Table 1. Inclusion and exclusion criteria for patients treated with SYST IL-2

Criteria	Atzpodien et al. (1990b)	Ravaud et al. (1994)	Sleijfer et al. (1992)	Tourani et al. (1996)
Inclusion criteria				
Patient written and informed consent	√	√	√	√
Proven advanced or disseminated RCC	√	√	√	√
RCC refractory to standard therapy	√			
Expected survival ≥ 3 months	√	√		
Karnofsky performance status ≥ 70%	√			
ECOG performance status score ≤ 2		√		√
White blood cell count ≥ 3 500/μl	√	√		
Platelet count ≥ 120 000/μl		√		
Platelet count ≥ 100 000/μl	√			
Hematocrit > 30%		√		
Hematocrit ≥ 28%	√			
Creatinine clearance ≥ 60 ml/min	√			
Creatinine concentration ≥ 150 μM		√		
Exclusion criteria				
Evidence of major organ system dysfunction		√		√
Evidence of serious cardiac disease	√	√		
Forced expiratory volume < 2 liters in 1 s	√			
CNS metastases		√		√
Evidence of CNS disease		√		
Evidence of seizure disorders		√		
Evidence of active infection*	√	√		
Requirement for corticosteroids	√	√		
Previous IL-2 therapy				√
Anticancer therapy within 4 weeks of entry	√	√		
Use of prostaglandin E2 synthesis inhibitors	√			

*Including human immunodeficiency virus and infectious hepatitis

Lifetec Jetair δ20 nebulizer (Hoyer Bremen, Bremen, Germany). Subcutaneous injections were administered by the patients themselves. Additional doses of either 5×10^6 IU IFN-α or 9×10^6 IU IL-2 were administered subcutaneously thrice weekly.

(b) *SYST IL-2 therapy.* Patients treated with SYST IL-2 received subcutaneous injections of IL-2 (with or without IFN-α treatment) according to one of four treatment protocols, as summarized in Table 2 (Atzpodien et al., 1990b; Sleijfer et al., 1992; Ravaud et al., 1994; Tourani et al., 1996).

Objective responses

Responses to treatment were assessed largely according to the criteria established by the World Health Organization. A complete response (CR) was defined as the complete disappearance of all clinical and/or radiological disease for at least 4 weeks. A partial response (PR) represented at least a 50% decrease in the sum of the products of the longest perpendicular diameters of measurable lesions for at least 4 weeks. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% in the aggregate area of measurable lesions, lasting for at least 3 months for patients receiving INH IL-2 treatment, and at least 4 weeks for patients treated with SYST IL-2. Progressive disease (PD) reflected more than a 25% increase in the aggregate area of measurable lesions, or the development of new lesions.

Toxicity

Toxicity related to IL-2 therapy was evaluated according to the criteria established by the World Health Organization. The severity of toxicity was expressed as Grades 1 through 4.

Statistical analysis

Survival curves were plotted using the Kaplan-Meier method, and statistical differences were calculated using a logrank test. Multivariate analysis of patient survival, adjusting for factors prognostic of survival, was performed using the Cox's proportional hazards model.

Table 2. Treatment protocols for SYST IL-2 therapy

Reference	Cycles	IL-2 (IU, sc)	IFN-α (IU, sc)
Atzpodien et al., (1990b)	6 weeks long, repeated every 10 weeks	$29 \times 10^6/m^2$ bid for 2 days (pulse phase) followed by $21.8 \times 10^6/m^2$ bid for 5 days (6-week maintenance phase)	$5 \times 10^6/m^2$ qd on days 1, 3 and 5 of the maintenance phase
Ravaud et al., (1994)	7 weeks long, separated by 2-week intervals	$9 \times 10^6/m^2$ bid for 7 days (induction phase) followed by $1.8 \times 10^6/m^2$ bid 5 days/week for 6 weeks (maintenance phase)	$5 \times 10^6/m^2$ qd 3 times a week during the maintenance phase
Sleijfer et al., (1992)	6 weeks long, separated by 3-week intervals	18×10^6 qd for 5 days during the first week (induction phase) followed by 9×10^6 qd for 2 days and 18×10^6 qd for 3 days during the next 5 weeks (maintenance phase)	
Tourani et al., (1996)	9 weeks long, separated by 2-week intervals	9×10^6 bid for 5 days during weeks 1 and 6; 9×10^6 bid for 2 days and qd for 3 days during weeks 2 – 4 and 7 – 9; no treatment during week 5	

