# Vinflunine in the treatment of advanced urothelial cancer: clinical evidence and experience

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***Abstract*:** Vinflunine (VFL) has been approved in Europe for second-line treatment of metastatic and advanced urothelial cancer after failure of platin-containing therapy. Since approval, the drug has been investigated in few clinical trials. Most of the currently available reports describe experiences with VFL in a daily clinical setting. This review gives a short overview on clinical experiences and clinical trials involving VFL since the approval of this drug in 2009.

***Keywords:*** metastatic urothelial carcinoma, second line, mTCCU, urothelial cancer, vinflunine

## Introduction

With an incidence of 429,700 new cases per year and a related mortality of 165,000 worldwide, urothelial carcinoma of the bladder is one of the most common malignancies overall [World Health Center, 2016]. Approximately 80% of the affected patients are aged 50–79 years [Aben *et al.* 2002]. Non-muscle-invasive bladder cancer and muscle-invasive locally confined tumors are best treated by surgical approaches. As urothelial carcinoma is a chemosensitive cancer, for metastatic disease cisplatin-based chemotherapy is the current standard of care, which, however is rarely curative [Bellmunt *et al.* 2014]. Relapse after first-line therapy for metastatic disease may occur even in the course of treatment and for affected patients, options for second-line treatment are limited. Two randomized trials in second line for urothelial cancer have been successfully concluded investigating either vinflunine (VFL) or the combination of paclitaxel/gemcitabine [Bellmunt *et al.* 2009; Albers *et al.* 2011].

In 2009 VFL was approved as second line treatment option in metastatic transitional cell carcinoma of the urothelium (mTCCU) by the European Medicines Agency (EMA) but not the US Food and Drug Administration (FDA) based on a 2.4 months median survival gain compared with best supportive care (BSC) in a randomized phase III clinical trial [Bellmunt *et al.* 2009]. Ever since, different classes of drugs, newly emerged targets and combination approaches have been investigated in phase II trials in second line with inconsistent results and trends [Petrylak *et al.* 2016; Gerullis *et al.* 2012]. However, VFL and paclitaxel remain the only drugs investigated in a randomized setting.

This review provides a short overview on the role of VFL in second-line urothelial cancer therapy and focuses on developments after the drug's approval in Europe in 2009.

## Vinflunine

### General

VFL was described first in 1998 by scientists at the Pierre Fabre research center in collaboration with the University of Poitiers in France. It is considered a third-generation member of the vinca alkaloid family besides vincristine, vinblastine, vindesine and vinorelbine which all are antimitotic agents and are currently used in cancer therapy [Kruczynski *et al.* 1998].

### Pharmacodynamics

The antineoplastic effect of VFL is explained by specifically binding to tubulin at vinca alkaloid binding sites, inhibiting microtubule polymerization leading to reduction of the microtubule network of interphase cells and subsequent induction

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of G2+M arrest *in vitro*, finally resulting in apoptosis by mitotic accumulation at the metaphase/anaphase transition [Kruczynski *et al.* 2002; Pourroy *et al.* 2004]. A weaker binding affinity to tubulin than other vinca alkaloids may explain the drugs reduced neurotoxicity [Kruczynski and Hill, 2001]. The *in vitro* antitumor effect of VFL is supposed to be superior to that of other alkaloids which has prioritized the further clinical development and evaluation of VFL [Bennouna *et al.* 2008]. In addition, compared with other vinca alkaloids, VFL is a less-potent inductor of drug resistance *in vitro* [Etievant *et al.* 2001]. Already at an early stage of development, those results indicated a possible role of the compound in the systemic treatment of urothelial carcinoma [Bonfil *et al.* 2002].

### Pharmacokinetics and metabolism

VFL is administered intravenously. Following administration, VFL shows an exponential elimination curve with a particularly rapid fall in the first hour. VFL is moderately bound to serum proteins with a mean terminal half-life of approximately 40 h. It does not require solvent formulation as it is freely water soluble. The area under the curve is correlated with its hematological toxicity. VFL and its compounds are excreted *via* the cytochrome P450 3A4 system and eliminated in feces (2/3) and urine (1/3), reducing the risk of accumulation in patients [Zhao *et al.* 2007].

