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Vinflunine–gemcitabine versus vinflunine–carboplatin as first-line chemotherapy in cisplatin-unfit patients with advanced urothelial carcinoma: results of an international randomized phase II trial (JASINT1)†

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Background: There is no standard first-line chemotherapy for advanced urothelial carcinoma (aUC) in cisplatin-ineligible (cisplatin-unfit) patients. The study assessed the efficacy and tolerability profile of two vinflunine-based cytotoxic regimens in this setting.

Patients and methods: Patients with aUC a creatinine clearance (CrCl) of <60 but ≥30 ml/min, performance status 0 or 1 and no prior chemotherapy for advanced disease were randomized (1 : 1). They received vinflunine 250 or 280 mg/m^2 (based on baseline CrCl) on day 1, plus either gemcitabine [750 mg/m^2 escalated to 1000 mg/m^2 in cycle 2 if no toxicity grade (G) ≥2 on days 1 and 8 (VG) or plus carboplatin area under the curve 4.5 day 1 (VC) every 21 days]. To detect a 22% improvement in each arm compared with H0 (41%) in the primary end point, disease control rate (DCR = complete response + partial response + stable disease), 31 assessable patients per arm were required ($\alpha = 5\%$, $\beta = 20\%$).

Results: Sixty-nine patients were enrolled (34 VG, 35 VC). Less G3/4 haematological adverse events (AEs) were reported with VG: neutropaenia was seen in 38% (versus 68% with VC) and febrile neutropaenia in 3% (versus 14% with VC) of patients. No major differences were observed for non-haematological AEs. DCR was 77% in both groups; overall response rate (ORR) was 44.1% versus 28.6%, with a median progression-free survival of 5.9 versus 6.1 months and median OS of 14.0 versus 12.8 months with VG and VC, respectively.

Conclusion: Both vinflunine-based doublets offer a similar DCR, ORR and OS. The better haematological tolerance favours the VG combination, which warrants further study.

ClinicalTrials.gov protocol identifier: NCT 01599013.

Key words: vinflunine, urothelial carcinoma, bladder cancer, cisplatin-ineligible, renal impairment

introduction

Urothelial carcinoma (UC) counts for 429 793 new cases per year with 165 068 related deaths worldwide [1]. The standard of care for advanced and metastatic disease is cisplatin-based chemotherapy [2]. The response rate with these regimens is ∼50% and median overall survival (OS) 13–15 months [3]. Up to 50% of the patients with advanced or metastatic UC are not eligible for cisplatin, generally due to impaired renal function and/or a performance status (PS) of ≥2, but also comorbidities such as congestive heart failure, peripheral neuropathy or hearing loss should be taken into account [3, 4]. So far, no standard treatment for such patients has been defined and there are currently only few ongoing trials, in particular phase II trials

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with immunotherapy that also include this patient population. Generally, carboplatin-based combinations or single agents are used in such patients. However, the benefit with carboplatin-based chemotherapy is modest, and OS usually does not exceed 8–9 months [2, 3, 5, 6]. Vinflunine, as a single agent, was approved by the EMA in 2009 for patients with advanced or metastatic UC after the failure of a platinum-based regimen [7, 8]. In addition, vinflunine has shown to be safe also in patients with significant renal impairment [7, 9].

Based on these data, a potential benefit of first-line vinflunine combinations in cisplatin-unfit patients with advanced or metastatic UC was hypothesized. Phase I trials assessed vinflunine combinations in different cancers [10, 11]. This randomized phase II study was aimed at exploring the feasibility as well as clinical efficacy and tolerability profiles of two vinflunine combinations in UC patients.

patients and methods

This was a randomized two-arm, open-label, multinational phase II trial.

patients

Eligible patients had histologically confirmed locally advanced or metastatic UC (transitional cell predominant, urinary bladder or upper tract) with measurable disease as defined by RECIST (version 1.1), age between 18 and 79 years and ECOG PS 0 or 1. No prior systemic chemotherapy was allowed except for perioperative chemotherapy if relapse occurred ≥6 months after the last dose. All patients had to be ineligible for a cisplatin-based therapy based on renal function impairment [calculated creatinine clearance (CrCl) by the Cockcroft–Gault formula of <60 ml/min but ≥30 ml/min] and/or congestive heart failure (NYHA Classification stages II–III). Adequate bone marrow function (absolute neutrophils ≥2000/mm^3, haemoglobin ≥10 g/dl, platelets ≥100 000/mm^3), normal hepatic function, absence of known brain metastases, leptomeningeal involvement and peripheral neuropathy Grade ≥2 by NCI Common Toxicity Criteria (CTC) were required.

