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Continuous Infusion of Recombinant Interleukin-2 With or Without Autologous Lymphokine Activated Killer Cells for the Treatment of Advanced Renal Cell Carcinoma

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Data have been analysed for 327 patients with advanced renal cell carcinoma receiving a continuous infusion of recombinant interleukin 2 (rIL-2) alone (225 patients) or rIL-2 plus lymphokine activated killer (LAK) cells (102) on a normal oncology ward. Eligibility criteria were uniform across protocols, all patients having advanced progressive disease, but with an ambulatory performance status. The baseline characteristics of patients receiving rIL-2 alone did not differ significantly from those receiving LAK, with the exception that the LAK treated patients had a better performance status. Despite similar treatment intensity, toxicity was more severe in the patients receiving LAK. The addition of LAK did not lead to higher response rates or to prolonged response duration, progression-free survival or survival. This review confirms the activity of rIL-2 for the treatment of advanced renal cell carcinoma and demonstrates that the addition of LAK cells does not lead to increased efficacy.
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INTRODUCTION

INTERLEUKIN-2 (IL-2) is a 15 500 D glycoprotein with key functions in immune regulation [1]. With the advent of recombinant biotechnology, it has been possible to produce large quantities of recombinant IL-2 (rIL-2). IL-2 is pleiotropic in action, and causes activation and proliferation of several lymphocyte subsets [2–4]. Culture of lymphocytes *in vitro*, with high concentrations of IL-2 results in the generation of lymphocytes with non-major histocompatibility complex restricted cytotoxicity to a variety of tumour cells, but not to normal cells [5]. This has become known as the lymphokine activated killer (LAK) cell phenomenon, and cells that have been stimulated with IL-2 have been called LAK cells, even though lymphocytes with this characteristic are not members of a unique lymphocyte subset [6]. In animal models, the administration of LAK cells in conjunction with IL-2 appeared to be more effective in mediating tumour rejection than the administration of the cytokine alone [7, 8].

A comprehensive clinical trials programme has been developed throughout Europe and North America, using rIL-2. To date, the majority of patients have been treated intravenously with Cetus rIL-2 (Proleukin), using either bolus or a continuous infusion schedule, with or without autologous LAK cells [9–15].

While the original work has led to successful treatment of patients with advanced renal cell carcinoma (RCC), the use of high-dose bolus regimens can result in severe toxicity, requiring intensive care unit (ICU) support in the majority of patients [9].

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Modifications of the original high dose bolus regimens have attempted to maintain antitumour activity, while reducing toxicity to a level that is manageable on a normal oncology ward. By using a continuous intravenous infusion regimen, as originally described by West *et al.* [10], patients can be treated on a normal oncology ward [11, 12, 14, 15].

Considerable controversy remains as to whether the addition of LAK cells to a rIL-2 regimen leads to enhanced antitumour activity, as predicted from the preclinical animal models. Since this may be dependent on the tumour type and the schedule of rIL-2 used, the present review is restricted to an analysis of patients with advanced RCC, treated with rIL-2 given by continuous intravenous infusion, both with and without autologous LAK cells.

PATIENTS AND METHODS

All patients were treated with rIL-2, given by continuous intravenous infusion with or without the addition of LAK. Patients were treated on Cetus and EuroCetus sponsored trials between September 1986 and June 1990 using the continuous intravenous infusion regimen as originally described by West *et al.* [10] Table 1 lists the studies included in this analysis. The treatment schedule was essentially very similar for all five studies. One cycle consisted of two 5 day periods of continuous intravenous rIL-2 infusion at 18×10^6 IU/m^2/day separated by a rest period. During the rest period, four leukaphereses were carried out in patients scheduled to receive LAK, in order to obtain a sufficient quantity of autologous peripheral blood mononuclear cells (PBMC) for *ex-vivo* generation of LAK cells as previously described [10, 16].

