CLINICAL INVESTIGATION

Vinflunine for the treatment of metastatic transitional cell carcinoma: recent evidence from clinical trials and observational studies

The microtubule inhibitor vinflunine is currently the only cytotoxic drug approved in Europe for the treatment of patients with metastatic transitional cell carcinoma who failed first-line platinum-based chemotherapy. Indeed, the only Phase III trial ever conducted in this setting demonstrated a benefit in progression-free and overall survival for patients receiving vinflunine plus best supportive care compared with best supportive care alone. Recent data from European studies performed in real life confirmed the efficacy of the drug, even in patient populations exhibiting adverse prognostic factors. Side effects were manageable, provided gastrointestinal prophylaxis is performed. The potential role of vinflunine in first-line treatment as maintenance therapy or as a partner in combination chemotherapy for patients unfit for cisplatin is currently being investigated.

Keywords: metastatic disease • platinum-resistant disease • second-line chemotherapy • transitional cell carcinoma • urothelial carcinoma • vinflunine

Camille Serrate[1,2], Damien Pouessel[1], Hélène Gauthier[1,2], Christine le Maignan[1], Luis Teixeira[1,2] & Stéphane Culine*[1,2]

[1]Department of Medical Oncology, Hôpital Saint-Louis, Paris, France
[2]Paris Diderot University – Paris 7, Paris, France
*Author for correspondence:
Tel.: +33 1 42 49 42 47
Fax: +33 1 42 49 98 95
stephane.culine@sls.aphp.fr

Bladder cancer is a major global health problem with an estimated 386,000 new cases worldwide resulting in 150,000 deaths in 2008 [1]. Transitional cell carcinoma (TCC) is the predominant histological type. Diagnosis is often made at early stage of the disease but 50% of patients in advanced stages (>T2) experience metastatic relapse. Untreated metastatic TCC is associated with a median survival times rarely exceeding 3–6 months. Following cisplatin-based front-line schedules including methotrexate, vinblastine, doxorubicin and cisplatin or gemcitabine plus cisplatin, high response rates (RR) of 40–70% are observed along with different toxicity profiles. However median progression-free survival (PFS) of approximately 8 months and median overall survival (OS) of 14–15 months are disappointing, even though some long survivors have been reported [2].

After failure of first-line chemotherapy, more than half of patients are unfit for cisplatin, due to renal dysfunction, cumulative neurotoxicity, poor performance status or refractory disease. Most studies evaluating other single-agent or combination regimens in this setting have included few patients and heterogeneous populations, limiting validation of standard second-line treatment. Modest RR of 10–20% and median OS of 6–9 months were reported [3]. Vinflunine was approved in Europe in recent years based on results of the first completed Phase III trial in the second-line setting [4]. This review provides an update of vinflunine data in metastatic TCC.

Preclinical & early clinical data

Vinflunine is a microtubule-inhibiting bifluorinated vinca alkaloid. *In vivo*, vinflunine showed greater antitumor activity than vinorelbine because of differences in its tubulin-properties and inhibitory effects on microtubule dynamics during mitosis. By inhibiting tubulin, vinflunine prevents microtubule assembly and induces apoptosis. Three Phase I trials were conducted between 1998 and 2003 in patients with refractory solid tumors (Table 1). Three administration schedules were

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Table 1. Results of Phase I studies with vinflunine in solid tumors.

Study	Patients (n)	Administration schedule	Recommended dose (mg/m²)	PR	Ref.
Delord *et al.*	34	D1 weekly	120–150	0	[5]
Bennouna *et al.*	31	D1 three weekly	350	3	[6]
Johnson *et al.*	16	D1–D8 three weekly	170	0	[7]

D: Days; PR: Partial response.

studied [5–7]. The three weekly (10 min intravenous infusion) regimen was retained for subsequent development, with a recommended dose of 350 mg/m². Dose limiting toxicities included mucositis, constipation and neutropenia [6].

