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Multicentre EORTC study 16997: Feasibility and phase II trial of farnesyl transferase inhibitor & gemcitabine combination in salvage treatment of advanced urothelial tract cancers

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Abstract

In this study, the feasibility and activity of combined chemotherapy of the farnesyl transferase inhibitor SCH66336 and gemcitabine was evaluated. This therapy was used as second-line treatment in patients with advanced urothelial tract cancer and the influence of SCH66336 exposure on the pharmacokinetics of gemcitabine was also determined. Patients who had received one previous chemotherapy regime for advanced urothelial cancer were treated with a combination of SCH66336 (150 mg in the morning and 100 mg in the evening) and Gemcitabine (1000 mg/m^2 on day 1, 8 and 15 per 28-day cycle). Dosages of gemcitabine and its metabolite dFdU were performed on day one of cycle 1 before exposure to SCH66336 and day one of cycle 2. A total of 152 cycles were administered in 33 patients (median 3, range: 1–15). No patients had severe hematological toxicity, defined as Grade 4 thrombocytopenia or febrile neutropenia. Nine partial responses and one complete response were achieved in 31 assessable patients and corresponded to an overall response rate of 32.3% [95% CI:17%–51%]. There was no influence of exposure to SCH66336 on the level of gemcitabine or dFdU in 11 assessable patients. In conclusion, a combination of SCH66336 and gemcitabine is feasible in terms of toxicity and active as second-line treatment in patients with advanced urothelial tract cancer. SCH66336 had no effect on the pharmacokinetics of gemcitabine. Randomised trials should be undertaken to clarify the role of SCH66336 in combination with gemcitabine in cancer treatment.

Keywords: Bladder cancer; Chemotherapy; Signal transduction modification; Farnesyl transferase inhibitor SCH66336; Gemcitabine

1. Introduction

Chemotherapy is the mainstay of treatment for advanced urothelial carcinoma. The combination of methotrexate, vinblastine, doxorubicin and cisplatin

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(M-VAC), which was developed in the early eighties, was a major breakthrough yielding an overall response rate (ORR) of 70% with a median survival of 12–14 months and 5–15% long-term survival [1,2]. However most patients relapse and the overall prognosis remains very poor and trials of new drugs are required. Single-agent gemcitabine, at weekly doses ranging from 875 to 1350 mg/m^2, yielded response rates of 23% and 28% in previously untreated patients [3–5] and of 21%, 23% and 11% in patients pre-treated with cisplatin [6–8]. Gemcitabine has since then been considered the most promising new drug for urothelial cancer and the popularity of M-VAC was challenged by the gemcitabine–cisplatin combination. Whereas it was possible to lower the toxicity of chemotherapy by shortening the duration of neutropenic fever, the new combination failed to improve the ORR and the overall survival [10]. The increasing diversity of new drugs has allowed research on the development of salvage treatments using not only conventional chemotherapy but also the more recently developed agents, aimed at altering the biological behaviour of cancer cells.

Mutated *ras* genes are thought to play a role in the pathogenesis of urothelial cancer. Ras protein is normally synthesised as pro-ras, which undergoes a number of post-translational modifications, the most prominent among them being farnesylation of a carboxy-terminal cystein residue by farnesyl transferase. Processed ras proteins localise to the inner surface of the plasma membrane, and function like a molecular switch that cycles between an inactive and an active form. In its active form, either because of binding of an external ligand or because of its constitutive activation, ras activates several downstream effectors, such as raf-1, rac, rho and phosphatidylinositol-3 kinase, which mediate important cellular functions, such as proliferation, cytoskeletal organization and others [9]. Prevention of ras membrane localization interrupts the *ras* signalling pathway. Inhibition of farnesylation prevents membrane localization and ablates the activity of the ras protein. Mechanisms of action of farnesyl transferase inhibitors, involving rho B, centromere-binding proteins and possibly other farnesylated proteins have recently been discovered. Farnesyl transferase inhibitors are ideal cancer drug candidates as they could potentially stop neoplastic transformations [10,11].