The duration of the rest period was originally chosen to last 6 days, in the first four studies listed in Table 1. The rest period

Table 1. Studies evaluated

Study	Reference*	Treatment	No. of eligible patients entered
IS-L287-25 (Multicenter USA)	9, 10	rIL-2 by continuous intravenous infusion + LAK	21
NC-L287-69 (Multicenter USA)	13	rIL-2 by continuous intravenous infusion + LAK	25
EC-L2-015 (Multicentre Europe)	12	rIL-2 by continuous intravenous infusion + LAK	56
EC-L2-008 (Multicentre Europe)	12, 14	rIL-2 by continuous intravenous infusion alone	92
EC-MP-001 (Multicentre Europe)	15	rIL-2 by continuous intravenous infusion alone	133
Total			327

* References provide details on the study protocols and interim results.

was subsequently reduced to 2 days on study EC-MP-001. This was done because the data demonstrated that the toxicity, resulting from the first 5 days rIL-2 treatment in each cycle, resolved quickly, thus allowing for the second 5 days treatment earlier. Moreover, this modification has led to a more 'user-friendly' schedule, since patients only require treatment during weekdays and not during the weekend.

All patients were scheduled to receive two cycles, and in the event of disease stabilisation or objective antitumour response, up to four maintenance cycles.

The eligibility criteria were very similar. The requirements included measurable or evaluable disease assessable by non-invasive procedures, an ambulatory performance status (ECOG 0-1), no brain metastases, and serum bilirubin, creatinine and haematological parameters within the institution's normal range. Patients with significant cardiovascular disorders, or patients requiring antibiotics for serious active infections, or corticosteroids for intercurrent disease, were all excluded. Prior antineoplastic therapy, if given, should have stopped at least 4 weeks prior to inclusion on study.

Evaluation of efficacy and toxicity

Antitumour response, response duration and toxicity assessment used the WHO criteria [17]. However, for toxicities not included in the WHO guidelines, a comparable grading system was used (grade 0 = absent, grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = most severe). Response to therapy was assessed after each cycle of therapy. Eligible patients, receiving at least one cycle of therapy, were evaluable for response. All eligible patients were evaluated for toxicity and survival. Progression free survival (PFS), for patients achieving stable disease (SD) or better, was calculated from the first day of treatment with rIL-2 to the date of documented relapse or the date of last follow-up if disease progression has not occurred. Survival was measured from the first day of treatment with rIL-2 to the date of death or to the date of last follow-up.

Statistical methods

For all statistical tests, differences at $P \leq 0.05$ were considered statistically significant. Baseline characteristics of the two treatment groups, including the demographic and potential prognostic factors have been compared using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous and ordered variables. Treatment intensity and safety data were compared using the Mantel–Haenszel χ^2 test for linear trend, or the Wilcoxon rank-sum test, when appropriate. Response rates were compared using the unadjusted χ^2 test. Confidence intervals for response rates were computed using the normal approximation of the binomial distribution. The Kaplan–Meier product limit estimator [18] was used to estimate the response duration, the progression free survival and the overall survival. Univariate tests of significance were performed using the logrank χ^2 test [19].

Multivariate analysis used the Cox proportional-hazards regression model [20] for analysing overall survival, and adjusting for any possible imbalance between the two treatment groups in important baseline prognostic variables. All factors listed in Table 2 were included in the model. A choice needed to be made between the time from diagnosis to treatment (DTI) and the time from diagnosis to the detection of metastases (DFI), since these time intervals are highly correlated ($P = 0.0001$, $r = 0.78$, Pearson correlation). The former was chosen to be included in the model, since the required dates can be more readily retrieved from hospital files.

Continuous variables were translated into 2-level categorical variables, with a cut-off for age at 60 years and for DTI at 24 months.

RESULTS

The majority of patients accrued to the studies, using the continuous intravenous infusion regimen, were treated in the ordinary oncology ward. Table 2 compares the baseline characteristics between patients treated with rIL-2 plus LAK versus patients treated with rIL-2 alone. The only significant difference between the two groups was the baseline performance status, which was worse for patients receiving rIL-2 alone ($P < 0.0001$).

The median cumulative dose of rIL-2 on cycle 1 was 160×10^6 U/m^2 (range 30×10^6 205×10^6 U/m^2) for patients receiving rIL-2 alone and 152×10^6 U/m^2 (range 18×10^6–225×10^6 U/m^2) for patients receiving rIL-2 plus LAK. For cycle 2, the median cumulative dose was 154×10^6 U/m^2 (range 28×10^6–205×10^6 U/m^2) for the former group and 150×10^6 U/m^2 (range 35×10^6–190×10^6 U/m^2) for the latter group. Both for cycle 1 and 2, the median cumulative doses were not significantly different.

