Vinflunine in the treatment of bladder cancer

Mark Bachner
Maria De Santis

3rd Medical Department – Center for Oncology and Hematology, Kaiser Franz Josef-Spital der Stadt Wien, and Ludwig Boltzmann-Institute for Applied Cancer Research Vienna (LBI-ACR VIEnna), Cluster Translational Oncology, Kaiser Franz Josef-Spital der Stadt Wien, and Applied Cancer Research – Institution for Translational Research Vienna (ACR-ITR VIEnna)/CEADDP, Vienna, Austria

Abstract: Vinflunine (VFL) is a third-generation bifluorinated semi-synthetic vinca alkaloid obtained by superacidic chemistry from its parent compound, vinorelbine. As with the other vinca alkaloids, the main antineoplastic effects of VFL arise from its interaction with tubulin, the major component of microtubules in mitotic spindles. In contrast to other vinca alkaloids, VFL shows some distinctive properties in terms of tubulin binding, possibly explaining its superior antitumor activity in vitro and in vivo compared with vinorelbine as well as its excellent safety profile. In transitional cell carcinoma (TCC), two single-agent phase II trials were performed testing VFL in platinum-pretreated patients, showing moderate response rates and promising disease control rates. Therefore, the first phase III trial in modern times for second-line TCC of the urothelium was designed in order to further investigate the activity of VFL. First results were presented at the 2008 ASCO conference. VFL appears to be a possible treatment option for patients with TCC progressing after first-line platinum-containing chemotherapy.

Keywords: vinflunine, transitional cell carcinoma (TCC) of the bladder, bladder cancer, chemotherapy, second-line chemotherapy

Bladder cancer – a brief overview

In 2002, 357,000 patients were newly diagnosed with transitional cell carcinoma of the urothelium (TCCU) worldwide, 274,000 males and 83,000 females, making it the ninth most common type of cancer for both sexes combined (Parkin et al 2005). In the same year, an estimated number of 145,000 patients died from this disease (108,000 males and 37,000 females).

The standard of care for muscle-invasive TCCU is radical cystectomy. Unfortunately, 5-year survival rates after surgery are only approximately 50% (Ghoneim et al 1997; Bassi et al 1999; Dalbagni et al 2001; Stein et al 2001; Stein 2006). About 50% of patients will relapse after surgery, depending on the pathological stage of the primary tumor, the nodal status, and the quality and extent of surgery performed. Local recurrence counts for about 30% of relapses whereas distant metastases are more common (Rosenberg et al 2005).

Trying to improve outcome after surgery, multiple randomized trials examined preoperative chemotherapy, leading to inconclusive and even controversial results. Therefore, 3 meta-analyses were performed (Advanced Bladder Cancer Meta-Analysis Collaboration 2003, 2005b; Winquist et al 2004), showing a small, but statistically significant overall survival (OS) benefit for neoadjuvant, cisplatin-containing combination chemotherapy.

Five randomized trials and 1 meta-analysis could not provide convincing results to support routine use of adjuvant chemotherapy (Advanced Bladder Cancer Meta-Analysis Collaboration 2005a).

Before the development of effective chemotherapy, the median survival of patients with metastatic urothelial cancer rarely exceeded 3 to 6 months (Sternberg et al 2003). In the early 1980s, cisplatin monotherapy doubled the median survival to about 8 months (Loehrer et al 1992). MVAC (methotrexate, vinblastine, doxorubicin,

Correspondence: Mark Bachner
3rd Medical Department – Center for Oncology and Hematology, Kaiser Franz Josef-Spital der Stadt Wien, Kundratstraße 3, A-1100 Vienna, Austria
Tel +43 1 60191 2308
Fax +43 1 60191 2309
Email mark.bachner@wienkav.at

and cisplatin) in the mid 1980s (Sternberg et al 1988), further improved OS to slightly over 1 year and became the standard of care for metastatic TCCU (Culine 2002).

In a phase III trial published in 2000, von der Maase et al (2000) established the combination regimen GC (gemcitabine, cisplatin) as an alternative to MVAC with comparable efficacy results but a favorable toxicity profile. Today, a median OS of 14 to 15 months can be expected.

