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ORIGINAL ARTICLE

A phase-II study of combination of pegylated interferon alfa-2a and capecitabine in locally advanced or metastatic renal cell cancer

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Abstract
Purpose Combination of capecitabine and interferon has shown activity in metastatic renal cell carcinoma. Pegylated interferons might have more clinical activity and fewer side effects. This study evaluated the efficacy, tolerability, and safety of the combination of capecitabine and pegylated interferon alfa-2a.
Methods In this open label, single institution, non-randomized phase-II first-line study, 26 patients were included. Capecitabine was administered 2,000 mg/m^2 daily for 14 days followed by 1 week rest. Pegylated interferon alfa-2a was given once as weekly injections with a fixed dose of 180 μg. Overall survival, progression-free survival, and response rates were evaluated; safety and tolerability were monitored.
Results Response rate was 27, with 4% complete responses. Stable disease was achieved in 42%. The treatment discontinued in 4 (15%) patients before first response evaluation because of toxicity. The median progression-free survival was 7.5 months; the median overall survival was 17 months. Grades 3–4 toxicity was seen in 46% of patients, but in 93% of cycles no serious toxicity was experienced. Dose reductions had to be done, but in 81% of cycles intensity of 70% or more was possible. Quality of life was better in cycle five than in the base line.
Conclusions The combination had moderate, but manageable toxicity. In the future studies, lower dose for capecitabine is recommended. The combination was active and the response rates seen here were in line with phase-II studies on former combinations of non-pegylated interferons. One complete remission was achieved.

Keywords Renal cell carcinoma · Immunotherapy · Interferon · Pegylated · Chemotherapy · Capecitabine

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Background

Until very recently, renal cell cancer (RCC) has had very few available oncological treatments with at least moderate efficacy. Interferon (IFN) has been reported to have antitumor activity against RCC already in 1983 producing partial responses (PRs) to 26% of patients in the early studies [1]. The mechanisms of action of IFN are various and still partly unclear. IFN modulates cancer cell growth and differentiation by regulation of cell cycle, affects cellular communication and intracellular signaling making cells to undergo apoptosis, but also induces non-apoptotic cell death. The effects of IFN are translated in the direct tumor cell growth inhibition or death and in the stimulation of an antitumor immune response. It also upregulates expression of MCH class I antigens which favors tumor cell recognition by specific cytolytic T cells as well as the activation of natural killer cells. IFN has postgenomic effects based on the regulation of protein synthesis and on the selective translation of proteins participating in growth arrest and apoptosis. IFN also produces a link between innate and adaptive immune responses and interferes with tumor-mediated angiogenesis [2]. However, IFN has moderate toxicity and the dosing is three to five times a week given as

subcutaneous injections. Therefore, new formulations have been developed and two pegylated interferons are now commercially available. These are chemically modified by covalent linkage of polyethylene glycol (PEG) polymer to enhance pharmacokinetic characteristics and reduce immunogenicity [3, 4].

Pegylated interferon-alfa-2a (Pegasys®) belongs to the second generation of pegylated interferons, with a 40 kDa PEG-moiety. After injection, serum concentrations are measurable in 6 h and stay close to peak from day three to eight allowing once-weekly dosing which might improve efficacy compared with non-pegylated interferons. Steady-state is seen from week five of therapy, but serum concentrations increase with chronic dosing to 2.5-fold. Side effects are most commonly fatigue, fever, headache, myalgia, nausea, and decreased appetite and elevated liver values, anemia, thrombocytopenia and leuko-/neutropenia. In phase-I studies PRs were seen in 19%, stable disease (SD) in 48%; 450 μg per week was recommend for further studies as a single-agent therapy [3]. In phase-II studies responses were seen in 13% of patients, complete response (CR) in 2.5%. The toxicity was mostly mild to moderate; grades 3–4 toxicity was seen as neutropenia, fatigue, nausea/vomiting, and elevated hepatic transaminase values [5].

