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Review

A systematic review of the relation between interleukin-2 schedule and outcome in patients with metastatic renal cell cancer

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Abstract

In Europe, interleukin 2 (IL-2) is one of the two treatment modalities officially approved for patients with metastatic renal cell cancer. Traditionally, IL-2 has been administered by three different routes: intermittent bolus injection (BIV), continuous intravenous infusion (CIV) and subcutaneous injection (SC). There have been few randomized trials designed to compare these routes of administration. This paper describes a systematic review of the literature in which an attempt has been made to determine which schedule of administration is superior. Heterogeneity of the data makes firm conclusions difficult. It appears that the number of complete remissions (CR) is similar between BIV and SC routes and that these are higher than for CIV schedules. The durability of the CRs induced by BIV appeared superior to those induced by SC IL-2 and definitely higher than with CIV protocols. This analysis highlights some of the difficulties of using evidence-based medicine to determine standard of care when the clinical-trial data are heterogeneous. These data emphasize the importance of randomized clinical trials in determining what should be regarded as optimum therapy.

Keywords: Renal cell cancer; Immunotherapy; Interleukin 2

1. Introduction

With an incidence of approximately 27 000 per year in Europe, renal cell carcinoma accounts for 2–3% of all malignancies [1]. Approximately 30% of patients present with systemic spread and a further 30–40% of patients with localised disease at presentation will eventually develop metastases [2]. The prognosis of patients with advanced renal cell cancer is very poor, with the median survival being less than 12 months [3]. This can, in part, be explained by the poor results achieved with anticancer therapies. So far, hormonal and chemotherapeutic agents such as 5-fluorouracil or vinblastine have been effective in only a minority of patients, with most responses being of short duration [4]. Although not being convincingly chemosensitive, metastatic renal cell carcinoma (MRCC) is considered to be an immune-responsive cancer. Some patients show spontaneous tumour regression, a phenomenon credited to immunological mechanisms. Moreover, the administration of the immune-modulating cytokines, interleukin 2 (IL-2) and interferon-α, as monotherapy or together, has yielded response rates of 10–30% in advanced renal cancer. A Cochrane review recently demonstrated that interferon provides a modest survival benefit compared to other commonly used treatments. In this review, no conclusion could be drawn concerning the effect of IL-2, because of the lack of controlled, randomised studies [5]. Although interferon treatment attains consistent response rates with an improvement in survival, it produces few documented long-term benefits. IL-2 based protocols may, however, be more promising. With maintenance of complete responses beyond 10 years having been documented, IL-2 may indeed have curative potential in disseminated renal cell cancer [6].

IL-2, discovered as a T-cell growth factor and an activator of T cells and natural killer cells in 1976, was

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first administered to patients with renal cell carcinoma as an intravenous bolus regimen in the mid-1980s [7,8]. Although response rates were encouraging, the protocol induced severe toxicity, being a considerable burden for both the patients and the medical staff with frequent admissions to the intensive care unit being required. Since then, trial design has been focused on improving response rates whilst at the same time reducing toxicity. A large number of phase I and phase II trials have been conducted, exploring the use of different doses, of co-administering several chemotherapeutic or immunological agents, and of alternative routes of administration. Unfortunately, few phase III trials have been conducted comparing the different routes of administration. This has made it difficult to be certain about the optimum dose and schedule for IL-2.

Nevertheless, a non-structured perusal of the literature suggested to us that the quantity and quality of complete remissions with short intensive intravenous IL-2 may be superior to both continuous intravenous infusion and subcutaneous treatment schemes [5,6]. Since this view is not based upon a systematic review of the literature, such an impression is likely to be biased. Therefore, until large randomised phase III trials have been performed, a systematic review of published data is the only means of gaining more insight into the optimal IL-2 route and schedule.

The objective of this study was to conduct a systematic review of the efficacy of IL-2 in patients with metastatic or locally advanced renal cell carcinoma in order to evaluate the effect of IL-2 dose, schedule and route of administration on outcome. Outcome measures of interest were: (1) quantity and durability of complete and partial responses; (2) median, progression-free and overall survival rates.

2. Methods

The search and selection strategy together with the data collection and analysis were prospectively defined in a protocol and subsequently performed by one reviewer.

2.1. Literature search

In order to identify the relevant studies the on-line databank NLM Gateway (http://gateway.nlm.nih.gov/gw/Cmd) was used. This database makes it possible to go through the following retrieval systems:

- MEDLINE/Pubmed (January 1967–October 2002)
- OLDMEDLINE (1957–1966)
- LOCATORplus, MEDLINEplus, DIRLINE, AIDS Meetings, Health Services Research Meetings, Space Life Sciences Meetings, and HSRProj.

Applied search terms were 'cancer, renal cell' and 'interleukin 2'. These were performed using subject headings (MeSH) and keywords. In this instance, no language, gender, age, study design or any other restrictions were applied. By keeping the search field broad, selection bias on a database level was minimised as much as possible.

2.2. Study selection

Subsequently, the selection strategy was executed in a two-step procedure.

At first, studies obviously irrelevant on the basis of title and subject headings were excluded. In a second round the remainder of studies were judged on their abstract. If exclusion could not be made with certainty on the basis of the abstract, detailed information from the full text publication was used. Any doubt as to whether an article should be included or excluded was resolved in a meeting with a second (a professor in oncology) and third reviewer (an epidemiologist).

Selected studies were considered eligible for this review if the following prospectively defined criteria were met:

- a clinical trial with an intravenous or subcutaneous IL-2-based treatment in at least one arm
- a phase II or III study design with prospectively defined inclusion and exclusion criteria
- the included patients should have progressive, metastatic or locally advanced renal cell carcinoma, inoperable due to technical or medical limitations
- response rate should be at least one of the presented primary outcome parameters.

After the first selection round it was decided to add the following exclusion criteria:

- non-full text, non-English written publications
- studies concerning IL-2 administration via inhalation
- IL-2-based studies with additional irradiation therapy in which it remained unclear whether the response was due to the radiotherapy or to the immunotherapy
- studies of which more than 5% of patients were under 18 or above 70 years of age. Yet, if age was linked to response per patient, the article reporting this for every treated patient, the 18- to 70-year-old persons were included.

When faced with multiple reports published from the same study, the most recent peer-reviewed full article was considered the primary reference and only this one was included in this review.

To make sure that every relevant article was included the reference lists of the identified articles was hand searched for additional eligible publications.

2.3. Quality assessment

Because of the inclusion of phase II studies, assessment of methodological quality in terms of internal validity was impossible. Instead, methodology was assessed by means of screening and tabulating the applied response definition and response assessment.

Concurrently, the quality of data presentation and data extraction was assessed, scoring the following items:

D1 Description of the eligibility criteria
D2 Description of the interventions with respect to type, duration, number and intensity
D3 Description of and report on the most important effect measures, i.e. responses
D4 Report on duration of follow up
D5 Report and description of withdrawal
D6 Report on the progressiveness of the advanced cancer
D7 Report if the diagnosis of included renal cell cancer patients is histologically or biopsy proven
D8 Report if patients with brain metastases were excluded
D9 Report if concomitantly use of steroids was not allowed.

A criterion was scored positive if adequately performed or negative if inadequately performed. Thus, a quality score was calculated with a possible range of 0–9.

Where there were any doubts about methods or data presentation the reviewer discussed the article with the oncologist and/or the epidemiologist. If controversy persisted a study was considered to be ineligible.

2.4. Data-abstraction and outcome measures

Patient characteristics including age, sex and prior treatment modalities were tabulated. The following outcome measures were extracted, where possible.

Quantity and quality of response rates using World Health Organisation (WHO) response criteria [9]:

(a) complete response (CR) = the disappearance of all known disease, determined by two observations not less than 4 weeks apart;
(b) partial response (PR) = 50% or more reduction in total tumour load, determined by two observations not less than four weeks apart; stable disease/no change (SD) = less than 50% tumour reduction or 25% tumour increase;
(c) progressive disease (PD) = 25% or more increase in tumour size or appearance of new lesions.