The most important exclusion criteria were any serious medical condition including infection or unstable cardiac disease, ongoing immune therapy, treatment with any potent cytochrome 3A4 inhibitor or inducer, the presence of other malignancies with a disease-free interval of <5 years with the exception of cured skin basal carcinoma, *in situ* cervix carcinoma and incidentally discovered localized prostate cancer (pT ≤2b, Gleason score ≤7).

The protocol was approved by the national and institutional ethics review boards of each participating institution, whatever applicable. Before randomization, written informed consent was obtained from all patients in accordance with the Declaration of Helsinki, applicable guidelines for good clinical practice and regulations of the participating countries.

treatment plan

Patients were centrally randomized 1 : 1 and stratified (minimization procedure) for study site, prior perioperative chemotherapy (yes or no), PS0 versus PS1 and pre-treatment CrCl (≥60 versus 40–60 versus 30–40 ml/min) and subsequently randomly assigned 1 : 1 to receive either vinflunine–gemcitabine (VG) or vinflunine–carboplatin (VC).

On the basis of the CrCl at randomization (<40 or ≥40 ml/min), patients received every 21 days vinflunine 250 or 280 mg/m^2 as a 20 min i.v. infusion on day 1, plus either a 30 min i.v. infusion of gemcitabine 750 mg/m^2 days 1 and 8, escalated to 1000 mg/m^2 in cycle 2 if no toxicity grade of ≥2 occurred (VG) or carboplatin area under the curve 4.5 day 1 over 1 h i.v. (VC). Treatment was continued until disease progression, intolerable toxicity or patient refusal. In case of complete response, two more cycles were to be given after the response confirmation and further treatment prolongation was left at the physician's discretion. Subsequent cycles were administered if ANC was >1500/mm^3 (2000 at baseline), and/or platelets count >75 000/mm^3 (100 000 at baseline); all study drugs were held if CrCl was below 20 ml/min and gemcitabine was held until recovery to a value of ≥30 ml/min. Secondary granulocyte colony-stimulating factor was given in case of febrile neutropaenia, G4 asymptomatic neutropaenia lasting >7 days or a neutropenic infection. One dose reduction was allowed for vinflunine, down to either 250 or 225 mg/m^2 (depending on the starting dose) in case of neutropaenia G4 >7 days, febrile neutropaenia, mucositis or constipation G2 ≥5 days or G ≥3 of any duration, any other G ≥3 toxicity related to the study drug (including G3–4 thrombocytopaenia with bleeding) except G3 inadequately treated or premedicated vomiting, nausea or fatigue. No dose re-escalation was allowed after a dose reduction.

objectives and clinical assessment

The primary objective of the study was to determine the disease control rate (DCR). This was defined by complete response (CR) + partial response (PR) + stable disease (SD) for both vinflunine-based combinations in the intent-to-treat (ITT) population (first assessment at week 6). Tumour assessment (RECIST1.1) and confirmation of response was carried out by the centre radiologist (chest, pelvic and abdominal and pelvic computed tomography scans or magnetic resonance imaging, bone scan and X-rays in case of bone lesions) at baseline and every 6 weeks. Patients who progressed before the first evaluation were classified as early progression and early death if dying before first treatment assessment.

Toxicity was evaluated according to NCI CTC (version 2.0) before each chemotherapy administration; pre-treatment electrocardiogram and audiogram were required.

Secondary efficacy endpoints included overall response rate (ORR, both best overall response and objective confirmed response), duration of disease control (DC), duration of SD, duration of response, time to first response, progression-free survival (PFS) and OS.

statistical methods

The null hypothesis H0 was based on the DCR observed with vinflunine single agent in the post-platinum setting. For H1, 38% ORR plus 25% SD rate was selected based on results observed with carboplatin and gemcitabine in unfit patients [12, 13]. With α 5% and β of 20%, 31 assessable patients per arm were needed to detect a DCR improvement of 22% within each arm compared with H0 (41%), the alternative hypothesis H1 being 63%. Assuming 10% non-assessable patients, a total of 68 patients were to be randomized. The primary efficacy analysis of the DCR was planned in the ITT population with 95% confidence interval (CI). Time-dependent parameters, OS, PFS, duration of response and DCR were analyzed with the Kaplan–Meier method. All treated patients were considered for the toxicity analyses. SAS® system software version 9.3 was used for the statistical analysis.

