological effector cells is limited by the blood–brain barrier. Our observation is in contrast to the relapse pattern reported in 37 responding melanoma patients treated with different IL-2 based protocols, in whom two thirds of the patients had a relapse at pre-existing sites, but in addition two thirds relapsed at new sites [4].

One reason for this difference may be that patients were re-evaluated only at 2–4 monthly intervals, while we saw our patients every 4 to 6 weeks during the first year following immunotherapy. In the same report, further therapy of 25 relapsing melanoma patients with IL-2 and LAK or TIL cells resulted in only one PR, whereas we observed four second PRs in 6 patients after retreatment with the identical IFNα/IL-2 protocol. One may only speculate that the addition of IFNα, which has potent immunomodulatory effects on the tumour [12], could be responsible for this difference.

There is a number of reports in the literature concerning surgical management of metastatic melanoma [5–7, 13–15]. Although there are a few reports of prolonged median survival in a selected group of patients, e.g. after resection of single pulmonary metastases [13], in most studies only a few patients had a disease-free interval longer than 1 year following surgery. Sherry and colleagues reported on a series of patients with metastatic melanoma with disease progression after response to immunotherapy, in whom tumour lesions were resected at the time of progression [8]. The median time to progression in 16 patients with malignant melanoma was 5 months, and all patients with melanoma had tumour progression within 10 months of surgery. In contrast to Sherry and colleagues, we performed surgery in our group of patients while they were in continuing remission, and the median time to progression in our group of patients is currently 10+ months. However, the number of patients is too small to draw further conclusions.

Of special interest is the histology of the resected lesions revealing almost complete tumour regression in 6/11 patients including 2/4 patients with SD. This demonstrates that tumour regression achieved by immunotherapy may not always be detectable by imaging procedures. In addition, the time to disease progression does not differ between patients with SD or PR.

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