An alternative to pegylated interferon-alfa-2a is pegylated interferon-alfa-2b (PEG-Intron®), which has a single PEG-moiety and a molecular weight of 12 kDa. As a single agent therapy it is well tolerated up to 6.0 μg/kg per week, which achieves an exposure comparable to 180 MIU non-pegylated interferon per week [4, 6]. In a phase-II study with single agent therapy with escalating dose 3.0–6.0 μg/kg per week, the overall response rate was 13.6%, with 4.5% CRs (one patient). Median overall survival (OS) was 13 months; in 9% of patients the response remained over 6 months. In this study, fatigue was the major dose-limiting factor; in 22.7% of patients grades 3–4 fatigue was reported. No grades 3–4 hematologic toxicity or liver enzyme elevations were seen, but 55% of patients required dose reductions [7].

Chemotherapy is considered mostly ineffective in RCC [8], but 5-fluorouracil as a continuous infusion has shown some (less than 10%) PRs [9]. Capecitabine is an oral fluoropyrimidine, a prodrug which is converted to 5-fluorouracil via enzyme pathway. Kidney cancer cells contain a considerable amount of thymidine phosphorylase (TP), a key enzyme converting capecitabine to active 5-FU [10]. As a single-agent capecitabine gives minor responses even in third-line therapy, but in most patients no response or only SD is observed [11, 12].

The rationale for combination of capecitabine and interferon is that cytokines, including interferon, increase intratumoral levels of TP especially given prior to fluoropyrimides. This increases the efficacy of capecitabine [13, 14]. The continuous infusion of 5-fluorouracil, similar to the effect of capecitabine, is reported to potentiate the action of interferon-alfa-2b producing a 43% response rate with 19% CRs, with mild toxicity. These responses were durable as the mean duration of response was almost 2 years [15]. However, the response rates in multicenter randomized trials are similar to those for cytokines alone [16].

Combinations of capecitabine and non-pegylated interferon-α has been tested in phase-I and -II studies, which have shown that this combination is most commonly well tolerated and it has some clinical activity and manageable toxicity [17–19]. PRs and SD even as a second- or third-line treatment are seen with capecitabine as a single-agent therapy or in combination with interferon-alfa [20, 21]. In triplet combinations immunomodulatory drug thalidomide is added to the combination [22]. Also combination of capecitabine, interferon-alfa-2a, IL-2, and oral 13-*cis* retinoic acid has been reported [23]. Only reported study on the combination of capecitabine (1,000 mg/m^2 twice daily, days 1–14, cycle 28 days) and pegylated interferon-alfa (50 μg weekly s.c.) is done with PEG-Intron®. In this phase-II study also subcutaneous low-dose interleukin-2 (IL-2) and oral 13-*cis* retinoid acid were in the treatment schedule. This treatment was well tolerated; responses were seen in 53.6% of patients [24]. The combination of capecitabine and pegylated interferon-alfa-2a is not reported in the literature before this study.

Patients and methods

This was an open-label, single institution, non-randomized phase-II study. Primary objective was to characterize efficacy, safety, and tolerability of PEG-IFN-alfa-2a given once weekly s.c. and capecitabine given per orally. For efficacy, progression-free survival (PFS), overall survival (OS), and response rate were assessed; for tolerability, premature withdrawals and dose reductions because of laboratory abnormalities or adverse events and for safety adverse events, laboratory test results, and vital signs were recorded. The study protocol was approved by the Pirkanmaa Hospital District ethical committee.

Eligibility criteria included: age 18–80 years, informed consent, histologically or cytologically verified locally advanced or metastatic RCC with or without prior nephrectomy, evaluable or measurable disease (RECIST), performance status of Zubrod 0-2 and adequate renal (serum creatinine less than 180 mmol/l), and hepatic function (bilirubin, aspartate aminotransferase (ASAT), and glutamyl transferase (GT) less than 1.5 times the upper limit of normal values).

Exclusion criteria included pregnant or lactating women, malignancies other than RCC excluding basal or squamous

cell carcinomas of the skin and carcinoma in situ of the uterine cervix; metastases in central nervous system (brain computed tomography was not required for asymptomatic patients); chronic heart failure (New York Heart Association status III–IV); instable angina pectoris; acute myocardium infarction within the past 12 months before study entry; history of difficult renal, hepatic, neurological, or psychiatric disease; untreated depression; serious infection or wide-field radiotherapy within the previous 4 weeks. Prior treatment with interferon was not allowed.