results

From February 2011 to August 2012, 69 patients were enrolled in 23 centres from 6 European countries and Taiwan: 34 in the VG arm and 35 in the VC arm (flow chart see supplementary Figure S1, available at *Annals of Oncology* online); all received at least one dose of the study drugs. The cut-off date for the final analysis was 10 April 2014. At that time, no more patients were on study treatment. The median follow-up was 25.9 months (95% CI 24.3–26.5) with 74% deaths in each arm.

patient characteristics

Baseline demographics were generally well balanced between the two treatment groups. There was a slight imbalance on the primary tumour location: upper urinary tract (UUT) 50% (VG) versus 43% (VC). Slightly more patients on VG had metastatic disease (88% on VG versus 77% on VC). All patients had a CrCl of <60 ml/min (median CrCl of 46 ml/min). Most patients had two or more comorbidities. Detailed patient characteristics are summarized in Table 1.

drug exposure

The median number of cycles was 5 (range1–17) for VG and 4 (range 1–11) for VC. Three patients (9%) in each arm received only one cycle. None of these early interruptions was a consequence of a drug-related adverse event (AE). The planned gemcitabine dose escalation from 750 to 1000 mg/m^2 in cycle 2 for the VG group was possible in 16/31 patients (52%). The median relative dose intensity for vinflunine was 97.4% and 91.3%. Vinflunine dose-reduction was indicated in 6 (17.6%) and 13 (37.1%) patients, in the VG and VC arms, respectively. Main reasons for stopping treatment were progression in 23 patients (14 on VG and 9 on VC) and a drug-related AE in 20 patients (8 on VG and 12 on VC).

Table 1. Patient demographics and clinical characteristics

Main baseline characteristics (all patients randomized)	VG ($N = 34$)	VC ($N = 35$)
Median age (years) [range]	68 [46–79]	72 [42–79]
ECOG PS 0/1, *n* (%)	15 (44%)/19 (56%)	14 (40%)/21 (60%)
Primary tumour site, *n* (%)		
Bladder	17 (50%)	19 (54%)
Upper urinary tract	17 (50%)	15 (43%)
Urethra	0	1 (3%)
Prior locoregional treatments, *n* (%)		
Major surgery[a] [involving kidney]	27 (79%) [50%]	29 (83%) [37%]
Radiotherapy	1 (3%)	4 (11%)
Prior neo- or adjuvant CT, *n* (%)	5 (15%)	6 (17%)
Disease extent, *n* (%)		
Locoregional	4 (12%)	8 (23%)
Metastatic	30 (88%)	27 (77%)
Visceral involvement, *n* (%)	18 (53%)	16 (46%)
Liver metastases, *n* (%)	10 (29%)	8 (23%)
Comorbidities, *n* (%)		
Cardiac disorders (at least 1)	8 (24%)	8 (23%)
Congestive heart failure: stage I/stage II	0 (0)/2 (6%)	4 (11%)/2 (6%)
Diabetes	7 (21%)	7 (20%)
Creatinine clearance: median [range] (ml/min), *n* (%)	47.5 [30.8–59.8]	45.0 [30.0–59.5]
≥60 ml/min	0	0
40–<60 ml/min	28 (82%)	28 (80%)
30–<40 ml/min	6 (18%)	7 (20%)

[a]Radical cystectomy, uretero-nephrectomy.

efficacy

The primary end point DCR was similar in both groups: 77% (Table 2). CR or PR were confirmed in 44% versus 29% of randomized patients ($P = 0.215$). Median PFS was of 5.9 versus 6.1 months and median OS was 14.0 versus 12.8 months ($P = 0.860$) on VG and VC, respectively.

At the time of analysis, 51 patients (25 on the VG and 26 on the VC arm) have died, 46 of which were due to disease progression. A 76-year-old woman died of a myocardial infarction in the setting of an underlying cardiovascular disease. Four additional patients died of non-drug-related reasons (worsening of general condition most probably secondary to unconfirmed disease progression in one case, death for unknown reasons that occurred several months after last study treatment in three patients).

safety

Myelosuppression was less pronounced with VG: G3–4 neutropaenia occurred in 38% and 68% of patients ($P = 0.028$) and this was febrile in only one patient (3%) versus 5 (14%) on the VG and VC arms, respectively (Table 3). G3–4 thrombocytopenia was more pronounced on VC (with 21% versus 6% on VG). No associated bleeding was seen in either group.