bid – the dose was given twice a day
qd – the dose was given once a day

Results

Patient characteristics

The characteristics of the studied patients are summarized in Table 3. Patients receiving INH or SYST therapy were similar with respect to mean age and distribution according to gender. The majority of the patients in both treatment groups had undergone a nephrectomy. Comparable proportions of patients in the two treatment groups had experienced metastasis of their renal cell carcinoma to their lungs and had received prior chemotherapy. However, the patients in the two treatment groups differed with respect to the IL-2 treatment received and the presence of risk factors. Substantially more patients in the INH IL-2 treatment group received IL-2 monotherapy versus IL-2/IFN-α combination therapy. Conversely, for the SYST IL-2 treatment group, substantially more patients received IL-2/IFN-α combination therapy than IL-2 monotherapy. In regard to the presence of risk factors, patients receiving INH IL-2 treatment tended to have a poorer overall performance status (i.e., higher ECOG score) than patients receiving SYST IL-2 treatment. Of the 75 patients receiving INH IL-2 treatment, 4 patients (5%) had an ECOG performance score of 0, and 71 (95%) had a score ≥ 1. In contrast, 91/202 patients (45%) receiving SYST IL-2 treatment had an ECOG performance score of 0, and 120/202 patients (55%) had a score ≥ 1. However, the patients in the two treatment groups were characterized by a similar diagnosis-to-treatment interval.

Objective responses to IL-2 treatment

Patients in both IL-2 treatment groups experienced objective responses to treatment (Table 4). The most common objective response observed for both treatment groups was SD. Of the patients in the INH IL-2 treatment group, 37 (49.3%) had an SD response, while 71 patients (35.1%) in the SYST IL-2 treatment group showed this response. A PR was achieved by 7 patients (9.4%) treated with INH IL-2 and by 36 patients (17.8%) treated with SYST IL-2. A single patient (1.3%) in the INH treatment group and 9 patients (4.4%) in the SYST treatment group achieved a CR.

The patient response to treatment as a function of the ECOG performance status is illustrated in Table 5. A poorer ECOG performance status (i.e., higher ECOG score) tended to be associated with a weaker response to treatment with INH IL-2. Thus, of the patients receiving INH IL-2 treatment and characterized by an ECOG score of 0, no patients achieved a CR, but 1/4 patients (25%) achieved a PR, 2/4 patients (50%) showed SD and 1/4 patients (25%) experienced PD. In comparison, smaller proportions of patients with an ECOG performance score of 2 manifested a PR (0/7, 0%) or SD (3/7, 42.9%), and a larger proportion experienced PD (4/7, 57.1%).

For patients receiving SYST IL-2 therapy, the response to treatment consistently reflected the ECOG performance scores (Table 5). An ECOG performance score of 0 was associated with higher proportions of patients achieving a CR or a PR than was a score of 1, and in turn, a score of 1 was associated with higher proportions of patients achieving a CR or PR than was a score of 2. Of patients with an ECOG performance score of 0, 1 or 2, 7/91 (7.7%), 2/102 (2%) and 0/9 (0%) achieved a CR, and 20/91 (22%), 15/102 (14.7%) and 1/9 (1.1%) experienced a PR, respectively. Conversely, an ECOG performance score of 2 was associated with higher proportions of patients experiencing PD than was a score of 1, and in turn, a score of 1 was associated with a greater proportion of patients experiencing PD than was a score of 0. Of patients with an ECOG performance score of 2, 1 or 0, 5/9 (55.6%), 47/102 (46.1%), and 27/91 (29.7%) were found to have PD, respectively.