Vinflunine and bladder cancer: present and future indications

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Abstract

Urothelial cancer (UC) frequently affects male sex over the sixth decade of life, and in about 30% of the cases, it is diagnosed as muscle-invasive disease. For patients with metastatic disease, the prognosis is grim and the typical treatment is polychemotherapy involving cisplatin. Second-line chemotherapy is often employed, but a standard scheme does not exist. Vinflunine (VFL) is a new generation vinca alkaloid able to reversibly link the subunits of tubulin, causing the arrest of mitotic spindle polymerization. In critical trials, VFL has shown good activity and manageable toxicity; in a phase III randomized trial, it significantly improved survival compared with the best supportive care (BSC). VFL has received European Medicines Agency (EMA) approval for use as second-line treatment in UC patients who progressed after a first-line cisplatin-containing chemotherapy. Due to its low toxicity and promising efficacy, VFL is under clinical experimentations aimed to assess its role in other disease settings.

Introduction

Urothelial cancer (UC) is the fifth most common cancer worldwide; its frequency is higher in the male sex and over the sixth decade of life.[1] UC of bladder may be divided in three main prognostic categories: non-muscle-invasive, non-metastatic muscle-invasive, and metastatic tumors.

The median overall survival (OS) in patients with metastatic disease is about one year, and the standard of care is polychemotherapy.[1] Metothrexate, vinblastine, doxorubicin and cyclofosfamide (MVAC), cisplatin, gemcitabine and paclitaxel (PCG), gemcitabine and cisplatin (GC) regimens are the three most commonly employed schemes able to obtain a median OS of about 13 months in clinical trials.[2] The GC regimen is often chosen rather than MVAC due to its lower toxicity.

Prognosis of patients who recur after first-line chemotherapy is poor and non-standard therapy options are available. The chemotherapy regimen offered as second-line strongly depends on what drugs have been used as first-line, and frequently a monochemotherapy is chosen. The active drugs explored in this setting include taxanes, gemcitabine, doxorubicin, ifosfamide, pemetrexed, and methotrexate.[3-12] Combined chemotherapy schemes such as paclitaxel plus gemcitabine, ifosfamide plus gemcitabine or carboplatin plus paclitaxel are very promising.

Unfortunely, in most trials (Table 1), the clinical outcomes were disappointing with median progression free survivals (PFS) of 2-3 months, and median OS of 6-9 months.[3-12] Recently, a second-generation vinca alkaloid, vinflunine (VFL), has been approved for use in second-line chemotherapy for patients with advanced UC.[13] VFL is able to induce apoptosis by blocking microtubule assembly during mitosis. Unlike other vinca alkaloids, it had a greater effect on mitotic rather than axonal tubulin so the use of VFL significantly reduced the rate of neurotoxicity by allowing to reach greater plasma concentrations.[13] The clinical activity of VFL in patients with metastatic UC was initially assessed in phase II and III trials showing good activity and a favorable toxicity spectrum (Table 2).[14-17]

As result of these studies, VFL was the first drug to receive approval from the European Medicines Agency (EMA) for use in platinum-resistant metastatic UC patients.

This review will focus on the promising role of VFL in advanced UC of the bladder and its possible future use in other settings of disease.

Vinflunine in clinical trials

Pharmacodynamics

Microtubules and tubulin are structural cellular components that play an important role in several cell functions, including division, signaling, and intracellular trafficking. Anticancer agents able to target microtubules constitute one of the most effective classes of drugs. The list of compounds that target either tubulin or microtubules comprises both molecules that bind to the tubulin dimers and destabilize microtubules (vinca alkaloids) and those that bind to the microtubule polymer and stabilize microtubules (taxanes).[13] VFL, a third-generation, semi-synthetic vinca alkaloid, interacts with the so-called vinca-alkaloid-binding-domain of tubulin, and is able to interfere with the mitotic spindle polymerization. Moreover, VFL disrupts newly formed blood vessels by blocking microtubule functions and seems to be able to reduce the metastatic process.[13] If compared with other members of its class, VFL links the tubulin subunits with a lower affinity but this low binding affinity does not influence its antitumor efficacy. On the other hand, the binding affinity to tubulin is correlated to the severity of neuropathies observed in clinical setting and the reversibility of VFL-tubuline binding is able to explain its lower toxicity, in particular with regard to neurotoxicity.[13-14]

Preclinical studies

Etievant *et al.*[18] found that VFL bound to tubulin by inducing structural changes that led to inhibition of microtubule assembly. Moreover, *in vitro* VFL reduced the

