Original Articles

Efficacy and Safety of Inhaled Recombinant Interleukin-2 in High-Risk Renal Cell Cancer Patients Compared with Systemic Interleukin-2: an Outcome Study

(renal cancer / lung metastasis / aerosol / interleukin-2 / inhalation / local therapy)

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Abstract. Systemic IL-2 is an effective treatment for low to intermediate risk mRCC patients, its efficacy is marginal in high-risk cases. Therefore, other treatment approaches are required for this population. Ninety-four high-risk patients with RCC and pulmonary metastases were treated with inhaled plus concomitant low-dose subcutaneous rhIL-2. Clinical response, survival and safety were compared with those from IL-2 given systemically at the registered dose and schedule in 103 comparable historical controls. In the rhIL-2 INH group, treatment consisted of 6.5 MIU rhIL-2 nebulized 5x/day and 3.3 MIU rhIL-2 SC once daily. The rhIL-2 SYS group received treatment which consisted of intravenous infusion of 18.0 MIU/m^2/day rhIL-2 or SC injection of 3.6-18.0 MIU rhIL-2. Some patients in both groups also received IFNα. Mean treatment durations were 43 weeks rhIL-2 INH and 15 weeks rhIL-2 SYS. Significantly longer overall survival and progression-free survival durations were observed in the rhIL-2 INH group. The probability of survival at 5 years was 21% for the rhIL-2 INH group. No patients survived 5 years in the rhIL-2 SYS group. A multivariate analysis of overall survival adjusting for differences in baseline characteristics between the two treatment groups resulted in a risk ratio of 0.43 (95% CI 0.30–0.63; P < 0.0001). The data suggested an association between the response (SD or better) and survival, especially in the rhIL-2 INH group. The inhalation regimen was well tolerated. This outcome study suggests that administration of rhIL-2 by inhalation is efficacious and safe in high-risk mRCC patients with pulmonary metastases, who have no other treatment option available.

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Abbreviations: CI – confidence intervals, CIV – continuous intravenous infusion, CR – complete response, DTI – disease to treatment interval, IFNα – interferon alfa, IL-2 – interleukin 2, INH – inhaled, IV – intravenous, LAK – lymphokine-activated killer, mRCC – metastatic RCC, NK – natural killer, PR – partial response, PS – performance status, RCC – renal cell carcinoma, rhIL-2 – recombinant human IL-2, SC – subcutaneous(ly), SD – stable disease, SYS – systemic.

Interleukin-2 (IL-2) is a 15 kD glycoprotein produced by T cells in response to stimulation by mitogens or antigens. It is a naturally occurring cytokine that induces T-cell proliferation via activation of high-affinity

IL-2 receptors located on the target cell membrane (Debatin et al., 1989; Kolitz, 1991). The IL-2 anti-tumour activity is thought to be based on the enhancement of tumour-specific cytotoxic T cells, natural killer (NK) cells and lymphokine-activated killer (LAK) cells (Bukowski, 1979; Cheever et al., 1982; Oldham 1984; Foa et al., 1992). Aldesleukin is a recombinant form of human IL-2 (rhIL-2) that has been shown to have similar biological activity to endogenous IL-2.

Metastatic renal cell carcinoma (mRCC) has a very poor prognosis, with a 74% mortality rate at 1 year and 96% at 3 years (Patel and Lavengood, 1977). The results of systemic chemotherapy, radiation therapy or hormonal therapy are generally disappointing (deKernion et al., 1983; Goepel and Rubben, 1991; Stahl et al., 1992). Following high-dose intravenous (IV) IL-2 on the other hand, response rates as high as 30% have been reported (Rosenberg et al., 1985; West et al., 1987; Négrier et al., 1989; Figlin et al., 1997). More importantly, survival rates were considerably greater than expected without IL-2 treatment (Jones et al., 1993; Figlin et al., 1997) and some complete responses were very durable.

A disadvantage of high dose IV (bolus) IL-2, however, is a dose-dependent toxicity, primarily due to a multi-system capillary leak syndrome. This limits the use of this treatment (Sosman et al., 1988; Lee et al., 1989; Rosenberg et al., 1989; Rosenberg et al., 1994), and other systemic routes of administration have therefore been investigated. It was later shown that treatment with subcutaneous (SC) IL-2 at lower doses is as effective as high-dose IV (bolus) IL-2, particularly when administered in combination with other immunotherapy and chemotherapy agents such as interferon alpha (IFNα), while at the same time significantly less toxicity is seen (Atzpodien et al., 1990; Atzpodien et al., 1993; Palmer et al., 1993; Ravaud et al., 1994; Atzpodien et al., 1995; Buzio et al., 1997).