For the large patient group regarded as unfit for cisplatin-containing chemotherapy (mainly due to impaired renal function and/or low performance status), there are only limited data and no approved standard of care.

Also, for patients progressing after first-line platinum-containing chemotherapy, there is still no approved second-line therapy.

Vinflunine – preclinical studies

Vinflunine (VFL, Javlor®) is a third-generation, semi-synthetic vinca alkaloid obtained through superacidic chemistry by the selective introduction of 2 fluorine atoms at the 20′-position of vinorelbine, a part of the molecule previously inaccessible by classical chemistry (Fahy et al 1997, 2008).

VFL interacts with the so-called vinca-alkaloid-binding-domain of tubulin, as judged by proteolytic cleavage patterns (Lobert et al 1998), and, more recently, confirmed by NMR spectroscopy (Fabre et al 2002).

Microtubules are an important target for anticancer therapy because of the crucial role they play during mitosis, coordinating chromosomal segregation; microtubule inhibitors include vinca alkaloids, taxanes, and epothilones.

VFL expresses some distinctive features: the affinity of VFL binding to tubulin is considerably lower than that of other vinca alkaloids. Also, VFL does not prevent other vinca alkaloids from binding to unassembled tubulin. The binding affinity of different vinca alkaloids to tubulin was classified as: vincristine > vinblastine > vinorelbine > vinflunine (Kruczynski et al 1998a; Lobert et al 1998), correlating well with the weekly intravenous drug doses of these vinca alkaloids used in the clinic.

Interestingly, the binding affinity of vinca alkaloids to tubulin is not necessarily related to the degree of antitumor efficacy. Singer et al (1992), for example, found an inverse correlation between relative binding affinities and inhibition of cell proliferation examining 4 different vinca alkaloids. Also, Jordan et al (1985) 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. This may be due to the fact that vinca alkaloids accumulate intracellularly several-fold to >100-fold or that they target other intracellular sites (Gout et al 1984; Jordan et al 1991; Etievant et al 1998; Jean-Decoster et al 1999; Ngan et al 2001). Of the tested vinca alkaloids, VFL reached the highest intracellular concentrations (Hill 2001). The significance of this finding is still unclear.

Lobert et al (1998) hypothesized that the drug affinity to tubulin may contribute to the severity of neuropathies observed clinically.

Microtubules display two types of characteristic behavior: "dynamic instability", a random switching of microtubules between phases of relatively slow growth and rapid shortening and "treadmilling", a net addition of tubulin subunits at one end of a microtubule (the fast-growing plus end) and the balanced net loss from the opposite end (the slow-growing minus end). Both phenomena appear crucial for progression through mitosis and the cell cycle.

Ngan and colleagues found that the effects of vinorelbine and VFL on microtubule dynamics differ significantly from those of the classic vinca alkaloid, vinblastine (Ngan et al 2000, 2001; Jordan et al 2008): VFL and vinorelbine suppress the rate and extent of microtubule growing, whereas vinblastine strongly suppresses the rate and extent of microtubule shortening. VFL inhibited the rate of treadmilling 4-fold less strongly than vinorelbine and 7-fold less strongly than vinblastine.

Ngan et al (2000) hypothesized that non-tumor cells with "normal" checkpoint proteins could tolerate the relatively less powerful inhibitory effects of VFL 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 VFL and vinorelbine than normal cells. This may account for the superior antitumor efficacy as well as a favorable safety profile of VFL.

VFL bound to tubulin induces structural changes favoring an inhibition of GTP hydrolysis and inhibition of microtubule assembly (Kruczynski et al 1998a; Hill 2001). In cell cultures, VFL reduced the microtubule network of interphase cells and induced G2+M arrest (Kruczynski et al 1998a), leading to mitotic accumulation at the metaphase/anaphase transition and finally resulting in apoptosis (Kruczynski et al 2002; Pourroy et al 2004; Braguer et al 2008; Jordan et al 2008). At higher concentrations, VFL – like other vinca alkaloids – aggregated microtubules, leading to paracrystal formations.

