Vinflunine as second-line treatment in platin-resistant metastatic urothelial carcinoma: a review

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The novel third-generation bifluorinated semisynthetic vinca alkaloid, vinflunine, is a microtubule inhibitor that shows superior antitumor activity and a favorable safety profile compared with other vinca alkaloids. The main antineoplastic effects of vinflunine arise from its interaction with tubulin, the major component of microtubules in mitotic spindles. Vinflunine is known to have low affinity for tubulin, high intracellular accumulation, and important effects on microtubule dynamics. It has been shown to have activity against transitional cell carcinoma of the urothelial tract. Vinflunine was investigated in a randomized phase III clinical trial comparing vinflunine and best supportive care versus best supportive care alone in patients with advanced transitional cell carcinoma of the urothelial tract, who were progressive after first-line platinum-containing therapy. At an acceptable safety profile without cumulative toxicity, second-line treatment with vinflunine has shown a survival advantage and has therefore been approved in 2009 for this indication.

This review gives a brief outline on vinflunine as a second-line treatment for platin-resistant advanced urothelial carcinoma; it describes pharmacology, efficacy studies, tolerance, and side effects and briefly discusses future clinical perspectives. *Anti-Cancer Drugs* 22:9–17 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

With approximately 136 000 newly diagnosed cases per year in Europe, with a three times higher risk for men than women, carcinoma of the urothelium is the second most common cancer of the urogenital tract and the fourth most common malignancy overall [1]. Nowadays, transitional cell carcinoma of the urothelial tract (TCCU) has a high prevalence in the elderly, which is why approximately 80% of those who are affected are aged 50–79 years [2]. Malignancies of the urinary tract are mostly transitional carcinoma, which in 90% of the cases are localized in the urinary bladder, whereas 10% are tumors of the ureter or renal pelvis. The majority of patients with bladder cancer are diagnosed with superficial tumors. Prognosis for superficial tumors depends on the degree of differentiation, size, and quantity of tumor lesions in the organ (bladder), the presence or absence of carcinoma *in situ*, and earlier lesions and respective recurrent tumors. Treatment of bladder carcinoma strictly follows the respective stage of disease. Even though superficial tumors can be completely resected by transurethral techniques, the risk of recurrence remains high: approximately 50–70% of these patients will develop tumor recurrence within 5 years after diagnosis, and almost 90% will have a recurrence of their disease within 15 years. Almost 25% of the patients with Ta and T1 noninvasive tumors will eventually develop invasive disease in the future. When diagnosed, 20–30% of transitional cell carcinomas (TCCUs) display muscle infiltration, of which 50% metastasize [3]. Patients with stage T2 tumors have a 5-year survival rate of 60%, but only 35% of patients with stage T3 tumors and 10% of patients with stage T4 metastatic tumors survive 5 years. The prognosis of patients with metastatic TCCU remains poor, with a median survival of only 12–14 months [4,5].

Treatment of bladder cancer strictly follows stage-dependent recommendations. Superficial tumors are normally resected transurethrally and a postoperative intravesical instillation therapy leads to a decreased risk of recurrence. Within a narrow time frame of 4–6 weeks after initial tumor resection, in the T1 or G3 tumors, a second transurethral reevaluation and resection is recommended to exclude residual tumors. For patients with invasive bladder cancer, radical cystectomy with bilateral lymphadenectomy and urinary diversion remains the surgical standard procedure.

Although a neoadjuvant chemotherapeutic approach may increase the 5-year survival rate by 5% [6,7], the effectiveness of adjuvant chemotherapy is currently under discussion [8]. As urothelial carcinoma is a chemosensitive cancer, treatment in the metastasized stage includes

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cytostatic approaches. First-line therapy based on cisplatin was shown to reach an overall survival rate of 14 months and has been the standard of care for urothelial TCCU for more than 20 years.