Because of the sometimes serious toxicity seen with high-dose systemic IL-2, the characteristics of the patients who benefited most from this treatment modality were determined. In a meta-analysis it was shown that systemic IL-2 therapy was less efficacious in patients with more advanced RCC; that is in patients with a performance status (PS) = ECOG 2, or a PS of ECOG 1 plus metastases in at least two sites plus a time from diagnosis of primary RCC to consideration for treatment of metastases (disease to treatment interval – DTI) of 24 months (Palmer et al., 1992).

Since high-risk mRCC patients have few other treatment possibilities, for those with pulmonary metastases the use of rhIL-2 by inhalation has been assessed (Huland et al., 1992). The rationale for regional therapy of lung metastases of RCC with rhIL-2 by inhalation is the exposure of tumour tissue and surrounding lymph nodes to immunomodulatory levels of IL-2 without the toxicity associated with systemic administration (Huland , 2001).

We have previously reported results with this combined treatment modality in patients with mRCC (Huland et al., 1992; Huland et al., 1997; Heinzer et al., 1999). We now present a comparison of rhIL-2 administered by inhalation with concomitant prolonged low-dose systemic administration in high-risk patients with mRCC (rhIL-2 INH group) and with rhIL-2 given only systemically in a historical group of high-risk patients in whom systemic treatment with rhIL-2 with registered dose and schedule would nowadays be contraindicated (rhIL-2 SYS group).

Methods

Patient population

High-risk patients with mRCC who received rhIL-2 by inhalation (rhIL-2 INH; N = 94) were retrospectively compared with historical controls that had received rhIL-2 as systemic treatment (rhIL-2 SYS; N = 103). High-risk patients were defined as those with ECOG performance status ≥ 2; or ECOG 1 and DTI ≤ 24 months and ≥ 2 sites of metastases (Palmer et al., 1992). The rhIL-2 INH data originate from patients treated between 1994 and 2001 in nine German centres. Out of 265 patients for whom data were collected on treatment with inhaled rhIL-2, 94 at four German centres were identified as being high-risk patients and are included in the present analysis. These patients were treated clinically and data were recorded in case notes during long-term patient follow-up.

For the rhIL-2 SYS control group, high-risk patients were identified from the data collected during seven clinical trials performed for registration purposes of rhIL-2 in Europe by Chiron BV. In total 103 out of 492 patients who had received rhIL-2 SYS between 1987 and 1994 were identified as being high-risk patients and were included in the analysis.

Inhalation treatment

All patients were treated with rhIL-2 (aldesleukin) (Proleukin® Chiron; 18 MIU per vial for reconstitution with diluting solution containing 5% glucose and 0.5% human serum albumin). The usual treatment regimen with rhIL-2 by inhalation was as follows. Two vials of rhIL-2 (36 MIU) were dissolved under aseptic conditions in 11 ml diluting solution. One ml (3.3 MIU) of the resulting solution was withdrawn and administered SC, and the remainder was inhaled in 5 portions of 2 ml (6.5 MIU) each at 3-hour intervals during the day. If there were problems tolerating 36 MIU per day, the dose could be decreased to 18 MIU per day. Treatment was administered 6 days per week, and could be supplemented with SC IFNα and a low dose of SC rhIL-2 for the treatment of distant metastases other than lung metastases. Doses were so small as to avoid significant

Table 1. Treatment schedules; rhIL-2 SYS group (N = 103)

N*	N**	IL-2 treatment	Treatment schedule
92	23	CIV	2 induction cycles (1-week treatment & 1-week rest) with a 3-week rest period between cycles. After a 3-week rest period, a maintenance cycle (1-week treatment) every 4 weeks.
133	29	CIV	2 induction cycles (2-week treatment & 1-week rest) with a 3-week rest period between cycles. Max. 4 maintenance cycles (1-week treatment) every 4 weeks.
39	6	SC	1 cycle of 10-week treatment, 2 weeks of rest. 4 maintenance cycles (1-week treatment) separated by 2-week rest periods.
65	11	SC	Either 4- or 6-week treatment cycles separated by either 2- or 3-week rest periods. Maximum 12 weeks of treatment.
54	12	SC + IFNα	2 cycles of 7-week treatment with 2–4 weeks of rest between cycles.
109	22	SC + IFNα	1 cycle of 6-week treatment. In case of SD, 1 more cycle after 2 weeks of rest.

IFNα – plus concomitant interferon-alfa

N* Patients (N = 492) who had received IL-2 SYS between 1987 and 1994 from the data collected during seven early clinical trials performed for registration purposes in Europe by Chiron BV (formerly EuroCetus)

N** High-risk patients (N = 103 from the above N = 492), defined as those with ECOG performance status ≥ 2; or ECOG 1 and DTI ≤ 24 months and ≥ 2 sites of metastases.

systemic toxicity. Treatment was given until the patient had progression of disease, could not tolerate treatment or did not wish to continue. Initially in 1994 the first doses of inhalational and SC study treatment were administered in hospital, where patients were instructed on the preparation of the medication. All further medication for inhalation was administered by the patients themselves at home. Later, the treatment was only given on an outpatient basis. Patients received prescriptions from the treating physician to be given to the local pharmacist plus a solution for dilution of the product. The inhaler used was Salvia Lifetec Jetair Delta 20 from Salvia Lifetec, with an intermittent positive pressure breathing (IPPB) tube system.