Table 3 compares the treatment intensity in terms of the percentage of the total planned dose given to patients on cycles 1 and 2. A Mantel–Haenszel χ^2 test for linear trend, revealed no significant difference in treatment intensity between patients receiving rIL-2 alone or rIL-2 + LAK ($P = 0.303$ on cycle 1, and $P = 0.124$ on cycle 2). The median number of cycles was 2 (range 1–6) both for patients receiving rIL-2 alone and those receiving rIL-2 + LAK. The median cumulative number of cells infused in patients, treated on the rIL-2 plus LAK studies was 7.5×10^{10} cells (range 0.5×10^{10}–32×10^{10}) on cycle 1 and 5.5×10^{10} cells (range 2×10^{10}–23×10^{10}) on cycle 2.

Table 4 compares the incidence and severity of toxicity experienced by the patients, on any cycle. This analysis shows that the administration of LAK cells in conjunction with rIL-2,

Table 2. Patients' characteristics

Characteristic	rIL-2 alone	rIL-2 + LAK	Statistical Wilcoxon rank sum test *P* value	χ^2 or *t*-test *P* value
No. of patients	225	102		
Age (years)				
Median	57	54	NS	
Range	(21–80)	(23–74)		
≤ 60 years	141 (63)	71 (70)		NS
> 60 years	84 (37)	31 (30)		
Sex				
Female	69 (31)	24 (24)		
Male	156 (69)	78 (76)		NS
Baseline performance status				
ECOG 0	94 (42)	76 (75)		
ECOG 1	131 (58)	26 (25)		< 0.0001
Time from diagnosis to first treatment with rIL-2 (months)				
Median	7.7	6.0		
Range	(1–236)	(0–233)	NS	
0–24 months	176 (78)	81 (79)		
> 24 months	49 (22)	21 (21)		NS
Time to diagnosis to first metastases (months)				
Median	2.2	3.6		
Range	(0–227)	(0–230)	NS	
0–24 months	183 (81)	87 (85)		
> 24 months	38 (17)	9 (9)		NS
Unknown	4 (2)	6 (6)		
Nephrectomy				
Yes	173 (77)	79 (77)		
No	52 (24)	23 (23)		NS
Prior chemotherapy	11 (5)	6 (6)		NS
Prior radiotherapy	40 (18)	12 (12)		NS
No. of organ sites involved				
1 organ site	75 (33)	29 (28)		
2 organ sites	81 (36)	31 (30)		
≥ 3 organ sites	69 (31)	42 (42)		NS
Organ sites				
Lung	156 (69)	71 (70)		NS
Liver	40 (18)	26 (25)		NS
Bone	38 (17)	25 (25)		NS
Other	159 (71)	74 (73)		NS

No. of patients (%). NS = not significant.

given by continuous intravenous infusion, results in a more pronounced toxicity profile. The LAK procedure did not lead to new toxicities, but the majority of the toxicities were of increased severity.

A profound rebound lymphocytosis occurred 24–48 h after interruption of rIL-2, a universal finding in all studies [9–15]. Biological activity, as measured by alterations in total lymphocyte and eosinophil counts, is not significantly enhanced by the addition of LAK to the CIV rIL-2 infusion regimen (data not shown). There was no correlation between objective response and baseline lymphocyte counts, or with the degree of rebound lymphocytosis (Table 5).

Table 3. Percentage of the planned dose received by patients: rIL-2 alone vs. rIL-2 + LAK, cycles 1 and 2

Cycle	Dose (%)	rIL-2 alone [*n* (%)]	rIL-2 + LAK [*n* (%)]
1 (n = 225 vs. n = 102)	≥ 80	150 (67)	75 (74)
	60–80	42 (19)	18 (18)
	≤ 60	33 (15)	9 (9)
2 (n = 164 vs. n = 61)	≥ 80	97 (59)	35 (57)
	60–80	21 (13)	14 (23)
	≤ 60	46 (28)	12 (20)

288 patients, from the cohort of 327 patients treated with continuous intravenous infusion of rIL-2 with or without LAK, were evaluable for response. Patients who did not receive at least one complete cycle of therapy (13 patients on rIL-2 alone and 5 patients on rIL-2 plus LAK) were considered inevaluable for response. In addition, 19 patients treated with rIL-2 alone and 2 patients treated with rIL-2 plus LAK had insufficient documentation available for an objective response assessment.