Phase II studies in patients with platinum-refractory metastatic TCC

The results of the two Phase II studies were quite similar (Table 2). In the European trial, the initial dose of 350 mg/m² every 3 weeks was reduced to 320 mg/m² after the occurrence of significant hematologic toxicities in the first six patients. RR was 18% with a median duration of response of 9 months while 50% of patients had stable disease. Better disease control was observed in patients who had previously experienced response to first-line chemotherapy or had a long interval from prior platinum treatment. Median PFS was 3 months whereas median OS was 6.6 months [8]. The American trial confirmed these results in 151 patients with more pejorative prognostic factors. About 80% of patients had developed a disease progression within 6 months after prior chemotherapy. A large proportion of patients (40%) presented with renal dysfunction (creatinine clearance between 20 and 60 ml/min). Most of them had comorbidities accounting for a lower initial dose of 280 mg/m² since only 26% of patients received an initial dose of 320 mg/m². Dose escalation to 320 mg/m² was still possible for 37% of patients while 20% had a dose reduction. The RR was 15% with a median duration of response of 6 months. In total, 64 patients (42%) achieved stable disease. Median PFS was 2.8 months while median OS was 8.2 months [9].

Phase III trial

A total of 370 metastatic TCC patients were randomly assigned to vinflunine plus best supportive care (BSC) or to BSC alone between May 2003 and August 2006 [4,10]. Patients with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 and without previous pelvic irradiation were treated at 320 mg/m² every 3 weeks. The initial dose was reduced to 280 mg/m² in patients with ECOG PS of 1 or with previous pelvic irradiation but a third of them subsequently experienced dose escalation to full dose. After a median follow-up time of 21 months, the objective of a median 2-month survival advantage was achieved but the difference was not statistically significant. In the eligible population excluding 13 patients with at least one major protocol deviations, median OS was significantly longer for vinflunine plus BSC compared with BSC alone (Table 3). Safety was acceptable. The most frequent grade 3–4 toxicity was neutropenia (50%), with neutropenic fever occurring in 6% of patients. Severe constipation (grade 3–4) was reported in 16% of patients, mainly observed during the first and second cycles and easily managed by prophylaxis.

Long-term results were recently published with a median follow-up duration of 42 months for the vinflunine arm and 45 months for the control arm [10]. In the eligible population, the addition of vinflunine

Table 2. Results of Phase II studies with vinflunine in patients with platinum-refractory metastatic transitional cell carcinoma.

Study	n	Age (years)			PS (n, %)			RI†	PR (n, %)	SD (n, %)	PD (n, %)	PFS (months; 95% CI)	OS (months; 95% CI)	Ref.
		Mean	< 65 (n, %)	≥ 65 (n, %)	0	1	2							
European	51	63	31 (60.8)	20 (39.2)	28 (54.9)	22 (43.1)	1 (2.0)	11 (21.6)	9 (18)	25 (49)	14 (28)	3 (2.4–3.8)	6.6 (4.8–7.6)	[8]
American	151	66	70 (46.4)	81 (53.6)	103 (68.2)	48 (31.8)	–	61 (40.4)	22 (15)‡	64 (42)‡	49 (32.5)‡	2.8 (2.6–3.8)	8.2 (6.8–9.6)	[9]

†Creatinine clearance between 20 and 60 ml/min.
‡According to the independent response review committee.
OS: Overall survival; PD: Progressive disease; PFS: progression-free survival; PR: Partial response; PS: Performance status; RI: Renal impairment; SD: Stable disease.

to BSC prolonged median OS by 2.6 months with statistical significance (Table 3). This benefit was not statistically significant in the intention-to-treat (ITT) population. However, in the preplanned multivariate analysis adjusting for prespecified prognostic factors on the ITT population, the addition of vinflunine had a significant independent effect on OS with a risk of death reduced by 23%.

Prognostic factors in second-line setting

A *post hoc*, observational analysis of the Phase III study was done in order to define a prognostic model for patients who failed after platinum-based chemotherapy [11]. Three prognostic factors were identified: ECOG PS (0 vs 1), liver involvement and hemoglobin (<10 vs ≥10 g/dl). The median OS varied from 14.2 months in the group without any risk factor to 1.7 months in patients with three risk factors (p< 0.001). More recently, a retrospective analysis of seven pooled prospective trials including 570 patients was performed to investigate the prognostic value of time from prior chemotherapy. Data from patients included in the Phase III trial with vinflunine confirmed that shorter time from prior chemotherapy was significantly associated with PFS and OS in multivariate analysis, such as ECOG PS, hemoglobin and liver involvement [12].