Survival:

(a) overall survival (1, 2, or 5 years, etc.);
(b) median survival.

2.5. Statistical analysis

Patients were divided into three groups according to the route of administration: continuous intravenous (CIV), subcutaneous (SC) or bolus intravenous (BIV). Statistical tests were performed to assess the differences in characteristics of the studies and the patients between the three groups. Response rates were compared in a weighted least-squares regression analysis, in which the number of patients who were intended to receive IL-2 in each study was used as the weighting variable and the three groups (i.e. CIV, SC and BIV) were recoded to two dummy variables. Comparisons of the proportion of patients responding >12 months, >24 months and >36 months were made in a similar way, using the number of responding patients as a weighting variable. To adjust for possible heterogeneity between the three groups, stratified analyses were performed according to the quality of the studies (quality score <6 versus >6), sex, age group (<60 versus >60), nephrectomy prior to IL-2, prior immunotherapy and prior chemotherapy. In all analyses, $P \geqslant 0.05$ was considered as statistically significant.

3. Results

3.1. Literature search and selection of studies

Of the 1188 journal citations yielded by the search in NLM Gateway, only 309 studies were found relevant on the basis of title and subject headings. On more detailed selection, 113 of these were ineligible because they were not (prospective) phase II or III trials. Another 23 studies were excluded because the full-text articles were not written in English. Six English articles were found ineligible because they concerned inhalation therapy. One study investigated the merits of a scheme combining continuous and bolus infusion and was therefore ruled out. Seventy-four studies could not be screened for their eligibility due to problems identifying them. The remaining 92 met eligibility criteria and all were included for analysis.

3.2. Characteristics of studies, patients and interventions

The 92 full-text articles reported on a total of 4946 patients divided over 112 cohorts. The median cohort size was 30 patients, the mean 44. IL-2 was administered CIV in 36 cohorts with a total of 1444 RCC patients, SC

Table 1a
Study characteristics, according to the route of administration of IL-2

Author	Ref.[a]	Study characteristics					Quality criteria for data presentation *3									Quality score	Patient characteristics					
		Year of public.	Phase of study	Therapy *1	No. ITT *2	No. LFU *2	D1	D2	D3	D4	D5	D6	D7	D8	D9	D1–9	Median age	Male	Female	Prior treatment		
																				Nephr	IT	ChT
CIV																						
Albertini	[2]	1990	2	2	10	NA	1	1	1	–	–	–	1	1	1	6	NA	NA	NA	NA	NA	NA
Besana	[14]	1994	2	2	23	6	1	1	1	1	1	1	1	1	1	9	58	17	6	23	4	1
Blay	[15]	1990	2	2	25	NA	–	1	–	–	–	–	–	–	–	1	NA	NA	NA	0	0	0
Clark	[19]	1990	2	2	4	0	1	1	1	–	1	–	1	–	–	5	NA	NA	NA	NA	NA	NA
Dillman	[22]	1993	2	NA	186	19	0	1	1	–	1	–	1	1	1	6	NA	NA	NA	NA	NA	NA
Elias	[25]	1999	2	5	16	3	1	0	1	–	1	–	–	1	–	4	53.5	9	7	6	2	NA
Elias	[26]	2000	2	5	35	NA	1	0	0	–	1	–	–	1	–	3	55	26	9	22	0	NA
Ellerhorst	[27]	1997	2	5	55	3	1	1	1	–	1	–	1	1	–	6	49	43	12	43	0	0
Engelhardt	[28]	1997	2	1	17	NA	1	1	1	–	–	–	–	1	–	4	NA	NA	NA	NA	NA	NA
Escudier	[29]	1993	2	2	33	NA	1	1	0	1	1	1	1	1	–	7	NA	23	10	27	0	16
Figlin	[31]	1992	2	2	30	0	1	1	1	1	1	–	1	1	1	8	57	25	5	24	0	1
Figlin	[32]	1999	3	1	68	NA	1	1	0	–	1	–	–	1	1	5	NA	NA	NA	68	NA	NA
Figlin	[32]	1999	3	2	72	NA	1	1	0	–	1	–	–	1	1	5	NA	NA	NA	72	NA	NA
Fossa	[35]	1993	2	2	16	3	0	1	1	0	1	–	–	–	–	3	52	12	4	15	NA	NA
Geertsen	[37]	1992	2	1	31	1	1	1	1	–	1	–	1	1	1	7	58	17	14	20	NA	NA
Gore	[39]	1994	2	1	133	24	1	1	1	–	1	–	1	1	1	7	56	97	36	89	6	22
Ilson	[42]	1992	2	2	34	NA	1	1	1	–	–	–	–	1	1	5	54	25	9	20	1	0
Kradin	[44]	1989	2	2	7	NA	1	1	0	–	–	–	–	1	1	4	55	NA	NA	7	NA	NA
Kuebler	[46]	1993	2	2	15	NA	1	1	1	–	1	–	–	–	–	4	59	13	2	12	NA	NA
Law	[47]	1995	3	1	36	2	1	1	1	–	1	–	–	1	–	5	53	31	5	30	2	0
Law	[47]	1995	3	2	35	3	1	1	1	–	1	–	–	1	–	5	53	24	11	31	4	2
Mittelman	[55]	1991	2	2	15	3	1	1	1	–	1	–	–	1	–	5	61	8	7	9	0	0
Négrier	[56]	1992	2	1	17	3	1	1	1	–	1	1	1	1	–	7	68.5	9	8	15	0	0
Négrier	[57]	1998	3	1	132	NA	1	1	0	1	1	1	1	1	1	8	56	NA	NA	128	0	1
Négrier	[57]	1998	3	2	136	NA	1	1	0	1	1	1	1	1	1	8	56	NA	NA	131	0	1
Paciucci	[60]	1989	2	2	9	NA	0	0	1	–	–	–	–	–	1	2	NA	NA	NA	NA	NA	NA
Pichert	[61]	1991	2	2	6	NA	1	1	1	–	–	–	–	1	–	4	47	5	1	6	0	NA
Shulman	[75]	1996	2	1	17	NA	1	1	0	–	–	–	1	–	–	3	48	13	4	NA	7	NA
Stoter	[80]	1989	2	1	27	9	1	1	1	–	0	–	1	–	–	4	53	NA	NA	15	NA	0
Sznol	[81]	1992	2	5	44	2	1	1	1	–	1	–	1	1	1	7	55	35	7	34	4	4
Thomas	[84]	1992	2	2	22	NA	–	0	1	–	–	–	–	–	–	1	53	16	6	NA	NA	NA
Thompson	[85]	1989	2	2	8	NA	1	1	1	–	–	–	1	–	1	5	NA	NA	NA	NA	NA	NA
Thompson	[86]	1992	2	2	20	NA	1	1	1	–	–	–	1	–	1	5	56	NA	NA	NA	1	2
Thompson	[86]	1992	2	2	22	NA	1	1	1	–	–	–	1	–	1	5	55	NA	NA	NA	2	1
Wang	[92]	1989	2	2	40	4	1	1	1	–	0	–	1	1	1	6	55.5	30	10	34	NA	NA
Weiss	[93]	1992	3	2	48	5	1	1	1	–	1	1	1	1	1	8	49	35	13	47	7	9

(*continued on next page*)

Table 1a (*continued*)