Systemic treatment

In five of the registration trials, rhIL-2 was given alone by continuous intravenous infusion (CIV) or SC administration. In two further trials, IFNα was used concomitantly with SC rhIL-2. The treatment regimens of the control group and the number of patients per regimen are presented in Table 1. The CIV treatment schedule consisted of two 5-day periods of rhIL-2 infusion at 18 MIU/m^2/day, separated by a rest period. The duration of the rest period was originally 6 days, but was later shortened to 2 days. This so-called induction cycle could be repeated after 4 weeks of rest, and for patients with a response or stable disease this was followed by up to 4 monthly 5-day maintenance cycles until progression of disease. The SC treatment schedule consisted of treatment cycles of 4–10 weeks (mostly 6–7 weeks), interrupted by rest periods of 2–4 weeks. The dosage and regimen of the SC treatment were adapted to the patient's condition and tolerance of the treatment. The daily SC rhIL-2 dose administered was 3.6–18 MIU, independent of body weight or body surface area. The SC IFNα dose could be up to 3 times 5–7 MIU per week. As a result, hospitalization and intensive care facilities were required to manage the associated toxicity.

Measurements of response

To assess the response in the rhIL-2 SYS historical control patients, tumour measurements by chest X-ray, CT scan or ultrasound had been obtained at baseline prior to treatment, and repeated at regular intervals. For the majority of rhIL-2 INH patients, the extent of pulmonary metastases was radiologically evaluated by CT scan or chest X-ray prior to treatment and at regular intervals after treatment start, reflecting normal clinical practice.

The primary efficacy parameter was survival (months), calculated from the start of study treatment to the date of death or the latest date on which the patient was known to be alive. Progression-free survival was calculated for patients with complete response (CR), partial response (PR) and stable disease (SD), and determined as the time (months) between the first day on treatment and the subsequent date on which disease progression was first noted.

The tumour response was evaluated according to the WHO criteria. A CR was defined as total disappearance of all tumours for at least four weeks, and absence of

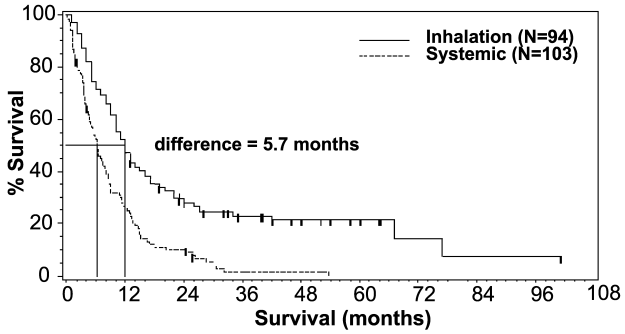

Fig. 1. Kaplan-Meier survival curve of patients with mRCC treated with inhaled and very low-dose SC rhIL-2 (rhIL-2 INH group, solid line) and systemically administered IL-2 (rhIL-2 SYS group, dotted line).

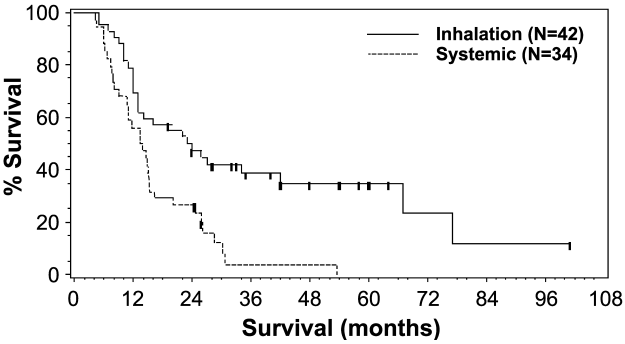

Fig. 2. Kaplan-Meier survival curve of responding patients (CR/PR/SD) with mRCC treated with inhaled and very low-dose SC rhIL-2 (rhIL-2 INH group, straight solid line) and systemically administered IL-2 (rhIL-2 SYS group, dotted line).

new lesions. PR was defined as a decrease of at least 50% in the surface area of the measured tumour, documented on two occasions at least four weeks apart, without appearance of new lesions or enlargement of any existing lesion by at least 25%. SD was defined as a decrease of less than 50% or increase of less than 25% in the sum of the products of the two longest perpendicular diameters of all measurable lesions, and no new lesions detected or progressive disease in any existing lesion, for at least 4 weeks.