In preclinical in vivo studies, VFL showed definite (high or moderate) antitumor activity against 7/11 (64%) of

subcutaneously implanted human tumor xenografts compared with vinorelbine, which showed only moderate activity against 3/11 (27%) of the xenografts (Kruczynski et al 1998b; Hill et al 1999), suggesting a broader spectrum of activity for VFL. VFL led to significant survival prolongation of tumor-bearing mice and tumor growth inhibition with optimal T/C (treated vs control) values of up to 457% in the absence of any significant body weight loss, providing evidence of a high level of tolerance to these effective antitumor doses of VFL.

Following the clinical success of vinorelbine and its efficacy in combination with other anticancer drugs (Johnson et al 1996; Bunn et al 1998; Gregory et al 2000; Hortobagyi 2000), Barret et al (2000) studied in vitro synergistic effects of several VFL combinations in a human non-small-cell lung cancer (NSCLC) line and a human leukemia cell line. They incubated VFL with camptothecin, cisplatin, doxorubicin, etoposide, 5-fluorouracil, gemcitabine, mitomycin C, paclitaxel, or vinorelbine. A high level of synergistic cytotoxicity of VFL was observed when combined with the DNA-damaging agents cisplatin and mitomycin C, the DNA-intercalating agent doxorubicin, and the antimetabolite 5-fluorouracil, all of which induce DNA damage directly or indirectly and induce cell death predominantly via a p53-dependent pathway. Moderate synergy was identified with the combination of VFL and the topoisomerase I inhibitor camptothecin. Only additivity but no synergy could be shown for combinations with the topoisomerase II inhibitor etoposide, the antimetabolite gemcitabine, and either of the two tubulin-interacting agents paclitaxel and vinorelbine.

These results are promising and may implicate manifold possibilities for combination therapies including VFL. A large 3-armed study for NSCLC patients could already demonstrate significantly higher response rates (RR) for the parent compound, vinorelbine, when combined with cisplatin compared to vinorelbine alone and compared to the combination of vindesine and cisplatin (Le Chevalier et al 1994). First results of a combined phase I/II trial of VFL in combination with cisplatin – again for patients with NSCLC – were also very encouraging with a RR of 33% and a disease control rate of 77% (Ramlau et al 2004).

Following earlier studies that showed definite antivascular effects of vinblastine and vinorelbine (Baguley et al 1991; Hill et al 1993), Holwell et al studied the influence of VFL on tumor vascularization in vivo using a transplantable murine tumor model (Holwell et al 2001). Morphologic changes after VFL-treatment included extensive hemorrhagic necrosis. Perfusion studies showed a vascular shutdown over a minimum of 24 hours at doses considerably lower than the maximum tolerated dose, suggesting that VFL mediates its antitumor activities – at least in part – via an antivascular pathway (Braguer et al 2008).

Resistance of tumor cells to multiple cytotoxic drugs, termed MDR, is a major limitation to effective chemotherapy. Results of a series of studies involving both in vitro and in vivo experimental tumor models suggested that VFL, like the other vinca alkaloids, belongs to the P-glycoprotein-dependent multidrug resistant (MDR) family of anticancer agents. However, it was clearly shown that among various P-glycoprotein-overexpressing multidrug resistant human tumor sublines tested in vitro, the level of cross-resistance expressed with VFL was generally far lower than that of vinorelbine or vincristine. Testing human leukemia cells in vivo, it was demonstrated that VFL induced drug resistance far less readily than vinorelbine, both in terms of time taken for resistance to be established and the level of resistance ultimately obtained (Etievant et al 1998, 2001; Kavallaris et al 2008).

In order to investigate the feasibility of systemic treatment of TCC of the bladder with VFL, Bonfil et al (2002) examined the effect of VFL on a murine bladder cancer cell line, which was transurethrally implanted. They found clear antitumor activity of VFL against this superficial bladder cancer model superior to that of vinorelbine with a good overall tolerance, suggesting that VFL might be a good candidate for the systemic treatment of bladder cancer.

Vinflunine – phase I trials

Starting in 1998, 3 initial phase I trials with different schedules of intravenous administration were performed in order to determine the recommended dose (RD) for single agent VFL:

- day 1 in a 3-week schedule: RD at 350 mg/m^2 every 3 weeks (Bennouna et al 2003)
- weekly administration:
  - previously treated patients: RD at 120 mg/m^2 (Delord et al 2001; Puozzo et al 2001)
  - previously untreated patients: RD at 150 mg/m^2 (Vermorken et al 2003)
- day 1 and day 8 every 3 weeks: RD at 170 mg/m^2 (Zorza et al 2001; Johnson et al 2001, 2006)

Dose-limiting toxicities (DLT) in these classical single agent phase I trials included grade 4 neutropenia, febrile neutropenia, grade 3/4 constipation, grade 3 myalgia,

grade 3 chest pain, grade 4 infection, and grade 3 rise in transaminases.