SCH66336 (lonafarnib) is an orally administered tricyclic farnesyl transferase inhibitor that has been shown to have significant anti-tumor activity in a variety of human tumor xenograft models in nude mice [12–14]. Phase I studies of continuous, daily administration were conducted with gradual dose escalation. The administration at a dose of 200 mg BID was found to be safe and well tolerated. A dose of 300 mg BID was associated with dose-limiting toxicities, including gastro-intestinal toxicity (nausea, vomiting and diarrhea), hematological toxicity (Grade 4 neutropenia and thrombocytopenia) and neurological toxicity (confusion and fatigue) [15,16]. A phase I study of oral SCH66336 and gemcitabine combination in weekly intravenous infusion for 3 out of 4 weeks was carried out in 18 patients with chemotherapy-refractory cancer. The maximum tolerated dose (MTD) was 1000 mg/m^2 for gemcitabine and 150 mg for SCH66336 in the morning and 150 mg in the evening with 7 patients treated at this dose level [17]. As it was unlikely that gemcitabine alone would be sufficient to dramatically alter the prognosis of advanced urothelial carcinoma, we decided to investigate the safety and efficacy of SCH66336 and gemcitabine combination therapy in previously treated patients with advanced urothelial carcinoma.

2. Patients and methods

2.1. Patients

Patients with pathologically confirmed metastatic or unresectable transitional cell carcinoma (TCC) of the urothelium (renal pelvis, ureter, bladder or urethra), who had previously received one line of chemotherapy for advanced disease, were recruited for the study. The following eligibility criteria were required: ECOG performance status $\leqslant 2$, life expectancy $\geqslant 3$ months, measurable lesion $\geqslant 20$ mm, absolute granulocyte count $>2000/\mu l$, platelet count $\geqslant 100\,000/\mu l$, bilirubin <1.5 upper limit of normal range (ULN), alkaline phosphatase and transaminases 2.5 times ULN in the absence of liver metastases and $\leqslant 5$ times ULN level in case of liver metastases, creatinine $<150\ \mu M$, clinically normal cardiac function, no previous administration of gemcitabine and written informed consent.

2.2. Treatment plan

Hospitalization was not required for treatment. Gemcitabine was administered on day 1, 8 and 15 of a 28-day cycle and SCH66336 was continuously given orally starting on day 2 of cycle 1 at a dose of 150 mg in the morning and 100 mg in the evening. Treatment was pursued until severe toxicity or disease progression occurred or if the patient refused to continue the investigated treatment.

2.3. Toxicity criteria

Toxicity was evaluated in all patients who started treatment. Toxicity was graded according to the National Cancer Institute toxicity criteria (version 2.0). Dose and schedule modifications were based on weekly blood counts and 4 weekly assessments of clinical toxicity. The worst grade of toxicity was recorded at each

cycle. Severe toxicity was defined as fever $\geqslant 38.5°$ with neutropenia $<1 \times 10^9$/l, or Grade 4 thrombocytopenia (platelets $<10 \times 10^9$/l). In case of hematological (Grade $\geqslant 2$) or non-hematological toxicity (Grade $\geqslant 3$), treatment was interrupted until the resolution of symptoms. In case of hematological toxicity Grade $\geqslant 2$, SCH66336 was reduced to 100 mg BID and gemcitabine to 800 mg/m^2. In the event of severe toxicity, the patient was withdrawn from the study.

2.4. Definition of response

Response to treatment was assessed in all patients who received at least one complete cycle of treatment with dose reductions when necessary. The assessment of activity was based on the response rate (RR) according to RECIST criteria. A complete response (CR) was defined as the complete disappearance of all target lesions. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter (LD) of target lesions with the baseline sum of the LD of target lesions as the reference. Progressive disease was defined as at least a 20% increase in the sum of the LD of target lesions. The duration of response was measured from the date of the start of treatment to the date of documented progression. Time to progression (TTP), overall survival (OS) and progression-free survival (PFS) were estimated by the Kaplan–Meier method and calculated from the day of the start of treatment.