Pretreatment evaluation included a medical history (including primary TNM classification and grade, sites of metastases, type of surgery, given radiotherapy), clinical examination, electrocardiography, complete blood count, assessment of plasma creatinine, calcium and protein levels and liver function tests: alkaline phosphatase (AFOS), alanine aminotransferase (ALAT), ASAT, GT, bilirubin. Radiographic studies (bone scan, thorax X-ray, and abdominal ultrasound or whole body computed tomography) were assessed within 14 days prior to the initiation of therapy. In first six patients, laboratory studies were performed on a weekly basis during the first three cycles, and at the end of each cycle thereafter. Radiographic studies, as required for assessment of measurable disease, were performed after two cycles, then every three cycles thereafter. Response was assessed according to RECIST criteria [25]. No external verification of response was employed. Toxicity was assessed according to NCI-CTCAE criteria [26] and quality of life according to EORTC QLQ-3 criteria [27], both in base line and after every cycle. Treatment was continued until 52 weeks or clinically significant progression, patient's withdrawal, unacceptable toxicity, or 12 weeks after confirmation of CR.

Between 2003 and 2008, 26 patients with advanced RCC entered trial (demographics in Table 1). The median age of patients was 63.5 years (range 46–81). One patient was older than the inclusion criteria required. However, this patient tolerated the treatment well and achieved complete response. Two patients were not operated before this trial.

PEG-IFN-alfa-2a was administered by subcutaneous injection at a fixed dose of 180 μg once weekly. As the study combination is not reported in the literature, PEG-IFN dosing was chosen to be the smallest with clinical efficacy [3]. No dose modifications were done, but the injection was withheld for grades 3–4 toxicity and for grade 2 toxicity if it was related to interferon. Capecitabine was administered twice daily at a dose of 2,000 mg/m^2 per day on days 1–14 of a 21-day cycle. Treatment was withheld in the event of any toxicity with severity exceeding grade 2. With grade 1 toxicity, no delays or dose modifications were done. With grade 2 toxicity, treatment was withheld until toxicity improved to grade 1 or better, if the event was not treatable with symptomatic medication. If the same event reappeared, treatment was again withheld until toxicity improved to grade 1 or better, then restarted with 25% lower dose of capecitabine. Grade 3 toxicity led to withhold of therapy until it resolved to grade 1 or better, then restarted with 25% lower dose of capecitabine. The reductions were made with 500 mg steps (the tablet size). As a dose reduction, the lower dose of given therapy or shorter administration of capecitabine or omitted injection were recorded. Grade 4 toxicity led to discontinuation of the therapy.

Table 1 Patient demographics

Demographics	*N* (%)
Sex	
Female	10 (38)
Male	16 (62)
Zubrod	
0	10 (38)
1	16 (62)
Palliative radiotherapy	
Given	5 (19)
Not given	21 (81)
Primary nephrectomy	
Radical	12 (46)
Non-radical	12 (46)
Not done	2 (8)
Grade of the primary tumor	
G1	0 (0)
G2	8 (31)
G3	4 (15)
G4	12 (46)
Not specified	2 (8)
T class of the primary tumor	
T1	1 (4)
T2	6 (23)
T3	16 (62)
T4	1 (4)
Not specified	2 (8)
N class of the primary tumor	
0	10 (38)
1	3 (12)
2	2 (8)
Not available	11 (42)
M status of the patients	
Primarily metastatic	13 (50)
Single site of metastases	9 (35)
Multiple sites of metastases	17 (65)
Abdominal metastases	13 (50)
Pulmonary or mediastinal	19 (73)
Lymph nodes, soft tissues	12 (46)
Other	4 (15)

The follow-up was every 2 months until 6 months after the end of the study treatment and then every 3–6 months up to 2 years. The progression date and the cause and date of death were recorded.

The investigators designed and initiated the study, collected, analyzed, and maintained the data. PEF-IFN (Pegasys®) and capecitabine (Xeloda®) were received from Roche Finland and grants from the Competitive Research Funding of Tampere University Hospital, Pirkanmaa Hospital District.

Results

The median of given cycles was 5.5 (range 1–18). In 30% of patients the treatment discontinued before the third cycle because of toxicity or progressive disease. The median follow-up was 10.5 months (range 0–50 months).