The overall response rate was 16% with a complete response rate of 5%. Table 6 compares the response rates using continuous intravenous infusion rIL-2 plus LAK versus continuous intravenous rIL-2 infusion alone. The small difference in overall response rate between rIL-2 alone and rIL-2 plus LAK treated patients (15% versus 18%), is not statistically significant. There is also no evidence of increased efficacy in terms of complete response (CR).

Table 7 compares response duration, progression free survival (PFS) and overall survival between patients receiving rIL-2 plus LAK versus rIL-2 alone. Durable responses were seen, both in patients treated with rIL-2 alone and in patients treated with rIL-2 plus LAK. However, a statistical comparison of response duration is complicated by the more limited follow-up of patients in the former group and the small number of patients who have achieved an objective remission. Bearing these limitations in mind, the durability of responses did not differ significantly between the 2 groups [P = 0.17 for CR and P = 0.18 for partial response (PR)].

Median PFS was 8.6 months [range 1.7–25.9(+)] for patients receiving rIL-2 alone versus 9.4 months [range 2.0–40.4(+)] for patients receiving rIL-2 + LAK. This difference is not significant (P = 0.52).

Patients treated with rIL-2 alone or rIL-2 plus LAK had a comparable survival (P = 0.12 in univariate analysis). Figure 1 shows the survival curves of the patient populations. Since treatments from non-randomised studies are compared and the baseline prognostic factors differed in terms of performance status, a multivariate analysis was performed [20], adjusting for prognostic factors (Table 8). This analysis did not show any significant survival difference between rIL-2 alone and rIL-2 plus LAK treated patients (P = 0.71).

DISCUSSION

The antitumour efficacy of rIL-2 in patients with advanced RCC is now well described [9–15]. However, some controversy remains as to whether the addition of *ex-vivo* generated LAK cells to the continuous intravenous infusion of rIL-2 can lead

Table 4. Toxicity

	rIL-2 alone (%)				rIL-2 + LAK (%)				
Severity grading	0	I–II	III–IV	NR¶	0	I–II	III–IV	NR (6)	*P*-value**
Anaemia	23	68	9	—	5	70	25	—	< 0.001
Thrombocytopenia	88	11	1	—	47	40	13	—	< 0.001
Leukopenia	92	8	—	—	75	25	—	—	< 0.001
Hypercreatinaemia	34	64	3	—	10	78	12	—	< 0.001
Hyperbilirubinaemia	65	34	2	—	46	46	8	—	0.004
Aspartate aminotransferase	49	47	4	—	35	62	3	—	< 0.001
Alkaline phosphatase	40	46	14	—	21	61	17	—	0.029
Hypotension	31	42	27	—	4	34	62	—	< 0.001
Arrythmias	92	6	3	—	81	5	11	3	0.02
Tachycardia	91	7	2	1	68	19	5	8	< 0.001
Myocardial infarction	99	1	1	—	98	—	2	—	NS
Weight gain	67	26	7	—	54	34	12	—	0.063
Pulmonary oedema	97	2	2	—	87	9	2	2	0.009
Periferal oedema	89	9	1	1	57	32	4	7	< 0.001
Fever	7	72	20	—	9	55	36	—	0.002
Influenza symptoms*	43	39	17	1	12	58	26	4	< 0.001
Central neurotoxicity	73	15	11	1	37	42	16	5	< 0.001
Peripheral neurotoxicity	97	2	2	—	93	3	1	3	NS
Nausea/vomiting	41	49	9	1	10	61	19	10	< 0.001
Diarrhoea	55	40	5	1	15	67	8	10	< 0.001
Other gastro-intestinal toxicity†	98	2	—	—	81	14	1	4	< 0.001
Skin toxicity‡	44	49	8	—	22	59	13	6	< 0.001
Mucous membrane toxicity§	70	25	3	2	19	19	1	1	< 0.001
Alopecia	99	1	—	—	98	2	—	—	NS
Dyspnoea	80	9	11	1	52	27	19	2	< 0.001
Other pulmonary events‖	95	3	2	—	43	36	10	11	< 0.001
Central line sepsis	—	—	—	10	—	—	—	16	NS
Pain	94	3	3	—	64	26	4	6	< 0.001
Death	—	—	—	4	—	—	—	1	NS