2.5. Statistical methods

The primary endpoint was the feasibility of the combination in terms of toxicity. The two-stage accrual design described by Simon [18] was chosen to determine the total number of patients required for the study. This design ensured that the total number of patients exposed to the therapy would be minimised if the therapy proved to be too toxic. A severe toxicity rate of 20% was set as the limit beyond which the toxicity profile of the combination did not warrant further investigation. A preliminary test was planned to assess 7 patients for toxicity. The study was to be stopped if two or more patients had developed severe toxicity. Otherwise, 31 patients were to be recruited for a second test.

2.6. Pharmacokinetics

Blood samples (3 ml) were collected in tubes at day one of cycle 1 and cycle 2 before and after 30 min, 2, 4 and 24 h after the administration of gemcitabine. The tubes were chilled, heparinised and contained tetrahydrouridine in order to prevent the degradation of gemcitabine. Centrifugation at 2000 g for 15 min at 4 °C was performed before freezing and transfer to the laboratory. Gemcitabine and dFdU were analysed as described previously [19]. Briefly, 150 μl of plasma were extracted as described and stored at −20 °C until analysis. Separation and quantification of gemcitabine and dFdU from the plasma was achieved with an isocratic reversed-phase high-performance liquid chromatography (HPLC) system using a μBondapak C18 column (length 300 mm, internal diameter 3.9 mm and particle size 10 μm). Peak areas were quantified using the data acquisition program Chromeleon version 3.02 (Chromeleon Chromatography Data Systems, Gynkotek HPLC, Germering, Germany). Retention times of gemcitabine and dFdU were 7.1 and 13.5 min, respectively. The limit of quantification was about 25 pmol/50 μl (0.5 M) for both gemcitabine and dFdU.

The area under the plasma concentration *versus* time curve from $t = 0$ (start of the infusion) to 120 min and to infinity were calculated using the linear trapezoidal analysis according to the WinNonlin computer program (version 1.5, Scientific Consulting, Inc). The half-life of the terminal log-linear phase ($T_{1/2\gamma}$) was calculated as $0.693/_z$, where λ_z is the terminal elimination rate constant, the absolute value of the slope of the terminal log-linear phase. Peak plasma concentrations (C_{max}) of dFdC and dFdU are the mean of measured values. Differences between data were evaluated using the Student's t, Wilcoxon signed ranks and Mann–Whitney U test.

3. Results

From June 2000 to December 2001, 34 patients from eight institutions were enrolled onto the study. One patient withdrew consent before the start of treatment.

3.1. Patient and treatment characteristics

Baseline patient characteristics are summarised in Table 1. Thirty-one patients had pure transitional cell carcinoma (TCC), while 3 patients had TCC with adenocarcinoma, squamous cell carcinoma or undifferentiated carcinoma components. Five patients were in the poor prognosis category associated with an ECOG 2 performance status and visceral metastases. Median time between study treatment and previous chemotherapy was 5 months (range 1–87 months). Twenty-nine patients had received chemotherapy during the previous 12 months, M-VAC being predominantly administered in 25 patients. Carboplatin-based chemotherapy was previously administered in 6 patients, which included a combination of paclitaxel and carboplatin in 3 patients and a combination of doxorubicin, vinblastine, methotrexate and mitomycin C in one patient.