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microtubule network of interphase cells and induced G2/M arrest, leading to apoptosis. In *in vivo* studies, on orthotopic bladder cancer xenografts, VFL resulted more potent than vinorelbine in inducing tumor growth inhibition, suggesting a broader spectrum of activity for VFL.[18] Moreover, VFL significantly prolonged survival of tumor-bearing mice and inhibited tumor growth without inducing significant toxicity. These results suggested that VFL could represent a good strategy for the systemic treatment of bladder cancer.[18]

Interestingly, VFL treatment induced chemoresistance more rarely than other drugs.[18] A possible explanation takes into account the role of the P-glycoprotein (P-Gp), which is an enzyme able to pump drugs outside the cell, thus being responsible for the multi-drug-resistance (MDR) phenomenon. For largely unknown reasons, VFL induces P-Gp up-regulation less frequently than other vinca alkaloids.[18] These features make VFL the optimal choice for patients with UC in progression after first-line chemotherapy.

Other studies[19] investigated the *in vitro* effects of VFL in combination with several chemotherapeutic drugs (such as DNA-damaging agents, DNA-intercalating agents, antimetabolites, topoisomerase I or II inhibitors, *etc.*). In particular, the combinations of VFL with cisplatin, mitomycin C, doxorubicin, and 5-fluorouracil, were highly synergistic, the combination of VFL and camptothecin showed a moderate synergy while no synergy could be registered for combinations with etoposide and gemcitabine or paclitaxel and vinorelbine.

In a retrospective trial, De Velasco *et al.*[20] described the activity of VFL in a group of 45 patients with metastatic UC who had experienced disease progression after first-line chemotherapy. The observed overall response rate (ORR) was 27%, with a median OS of 11 months. Neutropenia (13%) and abdominal pain (9%) were the most frequent side effects described.[20]

Phase I trials

VFL has been evaluated both as single agent and in combination in a number of phase I trials enrolling patients with different solid tumors, comprising non-small-cell lung cancer, prostate cancer, breast cancer, renal cell carcinoma, gastric cancer, malignant pleural mesothelioma and UC.[19] The recommended dose (RD) for single agent VFL was determined by performing 3 initial phase I trials with different schedules of intravenous administration. First, an intravenous administration every 3 weeks at 350 mg/m^2 was selected for phase II studies.[19] After an analysis of data obtained from the first patients enrolled in phase II trials, the recommended doses for clinical studies was lowered to 320 mg/m^2 every 21 days, or 280 mg/m^2 for patients with a lower performance status or those treated with prior pelvic irradiation.[19] Pharmacokinetic data in five patients treated with radio-labeled VFL given iv at 250 mg/m^2 showed that two thirds of the dose was eliminated through bile and one third by the kidneys.[19] Preliminary data of a phase I trial with oral VFL showed that the bioavailability of this oral form was 57% and 300 mg/day represented the maximum tolerated dose but this study did not define the recommended dose.[19] Recently, a phase I trial has tested the combination of VFL and pazopanib, a multikinase inhibitor which acts mainly on VEGFR family. The results, in terms of toxicity, have not been impressive. The study was interrupted early due to grade 3-4 hematologic side effects.[21]

Phase II trials

Due to the promising activity and toxicity spectrum, single-drug VFL has been tested in some phase II trials. Culine *et al.*[14] treated 51 patients with progressive disease after a platinum-containing regimen with single-agent VFL at doses of 320 mg/m^2. They observed an ORR of 18% and a disease control rate (DCR) of 67%. Median OS was 6.6 months, with a time to progression (TTP) of 3 months. Toxicity observed was manageable; grade 3 neutropenia was the most frequent adverse event. Interestingly a very low rate of neurotoxicity was seen.

Vaughn *et al.*[15] performed a similar trial enrolling more patients (151) who developed disease progression within 12 months after first-line platinum-containing chemotherapy. The patients received a starting dose of 280 mg/m^2 in first cycle, which escalated to 320 mg/m^2, if well tolerated, in the second cycle. ORR was considered the main endpoint and resulted in 15%, with a DCR of 57%. Median OS was 8.2 months. Neutropenia and anemia were the most frequent toxicities.[15]

Table 1. Trials with chemotherapeutic agents used in the second-line setting for urothelial carcinoma.

Drug	Study (year)	Patients (n)	ORR (%)	OS (months)
Ifosfamide	Witte *et al.* (1997)[3]	60	20	5.1
Gemcitabine	Lorusso *et al.* (1998)[4]	35	23	5
Topotecan	Witte *et al.* (1998)[5]	44	9	6.2
Gemcitabine	Gebbia *et al.* (1999)[6]	24	29	13
Pyrazoloacridine	Dodd *et al.* (2000)[7]	14	0	9
Gemcitabine	Albers *et al.* (2002)[8]	30	11	8.7
Piritrexim	Roth *et al.* (2002)[9]	35	7	7
Paclitaxel	Vaughn *et al.* (2002)[10]	31	10	7.2
Pemetrexed	Sweeney *et al.* (2006)[11]	47	27.7	9.6
Pemetrexed	Galsky *et al.* (2006)[12]	13	8	nd

ORR, objective response rate; OS, overall survival.