Safety measurements

A physical examination and ECG were performed before study treatment. Complete urine and blood analyses were performed at baseline and at regular intervals thereafter. For the IV treated patients this was on a daily basis during rhIL-2 infusion. For the SC treated patients and the rhIL-2 INH group, this was done weekly during treatment or as clinically indicated. The severity of adverse events was assessed in terms of WHO grades. For the rhIL-2 SYS patients and for the rhIL-2 INH patients, an assessment of relationship with the study drug was made by the treating physician. In addition for the rhIL-2 INH patients, safety data were collected through patient diaries. These patients were asked specifically for the occurrence of adverse events like nausea and vomiting, pain, cough, fatigue and anorexia, etc., which they were asked to grade with the help of a written description of the severity of adverse events on a scale of 0 (absent) to 4 (WHO grade 4 severity).

Statistics

All efficacy data were summarized. For continuous variables, baseline characteristics were compared using a t-test. For categorical variables, the chi-square test was used, or Fisher's exact test if 20% of the cells had an expected cell frequency less than 5 or if any expected cell frequency was less than 1. Overall and progression-free survival were calculated using the Kaplan-Meier method, and differences between the two treatment groups were assessed by means of the logrank test. Progression-free survival was calculated only for patients with SD or better. Clopper-Pearson 95% confidence intervals (95% CI) were calculated for

Table 2. Baseline characteristics

	rhIL-2 INH (N = 94)	**rhIL-2 SYS (N = 103)**
Age (years)		
mean	60	56**
range	37-77	24-80
Gender; N (%)		
female	20 (21)	65 (63)***
male	74 (79)	38 (37)
ECOG PS; N (%)		
1	68 (72)	94 (91)***
2	26 (28)	9 (9)
DTI; N (%)		
≤ 24 months	82 (87)	102 (99)**
> 24 months	11 (12)	1 (<1)
unknown	1 (1%)	
Metastatic sites; N (%)		
≥2	51 (54)	51 (50)
lung only	3 (3)	0 (0)
lung and other site(s)	91 (97)	103 (100)
Prior nephrectomy; N (%)		
yes	64 (68)	64 (62)
no	29 (31)	39 (38)
unknown	1 (1)	
Prior chemotherapy; N (%)		
yes	10 (11)	2 (2)*
no	84 (89)	101 (98)
Prior immunotherapy; N(%)		
yes	16 (17)	6 (6)*
no	78 (83)	97 (94)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 3. Exposure to rhIL-2

	rhIL-2 INH (N = 94)	rhIL-2 SYS (N = 103)
Days on study		
mean	301	102
range	15-3059	3-385
median	161	85
Total inhaled dose (MIU)		
mean	6055	
range	33-77770	
Total systemically administered dose (MIU)		
mean	711	567
range	0-9709	86-2016
Total cumulative dose (MIU)		
mean	6766	567
range	36-77770	86-2016

Table 4. Exposure to IFNα

	rhIL-2 INH (N = 38)	rhIL-2 SYS (N = 34)
Days on study		
mean	495	67
range	30-3059	8-340
median	337.0	50.0
Total cumulative dose (MIU)		
mean	730	161
range	6-7433	86-2016

the response rate. To better estimate the effect on overall survival and to take into account the differences in baseline characteristics between the two treatment arms, a multivariate analysis using Cox proportional hazards was undertaken to adjust for these differences. All reported and elicited adverse events were summarized.

Results

A summary of the patients' demographic and baseline characteristics is presented in Table 2. The results show that there were imbalances between the two groups. There were more male patients in the rhIL-2 INH group, and rhIL-2 INH patients were older, had a poorer performance status, and their DTI was more frequently > 24 months. More patients have had prior chemotherapy and prior immunotherapy in the rhIL-2 INH group.

Exposure to treatment

Table 3 shows the exposure to rhIL-2 of patients in the two groups. The mean duration of rhIL-2 treatment was approximately 3 times longer in the rhIL-2 INH group than in the rhIL-2 SYS treated patients, and the total cumulative dose of rhIL-2 administered was more than 10 times larger (Table 3). Ninety percent of the mean total dose was administered by inhalation. The remaining 10% administered SC to these patients (mean 711) exceeded the mean total cumulative dose administered to the systemic group (mean 567). This total dose was however administered over a longer period of time to the rhIL-2 INH group, resulting in lower average weekly SC rhIL-2 doses.

IFNα was co-administered during the study to 38 patients in the rhIL-2 INH group and to 34 patients in the rhIL-2 SYS group (Table 4). Similar differences in exposure to IFNα between groups were seen. The patients of the rhIL-2 INH group who received SC IFNα concomitantly received approximately a five times higher (mean) cumulative dose during an approximately seven times longer period than the patients of the rhIL-2 SYS group, resulting in lower average weekly IFNα doses.