For patients who are suitable for this cytostatic approach, several combinations of cytostatic agents are offered as first-line treatment, such as M-VAC (methotrexate, vinblastin, doxorubicin, cisplatin), high-dose intensity (HD)-M-VAC, MC (methotrexate, cisplatin), and GC (gemcitabin, cisplatin). Among these, MC, HD-M-VAC (+ G-CSF), and GC were shown to be less toxic compared with the classic M-VAC regimen. For patients who are not adequate candidates for a cisplatin-containing therapy, combination therapy or monotherapy with carboplatin is currently recommended [8]. Patients who are progressive under or after platin-containing therapy have a very poor prognosis. Until recently, for these patients no established second-line treatment was available. However, different cytostatic, biologic, and targeted drugs were evaluated in clinical trials. Tables 1 and 2 give an overview of clinical trials investigating different second-line approaches as single-agent or combination therapy for platinum-refractory advanced or metastasized TCCU. However, these trials were not randomized and included a few patients with earlier heterogeneous therapies, thus not allowing a definitive validation. Therefore, for patients at this stage of disease, different empirically developed therapies were applied. Most recently, vinflunine (Javlor), an innovative cytostatic drug for the treatment of recurrent, advanced, disseminated urothelial carcinoma, after the failure of platin-containing first-line therapy, was successfully investigated in a phase III trial and approved for this indication in September 2009, offering an evidence-based therapeutic option for this long-standing unsatisfying therapeutic situation [34]. This review gives a brief outline on vinflunine as a second-line treatment for platin-resistant advanced urothelial carcinoma; it describes pharmacology, efficacy studies, tolerance, and side effects and discusses current clinical implications and possible therapeutic perspectives.

Mode of action and preclinical studies

Vinflunine was discovered in 1998 by scientists of the Pierre Fabre research center in collaboration with the University of Poitiers in France.

Using superacidic chemistry, the third-generation semisynthetic vinca alkaloid vinflunine (Javlor) was primarily obtained by the selective introduction of two fluorine atoms at the C20′-position of vinorelbine, a part of the molecule, inaccessible earlier by classical chemistry [35,36]. Under hyperacidic circumstances, the molecule vinflunine remains stable and functionally active (Fig. 1).

Table 1 Single agent second-line treatment (targeted therapy)

Trial	Regimen	*N* (evaluable)	RR (%)	TTP (months)	OS (months)
Gomez-Abuin *et al.* [9]	Bortezomib	18 (11)	0	NR	NR
Wülfing *et al.* [10]	Lapanitib	59 (59)	2	2.0	4.1
Cheung *et al.* [11]	Vorinostat	14 (12)	0	1.1 (DFS)	2.1
Dreicer *et al.* [12]	Sorafenib	27 (22)	0	2.2 (PFS)	6.8
Gallagher *et al.* [13]	Sunitinib	45 (41)	7.3	NR	NR
Rosenberg *et al.* [14]	Bortezomib	25 (24)	0	1.4	5.7
McCaffrey *et al.* [15]	Docetaxel	(30)	13	NR	9.0
Lorusso *et al.* [16]	Gemcitabine	(31)	23	3.8	5.0
Witte *et al.* [17]	Ifosfamid	(56)	20	2.2	5.1
Moore *et al.* [18]	Oxaliplatin	(18)	6	NR	NR
Vaughn *et al.* [19]	Paclitaxel	(31)	10	2.2	7.2
Sweeney *et al.* [20]	Pemetrexed	(47)	28	2.9	9.6
Roth *et al.* [21]	Piritrexim	(27)	7	2.1	7.0
Dodd *et al.* [22]	Pyrazoloacridin	(14)	0	NR	9.0

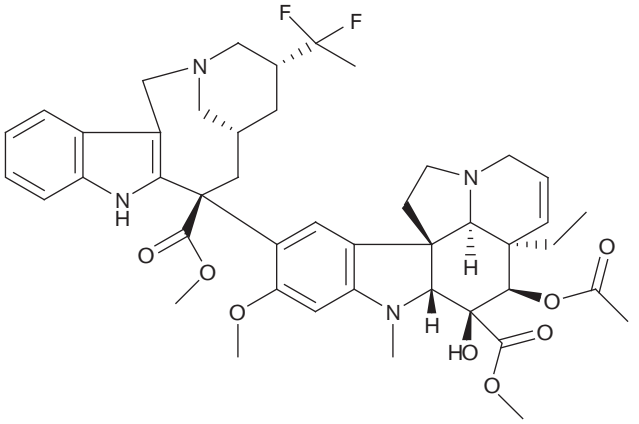
DFS, disease-free survival; NR, non reported; OS, overall survival; PFS, progression free survival; RR, response rate; TTP, time to progression.