### Clinical trials

*Phase I clinical trials on dosage and schedule.* Phase I clinical trials in patients with solid tumors have been conducted to define the maximum tolerated dose/recommended dose for intravenous administration of VFL as a single agent [Bennouna *et al.* 2003; Johnson *et al.* 2006]. As a result, the classic dosing schedule for VFL is an intravenous infusion of 320 mg/m$^2$ over 15–20 min once every 3 weeks in most patients and indications. A dose reduction to 280 mg/m$^2$ according to the patient's performance status or reasons such as reduced Karnofsky Performance Score, past irradiation, renal impairment or age >75 years is considered acceptable. Most relevant toxicities in those dose-defining single-agent VFL trials were neutropenia, febrile neutropenia, myalgia and gastrointestinal disorders (constipation, nausea, vomiting, constipation, stomatitis and anorexia). In subsequent trials combination therapy of VFL with other drugs increased adverse event rate, in particular bone marrow suppression [Souquet *et al.* 2010; Bennouna *et al.* 2006; Tournoux-Facon *et al.* 2011].

*Phase II and III clinical trials on efficacy.* Clinical efficacy for VFL in patients with platinum-resistant urothelial cancer was shown in a clinical program including two phase II trials ($n$ = 202) and one randomized phase III trial ($n$ = 253) which finally lead to approval of VFL in the second-line setting of mTCCU.

In the European multicenter phase II trial (VFL 202) 58 patients were recruited in 16 European centers between November 2000 and September 2002 [Culine *et al.* 2006]. On the basis of 51 evaluated patients the authors reported a median progression-free survival (PFS) of 3.0 months and a median overall survival (OS) of 6.6 months. VFL-related side effects were grade 3–4 neutropenia, observed in 67% of patients, febrile neutropenia in 10% of patients. Constipation was frequently observed and the incidence of grade 3 nausea and vomiting were low (4% and 6% of patients, respectively). The authors concluded that based on their results phase III trials were justified.

A second phase II trial (CA001) included 175 patients mainly from the US, of which only 151 received treatment and were included in the analysis [Vaughn *et al.* 2009]. Stable disease was observed in 46 patients (42%). The median PFS was 2.8 months, and the median OS was 8.2 months, comparable with the VFL 202 trial. Myelosuppression was the most frequent adverse event, with grade 3 neutropenia reported in 58% of the patients, grade 3 febrile neutropenia in 10 (7%) patients. Nonhematologic treatment-related events (grade 3 of 4) were generally manageable and included constipation (17%), asthenia/fatigue (13%), ileus (5%) and abdominal pain (5%) [Vaughn *et al.* 2009]. In conclusion, the results of CA001 appeared consistent with VFL 202.

In the subsequent randomized, phase III trial (VFL 302) 370 patients were randomized (2:1) to either VFL and BSC or BSC alone [Bellmunt *et al.* 2009]. Patients were recruited from 83 institutions in 21 countries demonstrating the complexity of conducting a phase III trial in this indication. VFL was given 3-weekly in a dose of 320 mg/m$^2$ for PS0 patients or initially at 280 mg/m$^2$ with subsequent escalation to 320 mg/m$^2$ in PS1 or two patients. The statistical hypothesis

in this trial was to prolong OS by a median of 2 months in the VFL group. In the intent-to-treat population, the 2-month survival advantage for arm A was achieved (6.9 *versus* 4.6 months) but failed statistical significance ($p = 0.29$).

Adjusting for prognostic factors a multivariate Cox analysis demonstrated a statistically significant effect of VFL on OS ($p = 0.036$), reducing the death risk by 23% [hazard ratio (HR) = 0.77; 95% confidence interval (CI) 0.61–0.98]. For the eligible population ($n = 357$), the median OS was significantly ($p = 0.040$) longer for VFL + BSC compared with BSC alone (6.9 *versus* 4.3 months, respectively).

Overall response rate (ORR), disease control and progression-free survival were all statistically significantly favoring VFL + BSC ($p = 0.006$, $p = 0.002$, and $p = 0.001$, respectively) [Bellmunt *et al.* 2009]. The toxicity profile in this study was manageable with most common grade 3/4 toxicities being neutropenia in 50% of patients, febrile neutropenia in 6%, anemia in 19%, fatigue/asthenia in 19% and constipation in 16%. In this phase III trial VFL did not induce a decrease in health-related quality of life when compared with BSC alone.

On the basis of the data of those two phase II and one phase III trials VFL (Javlor) was officially approved by the EMA on 21 September 2009 for the treatment of advanced mTCCU after failed platin-containing therapy [European Medicines Agency, 2009]. In addition, VFL appears to be safe also in patients with significant renal impairment [Bellmunt *et al.* 2009; Isambert *et al.* 2014].

In 2013 Bellmunt and colleagues published long-term updated OS data of their phase III trial and confirmed their initially positive results by describing an OS of 6.9 *versus* 4.3 months in the eligible population [Bellmunt *et al.* 2013].