Grade 3–4 non-haematological AEs (in >3% of patients) were reported in both arms, including asthenia/fatigue (22%), infection

Table 2. Efficacy parameters and disease status

	VG ($N = 34$)	VC ($N = 35$)
Best ORR	52.9%	42.9%
Confirmed ORR	44.1%	28.6%
Duration of confirmed ORR [median], months	8.2	7.7
Tumour assessments, *n* (%)		
Complete response	3 (8%)	5 (14%)
Confirmed CR	2 (6%)	4 (11%)
Unconfirmed CR	1 (3%)	1 (3%)
PR	15 (44%)	10 (29%)
Confirmed PR	13 (38%)	6 (17%)
Unconfirmed PR	2 (6%)	4 (11%)
Stable disease	8 (24%)	12 (34%)
Progression	6 (18%)	5 (14%)
Non-evaluable	2 (6%)	3 (9%)
Disease control, *n* (%)	26 (77%)	27 (77%)
95% CI	58.8–89.3	59.9–89.6
Duration of DC [median], months	7.2	8.3
PFS [median, months] (censored 20)	5.9 [4.2–9.4]	6.1 [4.6–10·4]
OS [median, months] (censored 23)	14.0 [8.3–20.1]	12.8 [9.5–17.7]
Survival status, *n* (%)		
Alive	7 (21%)	9 (26%)
Dead	25 (74%)	25 (71%)
Lost to follow-up	2 (6%)	0

ORR, objective response rate; CR, complete response; PR, partial response; DC, disease control; PFS, progression-free survival; OS, overall survival.

Table 3. Adverse events (AE)

Possibly related AEs in ≥6% patients in at least one arm (NCI CTC V2)	VG (*N* = 34)				VC (*N* = 35)			
	All G		G3/4		All G		G3/4	
	N	%	*N*	%	*N*	%	*N*	%
Neutropaenia	28	82	13	38	30	88	23	68
Anaemia	33	97	9	27	34	100	9	27
Thrombocytopaenia	24	71	2	6	22	65	7	21
Febrile neutropaenia	1	3	1	3	5	14	5	14
Bleeding or platelet transfusion with Thrombocytopaenia G3–4	0				0			
Asthenia—Fatigue	20	58.8	8	23.5	15	42.9	7	20.0
Infection	4	11.8	4	11.8	1	2.9	1	2.9
Constipation	10	29.4	1	2.9	14	40.0	2	5.7
Ileus	0	0	0	0	1	2.9	1	2.9
Flatulence	3	8.8	0	0	3	8.6	0	0
Abdominal pain	1	2.9	1	2.9	4	11.4	0	0
Diarrhoea	2	5.9	0	0	3	8.6	0	0
Dysphagia	3	8.8	0	0	0	0	0	0
Stomatitis	7	20.6	1	2.9	7	20.0	1	2.9
Nausea	12	35.3	0	0	16	45.7	0	0
Vomiting	7	20.6	0	0	9	25.7	0	0
Weight decrease	9	26.5	1	2.9	8	22.9	0	0
Decreased appetite	10	29.4	0	0	11	31.4	0	0
Musculoskeletal disorders, pain	3	8.8	1	2.9	6	17.1	1	2.9
Phlebitis (deep and superficial)	4	11.8	0	0	1	2.9	0	0
Pyrexia	5	14.7	0	0	2	5.7	0	0
Alopecia	9	26.5	0	0	9	25.7	0	0

AE, adverse events.

(7%) and constipation (4%) without major differences between arms (details in Table 3). Regarding events of special interest, no motor neuropathy was reported. One patient in each arm reported a G1 peripheral sensory neuropathy.

discussion

JASINT1 is the first study assessing the use of vinflunine combinations in this population of patients. The trial focuses on a homogeneous population of patients with good PS (0/1) and with impaired renal function as the single reason for being considered unfit for cisplatin.

Our trial population differs from that in two other published randomized studies in which patients with PS2 and/or renal impairment were enrolled [13, 14]. In these two studies, gemcitabine–carboplatin (GC) versus methotrexate, carboplatin, vinblastine [13], and gemcitabine–oxaliplatin versus gemcitabine alone [14], were compared.

Other smaller sized uncontrolled trials also differ with respect to the definition for patients being unfit for cisplatin [6]. One trial with 25 patients who received sequential doxorubicin–gemcitabine followed by paclitaxel–carboplatin was conducted in favourably selected patients with PS ≤1 and inclusion criteria allowed for a solitary kidney as a reason for cisplatin ineligibility in addition to CrCl of <60 ml/min [15]. This is contrasted by our study in which distant metastases were present in 88% of patients and visceral disease in 49%. Such differences of inclusion criteria preclude any cross study efficacy comparison [16].

Another study by Balar et al. assessed the combination of bevacizumab with GC in 51 platinum-ineligible patients. This study included patients with a good Karnofsky index (92% of patients) but with renal dysfunction (76%). A solitary kidney or the presence of visceral metastases was also considered as the criterion for cisplatin ineligibility [17].