Table 2 Combination chemotherapy as second-line treatment (targeted therapy)

Trial	Regimen	*N* (evaluable)	RR (%)	OS (months)
Sella *et al.* [23]	5-FU/α-interferon/cisplatin	28 (NR)	61	NR
Tu *et al.* [24]	Paclitaxel/methotrexate/cisplatin	25 (25)	40	NR
DeMulder *et al.* [25]	5-FU/α-interferon/cisplatin	43 (40)	13	4.9
Krege *et al.* [26]	Docetaxel/ifosfamid	22 (20)	25	4.0
Bellmunt *et al.* [27]	Methotrexat/paclitaxel	20 (19)	32	5.0
Pagliaro *et al.* [28]	Cisplatin/gemcitabine/ifosfamid	51 (49)	41	9.5
Chen *et al.* [29]	Docetaxel/gemcitabine/carboplatin	NR (9)	56	NR
Lin *et al.* [30]	Gemcitabine/ifosfamid	23 (23)	22	4.8
Sternberg *et al.* [31]	Gemcitabine/paclitaxel	41 (40)	60	14.4
Takahashi *et al.* [32]	Gemcitabine/paclitaxel	23 (23)	30	12.1
Suyama *et al.* [33]	Gemcitabine/paclitaxel	33 (30)	33	11.3

NR, non reported; OS, overall survival; RR, response rate.

Fig. 1



Structure of vinflunine.

Vinflunine interacts with the so-called vinca-alkaloid-binding domain of tubulin, as judged by the proteolytic cleavage patterns [37], and, more recently, confirmed by nuclear magnetic resonance spectroscopy [38]. As formerly shown, microtubules are an important target for anticancer therapy. They play a crucial role during mitosis, coordinating chromosomal segregation. The respective microtubule inhibitors are manifold and include vinca alkaloids, taxanes, and epothilones. Distinctive features are expressed by vinflunine such as the affinity to bind to tubulin, although it is considerably lower than that of the other vinca alkaloids. In addition, binding to unassembled tubulin by other vinca alkaloids is not prevented by vinflunine. The binding affinities of different vinca alkaloids to tubulin were classified as vincristine, vinblastine, vinorelbine, vinflunine, which correlated well with the weekly intravenous drug doses of these vinca alkaloids used in the clinic for different indications [39].

Singer *et al.* [40] found an inverse correlation between the relative binding affinities and inhibition of cell proliferation when examining four different vinca alkaloids, suggesting that the binding affinity of vinca alkaloids to tubulin is not necessarily related to the degree of antitumor efficacy. This hypothesis was supported by Jordan *et al.* [41] who described that, in contrast to their relative abilities to inhibit microtubule assembly *in vitro*, vinblastine and its derivative, vindesine, were more potent than vincristine and vinepidine in inhibiting cell proliferation in culture. The affinity of vinflunine binding to tubulin is considerably lower than that of the other vinca alkaloids reaching high intracellular concentrations [42]. Microtubules display two types of characteristic behavior, both crucial for progression through mitosis and the cell cycle: first 'dynamic instability', which displays a random switching of microtubules between phases of relatively slow growth and rapid shortening and second, 'treadmilling', which is a net addition of tubulin subunits at the fast-growing plus end of a microtubule and the balanced net loss from the opposite slow-growing minus end.

Vinflunine and vinorelbine have different effects on microtubule dynamics that significantly differ from those of the classic vinca alkaloid, vinblastine [43,44]. Suppression of the rate and extent of microtubule growth was supported by vinflunine and vinorelbine. Vinflunine was shown to inhibit the rate of treadmilling four-fold less strongly than vinorelbine and seven-fold less strongly than vinblastine, which led to the hypothesis that nontumor cells with 'normal' checkpoint proteins could tolerate the relatively less powerful inhibitory effects of vinflunine and vinorelbine on microtubule dynamics rather than the more powerful effects of vinblastine, whereas tumor cells with frequently 'faulty' checkpoint mechanisms may be more susceptible to vinflunine and vinorelbine than normal cells. This theory was considered to explain the superior antitumor efficacy and the favorable safety profile of vinflunine.

When binding to tubulin, vinflunine induces structural changes inhibiting guanosine-5′-triphosphate hydrolysis and microtubule assembly, thereby reducing the microtubule network of interphase cells and inducing G2 + M arrest *in vitro*. Finally, this mode of action results in apoptosis by mitotic accumulation at the metaphase/anaphase transition [45–47].