The overall response rate was 27%: PR was achieved in 23% and CR in 1 patient (4%). SD was seen in 42% of patients and progressive disease in 15%. No response evaluations were done in 4 (15%) patients because of toxicity-related early discontinuation of the study treatment. In the end of study treatment, PR remained in 15% and SD in 27%, others progressed. CR remained throughout the follow-up period. The median PFS was 7.5 months (range 1–51+ months). Four patients have not progressed in the follow-up. The median OS was 17 months (range 2–55+ months). The 1-year survival was 77%; the 2-year survival rate was 38%. Kaplan–Meier estimates of overall and progression-free survival are shown in Fig. 1. Second-line treatment was given to 72% of patients.

In seven responders (CR + PR) the median age was 66 (range 49–81). Previous nefrectomy was performed to 86% of these patients. Single site of metastases was seen in 86% and only pulmonary metastases in 43%. Primarily metastatic disease was noticed in 43% of responders. One patient with CR had T2N0M0 grade IV disease operated 6 months before relapse (abdominal lymph nodes) was noticed.

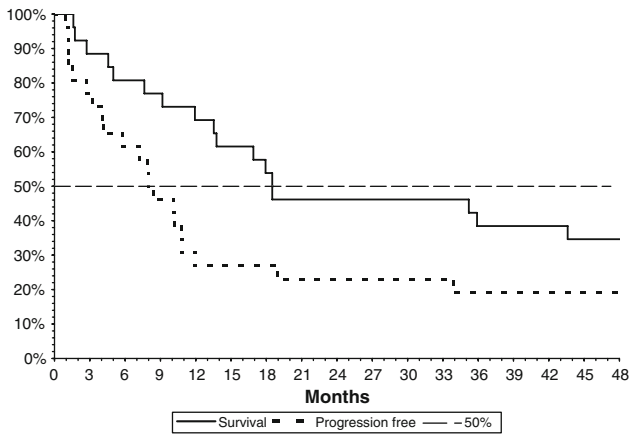

Fig. 1 Kaplan–Meier estimates of overall and progression-free survival

The clinical toxicity of the study combination is shown in Table 2, percentages are shown per patient ($n = 26$) and per given cycle ($n = 183$): grades 1–2 and grades 3–4 toxicities are combined. Fatigue and nausea were the most common toxicities. Only 12% of patients did not experience nausea at all and 4% did not experience fatigue. When counted per cycle, in 66% of given cycles patients experienced fatigue of any grade, nausea of any grade was seen in 33% of the treatment cycles. Hand–foot syndrome was seen in 39% of cycles, but 83% of the patients did not experience this toxicity. The grades 3–4 toxicity (% of patients) was recorded on fatigue (23%), nausea (12%), constipation (4%), diarrhea (15%), stomatitis (4%), and hand–foot syndrome (4%). Also one treatment-related pulmonary embolus and one hematoma of the gall bladder were recorded (grade 4), one patient experienced grade 3 dyspnea. No treatment-related deaths occurred. Other, miscellaneous toxicity of any grade was experienced by 77% of patients during the study treatment; mostly these were grades 1–2. The following toxicities were listed: thrombophlebitis, decreased appetite, nail problems, dryness of mouth, abdominal pain, conjunctivitis, and blurriness of the vision.

The hematological and blood chemistry toxicity are shown in Table 3, percentages are shown again per patient and per given cycle. The most common toxicities were anemia, leukopenia, neutropenia, hypoalbuminemia, and the elevation of liver values (ASAT). Leukopenia was seen in 69% of patients, anemia in 65%, and elevation of liver values were seen in 62%. Anemia was also the most common toxicity when counted per given cycle: in 54% of cycles. Neutropenia and thrombocytopenia were seen in 46% and hypoalbuminemia in 45% of cycles. Grades 3–4 toxicity was seen as neutropenia, leukopenia, and elevation of liver values.

Altogether 46% of patients experienced grades 3–4 toxicity. However, in 93% of cycles patients experienced only mild or no toxicity. Three patients (11.3%) experienced grade 4 toxicity which led to discontinuation of the study treatment: bloody diarrhea in two patients and synchronous pulmonary embolus and hematoma of the gall bladder in one patient.

In the evaluation of quality of life, patients experienced the physical and psychologically stable well being (Fig. 2). There was no statistically significant difference in the quality of life when tested in base line and in cycles five and ten ($P = 0.76$).