The VFL dose and schedule selected for phase II studies were 1 intravenous administration every 3 weeks at 350 mg/m^2 (Bennouna et al 2003), since the other schedules did not result in a higher dose intensity. However, after an analysis of data from the first 24 patients enrolled in phase II trials, the initial RD was lowered to 320 mg/m^2 every 3 weeks in patients with good performance status (PS) and no prior extended pelvic irradiation, and to 280 mg/m^2 for other patients.

In 2002, Focan et al (2002) presented pharmacokinetic results of five patients treated with radiolabeled, tritiated VFL given iv at 250 mg/m^2. They described 11 metabolites of VFL, the predominant and only active one being 4-O-deacetyl-vinflunine (DVFL). Two thirds of the dose was eliminated through bile and one third by the kidneys (Focan et al 2002; Lobert et al 2008).

Different phase I trials with VFL in combination with other anticancer drugs were performed or are still ongoing, including pemetrexed (Shah et al 2008), trastuzumab (Paridaens et al 2007), carboplatin (Tourani et al 2005), gemcitabine (Lemarie et al 2005), cisplatin (Ramlau et al 2004), capecitabine, erlotinib, and cetuximab (www.clinicaltrials.gov).

Paule et al (2007) performed a phase I trial in 30 patients to determine VFL dose adjustments in cancer patients with various degrees of liver dysfunction. They found that pharmacokinetic parameters of VFL and DVFL did not appear to be affected by the degree of liver disease. Saliba et al (2007) presented a subgroup analysis of the 18 patients with hepatocellular carcinoma taking part in the above mentioned trial and concluded that VFL could be given safely at 320 mg/m² in this patient cohort. The disease control rate was promising (66.7%) with one partial response (PR).

At the 2008 ASCO annual meeting Bennouna et al (2008) presented preliminary data of a phase I trial with oral VFL given twice a day for 2 consecutive days every week. The bioavailability of this oral form was 57%, the maximum tolerated dose was reached at 300 mg/day, when 2 patients experienced febrile neutropenia concomitant with grade 3 diarrhea. The recommended dose for oral application has not yet been defined.

Vinflunine in bladder cancer – phase II trials

In 2006, Culine et al published results of a phase II study of VFL as a 10-minute infusion 3-weekly in bladder cancer patients failing or progressing after first-line platinum-containing chemotherapy or after platinum-containing regimens given with adjuvant or neoadjuvant intent (Culine et al 2006). Fifty-eight patients were recruited in this multi-center trial by 16 European centers between November 2000 and September 2002. The primary objective was overall response rate (ORR), secondary objectives were duration of response, progression-free survival (PFS), OS, and safety. Eligibility criteria included a Karnofsky performance status (KPS) of 80 or greater and a glomerular filtration rate of at least 40 mL/min.

One patient died before receiving treatment and was not included in the analysis. At the beginning of the study, 6 patients were treated with intravenous (iv) VFL at 350 mg/m^2 based on the above described phase I trial (Bennouna et al 2003). The most frequent adverse events at this dose included leucopenia, neutropenia, and anemia, which were observed in all 6 patients (100%) with 1 fatal febrile neutropenia. A preliminary safety evaluation, performed across all ongoing VFL phase II trials, led to a dose reduction to 320 mg/m^2 3-weekly (the next lower dose level of the preceding phase I trial). The 6 patients treated at 350 mg/m^2 were not included in the analysis.

The median age of the analyzed 51 patients was 63 years; 55% had a KPS of 100 or 90. As prior chemotherapies, 22 patients (43%) had received MVAC or CMV (cisplatin, methotrexat, vinblastin) and 25 patients (49%) GC; prior therapy was for advanced disease in 34 patients (67%) and as adjuvant or neoadjuvant chemotherapy in 17 patients (33%). The median treatment-free interval between completion of initial chemotherapy and VFL treatment was 7.5 months. All patients enrolled in the study had clear evidence of progressive disease (PD), 61% had 2 or more metastatic lesions at entry, and 49% had visceral involvement.