A broad spectrum of its activity was suspected when, in preclinical in-vivo studies, vinflunine showed definite antitumor activity against seven of the 11 (64%) subcutaneously implanted human tumor xenografts compared with vinorelbine that had shown only moderate activity against three of the 11 (27%) xenografts [48,49]. Vinflunine led to significant prolongation of survival of tumor-bearing mice and tumor growth inhibition with optimal, treated versus control, values of up to 45% in the absence of any significant body weight loss, providing evidence of a high level of tolerance to these effective antitumor doses of vinflunine. Synergistic effects of several vinflunine combinations in a human nonsmall cell lung cancer (NSCLC) line and a human leukemia cell line after incubation of vinflunine with camptothecin, cisplatin, doxorubicin, etoposide, 5-fluorouracil, gemcitabine, mitomycin C, paclitaxel, or vinorelbine were observed, [50] whereas relevant synergistic cytotoxicity of vinflunine was observed when combined with the DNA-damaging agents cisplatin and mitomycin C and the p-53 triggered cell death-inducing agents doxorubicin and the antimetabolite 5-fluorouracil. In a transplantable murine tumor model, Holwell *et al.* [51] investigated the influence of vinflunine on tumor vascularization and showed morphologic changes after treatment with vinflunine in terms of extensive hemorrhagic necrosis, which could be supported by the finding of a vascular

shutdown over a minimum of 24 h at doses considerably lower than the maximum tolerated dose, suggesting that antitumor activities of vinflunine are mediated through an antivascular pathway showing relevant antiangiogenic effects [52].

It is assumed that vinflunine belongs to the p-glycoprotein-dependent multidrug resistant family of anticancer agents. However, the level of cross-resistance expressed with vinflunine was generally lower than that with vinorelbine or vincristine. It was observed that vinflunine induces drug resistance far less readily than vinorelbine, both in terms of the time taken for resistance to be established and the level of resistance ultimately obtained [53,54]. Bonfil *et al.* [55] examined the effect of vinflunine on a murine bladder cancer cell line to investigate the feasibility of systemic treatment of transurethrally implanted transitional carcinoma of the bladder with vinflunine. The results of their studies showed clear antitumor activity of vinflunine against this superficial bladder cancer model, superior to that of vinorelbine, with a good overall tolerance, suggesting a possible role for vinflunine in the systemic treatment of bladder cancer.

The results of in-vitro and in-vivo studies were promising and implicated manifold possibilities for combination therapies with vinflunine in different types of cancer resulting in incipient clinical trials. Initially, a large, three-armed study in NSCLC patients showed significantly higher response rates (RRs) for the parent compound, vinorelbine, when combined with cisplatin, compared with either vinorelbine alone or the combination of vindesine and cisplatin [56]. Another early combined phase I/II trial in NSCLC patients combining vinflunine with cisplatin was very encouraging with a RR of 33% and a disease control rate of 77% [57].

Pharmacology

The pharmacokinetic profile of vinflunine was investigated in 500 cancer patients with different solid tumors receiving 800 treatment cycles of vinflunine. An intravenous infusion of 320 mg/m^2 vinflunine over 15–20 min once every 3 weeks is the classic dosing schedule of vinflunine in most patients. Depending on the performance status (PS) of the patient, an initial or reduced dose of 280 mg/m^2 was applied. In contrast to other microtubule inhibitors, vinflunine is freely water soluble and does not require solvent formulation, which eliminates the risk of solvent-related hypersensitivity reactions and the need for steroid or antihistaminic premedication. In patients with different solid tumors participating in phase I trials, the mean terminal half-life of vinflunine was shown to be approximately 40 h; the only active metabolite of vinflunine, 4-*O*-deacetylvinflunine (DVFL), has a terminal half-life of 4–6 days. Vinflunine exhibited moderate binding to serum proteins. Vinflunine excretion is higher in feces (2/3) than in urine (1/3), which reduces the risk of accumulation in patients with renal or hepatic impairment. After infusion, vinflunine diffuses rapidly and extensively; the volume of distribution is estimated at approximately 2.422 ± 676 l (35 l/kg), suggesting a large tissue distribution and cellular uptake [58–60]. Plasma protein binding is 67% and is not saturable. The active metabolite of vinflunine, 4-*O*-deacetylvinflunin, is metabolized under the influence of CYP3A4.

Applied in doses from 30 to 400 mg/m^2 plasma concentrations of vinflunine and DVFL, respectively, increase proportionally to the applied doses [61,62]. Pharmacokinetic studies in elderly patients ($\geq$ 75 years) did not show any differences with regard to safety, thus no specific dose recommendation for this age group was necessary.