Efficacy

The overall response rate (CR/PR/SD) in the rhIL-2 INH group was 45% (95% CI: 34%–55%) versus 33% (95% CI: 24%–43%) in the rhIL-2 SYS group. Around 60% (95% CI: 49%–72%) of the patients in the rhIL-2 INH group showed a pulmonary response (CR/PR/SD). The Kaplan-Meier survival curves for the two treatment groups are presented in Fig. 1. The 1-, 2- and 3-year survival rates were estimated to be 47% and 26%; 28% and 10%; and 23% and 1%, respectively, for the rhIL-2 INH and rhIL-2 SYS groups. The probabilities of survival at 5 years were calculated to be 21% for the rhIL-2 INH group and 0% for the rhIL-2 SYS group. A multivariate analysis adjusting for the imbalances in baseline characteristics (gender, ECOG PS, DTI) resulted in a hazard ratio of 0.435 (95% CI: 0.30–0.63). In other words, the risk of dying at any time during the course of the disease with rhIL-2 INH treatment was estimated to be 44% of the risk of dying with rhIL-2 SYS treatment.

An association was found between tumour response in the first 6 months of treatment and survival duration. This association is more evident in the patients treated with rhIL-2 by inhalation than in those treated systemically. The overall survival for the responding rhIL-2 INH-treated patients was substantially longer compared to the responding patients in the rhIL-2 SYS group, as illustrated in Fig. 2. The 1-, 2- and 3-year survival rates for the responding patients were estimated to be 69% and 57%; 47% and 26%; and 39% and 4%, respectively, for the rhIL-2 INH and rhIL-2 SYS groups. The probabilities of survival at 5 years were calculated to be 35% for the inhaled group and 0% for the systemic group (logrank 11.60, $P < 0.001$).

Toxicity

For both patient groups, detailed information about safety is available. For 79 patients of the rhIL-2 INH group, adverse events were evaluated predominantly by weekly patient questionnaires. In the rhIL-2 SYS patients who received rhIL2 as monotherapy, adverse events were analysed in 16 patients treated by the SC route and 52 treated with CIV.

Almost all patients experienced one or more adverse events following one of the three treatment modalities. The profiles of the toxicity of inhaled and SC administered regimens differed considerably. In general, inhaled with concomitant low-dose systemic rhIL-2 +/- IFNα was well tolerated by these high-risk patients, and this was reflected by the long period over which treatment continued. In general, patients were able to continue with work or child care or daily activities during treatment.

Cough was a major toxicity in the rhIL-2 INH group, noted mainly during the last inhaled dose of the day and seen during the first 4–8 weeks of the treatment. This was the major reason for dose reductions in the INH group. Reaction to injection sites, skin disorders and fever were reported in both groups, as well as gastrointestinal disorders, which included constipation, diarrhoea, nausea and vomiting, and fatigue and malaise.

No treatment-related severe or life-threatening adverse events were identified in patients treated with inhaled and low-dose systemic therapy; especially no serious adverse event related to the vital organs (hypotension, renal insufficiency). Toxicities of grade 3 were reported for fever, nausea, anorexia and cough in less than 30% of all patients and grade 4 toxicities were limited to anorexia in less than 10% of the patients.

Discussion

The results of this historical comparison suggest longer overall survival and progression-free survival durations for the rhIL-2 INH group. The 1- and 2-year survival rates of 55% and 28% following treatment with rhIL-2 by inhalation combined with SYS IL-2 +/- IFNα found in the present study are similar to those we reported previously (Huland el al., 2000a).

In the present study comparing inhaled and systemic therapy, 28% of the rhIL-2 INH had an ECOG performance status of 2 compared to 9% in the rhIL-2 SYS group (Table 2). All patients from the rhIL-2 INH group were considered unsuitable for complete resection of their pulmonary metastases. Following incomplete surgical resection, low survival times have been reported; from one month to a maximum of 29 months (Piltz et al., 2002).

Survival in high-risk patients with mRCC treated with cytokine-based immunotherapy has consistently been reported to be 6 months or less, which is quite similar to the survival when no immunotherapy was given (Elson et al., 1988). Motzer reported in 2000 a figure of 6 months for high-risk patients treated with cytokines compared to 3 months for chemotherapy in a review of the literature of systemic therapy for patients with RCC (Motzer et al., 2000). In their own patients Motzer (1999) reported a median survival of 4 months in the high-risk group (Motzer et al., 1999). IFNα does not improve survival in high-risk patients, either. Fossa et al. (1994) reported a survival below 6 months in the high-risk group using either IFNα or chemotherapy. Systemic low-dose rhIL-2 plus IFN-α-2b also failed to prolong survival in high-risk patients. In a phase II pilot study (Clark et al., 1999), a very low combination of daily SC rhIL-2 with IFN-α-2b was used in patients who were incapable of tolerating high-dose IV rhIL-2, and median survival was reported to be 6 months and one-year survival was 16%. No major response was observed.

Whilst it was intended to compare two populations with similar baseline characteristics, especially with respect to the defined high-risk criteria (Palmer et al., 1992), the results indicated that the risk characteristics of the two groups were not completely identical. However, adjustments for these differences were made in the multivariate analyses performed.