The dose reductions are shown in Table 4. The most common indications for dose reductions were elevation of liver values and neutropenia. No dose reductions were

Table 2 Clinical toxicity

Toxicity	Grades	Per patient *n* (%)	Per cycle *n* (%)
Fatigue	0	1 (4)	62 (34)
	1–2	19 (73)	115 (63)
	3–4	6 (23)	6 (3)
Muscle pain	0	19 (73)	148 (81)
	1–2	7 (27)	35 (19)
	3–4	0 (0)	0 (0)
Fever	0	13 (50)	153 (84)
	1–2	13 (50)	30 (16)
	3–4	0 (0)	0 (0)
Neuropathy	0	17 (65)	157 (86)
	1–2	9 (35)	26 (14)
	3–4	0 (0)	0 (0)
Constipation	0	12 (46)	156 (85)
	1–2	13 (50)	26 (14)
	3–4	1 (4)	1 (1)
Stomatitis	0	15 (58)	161 (88)
	1–2	10 (38)	21 (11)
	3–4	1 (4)	1 (1)
Nausea and vomiting	0	3 (12)	124 (68)
	1–2	20 (77)	56 (31)
	3–4	3 (12)	3 (2)
Diarrhea	0	12 (46)	157 (86)
	1–2	10 (38)	22 (12)
	3–4	4 (15)	4 (2)
Infection	0	13 (50)	160 (87)
	1–2	13 (50)	23 (13)
	3–4	0 (0)	0 (0)
Alopecia	0	21 (81)	171 (93)
	1–2	5 (19)	12 (7)
	3–4	0 (0)	0 (0)
Rash	0	13 (50)	146 (80)
	1–2	13 (50)	37 (20)
	3–4	0 (0)	0 (0)
Allergic symptoms	0	26 (100)	183 (100)
	1–2	0 (0)	0 (0)
	3–4	0 (0)	0 (0)
Hand–foot syndrome	0	15 (58)	112 (61)
	1–2	10 (38)	70 (38)
	3–4	1 (4)	1 (1)
Other symptoms	0	6 (23)	130 (71)
	1–2	18 (69)	51 (28)
	3–4	2 (8)	2 (1)

Table 3 Hematological and serum chemistry toxicity

Value	Grades	Per patient *n* (%)	Per cycle *n* (%)
Anemia	0	9 (35)	84 (46)
	1–2	17 (65)	99 (54)
	3–4	0 (0)	0 (0)
Leukopenia	0	8 (31)	116 (63)
	1–2	17 (65)	66 (36)
	3–4	1 (4)	1 (1)
Neutropenia	0	10 (38)	100 (55)
	1–2	15 (58)	82 (45)
	3–4	1 (1)	1 (1)
Thrombocytopenia	0	13 (50)	99 (54)
	1–2	13 (50)	84 (46)
	3–4	0 (0)	0 (0)
S-AFOS	0	19 (73)	158 (86)
	1–2	7 (27)	25 (14)
	3–4	0 (0)	0 (0)
S-ASAT	0	10 (38)	117 (64)
	1–2	15 (58)	64 (35)
	3–4	1 (4)	1 (1)
	ND		1 (1)
S-ALAT	0	15 (58)	146 (80)
	1–2	11 (42)	37 (20)
	3–4	0 (0)	0 (0)
S-GT	0	13 (52)	109 (60)
	1–2	11 (44)	62 (34)
	3–4	1 (4)	1 (1)
	ND		11 (6)
S-Krea	0	13 (50)	152 (83)
	1–2	13 (50)	30 (16)
	3–4	0 (0)	0 (0)
	ND		1 (1)
Hypocalcemia	0	6 (23)	105 (57)
	1–2	20 (77)	78 (43)
	3–4	0 (0)	0 (0)
	ND		1 (1)
Hypercalcemia	0	24 (92)	180 (98)
	1–2	2 (8)	3 (2)
	3–4	0 (0)	0 (0)
S-Alb	0	5 (19)	98 (54)
	1–2	21 (81)	82 (45)
	3–4	0 (0)	0 (0)
	ND		3 (2)

ND not done

needed in 15% of patients and in 39% of cycles. In 50% of patients and in 39% of given cycles one dose reduction was needed. Altogether 64% of dose reductions were because of abnormal laboratory values (anemia, leuko- or neutropenia, thrombocytopenia, elevated liver values) which did not cause any clinical problems, but delayed the next cycle. One patient needed dose reduction five times, but continued in the study because of clinical benefit. In some cases there were multiple reasons to dose reductions. Dose delays were needed in 46% of patients and in 14% of given cycles.