Author	Ref.[a]	Study characteristics					Quality criteria for data presentation *3									Quality score	Patient characteristics					
		Year of public.	Phase of study	Therapy *1	No. ITT *2	No. LFU *2	D1	D2	D3	D4	D5	D6	D7	D8	D9	D1–9	Median age	Male	Female	Prior treatment		
																				Nephr	IT	ChT
SC																						
Allen	[3]	2000	2	5	55	13	1	1	1	–	1	–	1	1	1	7	52	44	11	49	6	NA
Atzpodien	[6]	1990	2	2	17	3	1	1	1	–	1	1	–	–	1	6	55	NA	NA	NA	NA	NA
Atzpodien	[7]	1991	2	2	32	0	1	1	1		1	1	1		1	7	52	19	13	32	5	10
Atzpodien	[8]	1993	2	5	35	0	1	1	0		1	1	1	–	5	61	25	10	34	2	4	
Atzpodien	[9]	1995	2	5	24	0	1	1	0		1	1	1	1	1	7	53	17	7	24	7	3
Atzpodien	[10]	1995	2	2	152	NA	1	1	1		1	1		1	1	7	58	92	60	148	11	6
Atzpodien	[11]	2001	3	5	41	NA	1	1	1	1	1	1	1	1		8	54	NA	NA	41	7	2
Atzpodien	[12]	2002	2	12	443	NA	1	1	1	1	0	1	1		1	7	58	323	120	430	61	38
Buzio	[17]	1997	2	2	21	1	1	1	1	–	1	1	–	1		6	64	16	5	21	NA	NA
Buzio	[18]	2001	2	2	50	9	1	1	1	1	1	–	–	1	–	6	NA	36	14	50	NA	NA
Clark	[20]	1999	2	2	19	0	1	1	1	1	1		1	1	1	8	64	14	5	9	0	0
Dutcher	[24]	2000	2	5	50	0	1	1	1	–	1	1	1	1	1	8	54	41	9	37	NA	NA
Facendola	[30]	1995	2	2	50	6	1	1	1	1	1		1	1		7	57	37	13	36	9	0
Gez	[38]	2002	2	5	67	5	1	1	1	–	1		1	1		6	63	NA	NA	54	0	0
Henriksson	[40]	1998	3	5	65	NA	1	1	0	1	–	–	1	1	1	6	61	43	22	54	NA	NA
Hofmockel	[41]	1996	2	5	34	0	1	1	1	1	1	1		–	–	6	NA	25	9	28	4	NA
Jayson	[43]	1998	3	1	30	1	1	1	1	–	1	1	–	1	1	7	53	19	11	30	0	0
Jayson	[43]	1998	3	2	30	2	1	1	1	–	1	1	–	1	1	7	56	18	12	30	0	0
Lissoni	[50]	1998	2	1	20	1	1	1	1	–	1	–	1	–	1	6	61	14	6	NA	NA	NA
Lissoni	[51]	2000	3	1	16	0	1	1	1	1	1		1	1	1	8	54	11	5	NA	NA	NA
Lissoni	[51]	2000	3	1	14	0	1	1	1	1	1	–	1	1	1	8	56	10	4	NA	NA	NA
Lopez	[52]	1996	2	1	16	NA	1	1	1	1	1	1	1	–	1	8	54	13	3	16	4	2
Lopez	[52]	1996	2	2	79	NA	1	1	1	1	1	1	1		1	8	57	53	26	75	16	7
Lopez	[52]	1996	2	5	120	NA	1	1	1	1	1	1	1	–	1	8	60	86	34	116	19	16
Lummen	[53]	1996	2	2	30	NA	1	1	1	1	1	1	1	1		8	58	22	8	23	0	0
Négrier	[58]	2000	3	2	70	3	1	1	0	1	1	1	1	1	1	8	58.9	54	16	55	0	NA
Négrier	[58]	2000	3	5	61	5	1	1	0	1	1	1	1	1	1	8	61.6	39	22	53	0	NA
Neri	[59]	2002	2	5	16	1	1	1	1	–	1	–	–	1	1	6	NA	12	4	16	NA	NA
Piga	[62]	1997	2	2	20	0	1	1	1	1	–	–	1	1	1	7	60	17	3	11	0	0
Ravaud	[63]	1994	2	2	38	NA	1	1	1	1	1		1	0	1	7	58	28	10	30	4	3
Ravaud	[64]	1998	2	5	110	5	1	1	1	1	1	1	1	1	1	9	60	NA	NA	97	NA	5
Reese	[65]	2000	2	3	15	NA	1	1	1	–	–	–	1	1	–	5	59	10	5	12	0	0
Rogers	[66]	2000	2	2	33	0	1	1	1	1	1	1	1	–	1	8	58	25	8	27	NA	1
Ryan	[70]	2000	2	2	20	0	1	1	1	–	–	–	1	1	–	5	61.5	14	6	12	0	0
Ryan	[70]	2000	2	5	21	1	1	1	1	–	–	–	1	1	–	5	62	12	9	7	0	0
Ryan	[71]	2002	2	5	41	4	1	1	1	–	1	–	1	1	–	6	58	29	12	29	6	1
Samland	[72]	1999	2	5	47	0	1	1	1	1	1	1	1	–	–	7	NA	38	9	46	2	3
Schmidinger	[73]	2000	2	2	70	7	1	1	0	1	1	1	1	0		6	62	NA	NA	57	0	0
Sleijfer	[76]	1992	2	1	27	1	0	1	1	–	1	1	1	–	–	5	NA	15	12	23	0	1

(*continued on next page*)

Table 1a (*continued*)

Author	Ref.[a]	Study characteristics					Quality criteria for data presentation *3									Quality score	Patient characteristics					
		Year of public.	Phase of study	Therapy *1	No. ITT *2	No. LFU *2	D1	D2	D3	D4	D5	D6	D7	D8	D9	D1–9	Median age	Male	Female	Prior treatment		
																				Nephr	IT	ChT
Stadler	[77]	1998	2	5	48	1	1	1	1	–	1	–	1	1	1	7	53	NA	NA	32	0	2
Stein	[79]	1991	2	1	9	NA	1	1	1	–	–	–	–	–	–	3	NA	NA	NA	NA	NA	NA
Tagliaferri	[82]	1998	2	1	12	NA	1	1	1	–	1	–	1	1	–	6	NA	NA	NA	NA	3	1
Thiounn	[83]	1995	2	2	15	NA	1	1	1	1	1	–	–	0	1	6	v	10	5	15	6	NA
Tourani	[87]	1996	2	1	39	0	1	1	1	1	1	1	1	–	–	7	58	30	9	39	10	6
Tourani	[88]	1998	2	5	62	7	1	1	1	1	1	–	1	1	–	7	57	49	13	55	0	1
van Herpen	[89]	2000	2	5	52	5	1	1	1	–	0	1	1	1	1	7	57	39	13	52	0	0
Vogelzang	[90]	1993	2	2	42	NA	1	1	1	–	1	–	1	1	1	7	55	31	11	29	0	1
Vuoristo	[91]	1994	2	2	16	3	1	1	1	–	1	–	1	–	–	5	58	9	7	NA	4	11
BIV																	NA	NA	NA	NA	NA	NA
Abrams	[1]	1990	2	1	16	NA	1	1	1	–	–	1	1	1	1	7	48	10	6	14	0	1
Atkins	[5]	1993	2	1	71	NA	1	1	1	–	–	1	1	1	1	7	54	52	19	61	1	2
Atkins	[5]	1993	2	2	28	NA	1	1	1	–	–	1	1	1	1	7	51.5	20	8	26	1	2
Bergmann	[13]	1993	2	2	36	6	1	1	1	–	1	1	–	1	–	6	60	NA	NA	NA	3	NA
Bukowski	[16]	1990	2	1	41	8	1	1	1	–	1	–	1	1	1	7	56	29	12	23	0	4
Creagan	[21]	1998	2	3	22	3	1	1	1	1	1	–	–	–	1	6	59	15	7	NA	4	NA
Du Bois	[23]	1997	3	1	7	1	1	1	1	–	1	–	1	1	1	7	NA	NA	NA	NA	NA	NA
Du Bois	[23]	1997	3	2	2	0	1	1	1	–	1	–	1	1	1	7	NA	NA	NA	NA	NA	NA
Fisher	[34]	1988	2	2	35	3	1	1	1	–	1	–	1	1	1	7	50	25	10	26	9	8
Fujioka	[36]	1994	2	2	10	NA	1	1	1	–	–	–	1	0		4	61.5	10	0	9	7	NA
Krigel	[45]	1990	2	2	24	2	1	1	1	–	1	–	1	1	1	7	61	20	4	14	1	3
Kuebler	[46]	1993	2	1	19	2	1	1	1	–	1	–	–	–	–	4	61	16	3	11	NA	NA
Kuebler	[46]	1993	2	3	15	6	1	1	1	–	1	–	–	–	–	4	59	10	5	7	NA	NA
Lindemann	[49]	1989	2	3	14	NA	1	1	0	–	–	–	–	1	–	3	NA	NA	NA	NA	NA	NA
Marincola	[54]	1995	2	2	11	NA	1	1	1	1	1	–	–	1	–	6	NA	NA	NA	NA	0	NA
Marincola	[54]	1995	2	2	28	NA	1	1	1	1	1	–	–	1	–	6	NA	NA	NA	NA	0	NA
Rosenberg	[67]	1993	3	1	48	7	1	1	1	1	1	–	1	1	–	7	NA	NA	NA	NA	NA	NA
Rosenberg	[67]	1993	3	2	49	3	1	1	1	1	1	–	1	1	–	7	NA	NA	NA	NA	NA	NA
Rosenberg	[68]	1994	2	1	149	NA	1	1	1	1	0	1	–	1	–	6	NA	101	48	140	27	16
Rosenberg	[69]	1998	2	1	227	NA	1	1	1	1	0	1	–	1	1	7	NA	156	71	215	35	22
Schoof	[74]	1993	2	2	12	NA	1	1	1	–	–	–	–	–	–	3	NA	NA	NA	NA	NA	12
Stahel	[78]	1989	2	2	14	NA	1	1	1	–	–	–	1	–	–	4	48	9	5	12	0	0
Thompson	[85]	1989	2	2	3	NA	1	1	1	–	–	–	1	–	1	5	NA	NA	NA	NA	NA	NA
Weiss	[93]	1992	3	2	46	4	1	1	1	–	1	1	1	1	1	8	51	38	8	45	4	2
Yang	[94]	1994	3	1	60	NA	1	1	1	1	1	–	1	–	–	6	NA	42	18	58	NA	NA
Yang	[94]	1994	3	1	65	2	1	1	1	1	1	–	1	–	–	6	NA	45	20	63	NA	NA
Yang	[95]	1995	3	1	27	NA	1	1	1	1	–	–	–	–	–	4	NA	NA	NA	NA	NA	NA
Yang	[95]	1995	3	1	29	NA	1	1	1	1	–	–	–	–	–	4	NA	NA	NA	NA	NA	NA