Notwithstanding all of these caveats, the size of the survival advantage shown in the analysis is impressive and demands further evaluation of inhaled IL-2 combined with systemic IL-2 +/- IFNα. This is challenging since mRCC is a rare disease, and high-risk patients with lung involvement rarer still.

As part of the risk-benefit assessment, safety data were collected as far as available. The systemic group comprised patients participating in prospective clinical trials. In the inhalation group cases were treated clinically, but detailed additional safety and efficacy data were recorded as part of an off-label quality management standard operating procedure in most patients. This resulted in comprehensive information in both groups. The toxicity profile of rhIL-2 administered by CIV can be severe, with hypotension, pulmonary and renal failure as dose-limiting toxicities as a result of a capillary leak syndrome (Sosman et al., 1988; Rosenberg et al., 1989; Rosenberg et al., 1994). Following SC administration, fewer and less severe side effects are observed, especially fever, fatigue and malaise, nausea and vomiting, and anorexia (Atzpodien et al., 1990; Atzpodien et al., 1993; Palmer et al 1993; Ravaud et al., 1994; Atzpodien et al., 1995; Buzio et al., 1997). Inhalation of IL-2 is known to produce local toxicity such as a dose-dependent cough, but hardly any systemic adverse events (Lorenz et al., 1996; Zissel et al., 1996).

Earlier work has also shown that combination of inhalation with low-dose systemic IL-2 also induces a relatively low incidence of side effects (Huland et al., 1997; Nakamoto et al., 1997; Heidenreich and

Neubauer, 1999; Heinzer et al., 1999; Roigas, 1999; Varga, 1999; Huland et al., 2000; Pizza et al., 2001).

Grade 1 and grade 2 adverse events in patients treated with the inhaled/low-dose systemic regimen in the current trial were reported in a number of patients, but it has to be kept in mind that the prolonged treatment period gave more time for events to arise, that the method of coding adverse events was not the same as for the clinical trial cases, as the patients were specifically asked to weekly record the occurrence of adverse events. It is well recognized that using patient questionnaires results in a significantly higher apparent incidence of the specified adverse events than does spontaneous reporting (Grootendorst et al., 1997).

Immunotherapy-associated severe or life-threatening adverse events related to the vital organs (hypotension, renal insufficiency) did not occur in patients treated with inhaled and low-dose systemic therapy. The limited number of reported grade 3 and 4 toxicities were related to symptoms commonly seen in advanced cancer patients as well as during cytokine-based immunotherapy; such as fatigue/malaise, fever, anorexia and cough.

The total cumulative dose of rhIL-2 administered in the rhIL-2 INH group was more than 10 times larger than in the rhIL-2 SYS group, while treatment times were 3 times longer only. Today, new inhalation devices are available, which adjust aerosol delivery to the lung function and breathing pattern and require 25–50% only of the aerosol medication used in this study, resulting in a significant saving in cost-intensive medication.

In conclusion, treatment with rhIL-2 by inhalation together with administration of low systemic doses may contribute to long-term stabilization of progressive disease in these high-risk mRCC patients. Survival benefits seem greater in those showing an early clinical response. The relatively benign toxicity profile permits use of this modality for prolonged periods in high-risk patients.

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References

Atzpodien, J., Korfer, A., Franks, C. R., Poliwoda, H., Kirchner, H. (1990) Home therapy with recombinant interleukin-2 and interferon-alpha 2b in advanced human malignancies. *Lancet* **335,**1509-1512.

Atzpodien, J., Kirchner, H., deMulder, P., Bodenstein, H., Oliver, T., Palmer, P. A., Franks, C. R., Poliwoda, H. (1993) Subcutaneous recombinant interleukin-2 and α-interferon in patients with advanced renal cell carcinoma: results of a multicenter phase II study. *Cancer Biother.* **8,** 289-300.

Atzpodien, J., Lopez Hänninen, E., Kirchner, H., Bodenstein, H., Pfreundschuh, M., Rebmann, U., Metzner, B., Illiger, H. J., Jakse, G., Niesel, T., Scholtz, H.-J., Wilhelm, S. (1995) Multiinstitutional home-therapy trial of recombinant interleukin-2 and interferon alfa-2 in progressive metastatic renal cell carcinoma. *J. Clin. Oncol.* **13,** 497-501.

Bukowski, R. M. (1997) Natural history and therapy of metastatic renal cell carcinoma: the role of interleukin-2. *Cancer* **80,** 1198-1220.

Buzio, C., Palma, G. de., Passalacqua, R., Potenzoni, D., Ferrozzi, F., Cattabiani, M. A., Manenti, L., Borghetti, A. (1997) Effectiveness of very low doses of immunotherapy in advanced renal cell cancer. *Br. J. Cancer* **76,** 541-544.