On account of the reduced vinflunine clearance in patients with renal damage, a dose of 280 mg/m^2 (40 ml/min $\leq$ ClCR $\leq$ 60 ml/min) every 3 weeks and 250 mg/m^2 (20 ml/min $\leq$ ClCR $\leq$ 40 ml/min) every 3 weeks is recommended in cases of moderate and severe kidney impairment, respectively [63]. In patients with impaired liver function, pharmacokinetics of vinflunine and DVFL remain unaltered. However, in cases of moderate or severe hepatic alteration (level 2–3), a dose reduction to 250 or 200 mg/m^2 every 3 weeks is recommended. As vinflunine is metabolized over CYP3A4, strong inhibitors of CYP3A4 (e.g. ketoconazol, itraconazol, ritonavir, and grapefuit juice) may increase the blood exposition of vinflunine and DVFL to a large extent. Therefore, vinflunine should neither be given in combination with these drugs nor with CYP3A4 inducers such as rifampicin. Possible interactions with taxanes as substrates for CYP3A4 resulting from an in-vitro study as an inhibition of vinflunine metabolism were shown. However, no specific clinical results are currently available to support this hypothesis. In contrast to conventional doxorubicin, which does not influence the pharmacokinetics of vinflunine, a phase I trial suspected interactions with pegylated/liposomic doxorubicin resulting in an increased vinflunine exposition of 15–30% and a reduced area under the curve of concentration over time by 2–3 times for doxorubicin. A combination of both components should therefore be applied taking strict precautions.

Clinical trials

Clinical development of vinflunine started in 1998 with the initiation of three phase I clinical trials with different schedules of intravenous administration to define the maximum tolerated dose/recommended dose for vinflunine as a single agent. Vinflunine was applied in patients with solid tumors. The results of these trials are summarized in Table 3.

Dose-limiting toxicities in these classical, single-agent phase I trials included grade 4 neutropenia, febrile

Table 3 Phase I trials with Javlor

Author	Number of patients	Time schedule	Dose (mg/m^2)	Recommended dose (mg/m^2)
Bennouna *et al.* [58]	31	D1, q3w[a]	30–400	350
Vermorken *et al.* [64]	34	Weekly	120–250	120–150
Johnson *et al.* [60]	16	D1, D8, q3w[b]	170–210	170

[a]D1, q3w: day 1 in a 3-week schedule: recommended dose at 350 mg/m^2 every 3 weeks.
[b]D1, D8, q3w: day 1 and day 8 every 3 weeks: recommended dose at 170 mg/m^2.

neutropenia, grade 3/4 constipation, and grade 3 myalgia. In patients with kidney cancer and breast cancer, the first evidence for antineoplastic activity was documented. Different phase I trials with vinflunine in combination with other anticancer drugs were performed or are still ongoing. These trials include the combination of vinflunine with pemetrexed, trastuzumab, carboplatin, gemcitabine, cisplatin, capecitabine, erlotinib, and cetuximab [57,65–69].

The resulting recommended treatment schedule of 320 mg/m^2 every 3 weeks in patients with a good PS and no earlier extended pelvic irradiation, and 280 mg/m^2 for other patients (reduced Karnofsky Performance Score, past irradiation, renal impairment, age >75 years) was implemented in the following clinical investigations. Clinical efficacy for vinflunine in patients with platin-resistant TCCU was shown in a clinical program that included two phase II trials ($n = 202$) and one randomized phase III trial ($n = 253$).

European phase II trial (vinflunine 202)