See enclosed appendix ('Appendix to Table 1a and 2a') for comments and abbreviations.

[a] See further reading section for references

in 48 cohorts (2394 patients) and BIV in 28 (1108 patients) (Table 1a).

All studies with a randomisation protocol were considered phase III, including two studies termed 'randomised phase II' by the authors. Not considering route there was an average of 22% phase III designs. Yet, when weighted by the number of patients intended to treat, a significantly higher proportion of the patients in the studies on CIV and BIV were treated within a phase III study as compared to the studies on SC IL-2 (36% and 30% versus 14%, respectively) (Table 1b).

The mean sum score for the quality of data presentation appeared slightly, yet significantly, higher for the subcutaneous studies as compared to the intravenous studies (Table 1b). With the average year of publication being 1998, articles on the SC scheme were published later than the articles on the other two schemes (Table 1b).

Most studies gave the full details of applied entry criteria and patient characteristics (Table 1a). The most consistently stated items were age, sex, performance status and RCC-related prior treatment. Patients with brain and bone metastases and steroid dependency were excluded in most of the studies. The median age of the patients in the SC studies was significantly higher than in the CIV and BIV studies (Table 1b). Another statistically important parameter was the proportion of patients that had received prior immunotherapy, being approximately 15% higher in the studies on SC and bolus IL-2 than in the studies on IL-2 CIV (Table 1b).

The great majority of studies described the intervention schedule in detail. As regards content, intervention schemes varied widely, not only in time schedule but also in IL-2 dose and in co-administration of other immune or chemotherapeutic substances. Furthermore, the term 'analysis by intention to treat' was not used

Table 1b
Study, patient and intervention characteristics according to the route of administration of interleukin 2 (IL-2)

	CIV			SC			BIV			Level of significance (*P*-value)		
	No.	% ($)	($)	No.	% ($)	($)	No.	% ($)	($)	CIV versus SC	CIV versus BIV	SC versus BIV
Study characteristics												
No. of cohorts	36			48			28					
Phase II	29			40			19					
Phase III	7			8			9					
Patients intended to treat	1444			2394			1108					
Phase II	917	64%		2067	86%		775	70%		**0.016**	0.57	0.109
Phase III	527	36%		327	14%		333	30%				
Mean year of publication			1995			1998			1994	**<0.001**	0.46	**<0.001**
Median year of publication			1992			1998			1993			
Sum score of quality criteria for data presentation												
average weighted			6			7			6	**0.001**	0.44	**0.022**
median			5			7			6			
Patient characteristics												
Mean median age			55			58			55	**<0.001**	0.98	**0.008**
Male	513	73%		1439	71%		598	71%		0.46	0.47	0.91
Female	186	27%		581	29%		244	29%				
Intervention characteristics												
Patients lost to follow up	90	6.2%		84	3.5%		47	4.2%		0.07	0.27	0.68
Coadministration:												
IL-2 monotherapy	478	38%		183	9%		759	69%		**0.003**	**0.005**	**<0.001**
IL-2 with other IT	630	50%		804	41%		298	27%				
IL-2 with ChT	0	0%	15	1%	51	5%						
IL-2 with both IT and ChT	150	12%	949	49%	0	0%						
Prior treatment characteristics												
Prior nephrectomy	928	82%		2034	89%		724	88%		0.1	0.22	0.91
Prior immunotherapy	40	4%		186	9%		92	12%		**0.06**	**0.01**	0.31
Prior chemotherapy	60	7%		124	7%		72	11%		0.91	0.31	0.21

$Presented outcome is based on the studies reporting on the parameter and is weighted by the number of patients intended to treat. CIV, continuous intravenous infusion; SC, subcutaneous infusion; BIV, bolus intravenous infusion; IT, immunotherapy other than IL-2; ChT, chemo- and/or hormonal therapy. Numbers in bold are statistically significant (*P*-value $\leqslant 0.05$).