Table 2. Phase II and III trials assessing the clinical activity of vinflunine in patients with metastatic urothelial cancer.

Drug	Trial	Study (year)	Patients (n)	ORR (%)	OS (months)
VFL	Phase II	Culine *et al.* (2006)[14]	51	18	6.6
VFL	Phase II	Vaughn *et al.* (2009)[15]	151	15	8.2
VF+BSC *vs* BSC alone	Phase III	Bellmont *et al.* (2009)[16]	370	8.6	6.9
VFL *vs* BSC in patients who received or not first-line cisplatin	Phase III	Harshman *et al.* (2013)[17]	357	NR	6.9 in patients who received first-line cisplatin, 5.8 in patients who did not receive prior cisplatin

ORR, objective response rate; OS, overall survival; VFL, vinflunine; BSC, best supportive care; NR, not reported.

Phase III trials

On the basis of the two phase II trials, Bellmunt *et al.*[16] carried out a randomized phase III trial of VFL versus best supportive care (BSC), as second-line treatment for patients who relapsed after a platinum-containing chemotherapy. A total of 370 patients were randomized to receive VFL at doses of 320 mg/m^2 every 21 days, or to receive placebo. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 received 320 mg/m^2 VFL, while patients with ECOG PS 0 and prior pelvic irradiation or ECOG PS 1 received 280 mg/m^2 VFL. Both arms were well balanced, except there were more patients with PS 1 than in the BSC arm. A median 2-month survival advantage favoring the VFL+BSC group represented the primary objective. An advantage in favor of the experimental arm was achieved but was not statistically significant (P=.287). On the other hand, multivariate Cox analysis, adjusted for prognostic factors, suggested statistically significant effects of VFL on OS (P=.036), and a risk of death reduction of 23%. ORR, DCR and PFS were significantly better in the VFL arm. Grade 3-4 toxicities primarily included neutropenia (50%), febrile neutropenia (6%) and anemia (19%). Based on these results, VFL received EMA approval for use as second-line chemotherapy in advanced UC.[16] The drug evidenced a favorable safety profile. The most frequent grade 3-4 toxicities were hematologic (Table 3). Common non-hematologic adverse effects were asthenia and constipation. Importantly, VFL did not induced the dose-limiting neurotoxicity observed for other vinca alkaloids.[13-17]

More recently, Harshman *et al.*[17] studied the possible impact of a prior first-line cisplatin chemotherapy on the outcome of patients enrolled in the aforementioned trial.[16] As expected, the impact of VFL on the outcome was independent of prior chemotherapy; the drug was able to prolong OS among in both cisplatin-pretreated patients and those who did not receive cisplatin.

Future perspectives

VFL has demonstrated good efficacy and low toxicity in a poor prognosis category of patients, thus, its use is also under investigation in other settings.

Maintenance therapy

A phase II randomized trial is evaluating the role of VFL as maintenance chemotherapy after first-line cisplatin-based chemotherapy. The doses employed were 320 mg/m^2 in PS=0 patients, and 280 mg/m^2 in PS=1 and PS=0 with prior pelvic irradiation. Enrollment has been almost concluded and results are pending (http://clinicaltrials.gov/ct2/show/NCT01529411?term=vinflunine&rank=9).

First-line chemotherapy

A number of patients, especially elderly and low-PS patients, are unable to tolerate cisplatin-containing first-line chemotherapy. In this subgroup of patients, VFL may substitute for cisplatin and may be employed in association with gemcitabine. A phase III randomized trial comparing gemcitabine plus placebo versus gemcitabine plus VFL in chemotherapy-naïve patients is currently ongoing. The target accrual of this trial, named VINCENT (vinflunine in cisplatin-ineligible patients), is 450 patients; its results should be available soon.[16]

Second-line chemotherapy

First-line chemotherapy has demonstrated good results in the treatment of locally advanced or metastatic UC with the potential for long-term survival and possible complete responses.[2-6] However, different therapeutic strategies are needed for patients relapsing or refractory to first-line chemotherapy. Several phase II studies were performed in patients with recurrent UC, but no therapy demonstrated to improve survival.[7-12] Several factors could influence sensitivity to second-line chemotherapy therapy such as PS, chemosensitivity to first-line treatment, the presence of visceral metastases, the intent of prior treatment (perioperative vs metastatic), or a combination of these factors.[7-12] Interestingly, contrasting results were reported for patients included in second-line studies after failure of neoadjuvant or adjuvant therapy compared to patients at relapse after first-line.[14-19] Because of their good activity in UC, taxanes may be compared with VFL as second-line chemotherapy. A randomized, head-to-head, phase II trial, which started its enrollments in October 2012, is ongoing and is comparing VFL at standard doses versus cabazitaxel, a third-generation taxane. Results are pending (http://clinicaltrials.gov/ct2/show/NCT01830231?term=vinflunine&rank=3).