Table 1
Patient characteristics (number of patients = 34)

	SCH66336 (N = 34)
Age/years	
Median	63.6
Range	42–80.2
Sex/N (%)	
Male	27 (79.4)
Female	7 (20.6)
Primary tumour site/N (%)	
Bladder	28 (82.4)
Renal pelvis	4 (11.8)
Ureter	2 (5.88)
Initial performance status/N (%)	
WHO PS 0	3 (8.8)
WHO PS 1	26 (76.5)
WHO PS 2	5 (14.7)
Previous chemotherapy/N	
M-VAC	25
CMV	1
Cisplatin alone	1
Carboplatin-based CT	6
Other	1
Time between start of treatment and date of last chemotherapy/months	
Median	5.3
Range	0.9–87.7
N obs	33
Radiotherapy/N (%)	
No	27 (79.4)
Yes excluded haematopoietic sites	5 (14.7)
Yes included haematopoietic sites	2 (5.9)
Tumour sites/N	
Loco-regional disease	7
Distant metastases	27

3.2. Administration of therapy and analysis of toxicity

One patient withdrew consent and was not treated according to the protocol. A total of 152 cycles of protocol treatment was administered in 33 patients, with a median number of 3 cycles per patient (range 0–15). Nineteen patients (57%) completed more than two cycles of treatment. The relative dose intensity of SCH66336 was 82% (range 28–100%). The relative dose intensity of gemcitabine was 75.5% (range 29–104%).

Thirty-three patients were assessed for toxicity. On the whole, therapy was well tolerated. Hematologic toxicity is summarised in Table 2. None of the 33 patients experienced severe hematological toxicity, defined as Grade 4 thrombocytopenia or febrile neutropenia. Grade 3 neutropenia and thrombocytopenia was observed in 6 patients, respectively. Grade 3 anemia occurred in 9 patients. The predominant non-hematological toxicities were Grade 3 fatigue in 8 patients and Grade 3 diarrhea in 4 patients. Also, Grade 3 nausea and vomiting was observed in 3 patients, Grade 3 hepatic toxicity in 1 patient, gemcitabine-related congestive heart failure in 1 patient, gemcitabine-related interstitial pneumonitis in 1 patient and fever caused by a urinary infection without neutropenia in 1 patient. A dose reduction for SCH66336 was necessary in 16 patients (48.5%), during one cycle in 8 patients (24%), during two cycles for 7 patients (21.2%) and during three cycles in 1 patient (3%). A dose reduction of gemcitabine was necessary in 8 patients (24.2%) for one cycle and in 2 patients for 2 patients (6.1%). Gemcitabine dose delay was needed at day 1, day 8 and day 15 of cycle in 4 (12.1%), 6 (18.2%) and 10 patients (30.3%), respectively. Treatment was interrupted for non-hematological toxicity in 11 patients.

3.3. Activity

Treatment activity was assessed in 31 patients. One patient never started treatment and two patients were not eligible. Ten patients achieved an objective response (OR), including one complete response (CR) and nine partial responses (PR). The overall response rate (ORR) was 32.3% [95% CI:17–51%]. The median duration of response was 13.4 months. Kaplan–Meier survival curves for overall survival (OS) and time to progression (TTP) are shown in Figs. 1 and 2, respectively. Kaplan–Meier curve for TTP in responders is shown in Fig. 3. Median TTP was 7 months (Fig. 1). Median survival was 11.5 months. Ten patients are still alive including one patient with liver metastases, a non-responder to previous M-VAC chemotherapy who attained PR with this treatment protocol and a surgical CR following hepatic metastasectomy.

Table 2
Worst hematological toxicity per patient (n = 33)

Grade	0 No (%)	1 No (%)	2 No (%)	3 No (%)	4
Leukopenia	5 – (15)	13 – (38)	10 – (29)	4 – (12)	1 – (3)
Neutropenia	13 – (38)	7 – (21)	7 – (21)	6 – (18)	–
Thrombocytopenia	14 – (41)	5 – (15)	8 – (24)	6 – (8)	–
Anemia	5 – (15)	7 – (21)	12 – (35)	9 – (26)	–