Fifty-eight bladder cancer patients were recruited in a multicenter trial by 16 European centers between November 2000 and September 2002. Patients enrolled had earlier failed or progressed after first-line platinum-containing chemotherapy or after platinum-containing regimens given with adjuvant or neoadjuvant intent [70]. Patients received the recommended dose of vinflunine every 3 weeks. The primary objective of the trial was the overall response rate (ORR); secondary objectives were duration of response, progression-free survival (PFS), overall survival (OS), and safety. Eligibility criteria included a Karnofsky PS (KPS) of 80 or higher and a glomerular filtration rate of at least 40 ml/min. One patient died before receiving the treatment and was not included in the analysis. Eighty percent of the included patients were male, 61% had reached an advanced stage of disease (locally advanced or metastatsized), and 55% had a KPS of 100 or 90. Surgery had been performed earlier in 61% of the patients and 24% had earlier received irradiation of the pelvis resulting in the reduced dosage scheme described. Prior first-line approaches included GC (49%, $n = 25$) and M-VAC/CMV (cisplatin, methotrexate, vinblastin 43%, $n = 22$). In 34 (67%) patients, previous chemotherapy was performed because of disseminated disease (first line), whereas in 17 (33%) patients prior chemotherapy was performed with neoadjuvant/adjuvant intention. Twenty (59%) of the 34 patients with advanced disease had responded to their first-line therapy. The median treatment-free interval between completion of initial chemotherapy and vinflunine treatment was 7.5 months. All the patients enrolled in the study had clear evidence of progressive disease, 61% had two or more metastatic lesions at entry, and 49% had visceral involvement. The disease control rate was 67% with nine (18%) partial responses and 25 patients with stable disease. A correlation between the disease control rates and the interval from the last platinum treatment with better results in late relapsing or progressing patients was suspected. ORRs were eight of 34 (24%) and one of 17 (6%) in the patients treated earlier in the metastatic and neoadjuvant/adjuvant setting, respectively. In particular, patients who had responded to chemotherapy earlier, seemed to respond to vinflunine therapy. An objective response was achieved in five of the 25 (20%) patients with visceral involvement. The median duration of response was 9.1 months. Among the 51 patients treated with 320 mg/m^2, the median PFS was 3 months and median OS was 6.6 months. KPS improved in 11 patients (22%), decreased in 10 (22%) patients, and did not alter in 27 (53%) patients during the treatment. Toxicity was generally easily manageable and did not cumulate; the grade 3/4 hematological toxicity predominantly observed was neutropenia (67%), with five patients (10%) experiencing febrile neutropenia, two of whom died; both had received multiple courses of vinflunine. The grade 3/4 nonhematologic toxicities mainly seen included fatigue (10%), constipation (8%), and abdominal pain (8%). No grade 3/4 peripheral neurotoxicity and no grade 3/4 rise in serum creatinine were observed.

North American phase II trial (CA 001)

To confirm the results from the European phase II trial (vinflunine 202), Vaughn *et al.* [71] published in 2009 the results of a second international phase II trial, mainly recruiting in the United States. The eligibility criteria were comparable with vinflunine 202: patients included were restricted to no more than one platinum-based regimen in the past with disease progression within 12 months of treatment, a Karnofsky Performance Score of 80, and a creatinine clearance of 20 ml/min. However, the study population had a worse prognosis compared with vinflunine 202. Although representative for a population with advanced TCUU, CA 001 had more refractory patients (78%) showing progression or recurrent disease within 6 months after the initiation of first-line platinum-containing therapy. In addition, the included patients showed a higher rate of comorbidities such as renal impairment (40%), and metabolic and

cardiovascular disorders (69%). Ninety-three percent of the patients had undergone a surgery earlier and 12% had undergone irradiation of the pelvis.

The primary endpoint of the study was ORR. From the 175 patients enrolled initially, 151 received treatment and were included in the analysis. Vinflunine 320 mg/m^2 was administered once every 3 weeks as a 15- to 20-min intravenous infusion. Patients with KPS 90 or 80, earlier pelvic irradiation, over 75 years of age, or a creatinine clearance between 20 and 60 ml/min received an initial dose of 280 mg/m^2, which was escalated to 320 mg/m^2 from cycle II onwards, based on tolerance. The investigators reported *22* partial responses with a median duration of 6 months, equivalent to an ORR of 14.6%. Stable disease was seen in 64 patients (42.4%) with a median duration of 4 months, resulting in a disease control rate of 57.0%. Median PFS was 2.8 months and median OS was 7.9 months. Tolerability and adverse event profile were similar to the data resulting from vinflunine 202, with 58.1% of the patients experiencing neutropenia grade 3/4 and 10 patients (6.6%) with neutropenic fever. Grade 3/4 nonhematologic toxicities included constipation (16.6%), asthenia/fatigue (12.6%), ileus (4.6%), and abdominal pain (4.6%). The results of CA 001 were consistent with the European trial vinflunine 202.

Phase III randomized trial (vinflunine 302)

In September 2009, Bellmunt *et al.* [34] published the results of a prospective multicenter, randomized (2:1) phase III trial comparing vinflunine and best supportive care (BSC) (arm A) versus BSC alone (arm B) in platinum-pretreated patients. Enrollment of 370 patients with unresectable, locally advanced or metastasized TCCU between May 2003 and August 2006 was spread across 83 institutions in 21 countries. OS was defined as the primary endpoint; secondary endpoints included PFS, RR, disease control, clinical benefit, and quality of life (QoL). Stratification factors were center and refractory disease. 'Moderate neuropathy' was defined as an exclusion criterion. Vinflunine was administered intravenously at a dose of 320 mg/m^2 every 3 weeks, except for patients with a PS of one and/or earlier pelvic irradiation who started at 280 mg/m^2 with a subsequent dose escalation to 320 mg/m^2, if possible. Patient characteristics are summarized in Table 4, and were mainly well balanced except for the performance score that slightly favored arm B (PS 1 arm A 71.5%, arm B 61.5%). Bulky disease was observed in 40% of the patients, whereas 74% showed visceral involvement and over 80% of the involved patients had relapsed or progressed within 6 months after first-line platinum-containing chemotherapy.