There were 9 PR observed (18%), 25 patients had stable disease (SD), amounting to a disease control rate of 67%.

Disease control rates seemed to correlate with the interval from prior platinum treatment, with better results in late relapsing or progressing patients. ORR were 8/34 (24%) and 1/17 (6%) in patients previously treated in the metastatic and neoadjuvant/adjuvant setting, respectively. Responses were observed in 3/22 (14%) patients who had received prior vinca alkaloids as a part of the MVAC or CMV regimens. Responses were predominantly seen in patients who had previously responded to chemotherapy, although numbers were too small to exclude random variation. However, 5 out of 25 (20%) of patients with visceral involvement achieved an objective response and responses were also seen in patients with primary chemoresistant disease.

Median duration of response was 9.1 months. Among the 51 patients treated at 320 mg/m^2, median PFS was 3.0 months and median OS was 6.6 months.

During treatment, KPS improved in 11 patients (22%), 27 patients (53%) maintained their baseline status. Only 10 patients (20%) had a worsening of their KPS during treatment.

Toxicity was generally well manageable and non-cumulative; the predominant grade 3/4 hematological toxicity was neutropenia (67%), with 5 patients (10%) experiencing febrile neutropenia, 2 of whom died; both had received multiple courses of VFL. The main grade 3/4 non-hematologic toxicities included fatigue (10%), constipation (8%) and abdominal pain (8%). Of note, there was no grade 3 or 4 peripheral neurotoxicity observed and no grade 3/4 rise in serum creatinine.

At the 2008 ASCO Genitourinary Cancers Symposium, Vaughn et al (2008) presented results of a second international phase 2 trial conducted to confirm the results published by Culine et al (2006). Eligibility criteria were comparable: patients with no more than one prior platinum-based regimen with disease progression within 12 months of treatment, a KPS ≥80, and a creatinine clearance >20 mL/min. The primary endpoint was ORR. 175 patients were enrolled, of whom 151 received treatment and were included in the analysis. VFL 320 mg/m^2 was administered once every 3 weeks as a 15- to 20-minute intravenous infusion. Patients with KPS 90 or 80, prior 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 two onwards, based on tolerance.

Twenty-two PR with a median duration of 6.0 months were reported, equivalent to an ORR of 14.6%. Sixty-four patients (42.4%) had SD with a median duration of 4.0 months, resulting in a disease control rate of 57.0%. Median PFS was 2.8 months and median OS was 7.9 months.

Toxicity was similar to the data previously reported by Culine (2006), with 58.1% of patients experiencing neutropenia grade 3/4 and 10 patients (6.6%) with neutropenic fever. Grade 3/4 non-hematologic toxicities included constipation (16.6%), asthenia/fatigue (12.6%), ileus (4.6%), and abdominal pain (4.6%).

Table 1 summarizes adverse events seen in more than 1000 patients treated with VFL as a single agent. Table 2 summarizes clinical trials with single-agent second-line chemotherapy in TCCU patients. Table 3 summarizes clinical trials with second-line combination chemotherapy.

Table 1 Selected adverse events in ≥1% of patients (n = 1049) (derived from Bellmunt et al 2008)

	Overall incidence n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic			
Anemia	787 (84)	82 (8)	14 (1)
Leukopenia	773 (74)	231 (22)	121 (12)
Neutropenia	758 (72)	222 (21)	288 (27)
Thrombocytopenia	395 (38)	30 (3)	–
Febrile neutropenia	59 (6)	52 (5)	–
Neutropenia with infection	19 (2)	14 (1)	–
Non-hematologic			
Abdominal pain	255 (24)	56 (5)	–
Constipation	552 (53)	108 (10)	–
Diarrhea	116 (11)	8 (1)	–
Nausea	435 (41)	30 (3)	–
Vomiting	313 (30)	32 (3)	–
Stomatitis	351 (33)	16 (2)	–
Fatigue	566 (54)	128 (12)	–
Myalgia	195 (19)	32 (3)	–
Peripheral sensory neuropathy[a]	39 (4)	–	–
Injection-site reactions	100 (10)	–	–
Alopecia	307 (29)	–	–

A total of 880 patients were administered an initial dose of 320 mg/m^2, 169 patients were administered an initial dose of 280 mg/m^2.
[a]one case of grade 3 paresthesia (0.1%) has been reported.