Table 2a
Outcome, according to the route of administration of IL-2

Author	Ref.[a]	Response outcome																	
			Complete response duration *6				Ongoing complete response duration					Partical response duration				Ongoing partial response duration			
		No. of CR	No. *5	⩾12 m	⩾24 m	⩾36 m	No. *5	⩾12 m	⩾24 m	⩾36 m	No of PR	No. *5	⩾12 m	⩾24 m	⩾36 m	No. *5	⩾12 m	⩾24 m	⩾36 m
CIV																			
Albertini	[2]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	0	0	0	0	0	0
Besana	[14]	1	1	1	0	0	1	1	0	0	5	5	3	0	0	1	1	0	
Blay	[15]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	0	NA	NA	NA	NA	NA	NA	NA
Clark	[19]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	2	1	0	0	1	1	0	0
Dillman	[22]	3	0	NA	NA	NA	NA	NA	NA	NA	10	0	NA	NA	NA	NA	NA	NA	NA
Elias	[25]	1	1	0	0	0	1	0	0	0	3	3	2	1	0	1	0	0	0
Elias	[26]	1	0	NA	NA	NA	NA	NA	NA	NA	3	0	NA	NA	NA	NA	NA	NA	NA
Ellerhorst	[27]	4	4	3	1	0	2	2	1	0	12	12	8	1	0	1	1	1	0
Engelhardt	[28]	2	2	1	0	0	2	1	0	0	3	3	1	0	0	0	0	0	0
Escudier	[29]	0	NA	NA	NA	NA	NA	NA	NA	NA	7	7	7	0	0	5	5	0	0
Figlin	[31]	0	NA	NA	NA	NA	NA	NA	NA	NA	9	9	5	0	0	5	3	0	0
Figlin	[32]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Figlin	[32]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Fossa	[35]	0	NA	NA	NA	NA	NA	NA	NA	NA	3	3	0	0	0	0	0	0	0
Geertsen	[37]	2	2	1	0	0	1	1	0	0	4	4	0	0	0	0	0	0	0
Gore	[39]	4	4	2	0	0	3	2	0	0	11	5	1	0	0	4	1	0	0
Ilson	[42]	1	1	0	0	0	1	0	0	0	3	3	1	0	0	1	1	0	0
Kradin	[44]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	0	NA	NA	NA	NA	NA	NA	NA
Kuebler	[46]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	2	0	0	0	0	0	0	0
Law	[47]	1	1	1	1	1	1	1	1	1	2	2	0	0	0	0	0	0	0
Law	[47]	1	1	1	1	1	1	1	1	1	0	NA	NA	NA	NA	NA	NA	NA	NA
Mittelman	[55]	2	2	2	1	0	1	1	1	0	2	0	NA	NA	NA	NA	NA	NA	NA
Négrier	[56]	1	1	1	0	0	1	1	0	0	1	1	0	0	0	0	0	0′	0
Négrier	[57]	2	0	NA	NA	NA	NA	NA	NA	NA	7	0	NA	NA	NA	NA	NA	NA	NA
Négrier	[57]	5	0	NA	NA	NA	NA	NA	NA	NA	25	0	NA	NA	NA	NA	NA	NA	NA
Paciucci	[60]	0	NA	NA	NA	NA	NA	NA	NA	NA	3	0	NA	NA	NA	NA	NA	NA	NA
Pichert	[61]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Shulman	[75]	0	0	0	0	0	NA	NA	NA	NA	1	0	NA	NA	NA	NA	NA	NA	NA
Stoter	[80]	1	1	0	0	0	0	0	0	0	2	2	0	0	0	1	0	0	0
Sznol	[81]	0	NA	NA	NA	NA	NA	NA	NA	NA	8	8	2	1	0	2	2	1	0
Thomas	[84]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	1	0	0	0	0	0	0	0
Thompson	[85]	1	1	0	0	0	1	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA
Thompson	[86]	2	2	2	1	1	2	2	1	1	3	3	2	1	0	1	0	0	0
Thompson	[86]	2	2	0	0	0	2	0	0	0	7	7	2	0	0	3	2	0	0
Wang	[92]	2	2	2	0	0	1	1	0	0	5	5	0	0	0	2	0	0	0
Weiss	[93]	2	2	1	0	0	2	1	0	0	5	5	2	0	0	2	2	0	0

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Table 2a (*continued*)

Author	Ref.[a]	Response outcome																
			Complete response duration [*6]				Ongoing complete response duration					Partical response duration				Ongoing partial response duration			
		No. of CR	No. [*5]	⩾12 m	⩾24 m	⩾36 m	No. [*5]	⩾12 m	⩾24 m	⩾36 m	No of PR	No. [*5]	⩾12 m	⩾24 m	⩾36 m	No. [*5]	⩾12 m	⩾24 m	⩾36 m
SC																			
Allen	[3]	3	0	NA	NA	NA	NA	NA	NA	NA	14	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[6]	2	0	NA	NA	NA	NA	NA	NA	NA	3	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[7]	4	0	NA	NA	NA	NA	NA	NA	NA	6	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[8]	4	0	NA	NA	NA	NA	NA	NA	NA	13	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[9]	4	0	NA	NA	NA	NA	NA	NA	NA	6	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[10]	9	0	NA	NA	NA	NA	NA	NA	NA	29	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[11]	7	0	NA	NA	NA	NA	NA	NA	NA	9	0	NA	NA	NA	NA	NA	NA	NA
Atzpodien	[12]	37	0	NA	NA	NA	NA	NA	NA	NA	89	0	NA	NA	NA	NA	NA	NA	NA
Buzio	[17]	1	1	1	1	1	1	1	1	1	3	3	2	1	1	2	1	1	1
Buzio	[18]	2	2	1	1	1	2	1	1	1	4	4	1	1	1	2	0	0	0
Clark	[20]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Dutcher	[24]	2	2	1	1	1	1	1	1	1	7	0	NA	NA	NA	NA	NA	NA	NA
Facendola	[30]	6	6	5	0	0	3	3	0	0	3	3	1	0	0	0	0	0	0
Gez	[38]	4	4	4	4	2	4	4	4	2	14	0	NA	NA	NA	NA	NA	NA	NA
Henriksson	[40]	5	0	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Hofmockel	[41]	3	0	NA	NA	NA	NA	NA	NA	NA	10	0	NA	NA	NA	NA	NA	NA	NA
Jayson	[43]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	0	NA	NA	NA	NA	NA	NA	NA
Jayson	[43]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Lissoni	[50]	0	NA	NA	NA	NA	NA	NA	NA	NA	4	0	NA	NA	NA	NA	NA	NA	NA
Lissoni	[51]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	1	0	0	0	0	0	0	0
Lissoni	[51]	0	NA	NA	NA	NA	NA	NA	NA	NA	4	0	NA	NA	NA	NA	NA	NA	NA
Lopez	[52]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA	NA	NA	NA	NA	NA
Lopez	[52]	6	0	NA	NA	NA	NA	NA	NA	NA	16	0	NA	NA	NA	NA	NA	NA	NA
Lopez	[52]	13	0	NA	NA	NA	NA	NA	NA	NA	34	0	NA	NA	NA	NA	NA	NA	NA
Lummen	[53]	3	3	1	1	1	0	0	0	0	4	4	0	0	0	0	0	0	0
Négrier	[58]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	0	NA	NA	NA	NA	NA	NA	NA
Négrier	[58]	0	NA	NA	NA	NA	NA	NA	NA	NA	5	0	NA	NA	NA	NA	NA	NA	NA
Neri	[59]	1	1	1	1	0	1	1	1	0	3	0	NA	NA	NA	NA	NA	NA	NA
Piga	[62]	1	1	1	1	1	1	1	1	1	2	2	0	0	0	0	0	0	0
Ravaud	[63]	1	1	1	0	0	0	0	0	0	6	6	2	1	0	1	1	1	0
Ravaud	[64]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	0	NA	NA	NA	NA	NA	NA	NA
Reese	[65]	0	NA	NA	NA	NA	NA	NA	NA	NA	3	3	2	0	0	0	0	0	0
Rogers	[66]	0	NA	NA	NA	NA	NA	NA	NA	NA	3	3	3	2	1	0	0	0	0
Ryan	[70]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Ryan	[70]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	1	1	0	0	0	0	0	0
Ryan	[71]	1	0	NA	NA	NA	NA	NA	NA	NA	5	0	NA	NA	NA	NA	NA	NA	NA
Samland	[72]	7	7	2	1	0	3	1	1	0	2	2	1	0	0	0	0	0	0
Schmidinger	[73]	2	0	NA	NA	NA	NA	NA	NA	NA	5	0	NA	NA	NA	NA	NA	NA	NA
Sleijfer	[76]	2	2	2	0	0	2	2	0	0	4	4	0	0	0	1	0	0	0

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Table 2a (*continued*)