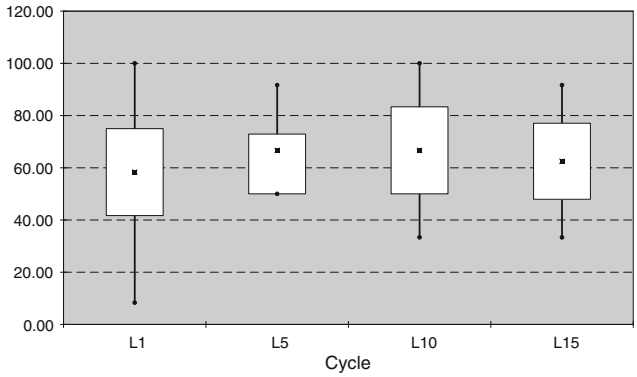

Fig. 2 Results of quality-of-life questionnaire in base line (L1), in cycle 5 (L5), and in cycle 10 (L10)

Table 4 The dose reductions

Dose reductions of capecitabine	Per patient (%)	Per cycle (%)
None	4 (15)	71 (39)
Once	13 (50)	72 (39)
Twice	4 (15)	21 (11)
Three times	3 (12)	14 (8)
Four times	1 (4)	2 (1)
Five times	1 (4)	3 (2)
Reasons for dose reductions of capecitabine		**Number of reductions**
Anemia		2
Leukopenia		2
Elevation of liver values		10
Lowered general condition		5
Diarrhea		2
Neutropenia		18
Nausea		1
Hand–foot syndrome		4
Thrombocytopenia		3
Rash		2
Vacation		1
Stomatitis		1
Multiple reasons		9
Dose intensity of capecitabine (%)		**Cycles (%)**
90–100		73 (40)
80–89		9 (5)
70–79		65 (36)
60–69		6 (3)
50–59		26 (14)
40–49		4 (2)
Reduction to pegylated interferon-alfa-2a	**Per patient (%)**	**Per cycle (%)**
Done	9 (35)	160 (87)
Not done	17 (65)	23 (13)

These delays were 1–2 weeks in duration. The dose intensity of capecitabine was 90–100% in 40% of cycles, 70–79% in 36% of cycles, and 50–59% in 14% of cycles. Some injections of pegylated interferon were omitted in 35% of patients and in 87% of cycles because of grades 2–3 hematological toxicity or elevated liver values.

The reason for discontinuation of the treatment was toxicity in 11 patients (38%), progressive disease in 10 (35%), and non-treatment-, non-cancer-related death in one (3%). In three patients (11.5%), treatment was given up to 1 year and then discontinued according to protocol. One patient discontinued the treatment in complete remission 12 weeks after the confirmation of the response. Also congestive heart failure, infection, and second malignancy were reasons for discontinuations, each in one patient. Three patients had two different reasons for discontinuation. Those who discontinued the study because of serious clinical side effects did it during the first cycles, after that there were mostly elevated liver values which prevented the continuation of the study treatment.

Discussion

The study combination with capecitabine and pegylated interferon-alfa-2a was active: 27% of patients achieved response including 4% of CRs. Most patients who responded here had only one site of metastases and half of them had only pulmonary metastases. Other single sites were abdominal and mediastinal lymph nodes. Typical responders to IFN are patients with only pulmonary metastases [1]. The current combination proved efficacy also in other patients. The age range of responders was wide and even the oldest patient (81 years) tolerated the treatment well.

The achieved response rate is in line with phase-II studies done with the combination of capecitabine and non-pegylated interferon: 12–24% overall response rates are reported, with 3–4% CRs; SD was seen in 36–38% of patients [18, 19]. The triplet combination with thalidomide does not produce better responses: PRs were seen in 20%, SD in 28% [22]. When IL-2 is added to the combination [23, 24] more responses and longer PFS and OS are achieved. With the four-drug combination (capecitabine, non-pegylated IFN, IL-2 and 13-cis retinoic acid) a response rate of 34% was reported, with 7% CRs and 40% of patients presented with SD [23]. In a phase-II study when IFN is changed to pegylated interferon-alfa-2b in otherwise similar four-drug combination, responses are reported in 53.6% of patients with 24% CRs. SD was achieved in 34%. The median PFS was 14.7 months and the median OS 27.9 months [24]. When capecitabine is combined with another chemotherapy agent gemcitabine,

responses are seen in 15.8–22% of patients in phases I–II studies [28, 29], which is quite comparable to responses in different combinations of chemoimmunotherapy with interferon.