Table 2 Single-agent second-line chemotherapies for advanced bladder cancer

Trial	Regimen	N (evaluable)	RR	TTP	Median survival (months)
(Khorsand et al 1997)	Piritrexim	17 (13)	23%	NR	NR
(McCaffrey et al 1997)	Docetaxel	31 (30)	13%	NR	9
(Papamichael et al 1997)	Paclitaxel	14 (14)	7%	NR	NR
(Pronzato et al 1997)	Ifosfamide	20 (20)	5%	6	8
(Witte et al 1997)	Ifosfamide	60 (56)	20%	2.2	5.1
(Lorusso et al 1998)	Gemcitabine	35 (31)	23%	3.8	5
(Witte et al 1998)	Topotecan	46 (44)	9%	1.4	6.3
(Gebbia et al 1999)	Gemcitabine	24 (24)	29%	NR	13.0
(Dodd et al 2000)	Pyrazoloacridine	14 (14)	0%	NR	9
(Albers et al 2002)	Gemcitabine	30 (28)	11%	4.9	8.7
(Roth et al 2002)	Piritrexim	35 (27)	7%	2.1	7.0
(Vaughn et al 2002)	Paclitaxel	31 (31)	10%	2.2	7.2
(Moore et al 2003)	Oxaliplatin	20 (18)	6%	NR	NR
(Joly et al 2004)	Paclitaxel	45 (37)	5%	NR	NR
(Sridhar et al 2005)	Bortezomib	18 (11)	0%	NR	NR
(Wülfing et al 2005)	Lapatinib	59 (59)	2%	2.0	4.2
(Sweeney et al 2006)	Pemetrexed	47 (47)	28%	2.9	9.6
(Culine et al 2006)	**VFL**	**58 (51)**	**18%**	**3.0 (PFS)**	**6.6**
(Dreicer et al 2007)	Epothilone B	45 (42)	12%	2.7 (PFS)	8
(Galsky et al 2007)	Pemetrexed	13 (12)	8%	NR	NR
(Vaughn et al 2008)	**VFL**	**175 (151)**	**15%**	**2.8 (PFS)**	**7.9**
(Bellmunt Molins et al 2008)	**VFL**	**253 (185)**	**9%**	**3.0 (PFS)**	**NR**

Abbreviations: RR, response rate; TTP, time to progression; NR, not reported; PFS, progression-free survival.

Second-line TCCU treatment – interpretation of trial results and open questions

For more than 20 years, cisplatin combination regimens have been the standard of care in the treatment of locally advanced or metastatic TCCU. Urothelial cancers are highly responsive to chemotherapy in the first-line setting with possible complete responses and the potential for long-term survival. Median survival of patients has been reported to be up to 15 months. Combination regimens have demonstrated a clear advantage compared to single-agent therapy.

However, cures are rare and therapeutic options for patients refractory to or relapsing after platinum-containing chemotherapy are clearly needed. Although there were several phase II studies performed in patients with recurrent TCC, there is still no approved treatment option in this setting and no therapy has proven to prolong survival.

There are no established predictive or prognostic factors for second-line treatment in TCCU. In a retrospective multivariate regression analysis performed by Bajorin et al (1999), the authors found a KPS less than 80% and the presence of visceral metastases to be two independent prognostic factors for survival and assigned patients to three risk categories according to the number of unfavorable characteristics. In this retrospective analysis, all but 12 patients were chemonaïve; whether these prognostic factors are also valid in second-line treatment remains unclear.

Response to second-line therapy might be influenced by chemosensitivity to first-line treatment (Albers et al 2002), PS (Meluch et al 2001), the presence of visceral metastases, the intent of prior treatment (perioperative vs metastatic), or a combination of these factors (Sternberg et al 2001).