Author	Ref.[a]	Response outcome																
			Complete response duration *6				Ongoing complete response duration					Partical response duration				Ongoing partial response duration			
		No. of CR	No. *5	⩾12 m	⩾24 m	⩾36 m	No. *5	⩾12 m	⩾24 m	⩾36 m	No of PR	No. *5	⩾12 m	⩾24 m	⩾36 m	No. *5	⩾12 m	⩾24 m	⩾36 m
Stadler	[77]	1	1	1	0	0	0	0	0	0	7	7	7	6	5	4	4	4	4
Stein	[79]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	2	0	0	0	0	0	0	0
Tagliaferri	[82]	1	1	1	1	1	1	1	1	1	3	3	3	0	0	0	0	0	0
Thiounn	[83]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Tourani	[87]	1	0	NA	NA	NA	NA	NA	NA	NA	6	0	NA	NA	NA	NA	NA	NA	NA
Tourani	[88]	1	1	1	0	0	0	0	0	0	11	11	7	0	0	5	4	0	0
van Herpen	[89]	0	NA	NA	NA	NA	NA	NA	NA	NA	6	0	NA	NA	NA	NA	NA	NA	NA
Vogelzang	[90]	1	1	1	1	0	1	1	1	0	4	4	2	0	0	4	2	0	0
Vuoristo	[91]	1	1	0	0	0	1	0	0	0	1	0	NA	NA	NA	NA	NA	NA	NA
BIV																			
Abrams	[1]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Atkins	[5]	4	4	3	1	0	3	3	1	0	8	8	7	2	0	7	7	2	0
Atkins	[5]	0	NA	NA	NA	NA	NA	NA	NA	NA	3	3	1	0	0	0	0	0	0
Bergmann	[13]	2	2	2	0	0	1	1	0	0	7	7	2	0	0	0	0	0	0
Bukowski	[16]	1	1	1	0	0	1	1	0	0	4	4	0	0	0	0	0	0	0
Creagan	[21]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	1	0	0	0	0	0	0	0
Du Bois	[23]	0	NA	NA	NA	NA	NA	NA	NA	NA	2	2	0	0	0	0	0	0	0
Du Bois	[23]	1	1	1	0	0	1	1	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA
Fisher	[34]	2	2	1	0	0	2	1	0	0	3	3	2	0	0	2	2	0	0
Fujioka	[36]	1	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0
Krigel	[45]	1	1	0	0	0	0	0	0	0	5	5	2	0	0	2	2	0	0
Kuebler	[46]	0	NA	NA	NA	NA	NA	NA	NA	NA	1	1	0	0	0	0	0	0	0
Kuebler	[46]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Lindemann	[49]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Marincola	[54]	3	3	3	3	2	3	3	3	3	1	1	0	0	0	0	0	0	0
Marincola	[54]	4	4	4	3	3	3	3	3	3	3	3	2	2	2	1	1	1	1
Rosenberg	[67]	4	4	4	3	3	3	3	3	3	6	6	5	4	1	1	1	1	1
Rosenberg	[67]	7	7	6	4	2	1	1	1	1	8	8	2	0	0	0	0	0	0
Rosenberg	[68]	10	10	9	7	5	7	6	6	5	20	20	9	5	2	7	3	1	1
Rosenberg	[69]	21	21	21	18	17	17	17	17	17	22	22	11	3	1	0	0	0	0
Schoof	[74]	0	NA	NA	NA	NA	NA	NA	NA	NA	5	5	0	0	0	3	0	0	0
Stahel	[78]	0	NA	NA	NA	NA	NA	NA	NA	NA	3	3	0	0	0	0	0	0	0
Thompson	[85]	0	NA	NA	NA	NA	NA	NA	NA	NA	0	NA	NA	NA	NA	NA	NA	NA	NA
Weiss	[93]	3	3	3	0	0	3	3	0	0	6	6	3	0	0	3	2	0	0
Yang	[94]	4	4	2	0	0	3	2	0	0	5	5	1	0	0	4	1	0	0
Yang	[94]	2	2	1	0	0	2	1	0	0	11	11	2	0	0	6	1	0	0
Yang	[95]	2	2	2	2	2	2	2	2	2	3	3	1	1	0	0	0	0	0
Yang	[95]	2	2	2	2	2	2	2	2	2	3	3	1	1	1	1	1	1	1

See enclosed Appendix ('Appendix to Table 1a and 2a') for comments and abbreviations.

[a] See further reading section for references

consistently. In our analysis all patients that received even a single dose of IL-2 were considered assessable for response. In view of the diversity in schedules, simplifications had to be made in order to gain some insight into the distribution of the applied interventions. Although it was considered unfeasible to take into account every single co-administered substance, analysis of co-administration could be performed. Therefore, intervention schemes were divided into: (1) IL-2 monotherapy; (2) IL-2 with other immunotherapy; (3) IL-2 with chemotherapy; (4) IL-2 with both other immunotherapy and chemotherapy. Altogether, mode of co-administration tended to vary with route of administration, the difference between IL-2 monotherapy versus triple therapy being highly significant (Table 1b).

3.3. Response rates and duration of response

All studies assessed the presence of response by means of the WHO criteria or extended derivations of these. In addition, almost all studies gave some indication concerning the duration of response, albeit not every study applied the WHO recommendations on this matter (Table 2a). Some investigators recorded both complete and partial duration from the first day of treatment; others measured from the initial date of observed response. The termination time of a response was consistently defined as the date progressive disease was first observed. If remissions persisted at study closure, they were termed 'ongoing'. Duration of remission per responding patient was presented for 139 of 251 complete responders and for 287 of 643 partial responders (Table 2a).

3.3.1. Complete response

In total, 251 of all 4946 included patients (5.1%) were stated to be in CR after receiving any schedule of IL-2-based therapy and regardless of route. When adjusted for the route of administration, the proportion of CR was approximately 3% and 4% higher for the SC and BIV schedules, respectively, as compared to the CIV schedule (Fig. 1). Although the SC yielded 1% fewer CR, this difference proved not to be significant (Table 2b). Response duration per responding patient

Table 2b
Response rates and duration of response according to route of administration of interleukin 2 (IL-2)

	Continuous intravenous infusion		Subcutaneous infusion		Bolus intravenous infusion		Level of significance (*P*-value)		
	No.	% (CI)	No.	% (CI)	No.	% (CI)	CIV versus SC	CIV versus BIV	SC versus BIV
No. of study arms	36		48		28				
No. of patients intended to treat	1444		2394		1108				
Complete remissions	41	2.8% (1.4–4.2%)	136	5.7% (4.5–6.9%)	74	6.7% (5.1–8.3%)	**0.002**	**0.001**	0.32
Response duration given per patient	30		35		74				
⩾12 months	18	60%	24	69%	65	88%	0.47	**0.01**	0.06
⩾12 months and being ongoing	15	50%	17	49%	50	68%	0.91	0.13	0.09
⩾24 months	5	17%	13	37%	43	58%	0.18	**0.003**	0.1
⩾24 months and being ongoing	5	17%	12	34%	38	51%	0.26	**0.012**	0.18
⩾36 months	3	10%	8	23%	36	49%	0.36	**0.002**	**0.03**
⩾36 months and being ongoing	3	10%	7	20%	36	49%	0.49	**0.003**	**0.02**
Partial remissions	154	11% (8–14%)	358	15% (13–17%)	131	12% (9–15%)	**0.02**	0.59	0.11
Response duration given per patient	93		63		131				
⩾12 months	38	41%	32	51%	51	39%	0.28	0.94	0.23
⩾12 months and being ongoing	20	22%	12	19%	21	16%	0.76	0.41	0.69
⩾24 months	4	4%	11	17%	18	14%	0.05	0.09	0.57
⩾24 months and being ongoing	2	2%	6	10%	6	5%	0.06	0.43	0.19
⩾36 months	0	0%	8	13%	7	5%	**0.01**	0.18	0.11
⩾36 months and being ongoing	0	0%	5	8%	4	3%	**0.03**	0.31	0.16
Complete and partial remissions	195	14% (10–18%)	494	21% (18–24%)	205	19% (15–23%)	**0.002**	0.07	0.39

NB: No. of responses is based upon every included study. No. of response durations is based only on studies reporting it. Proportion of remission: no. of responders weighted by the number of patients intended to treat. Proportion of response duration: no. of responders reaching a given point weighted by the number of responders. CI, 95%-confidence interval; CIV, continuous intravenous infusion; SC, subcutaneous infusion; BIV, bolus intravenous infusion. Figures in bold are statistically significant (*P*-value $\leqslant 0.05$).