* Includes fatigue/malaise, arthraligia/myalgia, chills, sweating, nasal congestion and headache.
† Includes gastritis, constipation, melaena, gi hemmorhage and hepato(spleno)megaly.
‡ Includes erythema, rash, pruritus, dry skin, and skin exfoliation.
§ Includes mucositis and conjunctivitis.
‖ Includes cough, cyanosis, hypoxia, rales/wheezing and pulmonary embolism.
¶ NR = severity grade was not recorded or is not applicable.
** Mantel–Haenszel χ^2 for linear trend.
NS = not significant.

to a clinical meaningful augmentation of efficacy [10–12, 14, 21–23].

In preclinical models, the use of rIL-2 and LAK appears to stimulate more responses than rIL-2 alone [7, 8]. The original clinical studies, reported by Rosenberg *et al.* [9, 16], used short (bolus) infusions of rIL-2 every 8 h, in an ICU setting. Although toxicity was manageable, and treatment related mortality remained low, the level of morbidity and the need for ICU facilities have inhibited the use of this approach in Europe, where rIL-2 is predominantly given by continuous intravenous infusion on a normal oncology ward. The latter schedule was first described by West *et al.* [10].

Table 5. Relationship between lymphocyte counts and tumour responses

	Responders (N = 24)*	Non-responders (N = 106)*	*P* value
Baseline lymphocyte counts (× 10⁹/l) mean (SD)	1.908 (0.793)	1.655 (0.814)	NS
Rebound lymphocytosis (× 10⁹/l) mean (SD)	8.846 (4.288)	7.645 (4.967)	NS
No. of patients with rebound lymphocytosis ≥ 6 × 10⁹/l	18 (67%)	62 (61%)	NS

* This analysis includes patients evaluable for response and for whom lymphocyte counts were available 24–48 h following therapy.

A number of collaborative groups have expanded the original data, confirming the manageability and treatment efficacy of the rIL-2 regimen with or without LAK [11, 12, 14, 15]. No prospective randomised trial has been reported using the continuous intravenous infusion schedule comparing rIL-2 alone versus rIL-2 plus LAK. In Europe, this could not be done due to logistic reasons. In addition, only a minority of centres could participate in studies which included LAK, and even then few patients could be treated at any particular time, due to the equipment and personnel requirements.

Results of two randomised trials, comparing high dose bolus rIL-2 with or without LAK, have recently been reported [22, 23]. One study [22] was conducted in patients with advanced RCC and melanoma. The overall response rates and response

Table 6. Response analysis rIL-2 alone vs. rIL-2 + LAK

Schedule	No. entered (evaluable)	Response (%) CR	PR	Overall CR + PR (%)	95% confidence limits	χ^2 test
rIL-2 alone	225 (193)	8 (4)	20 (10)	28 (15)	10–20	
rIL-2 + LAK	102 (95)	5 (5)	12 (13)	17 (18)	10–26	NS
Total rIL-2 with or without LAK	327 (288)	13 (5)	32 (11)	45 (16)	12–20	

NS = not significant, CR = complete response, PR = partial response.

Table 7. Response duration, PFS and survival

Schedule	Response duration: median (range) in months CR	PR	PFS: median (range) in months	Survival: median (range) in months
rIL-2 alone	9.6 + (1.6–19.6+)*	11.4 (4.6–18.6)	8.6 (0.9–31.6+)	9.1 (0.2–35.5+)
rIL-2 + LAK	30.5 +(12.8–30.7+)†	12.8 (4.5–40.4+)	9.4 (2.0–40.4+)	12.1 (0.7–48.3+)
Total rIL-2 with or without LAK	30.5 + (1.6–30.7+)	11.6 (4.5–40.4+)	8.6 (0.9–40.4+)	10.8 (0.2–48.3+)

* Duration of CRs (in months) were 19.6(+), 13.6(+), 9.6(+), 6.8, 4.6(+), 2.1(+), 1.6 and is unknown for 1 patient, † duration of CRs (in months) were 30.6(+), 30.4, 18.6(+), 15.0(+) and 12.7.

duration were similar in the two regimens both for patients with RCC and melanoma. However no information is currently available on PFS or overall survival. The second randomised study, reported by Rosenberg [23] showed an overall response rate for patients with RCC of 33% for high dose bolus rIL-2 plus LAK and 24% for high dose bolus rIL-2 alone. This difference is not significant. This study included patients with a variety of different tumour types. However, a stratified analysis was only presented for objective response, and not for response duration, PFS or overall survival.