A high incidence of neutropenia grade 3/4 was observed (50%) in the vinflunine arm, but only 6% of the patients suffered from febrile neutropenia. There was one toxic death. Table 5 gives an overview of the grade 3/4 adverse events.

Table 4 Patients' characteristics – phase III study (VFL 302)

	Javlor + BSC (n = 253)	BSC (n = 117)
Age		
Median age (years)	64.2	64.2
<65 years (%)	53.4	51.3
≥ 65 years (%)	46.6	48.7
Sex		
Male (%)	77.9	81.2
Female (%)	22.1	18.8
WHO performance score		
0 (%)	28.5	38.5
1 (%)	71.5	61.5
Earlier therapy		
Surgery (%)	89.7	88.0
Radiotherapy (%)	22.5	22.2
Tumor localization		
Renal pelvis, ureter (%)	20.6	14.5
Bladder (%)	79.4	84.6
Urethra (%)	0	0.9
Number of organs		
1 (%)	24.5	26.5
2 (%)	34.4	33.3
≥ 3 (%)	41.1	40.2
Visceral metastases (%)	73.9	74.4
Creatinine clearance (ml/min)		
<40 (%)	4.0	3.4
40–60 (%)	41.9	35.0
≥ 60 (%)	54.0	59.0

BSC, best supportive care; VFL, vinflunine.

Table 5 Treatment-related adverse events and hematological abnormalities for vinflunine second-line therapy in advanced urothelial carcinoma, Phase III study (VFL 302)

	VFL + BSC		BSC	
Adverse events and hematological abnormalities	Overall incidence (%)	Grade 3/4 (%)	Overall incidence (%)	Grade 3/4 (%)
Asthenia/fatigue	50.0	19.3	60.7	17.9
Constipation	47.6	16.1	24.8	0.9
Nausea	39.1	2.4	21.4	0.9
Injection site reaction	27.4	0.4	0	0
Alopecia	29.0	0	1.7	0
Vomiting	29.0	2.8	14.5	0
Stomatitis	28.6	1.6	1.7	0
Abdominal pain	15.7	4.0	17.9	6.0
Myalgia	16.1	3.2	6.8	0
Neuropathy sensory	12.1	1.2	11.1	0
Anemia	93.1	19.1	61.3	8.1
Thrombocytopenia	51.2	5.7	16.2	0.9
Neutropenia	77.2	50.0	2.7	0.9
Febrile neutropenia	6.0	6.0	0	0

BSC, best supportive care; VFL, vinflunine.

The statistical hypothesis in this trial was an OS benefit of 2 months in the vinflunine group (6 vs. 4 months). When analyzing the intent-to-treat-population, the 2-month survival advantage for arm A was achieved (6.9 vs. 4.6 months). However, it did not reach statistical significance (P value 0.29). In a preplanned analysis looking only at eligible/per protocol patients (13 patients not eligible, 19 patients not treated according to protocol), the median OS was 6.9 months in the vinflunine arm and 4.3 months in the BSC arm (P value of 0.04 for eligible patients and 0.02 for per protocol patients).

A multivariate analysis adjusting for prognostic factors also showed a statistically significant effect of vinflunine on OS ($P = 0.04$), although other factors such as hemoglobin level, visceral involvement, or PS had a stronger impact on survival than treatment with vinflunine. ORR in the vinflunine arm was 8.6%, which was clearly lower than that of the earlier phase II trials; the disease control rate was 41.1% and PFS was 3 months. Despite the low RR, these responses were durable as the median duration of response was 7.4 months and the median duration of disease control was 5.7 months. Patients in the vinflunine arm had a median duration of treatment of 9.5 weeks. QoL results have not yet been reported.

The intention-to-treat analysis of ORR, disease control, and PFS showed that treatment with vinflunine led to a prolonged disease control.