Repeatedly, promising phase II results could not be confirmed by other investigators. For example, in 1992 Logothetis et al (1992) reported a response rate of 61% for the combination of 5-FU, α-interferon and cisplatin in partly heavily pretreated patients. Unfortunately, a subsequent EORTC trial was unable to confirm these results, reporting a RR of only 12.5% (De Mulder et al 2000). This emphasizes that initial encouraging results of small phase II trials should be confirmed by other investigators.

Table 3 Second-line chemotherapies for advanced bladder cancer

Trial	Regimen	N (evaluable)	RR	Median survival (months)
(Logothetis et al 1992)	5-FU/α-interferon/cisplatin	28 (NR)	61%	NR
(Tu et al 1995)	Paclitaxel/methotrexate/cisplatin	25 (25)	40%	NR
(Sweeney et al 1999)	Paclitaxel/ifosfamide	13 (13)	15%	8
(De Mulder et al 2000)	5-FU/α-interferon/cisplatin	43 (40)	13%	4.9
(Kaufman et al 2000)	Gemcitabine/paclitaxel	6 (6)	0%	NR
(Krege et al 2001)	Docetaxel/ifosfamide	22 (20)	25%	4
(Meluch et al 2001)	Gemcitabine/paclitaxel	15 (15)	47%	NR
(Sternberg et al 2001)	Gemcitabine/paclitaxel	41 (40)	60%	14.4
(Bellmunt et al 2002)	Methotrexate/paclitaxel	20 (19)	32%	5
(Pagliaro et al 2002)	Cisplatin/gemcitabine/ifosfamide	51 (49)	41%	9.5
(Chen et al 2004)	Gemcitabine/docetaxel/carboplatin	NR (9)	56%	NR
(Vaishampayan et al 2005)	Carboplatin/paclitaxel	44 (44)	16%[a]	6
(Fechner et al 2006)	Gemcitabine/paclitaxel	30 (27)	44%	NR
(Lin et al 2007)	Gemcitabine/ifosfamide	23 (23)	22%	4.8
(Albers et al 2008)	Gemcitabine/paclitaxel	51 (29)	35%	7.5

[a]Including 4 unconfirmed PR.

Abbreviations: RR, response rate; TTP, time to progression; NR, not reported; PFS, progression-free survival.

As Sweeney pointed out elsewhere (Sweeney et al 2006), variability in RR reported in phase II trials is not only likely to be due to a variability in drug activity, but also to the confounding factor of differing patient populations between studies. For example, many trials in second-line TCC not only include patients after first-line therapy for metastatic disease, but also allow patients having relapsed after chemotherapy in the perioperative setting. In view of this, an exact description of the patient characteristics becomes critical to evaluate the results of clinical trials.

It has been a common understanding that patients after neoadjuvant or adjuvant chemotherapy would have a higher chance of response to second-line treatment than patients relapsing after first-line MVAC for metastatic disease. For example, Sternberg et al (2001) reported RR of 80% and 27% for these two patient groups, respectively.

Interestingly, other investigators reported comparable or even worse results for patients included in second-line studies after failure of neoadjuvant or adjuvant therapy compared to patients at relapse after first-line chemotherapy (Culine et al 2006; Sweeney et al 2006).

Vinflunine in bladder cancer – phase III trial

At the 2008 ASCO conference in Chicago, Bellmunt Molins et al (2008) presented data from a multicenter, randomized (2:1) phase III trial comparing VFL and best supportive care (BSC) (arm A) versus BSC alone (arm B) in platinum-pretreated patients. In a large international effort, 83 centers from 21 countries enrolled 370 patients between May 2003 and August 2006 with unresectable locally advanced or metastasized TCCU, making this the first second-line phase III trial in "modern" times.

The primary endpoint was OS; secondary endpoints included PFS, RR, disease control, clinical benefit, and quality of life (QoL). Stratification factors were center and refractory disease (PD within 2 cycles). "Moderate neuropathy" was an exclusion criterion.

VFL was administered intravenously at a dose of 320 mg/m^2 every 3 weeks, except for patients with a PS of 1 and/or previous pelvic irradiation, who started at 280 mg/m^2 with a subsequent dose escalation to 320 mg/m^2, where possible.