Cytokines have been tested in combinations without chemotherapy regimens in hope for achieving more efficacy. When PEG-interferon is combined with IL-2 alone, the response rate is 30.2% with 3.8% CRs, which is comparable to the four-drug combinations [23, 24] or high-dose IL-2 alone. The median duration of response was 11 months. This schedule consisted of PEG-IFN-2b 2.0 μg/kg per week and IL-2.5 MIU/m^2 three times on day 1, then once daily 5 days a week, both for 4 weeks followed by 2 weeks rest [30]. In other schedule the pegylated interferon-alfa-2b was given 3.0 μg/kg per weekly and IL-2.20 MIU/m^2 three times a week at weeks 1 and 4, and 5.0 MIU/m^2 three times a week during weeks 2–3 and 5–6. PRs were seen only in 15% of patients, SD was achieved in 68%. PFS was 9.0 months and OS 31.9 months [31].

Toxicity of the study combination was manageable, but grades 3–4 side effects were seen in 46% of patients. Dose reductions were needed in 85% of patients and in 39% of cycles. Despite reductions, the response remained in most patients. This need to reductions has been seen already in previous studies done with non-pegylated interferon. In the first phase-I trial the combination of capecitabine (825–1,000 mg/m^2 twice daily for 14 days, followed by 1 week rest) and non-pegylated interferon-alfa-2b (1.5–3.0 MIU/m^2 three times a week) had moderate toxicity, mostly mild nausea/vomiting, diarrhea, and hand–foot syndrome. The majority of patients experienced malaise, fever, and chills related to interferon. Grade 1 hepatic toxicity occurred infrequently and hematologic toxicity was generally mild: thrombocytopenia was seen in 33% of patients and neutropenia in 37% [17]. Since then, in phase-II study done with capecitabine (1,250 mg/m^2 twice daily for 14 days followed by 1 week rest) and non-pegylated IFN (6 MIU three times per week) grades 3–4 toxicities were seen in 48% including fatigue, nausea, hand–foot syndrome, anorexia, vomiting, anemia, and neutropenia. Toxicity was considered acceptable, but dose reductions had to do in 48% and dose delays were necessary in 16% of patients. Capecitabine dose of 1,000 mg/m^2 twice daily was recommended for further studies [18]. In another phase-II study the starting dose with capecitabine was 1,000 mg/m^2 twice daily on days 1–14, but because of toxicity requiring dose reductions during the first cycle the dose was reduced to 825 mg/m^2 twice daily. Interferon was given 3.0 MIU/m^2 thrice a week. Toxicity was considered moderate to severe; dose reductions were required in 88% of patients and 19% of patients discontinued therapy secondary to toxicity. Grades 3–4 toxicity was seen in 78%, most commonly gastrointestinal and hand–foot syndrome [19]. In the study of combination of capecitabine and pegylated interferon-alfa-2b grades 3–4 toxicity was seen in 21.9% including nausea and vomiting, neutropenia, anemia, and thrombocytopenia [24]. In the future, in this combination with pegylated interferon-alfa-2a the dose level for capecitabine should be 1,600 mg/m^2 per day as the dose intensity over 70% was here tolerable in 81% of cycles (Table 4).

In the triplet combination (capecitabine 1,900 mg/m^2 per day, days 1–14; cycle 21 days, IFN-α 1 MIU daily without interruptions and thalidomide 400 mg daily) the dose reductions of capecitabine were required in 76% of patients. The most common grades 3–4 toxicity was hand–foot syndrome; anemia occurred in 4%, but no other grades 3–4 hematological toxicity was seen [22]. In the four-drug combination of capecitabine, interferon-alfa-2a, IL-2, and oral 13-*cis* retinoic acid toxicity was mild [23]. When capecitabine is combined with gemcitabine, the combination is reported to be too toxic in phase-I study despite dose reductions [28], but in phase-II study this combination had moderate and manageable toxicity [29], even when gemcitabine was given with larger dose than in the phase-I study.