## Clinical trials and daily clinical practice reports after approval

### *Clinical trials*

Since its official approval by the EMA only few clinical trials involving VFL have been successfully concluded, predominantly in European countries were the drug has reached standard of care status in the second-line setting of platin-resistant mTCCU.

In 2013, a phase I clinical trial was concluded using VFL in combination with pazopanib [Gerullis *et al.* 2013]. The rationale for this trial resulted from previous data regarding pazopanib having potential as a single agent in the same indication [Necchi *et al.* 2012]. However, the trial had to be stopped for safety reasons after five enrolled patients, since two of those patients had shown dose-limiting toxicities in terms of grade 4 neutropenia and grade 3 hepatobiliary disorder at the lowest dose level for pazopanib (200 mg). Thus, according to the protocol the initially planned phase II study was therefore not carried out [Gerullis *et al.* 2013].

At the ASCO 2016 congress, Font and colleagues presented results of a phase II trial investigating the role of VFL as maintenance treatment following platin-containing first-line chemotherapy in patients with advanced urothelial cancer. This placebo-controlled randomized multicenter MAJA trial [ClinicalTrials.gov identifier: NCT01529411] aimed to demonstrate whether maintenance VFL therapy was able to delay tumor progression after response to initial platinum-based chemotherapy [ClinicalTrials.gov identifier: NCT01529411; Pérez-Valderrama1 *et al.* 2016]. Between April 2012 and January 2015, 88 patients from 21 institutions were randomized. Of those, 45 patients received at least two cycles of VFL compared with 43 patients receiving BSC. Patients in the VFL arm received a median of six cycles. The most common grade 3/4 adverse events were constipation (13.6%), neutropenia (15.9%), fatigue (15.9%) and one febrile neutropenia (2.3%). After a median follow up of 12.2 months, 59% of patients had progressed and 43% of patients had died in the VFL arm, compared with 81% and 62% of patients in the BSC arm, respectively. The median PFS was 6.5 months in the VFL arm and 4.6 months in the BSC arm. The authors concluded that maintenance VFL application in patients with disease control after first-line cisplatin-based chemotherapy significantly reduces the risk of progression at an acceptable tolerability profile. Survival data are expected in the future [Pérez-Valderrama1 *et al.* 2016].

In 2016, De Santis and colleagues published the results of the randomized phase II JASINT1 trial [De Santis *et al.* 2016]. This trial assessed the combination of VFL with gemcitabine and VFL with carboplatin in patients ineligible to cisplatin with advanced or metastatic urothelial cancer [ClinicalTrials.gov identifier: NCT01599013].

**Table 1.** Observations reporting on clinical outcome of VFL in daily clinical practice since the drug's approval in 2009.

| Author | Number of observed patients | OS/PFS (months) |
|---|---|---|
| Pistamaltzian *et al.* [2016] | *n* = 71, retrospective study | 11.9/6.9 |
| Moriceau *et al.* [2015] | *n* = 19, retrospective study | 4.0/2.9 |
| Medioni *et al.* [2016] | *n* = 134, retrospective study | 8.2/4.2 |
| Hegele *et al.* [2014] | *n* = 21, retrospective study | 6.2/4.4 |
| Retz *et al.* [2015] | *n* = 77, prospective study | 7.7/– |
| Castellano *et al.* [2014] | *n* = 102, prospective study | 10.0/3.9 |
| Palacka *et al.* [2014] | *n* = 16, prospective study | 5.2/2.3 |
| Summarized | *n* = 440, prospective and retrospective observations | 7.6/4.1 |
| Bellmunt *et al.* [2009] | *n* = 259, phase III trial | 6.9/3.0 |

OS, overall survival; PFS, progression-free survival.

The study enrolled a total of 69 patients. The 34 patients treated with VFL/gemcitabine did show significantly less hematological grade 3/4 adverse events whereas nonhematological adverse events did not show major differences between the two groups. The ORR was 44.1% (VFL/gemcitabine) *versus* 28.6% (VFL/carboplatin). Median PFS and median OS were 5.9 *versus* 6.1 months and 14.0 *versus* 12.8 months with VFL/gemcitabine and VFL/carboplatin, respectively. Authors favored the combination of VFL/gemcitabine based on the better hematological tolerance and higher ORR [De Santis *et al.* 2016].

### *Reports from daily clinical practice*

Various clinical reports, both retrospective and prospective in nature, exist about the implementation of VFL into daily clinical practice after the official approval and marketing authorization of the drug in 2009 (Table 1).