Cheever, M. A., Greenberg, P. D., Fefer, A., Gillis, S. (1982) Augmentation of the anti-tumour therapeutic efficacy of long-term cultured T lymphocytes by in vivo administration of purified interleukin-2. *J. Exp. Med.* **155,** 968-980.

Clark, J. I., Gaynor, E., Martone, B. (1999) Daily subcutaneous ultra-low-dose interleukin 2 with daily low-dose interferon-alpha in patients with advanced renal cell carcinoma. *Clin. Cancer Res.* **5,** 2374-2380.

Debatin, K. M., Woodroofe, C., Lahm, H., Fischer, J., Falk, W. (1989) Lack of interleukin-2 (IL-2) dependent growth of TAC positive T-ALL/NHL cells is due to the expression of only low affinity receptors of IL-2. *Leukemia* **8,** 566-571.

deKernion, J. B., Sarna, G., Figlin, R., Lindner, A., Smith, R. B. (1983) The treatment of renal cell carcinoma with human leukocyte alpha-interferon. *J. Urol.* **130,** 1063-1066.

Elson, P. J., Witte, R. S., Trump, D. L. (1988) Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. *Cancer Res.* **48,** 7310-7313.

Figlin, R., Gitlitz, B., Franklin, J., Dorey, F., Moldawer, N., Rausch, J., Kernion, J. de., Belldegrun, A. (1997) Interleukin 2-based immunotherapy for the treatment of metastatic renal cell carcinoma: an analysis of 203 consecutively treated patients. *Cancer J. Sci. Am.* **3,** S92-S97.

Foa, R., Guarini, A., Gansbacher, B. (1992) IL-2 treatment for cancer: from biology to gene therapy. *Br. J. Cancer* **6,** 992-998.

Fossa, S. D., Kramar, A., Droz, J. P. (1994) Prognostic factors and survival in patients with metastatic renal cell carcinoma treated with chemotherapy or interferon-alpha. *Eur. J. Cancer* **30A,** 1310-1314.

Goepel, M., Rubben, H. (1991) Adjuvant therapy in renal cancer. *World J. Urol.* **9,** 232-236.

Grootendorst, P. V., Feeny, D. H., Furlong, W. (1997) Does it matter whom and how you ask? Inter- and intra-rater agreement in the Ontario Health Survey. *J. Clin. Epidemiol.* **50,** 127-135.

Heidenreich, A., Neubauer, S. (1999) Interleukin-2 inhalation therapy in pulmonary metastases of renal cell cancer – Cologne experience. *Anticancer Res.* **19,** 2003-2004.

Heinzer, H., Mir, T. S., Huland, E., Huland, H. (1999) Subjective and objective prospective, long-term analysis of quality of life during inhaled interleukin-2 immunotherapy. *J. Clin. Oncol.* **17,** 3612-3620.

Huland, E. (2001) Interleukin-2 and cancer – physiological and pharmacological uses. *Folia Biol. (Praha)* **47,** 111-112.

Huland, E., Huland, H., Heinzer, H. (1992) Interleukin-2 by inhalation: local therapy for metastatic renal cell carcinoma. *J. Urol.* **147,** 344-348.

Huland, E., Heinzer, H., Mir, T. S., Huland, H.(1997) Inhaled interleukin-2 therapy in pulmonary metastatic renal cell carcinoma: six years of experience. *Cancer J. Sci. Am.* **3,** S98-S105.

Huland, E., Heinzer, H., Huland, H. (1999) Treatment of pulmonary metastatic renal-cell carcinoma in 116 patients using inhaled interleukin-2 (IL-2). *Anticancer Res.* **19,** 2679-2683.

Huland, E., Heinzer, H., Huland, H. (2000a) A comparison of systemic versus inhaled recombinant IL-2 administration for the treatment of metastatic renal cell carcinoma. *Folia Biol. (Praha)* **46,** 241-250.

Huland, E., Heinzer, H., Huland, H., Yung, R. (2000b) Overview of interleukin-2 inhalation therapy. *Cancer J. Sci. Am.* **6,** S104-S112.

Huland, E., Heinzer, H., Timm, S., Aalamian, M., Huland, H. (2002) Immunotherapy for metastatic renal-cell carcinoma in Germany: a nationwide survey. *Urologe A* **41,** 282-287.

Jones, M., Philip, T., Palmer, P., von der Maase, H., Vinke, J., Elson, P., Franks, C. R., Selby, P. (1993) The impact of interleukin-2 on survival in renal cancer: a multivariate analysis. *Cancer Biother.* **4,** 275-288.

Kolitz, J. E., Mertelsmann, R. (1991) The immunotherapy of human cancer with interleukin-2: present status and future directions. *Cancer Invest.* **9,** 529-542.

Lee, R. E., Lotze, M. T., Skibber, J. M. (1989) Cardiorespiratory effects of immunotherapy with interleukin-2. *J. Clin. Oncol.* **7,** 7-20.