A recent publication from Albertini *et al.* [21], reported on a relatively small population of 20 patients treated with continuous intravenous rIL-2 infusions (Roche rIL-2), using a less intensive regimen than described by West *et al.* [10]. This study included only 10 patients with RCC. The patient numbers are too small to determine whether the addition of LAK leads to enhanced therapeutic efficacy. Nevertheless, a significant increase in toxicity was noted in the patients receiving LAK [21].

Since the potential of adoptively transferred LAK cells to contribute to the efficacy of rIL-2 therapy, may be both dependent on tumour type and the schedule used, the present study was undertaken in order to compare safety and efficacy of a

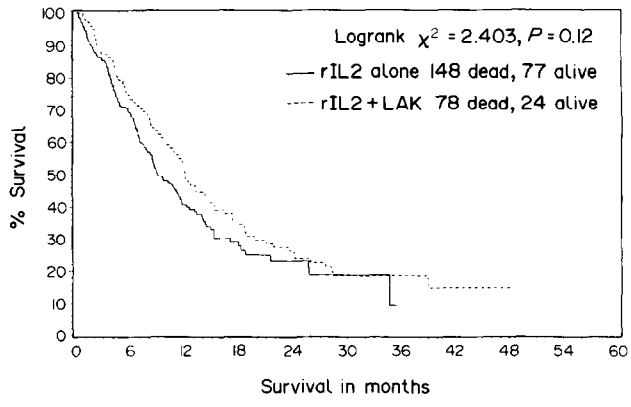

Fig. 1. The overall survival of patients treated with rIL-2 alone vs. rIL-2 + LAK.

Table 8. Multivariate analysis of prognostic factors for survival; rIL-2 alone vs. rIL-2 + LAK

Characteristic	Beta	Standard error	χ^2	P
Group (rIL-2 alone vs. rIL-2 + LAK)	−0.0621	0.1659	0.14	0.7082
ECOG PS (0 vs. 1)	0.6314	0.1678	14.16	0.0002
Age (≤ 60 years vs. > 60 years)	0.0867	0.1580	0.30	0.5834
Sex	−0.0307	0.1633	0.04	0.8506
DTI (> 24 months vs. ≤ 24 months)*	0.6213	0.2027	9.39	0.0022
Prior nephrectomy	−0.3892	0.1789	4.73	0.0296
Lung metastases	0.7253	0.2143	11.45	0.0007
Liver metastases	0.2781	0.2158	1.66	0.1975
Bone metastases	0.4947	0.2164	5.23	0.0222
Other metastases	0.5549	0.2519	4.85	0.0276
No. of metastatic sites (1 vs. 2 vs. ≥ 3)	−0.0424	0.1170	0.13	0.7172
Prior radiotherapy	0.0454	0.1957	0.05	0.8165
Prior chemotherapy	0.3342	0.3006	1.24	0.2663

* DTI = time from diagnosis to treatment.

continuous intravenous infusion regimen of rIL-2 in 327 patients, with advanced RCC, accrued in five concurrent studies. 225 patients received rIL-2 alone and 102 patients received LAK in addition. The baseline characteristics of the patients did not differ significantly between the two cohorts, with the exception of the performance status (PS), which was significantly worse for patients receiving rIL-2 alone. This may relate to patient selection. *A priori*, this could be anticipated, since the LAK procedure requires a significant investment of time and resources. Therefore patients with a better PS may have been preferentially entered in studies involving LAK. The LAK infusions clearly led to a more pronounced toxicity profile, despite equal treatment intensity, in terms of rIL-2 dosing. These findings confirm and extend the observations of Albertini *et al.* [21].

Rebound lymphocytosis and eosinophilia were not enhanced by the addition of LAK cells. West *et al.* [10] reported on the correlation of antitumour response with baseline lymphocyte counts and subsequent rebound lymphocytosis, following rIL-2. This was not confirmed in the present study (Table 5).