Indeed, in PS ≥2 patients, tolerance of chemotherapy is a relevant concern. It might differ substantially from that of good PS patients in whom efficacy usually is the driving end point. Interestingly, the only phase III trial in unfit patients, the EORTC trial 30986, that considered 2 criteria of cisplatin ineligibility (PS2 and/or GFR <60 ml/min) showed a high level of severe acute toxicities and a high degree of treatment abortion in patients presenting both criteria. These results prompted the authors to make a recommendation against the use of cytotoxic doublets in this particular patient group [13].

Comparing the baseline distribution of disease characteristics between the two treatment arms of our study, there was a slight imbalance concerning the primary tumour site and the presence of distant metastases favouring the VC arm. This imbalance limits the conclusions drawn for efficacy for the subgroups.

Our study population differs from others by a considerably higher rate of patients with UUT tumours (46%) [15, 17]. However, our trial, and despite an 'unfit' patient population, does not support the general assumption of a worse outcome of advanced or metastatic UUT tumours compared with those located in the urinary bladder. To date, no comparative prospective trial for metastatic UUT tumours versus bladder as the primary location has been published.

We chose a cautious gemcitabine dose-escalation approach for the VG combination [18]. The results revealed that gemcitabine could be escalated in cycle 2 in only 52% of patients, which supports our conservative approach. Of note, using our per-protocol dosing schedules, both vinflunine combinations were feasible with a high percentage of adequate relative dose intensity for all drugs.

Haematological toxicity clearly favoured the VG combination. Compared with the most commonly used GC combination (EORTC 30986 study arm), less G3–4 neutropaenia (38.2% versus 52.5%), febrile neutropaenia (2.9% versus 4.2%) and in particular less G3–4 thrombocytopaenia (5.9% versus 48.3%) were observed with VG [13] and no toxic death was reported. In our study, the gastrointestinal tolerance of both VG and VC was better than previously reported with vinflunine single agent in the post-platinum setting [8, 19].

Regarding activity of the two regimens in our study, the statistical assumption was met for both combinations with a similar 77% DCR. The confirmed response rate favoured VG and all other efficacy parameters, including a PFS of 5.9 months, suggested high levels of activity that compares favourably with the best available chemotherapy data in this setting [6].

Although OS was not the primary end point in this study, the observed 14 months' median OS in the VG group is promising in a cisplatin-unfit patient population with rather advanced and unfavourable disease characteristics. To put this into perspective, the most favourable subgroup out of the EORTC 30986 trial, 131 patients with PS0/1 and impaired renal function, showed a median OS of only 12 months [13].

There are clear limitations of our study. The absence of a non-investigational control arm precludes firm conclusions about any superiority of one of our treatment arms compared with other combination such as GC.

The primary end point of our study, DCR is not a standard end point for efficacy in this patient population. Therefore, the efficacy assumptions follow a general sense of clinically meaningful study end points in this disease but might be considered rather arbitrary. However, also other more commonly used end points for drug screening in small phase II single-arm UC trials like RECIST response have limited reliability [3, 20–24]. Duration of response or disease stabilization in the context of drug screening, as in our trial, might be more meaningful.

In conclusion, both vinflunine-based doublets were active while VG was better tolerated in cisplatin-unfit patients with a PS 0–1. The statistical assumption was met in both study groups with a DCR of 77%. The confirmed response rate of 44.1%, an OS of 14 months and less haematological toxicity favour the VG combination. These promising results warrant further development and are the basis for a planned comparison of VG with the widely used GC combination, for cisplatin-unfit patients.

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disclosure

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A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel

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Background: Few prognostic models for overall survival (OS) are available for patients with metastatic castration-resistant prostate cancer (mCRPC) treated with recently approved agents. We developed a prognostic index model using readily available clinical and laboratory factors from a phase III trial of abiraterone acetate (hereafter abiraterone) in combination with prednisone in post-docetaxel mCRPC.

Patients and methods: Baseline data were available from 762 patients treated with abiraterone–prednisone. Factors were assessed for association with OS through a univariate Cox model and used in a multivariate Cox model with a stepwise procedure to identify those of significance. Data were validated using an independent, external, population-based cohort.

Results: Six risk factors individually associated with poor prognosis were included in the final model: lactate dehydrogenase > upper limit of normal (ULN) [hazard ratio (HR) = 2.31], Eastern Cooperative Oncology Group performance status of 2 (HR = 2.19), presence of liver metastases (HR = 2.00), albumin ≤4 g/dl (HR = 1.54), alkaline phosphatase > ULN

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