Phase I combination trials

Sorafenib is a small molecule inhibiting several tyrosine kinases, among which VEGFR. It is currently employed in advanced kidney cancer, liver cancer, neuroendocrine tumors, and soft-tissue sarcoma. Taking advantage of its anti-angiogenic capability, some authors have designed a phase I trial aimed to assess the safety and activity of a combination sorafenib-VFL regimen in patients with advanced UC. Some biomolecular markers, especially those related to angiogenesis, will be evaluated concomitantly.

Among the drugs targeting microtubule functions, epothilones represent a class of anticancer agents which recently entered clinical development, especially in breast and lung cancer.[22] Epothilones share mechanisms of action similar to taxanes, but have non-overlapping mechanisms of resistance. Ixabepilone is a component of this class of compounds and it has been actively investigated in a number of clinical trials. Given the good activity shown by taxanes in UC,

Table 3. Grade 3-4 adverse events in patients with advanced or metastatic urothelial carcinoma treated with vinflunine.

	Patients	
	n	%
Hematologic		
Anemia	77	17
Leukopenia	96	21
Neutropenia	243	53
Thrombocytopenia	22	5
Febrile neutropenia	30	6
Non-hematologic toxicities		
Nausea	13	3
Vomiting	13	3
Constipation	69	15
Stomatitis	12	3
Asthenia/fatigue	72	16
Abdominal pain	21	4
Peripheral sensory neuropathy	4	1
Injection site reactions	2	1
Myalgia	14	3

Data derived by three clinical randomized trials (patients=455).

both in first- and second-line treatment, the combination of ixabepilone and VFL may be a valuable therapy choice. A phase I clinical trial is exploring the aforementioned drug combination in advanced tumors, among which UC. More in detail, the study is aimed to determine the maximum tolerated dose and to describe any dose limiting toxicities of ixabepilone and vinflunine in an alternating regimen (http://clinicaltrials.gov/ct2/show/NCT00362830?term=vinflunine&rank=11).

The use of targeted therapy in UC is currently uncommon; nevertheless, preclinical and early clinical studies have demonstrated that numerous potentially *targetable* molecular pathways exist, and one of these is the epidermal growth factor receptor (EGFR). Phase I and II studies have examined the impact of anti-EGFR drugs on advanced UC.[23] On the basis of these findings, a phase I trial assessing the combination of VFL and erlotinib has been designed. The trial has enrolled patients with advanced tumors, among which UC. The enrollment has been completed and results will be available briefly.

Conclusions

VFL is a well manageable drug, able to impact the survival and quality of life of patients with recurrent pretreated UC. Compared to other vinca alkaloids, VFL has shown a better safety profile, inducing a smaller degree of neuropathy and its early resolution after drug withdrawal.[13-18] Other adverse events reported were mucositis and neutropenia, which were of low grade and of prompt resolution after the appropriate therapy. In the phase III trial conducted by Bellmunt *et al*.,[16] VFL has demonstrated the ability to improve the outcome of patients with advanced UC which progressed after a first-line cisplatin-containing chemotherapy. In fact, the median OS reached by the single-agent VFL chemotherapy was 6.9 months, and its toxicity spectrum was manageable. The ORR and DRC were 8.6 and 41.1%, respectively, and are in line with those reached in previous phase II trials. Its indication remains as a second-line treatment, after prior cisplatin-based chemotherapy, but in the near future, it might also be used in other disease settings. Clinical trials evaluating the role of VFL as maintenance chemotherapy after first-line cisplatin-based chemotherapy or first-line chemotherapy in patients unable to tolerate platinum-containing combination regimens are ongoing in Europe and the United States. Phase I trials are assessing the safety and activity of VFL in combination with new targeted therapies or other chemotherapeutic agents. Moreover, phase II trials have shown a significant clinical activity of VFL in poor prognosis patients with breast and non-small cell lung cancer (NSCLC). Phase III trials are ongoing and results in breast and lung cancer are encouraging, suggesting that VFL might replace vinorelbine because of its improved efficacy and safety profile. To date, VFL has received European Medicines Agency (EMA) approval only for use as second-line treatment in UC patients who progressed after a first-line cisplatin-containing chemotherapy. A better understanding of the biology of chemotherapy-naive and chemotherapy-resistant UC, personalized approaches, better trial design, and assessment of quality of life as a study end point in this patient population will hopefully lead to the identification of tolerable and effective new regimens.

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