Rationale of vinflunine 202, CA 001, and vinflunine 302

The described phase II clinical trials (vinflunine 202 and CA 001) included a total of 202 patients with advanced TCCU. Demographic characteristics in both trials were comparable with the exception that CA 001 included more refractory patients.

As patients of the phase III trial (vinflunine 302) were diagnosed in a second-line setting, they had shown a more advanced stage of disease and were shown to be more refractory compared with the patients from the phase II trials. Including the secondary analyses, a statistically significant advantage in OS could be shown for vinflunine. Secondary endpoints, such as PFS, were favorable for suggesting an effective treatment option with vinflunine in this clinical setting. As the results for OS remained consistent after a 2-year follow-up in subgroup analyses, the clinical benefit for patients could be confirmed. In conclusion, the data received from these clinical trials showed a significant benefit for patients receiving vinflunine as a second-line treatment after the failure of first-line platinum-containing chemotherapy in advanced/metastasized TCCU, with focus on disease control, OS, and PFS at an acceptable side-effect profile. Thus, vinflunine (Javlor) was officially approved by the European Medicines Agency on 21 September 2009 for this indication.

Prognostic factors

All 370 patients with platinum-refractory TCCU participating in the vinflunine 302 trial were included in an analysis to identify the possible pretreatment prognostic factors for OS in patients with metastatic TCCU who had experienced treatment failure with the first-line platinum-based regimen and had subsequently received second-line treatment with vinflunine. Bellmunt *et al.* [72] used an univariate analysis to identify the clinical and laboratory factors that had significantly affected survival in their cohort. An Eastern Cooperative Oncology Group PS higher than 0, a hemoglobin level less than 10 g/dl, and the presence of liver metastasis were identified as the main adverse prognostic factors for OS. These prognostic factors were confirmed by external validation. The authors developed a scoring system classifying patients with platinum-refractory disease on second-line chemotherapy into four risk groups with different outcomes and concluded that similar to the first-line setting, the presence of visceral metastases and poor PS predicts a worse prognosis. These factors, together with low hemoglobin, were judged to be useful for the prognostication and stratification of patients in future clinical trials.

Perspective

In the future, with the extended application of neoadjuvant and adjuvant chemotherapy in localized and disseminated TCCU, the proportion of metastatic cancer patients with cisplatin-refractory disease at presentation is predicted to rise. The recent approval of vinflunine offers a therapeutic option for patients in this palliative setting. Vinflunine may be a new standard in this indication; at least, it is the drug that has reached the highest level of evidence ever reported for a single agent in second-line treatment of refractory advanced TCCU. Nevertheless, future plans have to be carefully considered. Having achieved these clinical results does not imperatively imply a second-line standard of care that needs to lead to the development of further phase III trials comparing vinflunine with other approaches, novel agents, and/or combinations. However, there is an interest in pursuing these additional comparative studies of other agents versus vinflunine in this palliative setting. It remains to be seen if the results of the phase III trial with vinflunine are going to alter the current treatment paradigms for this group of patients. Although superior to BSC, an OS benefit of 2 months has to be carefully balanced against the side effects at this end stage of disease. QoL remains the most important aim for this indication. It seems probable that many clinicians will still offer cytotoxic therapy with the aim of either improving or delaying the disease-related symptoms and will keep the BSC option reserved for the unfit patients. Therapy costs are an inevitable argument for or against a therapeutic approach. Other antineoplastic agents with similar objective activity (from phase II salvage studies) in advanced urothelial cancer are likely to provide comparable clinical benefit as vinflunine. This situation may lead to the conclusion that many of these palliative patients should/will be treated in clinical trials investigating these other agents compared with vinflunine or in combination, to identify more efficient treatment options for this patient group.

Conclusion

The novel third-generation bifluorinated semisynthetic vinca alkaloid, vinflunine, is a microtubule inhibitor that has been shown to have activity against transitional cell

carcinoma of the urothelial tract. In two phase II trials, moderate activity of vinflunine in TCCU could be proven and a consecutive, large, phase III trial comparing vinflunine with BSC versus BSC alone showed an improvement in OS in the vinflunine arm in the preplanned secondary analyses. As the drug shows an acceptable adverse event profile, being less neurotoxic compared with the other microtubule inhibitors, it was approved as a second-line option for patients with urothelial carcinoma resistant to first-line platinum-containing chemotherapy. The real clinical role of vinflunine has to be defined with the ongoing implementation of the drug into daily clinical practice and in clinical trials to identify more efficient treatment options for this palliative setting.

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