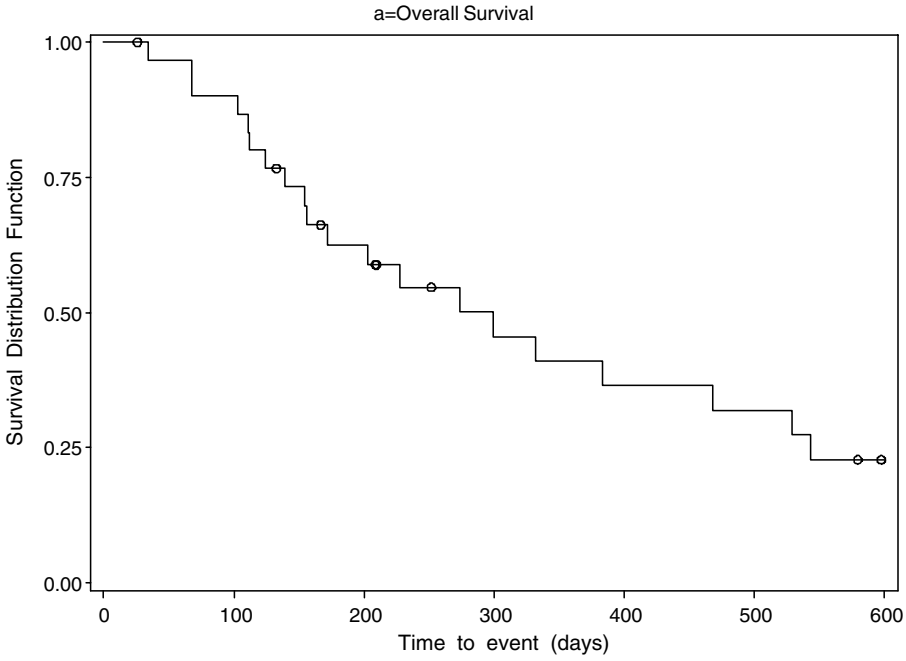

Fig. 1. Kaplan–Meier graph of overall survival. The estimated median overall survival is 11.5 months.

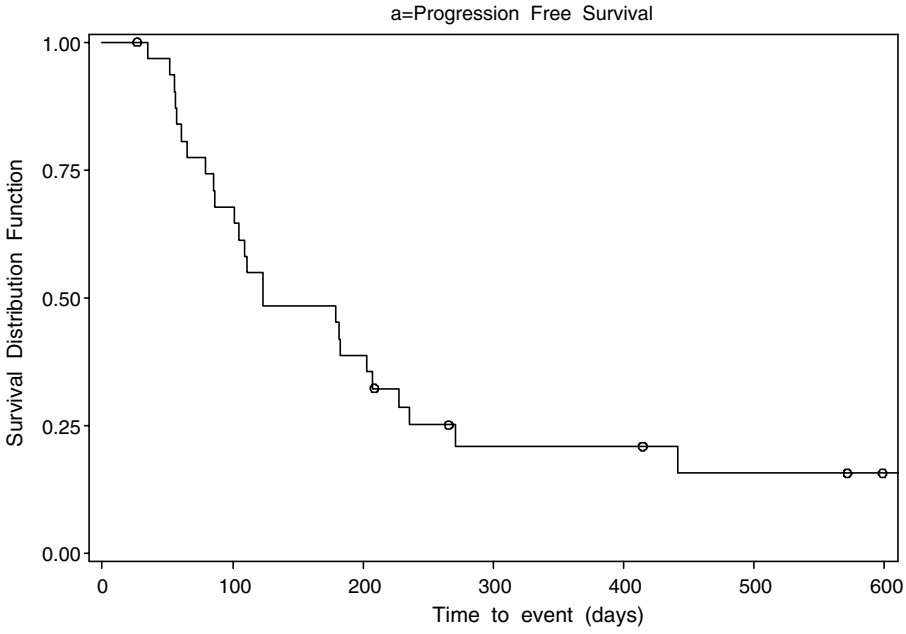

Fig. 2. Kaplan–Meier graph of time to progression. The estimated mean time to progression is 7 months.