Toxicity of pegylated interferon-alfa seems to be schedule-dependent and sometimes unpredictable. Also, it seems that two available pegylated interferons have different toxicity scales. This is probably in correlation with molecular weight. A 40-kd PEG moiety of interferon-alfa-2a cannot be excreted by the kidneys and is not quickly metabolized; therefore, the PEG may accumulate in the liver, which increases the risk for toxicity especially in the long-term administration [6]. The combination of pegylated interferon-alfa-2a and IL-2 produces in some schedules inacceptable toxicity: grades 3–4 cardiac toxicity was seen in 17% and central nervous system events in 11.3%. The schedule was abandoned because of the toxicity, which remained unexplained as the serum levels of either of the drugs were not increased. Some pharmacodynamic effect was suspected; capillary leak by IL-2 may have increased the end organ concentrations [30]. In other schedules, toxicity was moderate; the most common toxicities were nausea and vomiting, diarrhea, fatigue, fever, transient elevation in liver transaminases, leukopenia, thrombocytopenia, and anemia. Most of these side effects were mild [31].

Current treatment guide lines are recommending tyrosine kinase inhibitors (TKI), combination of bevacizumab and non-pegylated interferon, or temsirolimus as primary choices to the first-line treatment of metastatic RCC. The choice should be done according to tolerability of the treatment and prognostic factors [32]. With the combination of VEGF inhibitor bevacizumab and non-pegylated IFN, PFS was 10.2 months, OS 19.9 months, and response rate 31%. This combination is usually well tolerated, but grades 3–4 fatigue, diarrhea, anemia, neutropenia, and thrombocytopenia are seen. Proteinuria, thromboembolic events, and gastroin-

testinal perforation are additional side effects concerning treatment with bevacizumab [33]. TKI sunitinib has proved efficacy in the first-line treatment with response rate of 47%, PFS of 11 months, and OS of 26.4 months. With the current combination, sunitinib causes grades 3–4 diarrhea, fatigue, nausea and vomiting, and hand–foot syndrome, but additionally also hypertension. Grade 3 leuko- and neutropenia, thrombocytopenia, and elevated liver values are also seen [34, 35]. Temsirolimus is indicated to RCC patients with poor prognosis: median OS of 10.9 months and PFS of 5.5 months are reached. It also causes grades 3–4 hematological side effects and asthenia. Particular side effects concerning this treatment are hyperlipidemia, hyperglycemia, and pneumonitis [36]. The current study combination did not show any new side effects which were not known from the single-agent studies. We did not select patients according to risk factors, but the achieved response rate, PFS, and OS were better than with temsirolimus but lower than with sunitinib or with the combination of bevacizumab and interferon.

As pegylated IFNs are more convenient to use than non-pegylated IFN, they might find their place and more regular use in the treatment of RCC patients in combination with bevacizumab or in the second-line treatment after TKIs in the current combination. Usually, TKIs are more tolerable than this study combination but with lower starting dose of capecitabine the situation can be different. With lower dose of capecitabine, most of the clinically significant grade 4 side effects are probably prevented. As the clinical benefit was clear, we recommend a phase-III study to clarify the position of the current study combination.

Conclusions

The combination of capecitabine and pegylated interferon-alfa-2a produced clinical benefit of 69%, including 23% PRs and 4% CRs. Three responders had only pulmonary metastases and three had lymph node metastases, one patient had multiple sites. However, the response rate was not better than in studies including non-pegylated interferon. The median PFS was 7.5 months and OS 17 months. Dose reductions were needed in 85% of patients and dose delays in 46%, which is in line with previous studies. Toxicity was still manageable, but because of many reductions the dose for capecitabine should be 1,600 mg/m^2 per day in the future studies. The most common toxicities were fatigue, nausea, hematological toxicities, and elevated liver values. Because of more convenient dosing, the pegylated interferon-alfa-2a would be useful to be studied in combination with bevacizumab. The current combination might be applicable in the second-line treatment after TKIs, but a phase-III study is still needed. At the moment, patients unsuitable to treatment with sunitinib or bevacizumab (such as hypertensive patients or cases with previous arterial thromboembolic event or gastrointestinal perforation) could be candidates for this combination.

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