Vinflunine in routine practice: European experiences

One prospective and two retrospective observational studies have recently investigated the effectiveness and safety of vinflunine (Table 4).

The French retrospective CURVE study

This survey included 134 patients who were treated with vinflunine in 20 centers from January to December 2011 [13]. All but one had received a platinum salt as first-line chemotherapy. The study population exhibited a high percentage of adverse prognostic factors: 23% had an ECOG PS of 2, 24% a baseline hemoglobin <10 g/dl and 10% hepatic liver dysfunction. The median duration of treatment was 3 months and the median number of cycles was five (range: 1–23). The starting dose was 280 mg/m^2 in 55% of patients. In total, 16% of patients experienced at least one dose reduction. Most frequent grade 3–4 side effects were asthenia (20.9%), neutropenia (17.2%) and anemia (8.2%). The objective RR was 22% with 5% of complete responses (CR). The median PFS was 4.2 months and the

Table 3. Results of the Phase III trial of vinflunine versus best supportive care in patients with platinum-refractory metastatic transitional cell carcinoma.

Regimen	n	Age (n, %)		ECOG PS (n, %)		VI (n, %)	Hemoglobin (n, %)		RR (n, %)	DCR (n, %)	Median PFS (months)	ITTP median OS (months; n = 370)	EP median OS (months; n = 357)
		<65 years	≥65 years	0	1		<10 g/dl	≥10 g/dl					
BSC	117	60 (51)	57 (49)	45 (38)	72 (62)	87 (74)	14 (12)	103 (88)	0 (0)	29 (24.8)	1.5	4.6	4.3
Vinflunine + BSC	253	135 (53)	118 (47)	72 (28)	181 (72)	187 (74)	39 (15)	214 (85)	16 (8.6)*	104 (41.1)**	3.0†	6.9‡	6.9§
Vinflunine + BSC (long-term survival)	253	–	–	–	–	–	–	–	–	–	–	6.9¶	6.9#

*p = 0.006; **p = 0.002.
†HR: 0.68 (95% CI: 0.54–0.86); p = 0.0012.
‡HR: 0.88 (95% CI: 0.7–1.12); p = 0.2868.
§HR: 0.78 (95% CI: 0.61–0.99); p = 0.0403.
¶HR: 0.88 (95% CI: 0.7–1.10); p = 0.2613.
#HR: 0.78 (95% CI: 0.61–0.96); p = 0.0227.
BSC: Best supportive care; DCR: Disease control rate; ECOG PS: Eastern Cooperative Oncology Group performance status; EP: Eligible population; ITTP: Intent-to-treat population; OS: Overall survival; PFS: Progression-free survival; RR: Response rate; VI: Visceral involvement.
Data taken from [4,10].

Table 4. Results of European observational studies in real life with vinflunine in patients with platinum-refractory metastatic transitional cell carcinoma.

Study	n	Median age (years)	PS	VI (%)	RI† (%)	Cycles (n)	Neutropenic infections (%)	Anemia‡ (%)	Constipation‡ (%)	RR (%)	CR (%)	DCR (%)	Median PFS (months)	Median OS (months)	Ref.
German	77	67	Median Karnofsky: 80	60	NR	Average: 5	2.6	6.3	5.2	23	5	53	2.8	7.7	[15]
French	134	66	ECOG 0: 25% ECOG 1: 46% ECOG 2: 23% Missing: 5%	57 (lung and liver)	48	Median: 5 (1–23)	3	8	8	22	5	51	4.2	8.2	[14]
Spanish	66	67	ECOG 0: 32% ECOG 1: 61% ECOG 2: 7%	39 (lung) 26 (liver)	NR	Median: 5 (1–18)	NR	NR	6	27	1	70	4	10.4	[16]

†Creatinine clearance between 20–60 ml/min.
‡Grade 3–4.
CR: Complete response; DCR: Disease-control rate; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; PS: Performance status; RI: Renal impairement; RR: Response rate; VI: Visceral involvement.

median OS reached 8.2 months. Regarding prognostic factors, ECOG PS, hemoglobin and hepatic function were confirmed to select patients having higher benefit from vinflunine. Median OS was 11 months in the subgroup of patients with no adverse prognostic factor versus 2.3 months in those patients with three adverse prognostic factors [14].