3.4. Pharmacokinetics

Blood samples from 11 patients treated with gemcitabine (dFdC) and SCH66336 were analysed. No influence of SCH66336 on dFdC and dFdU (metabolite of gemcitabine) could be demonstrated when exposure on day 1 of cycle 1 was compared with that on day 1 of cycle 2. Levels of dFdC and dFdU did not differ significantly when given with or without SCH66336 (Table 3).

4. Discussion

The primary endpoint was the estimation of severe toxicity rate. Phase I studies of gemcitabine administered alone have shown that the once weekly administration for 3 weeks followed by a one week rest was safe but hematological, pulmonary, digestive and cardiac adverse effects were limiting toxicities [20]. Adding SCH66336 to gemcitabine was expected to possibly

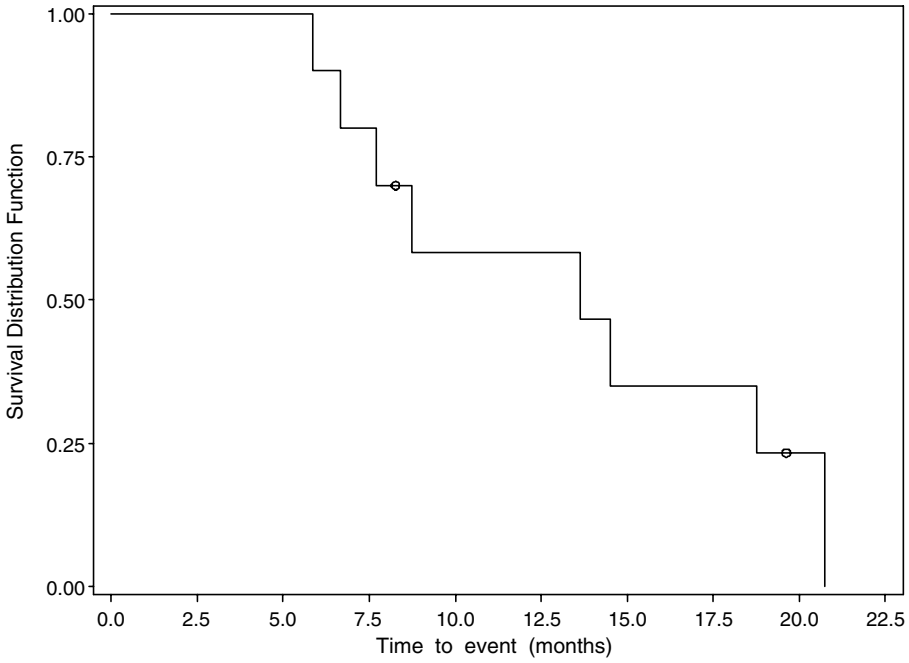

Fig. 3. Kaplan–Meier graph of time to progression for the responders. Median estimated duration of response from start of treatment was about 13.4 months (standard error = 2).

cause excessive hematological toxicity. Indeed, in the phase I study of SCH66336 [15,16], the MTD was 300 mg/m^2 with Grade 4 neutropenia and thrombocytopenia, diarrhea and fatigue as limiting toxicities. A phase I study of R115777, another farnesyl transferase inhibitor, combined with gemcitabine 1000 mg/m^2 and cisplatin 75 mg/m^2 on day one of a 21-day cycle was conducted in 30 patients. Dose-limiting toxicity was myelosuppression with thrombocytopenia alone in 4 patients, neutropenia alone in one patient or a combination of both in 3 patients [21]. Toxicity in our study is thus consistent with previous publications. Toxicities such as congestive heart failure and interstitial pneumonitis were primarily attributed to gemcitabine while, fatigue, abdominal pain and diarrhea were more likely related to SCH66336. Myelosuppression, nausea and vomiting could be caused either by gemcitabine, SCH66336 or both, but there appeared to be no excess toxicity, either in terms of intensity or incidence with this 2-drug combination. Since dose-limiting toxicity of gemcitabine may be related to its AUC and since the AUC of gemcitabine with SCH66336 was not different from that of gemcitabine alone, the lack of excess of toxicity fits with the PK pattern of gemcitabine. In addition to the lack of a difference between single agent gemcitabine and gemcitabine with SCH66336, the gemcitabine plasma concentrations and PK are in the same range as found earlier in combinations with SCH66336 [22] or with cisplatin and paclitaxel [23,24].