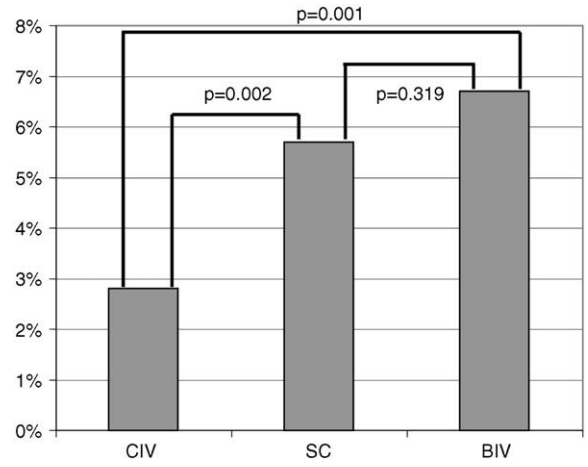

Fig. 1. Complete responses according to route of administration.

was presented for 55% of complete responders. Although the majority of intravenous studies presented duration per patient, investigators of the SC studies were not consistent in doing this (Table 2a). The proportion of CR reaching 1 year ranged between 60% and 88%, the average being 77% (Table 2b). The majority of these responses were still ongoing (Fig. 2). Albeit that responses of 3 years or more were seen in only one-third of cases, all but one were ongoing on study closure. When set off against CIV administration, the SC route only showed benefit for the 3-year response rate, whereas the bolus responses were significantly higher at all three time-points (Table 2b).

3.3.2. Partial response

PR of more than 50% occurred approximately two to four times more often than CR. With 15% against 11%, only the SC-induced responses were significantly more prevalent as compared to CIV-induced responses. Again, the difference between BIV and SC, now in favour for the latter, appeared not to be significant (Fig. 3; Table 2b). With regard to response durations, the willingness to present this parameter per responding patient was highest in BIV studies and rather low in SC studies (Table 2b). It also appeared that PR were much less stable than CR. Moreover, results indicated that not the BIV but rather the SC scheme yielded the most durable responses, although this could not be confirmed statistically. Overall response rates (CR + PR) were higher for SC and BIV IL-2 compared with CIV IL-2 with the comparison of SC with CIV reaching statistical significance (Fig. 4).

3.3.3. Survival

Only 55 of 112 cohorts, reporting on 2725 patients, presented median survival outcome and only 44 cohorts (2465 patients) gave overall 1-year survival. Frequently, survival statistics had to be extracted from survival plots. Moreover, reports of associated confidence interval or the number of patients at risk, required for statistical calculation, were omitted in more than 95% of these studies. Thus, analysis of survival parameters was regarded as not being feasible.

3.4. Stratified analyses

Stratified analysis according to sex and age group yielded response rates comparable to non-stratified analysis in all three routes of administration. Subgroup analysis comparing monotherapy versus co-administration therapy showed no significant differences in CR (data not shown). Attempts for detailed calculations on differences in IL-2 dose and time schedule failed due to small numbers.

Exclusion of patients who had not undergone nephrectomy prior to IL-2 treatment did not change the response rates and the duration of the responses for the three routes of IL-2 administration. Stratification for prior immunotherapy showed that having received no prior immunotherapy rendered comparable the CR outcome between the three regimens (Table 3). Although

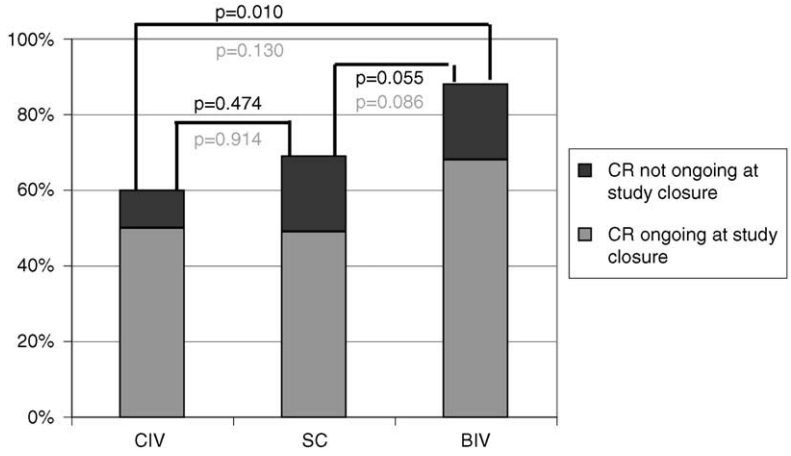

Fig. 2. Complete responses of 12 months or longer (either ongoing or not).

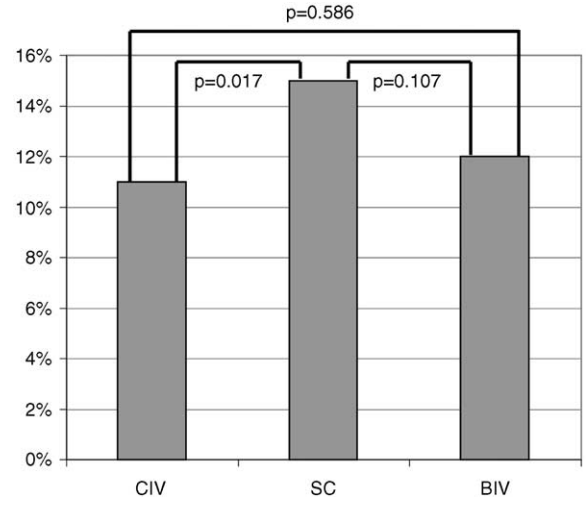

Fig. 3. Partial responses according to route of administration.

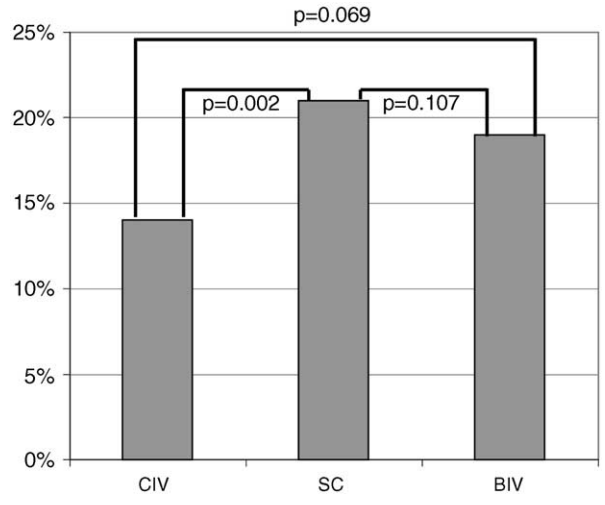

Fig. 4. All responses (complete and partial) according to route of administration.

receiving prior immunotherapy was associated with higher CR outcome in the SC studies as compared to the intravenous studies, these differences appeared not to be significant. Subgroup analysis per route showed that SC outcome significantly improved with prior immunotherapy. It is of note that the type of prior immunotherapy was heterogeneous, although in general it consisted of poorly described IL-2 or interferon-α-based regimens. In general, information concerning the response to previous treatment was lacking.

4. Discussion

With this systematic review we have attempted to gain some insight into which route of IL-2 administration produced the best prospects for MRCC patients. From the immense pool of published articles on this matter, no definite conclusions or preferences have emerged. By including both phase II and phase III trials in this review, statistical power was increased, so that a more carefully balanced appraisal on this issue could be given.