Lorenz, J., Wilhelm, K., Kessler, M. (1996) Phase I trial of inhaled natural interleukin 2 for treatment of pulmonary malignancy: toxicity, pharmacokinetics, and biological effects. *Clin. Cancer Res.* **2,** 1115-1122.

Motzer, R. J., Mazumdar, M., Bacik, J. (2000) Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma. *J. Clin. Oncol.* **18,** 1928-1935.

Motzer, R. J., Mazumdar, M., Bacik, J., Berg, W., Amsterdam, A., Ferrara, J. (1999) Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J. Clin. Oncol.* **17,** 2530-2540.

Nakamoto, T., Kasaoka, Y., Mitani, S., Usui, T. (1997) Inhalation of interleukin-2 combined with subcutaneous administration of interferon for the treatment of pulmonary metastases from renal cell carcinoma. *Int. J. Urol.* **4,** 343-348.

Négrier, S., Philip, T., Stoter, G., Fossa, S. D., Janssen, S., Iacone, A., Cleton, F. S., Eremin, O., Israel, L., Jasmin, C., Rugarli, C., von der Maasse, H. (1989) Interleukin-2 with or without LAK cells in metastatic renal cell carcinoma: a report of a European multicentre study. *Eur. J. Cancer Clin. Oncol.* **25,** S21-S28.

Oldham, R. K. (1984) Biological response modifiers program workshop, "In vivo-effects of IL-2". *J. Biol. Response Modif.* **3,** 455-532.

Palmer, P. A., Vinke, J., Philip, T., Negrier, S., Atzpodien, J., Kirchner, H., Oskam, R., Franks, C. R. (1992) Prognostic factors for survival in patients with advanced renal cell carcinoma treated with recombinant interleukin-2. *Ann. Oncol.* **3,** 475-480.

Palmer, P. A., Atzpodien, J., Philip, T., Negrier, S., Kirchner, H., von der Maase, H., Geertsen, P., Evers, P., Loriaux, E., Oskam, R., Roest, G., Vinke, J., Franks, C. R. (1993) A comparison of 2 modes of administration of recombinant interleukin-2: continuous intravenous infusion alone versus subcutaneous administration plus interferon alpha in patients with advanced renal cell carcinoma. *Cancer Biother.* **8,** 123-136.

Patel, N. P., Lavengood, R. W. (1977) Renal cell cancer: natural history and results of treatment. *J. Urol.* **119,** 722-726.

Piltz, S., Meimarakis, G., Wichmann, M., Hatz, R., Schildberg, F., Fuerst, H. (2002) Long-term results after pulmonary resection of renal cell carcinoma metastases. *Ann. Thorac. Surg.* **73,** 1082-1087.

Pizza, G., De Vinci, C., Lo, C. G. (2001) Immunotherapy of metastatic kidney cancer. *Int. J. Cancer* **94,** 109-120.

Ravaud, A., Négrier, S., Cany, L., Merrouche, Y., Guillou, M. Le., Blay, J. Y., Clavel, M., Gaston, R., Oskam, R., Philip, T. (1994) Subcutaneous low-dose recombinant interleukin 2 and alpha-interferon in patients with metastatic renal cell carcinoma. *Br. J. Cancer* **69,** 1111-1114.

Roigas, J. (1999) Inhalation of interleukin-2 as second-line treatment: Charité experience. *Anticancer Res.* **19,** 2010-2011.

Rosenberg, S. A., Lotze, M. T., Muul, L. M., Leitman, S., Chang, A. E. (1985) Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with cancer. *N. Eng. J. Med.* **313,** 1485-1492.

Rosenberg, S. A., Lotze, M. T., Yang, J. C., Abersold, P. M., Lineham, W. M, (1989) Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. *Ann. Surg.* **210,** 474-485.

Rosenberg, S. A., Yang, J. C., Topalian, S. L. (1994) Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA* **271,** 907-913.

Sosman, J. A., Kohler, P. C., Hank, J. A. (1988) Repetitive weekly cycles of interleukin-2. II. Clinical and immunologic effects of dose, schedule, and addition of indomethacin. *J. Natl. Cancer Inst.* **80,** 1451-1461.

Stahl, M., Wilke, H.-J., Seeber S., Schmoll, H.-J. (1992) Cytokines and cytotoxic agents in renal cell carcinoma: a review. *Semin. Oncol.* **19,** S70-S79.

West, W. H., Tauerm, K. W., Yanellim, J. R., Marshall, G. D., Orr, D.W., Thurman, G. B., Oldham, R. K. (1987) Constant infusion of recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. *N. Eng. J. Med.* **316,** 898-905.

Zissel, G., Aulitzky, W. E., Lorenz, J., Huber, C., Muller-Quernheim, J. (1996) Induction of accessory cell function of human alveolar macrophages by inhalation of human natural interleukin-2. *Cancer Immunol. Immunother.* **42,** 122-126.