The German prospective study

A total of 77 patients who failed platinum-based chemotherapy in 39 centers were included in a prospective noninterventional study. Vinflunine was predominantly administered as second-line chemotherapy. The average number of cycles was five. In 48% of patients, the starting dose was 320 mg/m^2, while 39% of patients received an initial dose of 280 mg/m^2. Toxicities were manageable in daily practice with simple gastrointestinal prophylaxis. The objective RR was 23.4% with 5.2% of CR. The median PFS was 2.8 months. The median OS was 7.7 months. Patients initially treated with a starting dose of 320 mg/m^2 tended to benefit most from treatment, with a median OS of 10.5 months [15] .

The Spanish retrospective study

Between April 2012 and February 2013, 66 patients with metastatic TCC receiving vinflunine were included (Table 5). All patients had been previously treated with platinum-based chemotherapy. The median number of cycles was five (range: 1–18). Most frequent grade 3–4 adverse events were neutropenia (9%), constipation (6%), abdominal pain (6%) and nausea/vomiting (6%). The objective RR was 27% including 1.5% of CR. The median PFS was 4 months. The median OS was 10.4 months. Liver involvement and ECOG PS were identified as prognostic factors for OS [16].

Vinflunine in the first-line setting

Maintenance therapy after platinum combination chemotherapy

An ongoing randomized Spanish study is assessing vinflunine maintenance therapy in patients with objective responses or stable disease after four to six cycles of the gemcitabine plus cisplatin combination. The results of a preplanned security analysis in 25 patients have recently been reported [17]. As expected, more adverse events were observed in the vinflunine arm when compared with no chemotherapy. However, maintenance appeared feasible with an acceptable security profile, leading to trial continuation.

Vinflunine-based chemotherapy in patients unfit for cisplatin

An international randomized Phase II study assessing the disease control rate of vinflunine/gemcitabine or

vinflunine/carboplatin chemotherapy in 69 patients was recently performed. Main eligibility criteria included creatinine clearance <60 ml/min but ≥30, ECOG PS 0 or 1, no prior chemotherapy for advanced disease. According to creatinine clearance (<40 or ≥40 ml/min), patients received vinflunine 250 or 280 mg/m^2 in combination with carboplatin (AUC = 4.5) or gemcitabine 750 mg/m^2 escalated to 1000 mg/m^2 in absence of toxicity grade ≥2. The safety data analysis of the first 43 patients showed a median vinflunine dose intensity of 93% in the carboplatin arm and 98% in the gemcitabine arm, with a median number of cycles of five (range: 1–12). The most frequent nonhematological grade ≥3 were asthenia (19%), infection (12%) and constipation (12%) without major difference between arms. Hematological grade ≥3 events were more frequent in the carboplatin arm (neutropenia 68 vs 43%, febrile neutropenia 9 vs 0%). Preliminary results regarding efficacy are interesting with an objective RR of 46% (confirmed 37%) and a disease control rate of 84% [18].

Present & future prospects for vinflunine in TCC

The second-line setting at present: a standard treatment?

Following the results of the Phase III trial demonstrating a benefit in PFS and OS for patients receiving vinflunine plus BSC as compared with BSC alone, vinflunine has obtained the European Medicines Agency approval in 2009 and is currently recommended by European guidelines for patients who failed platinum first-line chemotherapy for metastatic TCC. Although the objective of a 2-month median survival advantage was achieved together with a statistically significant treatment effect on the multivariate analysis, the lack of statistical significance in the log-rank test on the ITT population of the trial has limited the weight of the results and consequently impaired the recognition of the drug as a standard treatment in the second-line treatment of metastatic TCC. Should the brake be lifted in the light of recently published studies?