The ORR was higher than in most published studies of second-line chemotherapy for urothelial cancer. Tables 4 and 5 summarise the results of phase II studies

Table 3
Effects of SCH66336 on gemcitabine (dFdC) and its metabolite dFdU

	C_{max} (μM)		AUC total (μmol h/l)		AUC_{120} (μmol h/l)		$T_{1/2}$ (min)	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
dFdC								
Median	40.0	42.8	1562	1509	1612	1441	15.7	14.0
Mean	38.1	42.0	1407	1732	1402	1739	18.3	16.7
Std.	17.6	19.1	541	1063	531	1098	6.4	6.7
P value	0.97		0.67		0.62		0.24	
dFdU								
Median	96.4	94.9	48261	47707	17472	15396	497	468
Mean	100.9	95.6	49219	47523	16844	16253	510	497
Std.	16.3	13.5	15452	12418	3937	3216	81	47
P value	0.32		0.39		0.31		0.29	

Table 4
Second-line single-agent chemotherapy for urothelial cancer

Agent/mg/m^2	Patients/*N*	ORR/%	Ref.
Gemcitabine			
1000	24	29	[6]
1200	31	22.5	[7]
1250	28	11	[8]
Paclitaxel			
200	14	7	[25]
80	31	10	[26]
Docetaxel			
100	30	13	[27]
Ifosfamide			
5000	56	20	[28]
4500	20	5	[29]
Pyralozoacridine	14	0	[30]
Piritrexim			
400	27	7	[31]
Alimta			
500	47	27.7	[32]
Vinflunine			
320	51	18	[33]

Table 5
Phase II studies of salvage combinations in urothelial cancer

Agents	Patients/*N*	ORR/%	Ref.
Gemcitabine, ifosfamide,	34	21	[34]
Gemcitabine, cisplatin, ifosfamide	49	40	[35]
Gemcitabine, paclitaxel	41	60	[36]
5 FU, INFα, cisplatin	43	12	[37]
Ifosfamide, docetaxel	20	25	[38]
Ifosfamide 5 FU	15	0	[39]
Methotrexate, paclitaxel	19	31	[40]
Paclitaxel, methotrexate, cisplatin +5 FU, INF α, cisplatin	40	43	[41]

of second-line treatment in advanced urothelial carcinoma with single-agent and combination chemotherapy, respectively. The most active single agent is gemcitabine with an ORR varying from 29% in the first published report to 22% and 11% in more recent studies [6–8]. A 60% ORR was also reported with the gemcitabine-paclitaxel combination [36]. The most significant favourable prognostic factor was first-line adjuvant or neoadjuvant treatment *versus* first-line chemotherapy for advanced disease with an ORR varying from 80% to 27% for the same regime. Other prognostic factors in this patient population include first-line treatment with cisplatin, performance status, visceral metastases [41–44]. Patients assessed for treatment activity in our study were all previously treated for advanced disease with either no response to first-line treatment or a quick relapse. Most of them had distant metastases and only six of them had received carboplatin-based first-line chemotherapy. Therefore, the ORR in our study is at least among the best rates reported in other studies of second-line gemcitabine-containing chemotherapy in patients with advanced urothelial cancer. Since chance could not be ruled out as a possible explanation for the good ORR, only a randomised study could clarify the role of SCH66336 in this combination. However, beyond the question of what SCH66336 added to treatment with gemcitabine alone, our study shows that second-line therapy may be warranted in patients who fail first-line chemotherapy for advanced urothelial cancer.

Conflict of interest statement

None declared.

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