IL-2-induced CR were of special interest, because they were thought to be the best surrogate end point for cure from MRCC. The average proportion of CR based on all cohorts included was 5%. Although not astonishingly high, IL-2 does seem to have some merits in the treatment of otherwise lethal MRCC. Interestingly, BIV and SC schemes yielded twice as many CR compared to continuous infusion. Moreover, 50% of the BIV patients had ongoing responses of 36 months and more, indicating that these patients may have been cured. The other two routes of administration yielded less optimistic long-term outcomes. However, drawbacks in this analysis were the willingness of authors to present response duration per patient and the disappointingly low reporting of follow up. It was clear that, for some reason, the SC studies omitted to present the former parameter, and in theory this route had enough missing duration-outcome data to invert the observed effect. One also wonders what the outcome was of patients with an ongoing stable disease at study closure. Furthermore, different investigators applied differing definitions regarding the onset of response duration, this being either start of therapy or first confirmation of

Table 3
Proportion of patients with complete response according to route of administration and stratified according to prior use of immunotherapy

	Proportion complete responses			Level of significance (*P*)		
	CIV	SC	BIV	CIV versus SC	CIV versus BIV	SC versus BIV
No prior immunotherapy	3.10%	2.19%	7.27%	0.54	0.12	0.05
Prior immunotherapy	3.51%	8.38%	6.79%	0.4	0.16	0.67
Level of significance (*P*) for no prior IT versus prior IT	0.81	**<0.001**	0.85			

NB: the presented outcome is based on the studies reporting the parameter and is weighted in question and is weighted by the number of patients intended to treat. IT, immunotherapy; CIV, continuous intravenous; SC, subcutaneous; BIV. bolus intravenous.

response. Concerning response durations of 36 months or more, this difference may, however, be small.

It has to be noted that a great deal of possible factors, known and unknown, may have confounded the outcome of this analysis. Although on average the included studies extensively described intervention schedules and the patient characteristics, serious limitations were met in the final evaluation of them. First of all, the intervention schedules that the investigators applied were highly heterogeneous, which seriously hindered the systematic analysis of dose and time schedule. However, with a rough subdivision we were able to evaluate the interaction of co-administration with route. Indeed, with the intravenous studies taking the monotherapy line and SC studies preferring co-administration, mode of co-intervention differed significantly between the three routes. One explanation of this phenomenon might be the higher toxicities that occurred with (bolus) intravenous administration, making SC schemes more suitable for the addition of other agents. In the light of the above-mentioned facts, the impact of co-administration on response outcome was of special interest. Indeed, investigators of SC studies applied double or triple therapy more often.

The classification we made was, however, a simplified one. Differences in specific substances within a class could not be taken into account, because applied doses and schedules were too diverse to permit extensive analysis, let alone subgroup analysis. Because heterogeneity in intervention schedules resulted in analytic limitations, the possible confounding factors could not be traced. Thus, it remained unclear how serious a source of bias this heterogeneity might have produced. When designing this systematic review, it was realised that these limitations would to be encountered. However, it was also realised that in practice, co-administration and dose and time schedule were highly related to route. In deciding which schedule is to be preferred, investigators usually base the intervention strategy on phase I studies, favouring the regimen with the best balance between therapeutic effects and toxicity [6]. Schedule can thus be considered a marker for route, rather than a confounding factor. By investigating through which route IL-2 yields the best responses, one actually elucidates that balance between efficacy and toxicity, in addition to the benefits of a route. In addition, literature reviewers in the past could not find any substantial evidence about which scheme was to be preferred and the few two-arm studies investigating the response benefits of high over low dose were not convincingly in favour for any of either [10].

Within the scope of the above-mentioned discussion, other confounding factors gained importance. For example, it is acknowledged that administration by the SC route yields a more tolerable and safer toxicity profile. Not only does this allow home therapy, but it also allows the administration of IL-2 to a wider variety of patients, including the elderly, patients with lower performance status and those with concomitant systemic disease. In addition, other investigators have already demonstrated that performance status and also site of metastases are important factors in predicting response outcome [11]. Unfortunately, in our review any analysis of this potential of bias was not feasible, because included studies presented these characteristics both too heterogeneously and too infrequently. Notably in the larger, randomised studies included, the presented patient characteristics concerned the entered patients rather than the really eligible patients intended to treat. Hence, this information on population was useless for descriptive analysis of the three administration groups and statistical power for the final calculation of its impact was reduced.

We were, however, able to prove that median ages in the SC studies were significantly higher. On the assumption that performance status and median age were related, an analysis of response versus median age was performed, but no effect was seen. It has to be noted that subgroup analysis was seriously limited, due to problems with statistical power. Moreover, to perform linear regression of median age, these parameters had to be averaged. Although weighted by number of patients, calculating with such an average is of little value if confidence intervals are unknown. Concerning other patient characteristics, no significant differences between the three routes were seen, with the exception of prior immunotherapy. Subgroup analysis showed that prior immunotherapy was related to route in the same way as CR outcome. Thus, the so-called advantages of BIV and SC regimens could be explained. Indeed, SC studies explicitly allowing immune-based pretreatment had the highest CR proportions. One has, however, to realise that the term 'prior immunotherapy' included a large spectrum of immune modalities plus, by our definition, co-administered chemotherapeutics. Thus the validity of analysis is limited. In addition, the studies that were unclear about inclusion or exclusion of pretreatment might alter the level of the observed effects.

From the available data one may carefully conclude that BIV administration is the preferred route for IL-2 in MRCC, both in terms of the number and duration of complete remissions. The SC route yields as many CR as does the bolus and more than CIV infusion. It remains, however, unclear as to how stable and durable these SC remissions are. We can tentatively conclude that the most durable complete remissions have been observed with bolus IL-2 protocols.

It speaks for itself that all the confounding factors in this review make a reliable assessment of the optimum route of IL-2 administration problematic. The only way to bypass all the afore-mentioned problems and resolve

the issue of which IL-2 regimen yields the best outcome is by means of large randomised phase-III study trials. Following completion of this analysis and the first submission of this paper a randomised clinical trial addressing this issue was published [12]. Jang and colleagues demonstrated that high-dose BIV IL-2 produced higher response rates (21%) than low-dose BIV IL-2 (13%; P = 0.048). The response rate to SC IL-2 (10%) was also significantly lower than that of high-dose BIV IL-2 ($P = 0.033$). Furthermore, they reported that the durability of complete remissions was around 90% and 50% at 10 years for high- versus low-dose IL-2 ($P = 0.04$). The fact that this randomised clinical trial has produced similar conclusions to our systematic review is strong evidence that high-dose BIV IL-2 is superior to other doses and routes of administration of IL-2 and should therefore be the preferred treatment regimen for patients with MRCC.

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Appendix to Tables 1a and 2a

NA outcome concerning that parameter was not available

*1 classification of substances administered:

	1	IL-2 monotherapy. Note: In reference 34 (SC) 14 patients got melatonin. Note: In reference #142 (BIV) 29 patients got PEG-IL-2 in addition to IL-2.
x	2	IL-2 combined with another immunotherapeutic substance (mostly interferon-alpha)
x	3	IL-2 combined with a chemotherapeutic or hormonal substance
x	5	IL-2 combined with both immuno- and chemotherapeutic/hormonal substances
x	12	study protocol included several arms each in which at least IL-2 and interferon-alpha were administered

*2 **No. ITT:** number of patients on a intention to treat basis (every patient that received a dose of IL-2 based therapy was included)

No. LFU: number of patients ITT lost to follow-up due to variable reasons

*3 **Definition criteria:** D1 Description of the eligibility criteria;
D2 Description of the interventions with respect to type, duration, number and intensity;
D3 Description of and report on the most important effect measures, i.e. responses;
D4 Report on duration of follow-up;
D5 Report and description of withdrawal;
D6 Report on the progressiveness of the advanced cancer;
D7 Report if the diagnosis of included renal cell cancer patients is histologically or biopsy proven;
D8 Report if patients with brain metastases were excluded;
D9 Report if concomitantly use of steroids was not allowed.

Scoring: -: criterion was not met or not presented; **0:** criterion was not fully met; **1:** criterion was fully met.

*4 **Nephr.:** number of patients that received surgical nephrectomy prior to administration of the schedule
IT: number of patients that received immunotherapy or immuno-chemo-therapy for their renal cell cancer prior to inclusion
ChT: number of patients that received chemotherapy or hormonal therapy for their renal cell cancer prior to inclusion

*5 The number of patients for which the parameter was presented per patient

*6 >12 m: number of patients in which the response duration reached 12 months, either being progressive or ongoing.
>12+ m: number of patients in whom an ongoing response duration reached 12 months. Study closure limited follow-up.

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Further reading

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