The answer is certainly yes regarding European data from observational studies. The efficacy was confirmed in unselected populations, with median survivals ranging from 8 to 10 months. Additionally, the toxicity profile was safe provided a gastrointestinal prophylaxis and an adaptation of the initial dose to the performance status and history of pelvic irradiation are performed.

The answer is probably yes regarding the initial design of the Phase III trial. Three parameters (ECOG PS, liver metastases and hemoglobin level) have been subsequently shown as important prognostic factors for OS in this patient population. As this information was not available, patients were only stratified by study site and refractoriness to previous platinum regimens. This design led to an imbalance of 10% observed for ECOG PS in favor of the control arm. The use of these prognostic factors as stratification variables will be mandatory in future studies in order to avoid imbalances between treatment arms.

The answer is unknown considering the possibility of rechallenging a platinum salt first before delivering vinflunine. Retreatment with previously used agents is of unclear benefit in TCC. Some experiences have been reported with methotrexate, vinblastine, doxorubicin and cisplatin after failure of a platinum-based combination, suggesting some activity at the expense of significant toxicity [19]. It seems reasonable to consider the rechallenge of a platinum-based regimen in fit patients with a long time interval (≥12 months) after the first platinum-based chemotherapy given in a curative, perioperative or palliative, metastatic intent. Whether delaying the use of vinflunine in third-line in these patients could be detrimental is unknown.

The future in the first-line setting: for which patients?

The concept of maintenance has undergone a revival in recent years for lung cancer patients since a significant gain in OS has been shown. This approach includes two paradigms: continuation of maintenance therapy, wherein a component of the induction regimen, generally the nonplatinum cytotoxic drug is continued, and switch maintenance, wherein a new and potentially noncross-resistant agent is introduced immediately after the induction regimen. While continuation maintenance therapy has no role in the daily management of advanced TCC patients, the Spanish group is currently enrolling patients in a switch maintenance trial with vinflunine as described above. Mature results will be limited to safety concern since the planned number of patients is limited. Such an approach will require a larger trial in order to draw firm conclusion regarding the potential impact on OS.

There is no standard treatment in patients unfit for a cisplatin-based regimen as first-line chemotherapy in advanced or metastatic TCC. Only two randomized trials have been reported so far in this population. In a French randomized Phase II study, patients were treated with gemcitabine alone or gemcitabine plus oxaliplatin. The addition of oxaliplatin to gemcitabine did not appear to improve the activity as compared with gemcitabine alone, at least in terms of response rate [20]. A Phase III trial assessed the efficacy and toxicity of two carboplatin-based chemotherapy regimens. There were no significant differences in

efficacy but incidence of severe acute toxicities was lower in patients who received gemcitabine and carboplatin [21]. Therefore single agents or the gemcitabine/carboplatin doublet are frequently used. Considering that vinflunine can be safely administered as a monotherapy in patients with a creatinine clearance ≥20 ml/min, its combination with gemcitabine or carboplatin was a reasonable option to consider. Preliminary data from the randomized study described above support gemcitabine as the preferred partner regarding toxicity. While mature data on efficacy are awaited, a randomized study would be necessary to legitimize the use of vinflunine in patients unfit for cisplatin.

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Executive summary

- Vinflunine (Javlor®, Pierre Fabre Médicament) is the only single agent approved for patients who failed first-line platinum-based therapy in advanced transitional cell carcinoma.
- Results of the Phase III trial showed a benefit in progression-free survival and overall survival for patients receiving vinflunine plus best supportive care compared with best supportive care alone.
- Prognostic factors (performance status, liver involvement and hemoglobin level) could be of help for selecting those patients who are likely to benefit the most from vinflunine chemotherapy.
- Recent data of three European surveys in real life confirmed the efficacy and safety of vinflunine in unselected populations.
- Combination regimens including vinflunine are being studied in the first-line treatment of patients unfit for cisplatin.

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