Most of those daily clinical practice experiences result from inhomogeneous patient groups with inhomogeneous inclusion criteria. Also, the intervals between first- and second-line treatment are either not mentioned or inhomogeneous in the mentioned reports. Therefore, using those reports for comparative purposes remains critical.

In their retrospective analysis of 71 patients treated with VFL as a second-line approach after failure of platinum-containing therapy, Pistamaltzian and colleagues [Pistamaltzian *et al.* 2016] reported a median PFS of 6.2 months and OS of 11.9 months, respectively, and observed a complete remission in two patients (3%). The median of applied VFL cycles has been stated with 4 months at moderate side effect profile.

Moriceau and colleagues [Moriceau *et al.* 2015] retrospectively described 19 patients treated with VFL from 2010 until 2014 at a single institution within a compassionate use program which was implemented before the drug was available on the market and after it was withdrawn from the list of reimbursed medicines by the French national health insurance system in 2012. The median number of applied cycles was three. Median PFS was 2.9 months whereas the median OS was poor at 4.0 months which may be explained by the poor Eastern Co-operative of Oncology Group status of the patients. However, the authors report relevant toxicities with grade 4 adverse events as constipation (26%), three intestinal obstructions (16%), one mechanical ileus (5%) and asthenia and fatigue (21%).

Another retrospective analysis from France has been published by Medioni and colleagues [Medioni *et al.* 2016]. A total of 134 patients from 20 different centers in France were treated over 12 months in 2011. The majority of patients has had a performance status 0 and 1 (25% and 46%, respectively). Median OS was 8.2 months whereas median PFS was stated at 4.2 months. They applied a median number of five cycles VFL in this cohort.

In a retrospective report from Germany, Hegele and colleagues describe their experience with 21 patients originating from eight centers who have

been treated with VFL in the second-line indication [Hegele *et al.* 2014]. They observed a median PFS of 4.4 months and a median OS of 6.2 months at manageable toxicity profile with mostly hematologic adverse events. Interestingly, they reported a satisfaction rate with VFL treatment of 90.5% among patients and 62% among physicians, respectively.

Also from Germany, Retz and colleagues [Retz *et al.* 2015] published a prospective noninterventional study investigating safety and efficacy of VFL in platinum-pretreated urothelial cancer patients in routine clinical practice. In total 77 patients were treated in 39 different institutions over 13 months. VFL was given as second-line treatment in 66% of the patients, the average number of administered VFL cycles was 4.7 whereas one third of patients received at least six treatment cycles. The authors report a median OS of 7.7 months.

Castellano and coworkers reported on a group of 102 consecutive patients treated with VFL in second line from 2009 to 2013 in 15 different institutions in Spain [Castellano *et al.* 2014]. In their prospective observational study, they applied a median of four cycles VFL and observed as most common adverse events of any grade constipation in 70.6%, vomiting in 49.1%, neutropenia in 48.1% and abdominal pain in 34.3% of their patients. Antitumor efficacy in their cohort was comparable with other reports at a median PFS of 3.9 months and a median OS of 10 months leading to a clinical benefit rate with VFL of 65.7%.

Palacka and colleagues [Palacka *et al.* 2014] prospectively observed 16 patients with a median Karnofsky index of 90% receiving VFL as second-line treatment in advanced mTCCU at one single Slovak institution from 2011 to 2014. The reported median OS was 5.2 months and median PFS was 2.3 months. Remarkably, grade 3–4 adverse events were seen frequently in this study (neutropenia in 38%; leukopenia in 25%; constipation in 19%).

In summary, all of those reports from daily clinical practice with more heterogeneous patient populations present valuable sources of information on treatment modalities, risk stratification and side-effect management in this narrow indication. They confirm the results from pivotal trials with regard to safety and efficacy.

An interesting report was published by Guglieri-Lopez and colleagues. They performed an analysis of effectiveness, toxicity and economic evaluation of VFL for the treatment of patients with urothelial cancer in an outpatient setting in Spain [Guglieri-Lopez *et al.* 2016]. In their retrospective multicenter observational cohort study 37 patients with mTCCU were treated with VFL in second line. In addition to reproducing efficacy and tolerability data from previous trials the authors demonstrated a median-based cost-effectiveness ratio of €44,789 per progression-free year gained and €22,750 per life-year gained. Compared with other treatment approaches VFL seemed to have a higher cost at a lower OS effect [Guglieri-Lopez *et al.* 2016].

## Ongoing clinical trials and future perspective

With the introduction of check point inhibitors as potential therapeutic approaches in second-line mTCCU treatment, VFL is increasingly facing the role of the standard of treatment which those new drugs are compared with in clinical trials.