The statistical hypothesis was to demonstrate an OS benefit of 2 months in the VFL group (6 vs 4 months). Main characteristics of the patients were well balanced except for PS, that slightly favored arm B (PS 1 arm A 71.5%, arm B 61.5%). Fifty-three percent of the patients were under 65 years of age and only patients in PS 0 or 1 were eligible; on the other hand, 40% of patients had bulky disease, 74% suffered from visceral involvement and over 80% of the patients had relapsed or progressed within 6 months after first-line platinum-containing chemotherapy.

In the VFL arm a high incidence of neutropenia grade 3/4 was observed (50%), but only 6% of patients suffered from febrile neutropenia. There was one toxic death. Grade 3/4 non-hematological toxicities are summarized in Table 4.

Analyzing the intent-to-treat-population, the 2-month survival advantage for arm A was achieved (6.9 vs 4.6 months), but 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), median OS was 6.9 months in the VFL arm and 4.3 months in the BSC arm (p value 0.04 for eligible patients and 0.02 for per protocol patients). A planned multivariate analysis adjusting for prognostic factors also showed a statistically significant effect of VFL on OS ($p = 0.04$), although other factors such as hemoglobin-level, visceral involvement or PS had a stronger impact on survival in this analysis than the treatment with VFL.

ORR in the VFL-arm was 8.6% and therefore clearly lower than in the previous phase II trials, disease control rate was 41.1% and PFS was 3.0 months, all reaching statistical significance with p values < 0.01 compared to the control arm. Despite the low response rate those responses were durable, as the median duration of response was 7.4 months, the median duration of disease control was 5.7 months.

The median duration of treatment in the VFL-arm was 9.5 weeks, roughly amounting to the survival benefit shown. As the QoL results were not yet reported, the QoL-adjusted benefit for patients treated in the VFL arm remains to be seen.

Although there is no approved standard for second-line treatment and BSC was therefore chosen as control arm in this phase III trial, several other substances have proved activity in phase II trials as well as in daily clinical routine for this patient group (see Tables 2 and 3).

Conclusion

VFL showed very promising preclinical results with a broad spectrum of activity consistently superior to that of its parent compound, vinorelbine.

Phase I trials recommended a dose of 350 mg/m^2 as a short iv infusion on day 1 of a 3-week cycle (Bennouna et al 2003), later reduced to 320 mg/m^2.

In TCCU, VFL showed moderate activity in 2 phase II trials. In a large phase III trial, no statistically significant benefit was found for VFL in an intention to treat analysis; however, a preplanned secondary analysis did find an improvement in OS for patients in the VFL arm.

VFL has an excellent safety profile, the most common side effects being myelosuppression and constipation. Of note, VFL is far less neurotoxic in comparison to other vinca alkaloids and other microtubule inhibitors such as taxanes and epothilones. Therefore, VFL appears to be a reasonable option for patients with TCCU progressing after first-line platinum-containing chemotherapy.

However, treatment within clinical trials should be first choice whenever possible, in order to identify more efficient treatment options for this patient group.

Future indications for VFL in TCCU might include patients ineligible for first-line treatment with platinum-containing combination regimens. A trial comparing VFL plus gemcitabine versus gemcitabine alone has been initiated in the United States.

The role of VFL in NSCLC and metastatic breast cancer is under investigation.

Table 4 Non-hematological toxicities, n = 248 patients (derived from Bellmunt Molins et al 2008)

Adverse event	VFL + BSC		BSC	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Nausea	97 (39.1)	6 (2.4)	25 (21.4)	1 (0.9)
Vomiting	72 (29.0)	7 (2.8)	17 (14.5)	0
Abdominal pain	39 (15.7)	10 (4.0)	21 (17.9)	7 (6.0)
Constipation	118 (47.6)	40 (16.1)	29 (24.8)	1 (0.9)
Stomatitis/mucositis	71 (28.6)	4 (1.6)	2 (1.7)	0
Fatigue/asthenia	124 (50.0)	48 (19.3)	71 (60.7)	21 (17.9)
Myalgia	40 (16.1)	8 (3.2)	8 (6.8)	0
Neuropathy sensory	30 (12.1)	3 (1.2)	13 (11.1)	0
Alopecia	72 (29.0)	–	2 (1.7)	0
Infusion site reaction	68 (27.4)	1 (0.4)	0	0

Abbreviations: BSC, best supportive care; VFL, vinflunine.

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Neither author has conflicts of interest to disclose.

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