The efficacy data do not reveal evidence of additive or synergistic activity, when LAK cells are added to the continuous intravenous infusion regimen. Response rates, both in terms of CR and overall response (CR + PR), are not significantly different, despite the duration of CR recorded in the rIL-2 + LAK patients. Since the majority of rIL-2 alone patients continue to respond, it is possible that this apparent difference in response duration may not be maintained. In addition, this comparison lacks sufficient power due to the limited number of patients evaluable for this subgroup analysis.. However, more importantly, this possible trend did not translate into prolonged PFS or survival.

There is a growing consensus that objective antitumour response (CR or PR), may not be the most important endpoint to be used to evaluate efficacy of immunotherapy. It is apparent that in approximately 5% of patients, rIL-2 therapy results in a complete elimination of bulky tumour masses and that a significant (> 50%) reduction of tumour is obtained in a further 11% of patients. However, a retardation of tumour growth, resulting from a sustained immunological attack upon the tumour, may also result in patient benefit [24]. Therefore PFS and survival may be more appropriate parameters to use, when comparing treatment outcome. The lack of a benefit in terms of PFS or overall survival for patients treated with LAK, compared with rIL-2 alone, is in our view the most significant finding of this study.

To our knowledge this is the first report with sufficient patient numbers which compares toxicity, objective response and survival of a continuous intravenous infusion regimen of rIL-2 with or without LAK in patients with advanced RCC.

It is recognised that the comparison of results of rIL-2 alone and rIL-2 plus LAK, reported here, is done in a setting of concurrent trials and not in a prospective randomised trial. Although this approach has its limitations, the data show that *ex-vivo* generated LAK cells, when prepared according to the published conventional methodology [10, 16], do not appear to add significantly to efficacy when given to patients with advanced RCC, using a continuous intravenous rIL-2 infusion regimen.

It is not clear why the results from animal models showing a significant advantage for the addition of LAK cells [7, 8] could not be confirmed in the clinic. Perhaps this is related to the fact that conventional LAK cells target very poorly to sites of metastatic tumour [25]. It remains to be seen whether modifications of the methodology of adoptive transfer of rIL-2 activated lymphocytes using PBMC enriched in natural killer (NK) cells [26], or NK cells purified from PBMC [27], or tumour infiltrating lymphocytes [28], will lead to a meaningful enhanced antitumour activity in the clinical setting. Clearly, in view of the significant increase in toxicity, induced by the addition of *in vitro* generated conventional LAK cells, we do not believe that further clinical trials, using the adoptive transfer of these cells in conjunction with continuous intravenous rIL-2 are warranted in patients with advanced RCC.

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Phase II Study of Continuous Subcutaneous Interferon-Alfa Combined with Cisplatin in Advanced Malignant Melanoma

J. Richner, R.A. Joss, A. Goldhirsch and K.W. Brunner

Interferon-alfa (IFN-α) and cisplatin have shown synergism *in vitro* against tumour cell lines and optimal effects were observed with continuous and high IFN concentration. 20 patients with advanced malignant melanoma were treated with 10 MU IFN subcutaneously continuously, daily, plus cisplatin 50 mg/m² intravenously on days 8 and 9. Cisplatin was repeated every 4 weeks. The main toxic effects were myelosuppression, fatigue and weight loss. Toxicities always resolved completely after reduction/interruption of IFN and no life-threatening infection was observed. There were 1 complete and 6 partial responses. 6 patients had stable disease. Median time to progression was 7 months with a range of 16 to 2 months. The combined regimen of IFN-α and cisplatin is active in patients with multiple visceral and skeletal sites.
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INTRODUCTION

MELANOMA HAS a rising incidence, for which we lack effective treatment after definitive surgery. Chemotherapy has been of limited value in metastatic melanoma. Single agent treatment with dacarbazine, nitrosoureas or cisplatin have yielded response rates of 10 to 20% [1]. Encouraging reports of early results with combination chemotherapy regimens are rarely confirmed in sizeable series and the duration of response is generally short [2]. Interferons (IFN) have shown an inhibition of proliferation of melanoma cells *in vitro*. Objective regressions have been obtained in about 20%. The dose range was 10 to 50 MU interferon IFN three times weekly. Complete