The IMvigor211-Trial is an international multicenter, phase III, open-label, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with locally advanced or metastatic urothelial cancer of the bladder after failure with platinum-containing first-line therapy. The investigated drug is PD1 inhibitor atezolizumab but VFL is one of three active comparators as prior to randomization, the investigator will have the option of choosing one of three chemotherapy regimens (VFL *versus* paclitaxel or docetaxel) for each patient. The ratio of patients who are randomized to VFL *versus* patients who are randomized to a taxane (paclitaxel or docetaxel) is aimed to be approximately 1:1 [ClinicalTrials.gov identifier: NCT02302807].

Another phase III randomized clinical trial of pembrolizumab (MK-3475) *versus* paclitaxel, docetaxel or VFL in subjects with recurrent or progressive metastatic urothelial cancer (AP 48/15 of AUO] has been launched in Europe and the USA. Patients are required to have received a platinum-containing chemotherapy and line of treatment in this trial is supposed to be second or third [ClinicalTrials.gov identifier: NCT02256436; Rexer, 2015]. In this trial VFL is used as standard treatment approach and competitor to the investigated PD1

inhibitor pembrolizumab. Primary study goals are OS and PFS. However, again, although the trial is randomized 1:1 the choice between paclitaxel or docetaxel or VFL in the control group is up to the clinical investigator.

In Spain and the Netherlands, another clinical trial [ClinicalTrials.govidentifier:NCT01830231] is currently recruiting patients in the second-line setting of metastatic urothelial cancer after having received platinum-containing therapy as adjuvant or neo-adjuvant treatment approach in metastatic or locally advanced disease. Patients are randomized to receive cabazitaxel *versus* VFL. As experience with cabazitaxel in mTCCU is limited, the study started as a randomized phase II trial aiming to evaluate if the response rates (complete response + partial response) are sufficiently high to further study the treatment regimens in a subsequent phase III setting which is included in the protocol. The trial is estimated to be completed by November 2016.

The VINGEM trial is currently recruiting patients in Scandinavian countries. This multicenter, randomized phase II trial investigates the effectiveness of VFL and gemcitabine *versus* carboplatin and gemcitabine as first-line treatment in patients with metastatic urothelial cancer who are not fit for cisplatin-based chemotherapy due to impaired renal function. Based on 60 enrolled patients study completion is estimated by end of 2017 [ClinicalTrials.gov identifier: NCT02665039].

Also from Scandinavia, the VINSOR trial, an exploratory phase I study with sorafenib in addition to VFL in progressive locally advanced or mTCCU aims to analyze the tolerability of standard treatment (Javlor®) with the addition of a tyrosine kinase inhibitor: sorafenib (Nexavar®). Although this is just a phase I dose-finding study investigators also aim to investigate sophisticated imaging methods such as PET-CT and biomarkers with regards to outcome predictability [ClinicalTrials.gov identifier: NCT02665039]. However, on the basis of already-concluded comparable protocols, the tolerability of the combined approach needs to be confirmed before concluding outcome predictors.

As a future perspective, Calvo and coworkers conducted a phase I trial in patients with advanced malignancies to investigate the administration of VFL as hard capsules given twice a day on day 1–2 every day within 3-week cycles [Calvo *et al.* 2012]. This approach has been shown feasible and the recommended dose for further investigations has been established at 270 mg/day.

## Other urologic malignancies

As VFL is approved in various tumor entities, the number of urologic malignancies which have been targeted *via* VFL including clinical trials is limited. However, two clinical trials in urologic malignancies different from transitional carcinoma have been identified:

The currently recruiting multicenter single-arm phase II VinCaP-Trial in the United Kingdom aims to determine the clinical benefit and toxicity of VFL in patients with inoperable (locally advanced or metastatic) cancer of the penis. Recruitment end is supposed to be in March 2017 as 22 patients will receive VFL chemotherapy over four cycles prior formal restaging [ClinicalTrials.gov identifier: NCT02057913]. In a phase II clinical trial of the Sarah Cannon Research Consortium, single-agent VFL has been used in the salvage treatment of patients with castration-resistant prostate cancer. Oncologic outcome was poor as only 1 of 36 treated patients had partial response at a median PFS of 2.1 months. Thus, VFL did not show any potential in this indication [Hainsworth *et al.* 2010].

## Conclusion

Since its approval for second-line treatment in urothelial cancer VFL has been investigated in few clinical trials whereas several European groups have reproduced survival data from the phase III trial in their daily clinical practice reports. In Europe VFL is the currently approved second-line treatment of advanced or metastasized urothelial cancer and the drug is more and more becoming a comparator to new evolving drugs in clinical trials.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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