REVIEW

Critical evaluation of vinflunine in the treatment of refractory metastatic urothelial carcinoma

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Abstract: Urothelial carcinoma (UC) accounts for 5% to 10% of malignancies in men in Europe and the United States. For locally advanced or metastatic disease, there are two standard first-line chemotherapy regimens: MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) and gemcitabine/cisplatin. For refractory disease, there is currently no standard treatment. Vinflunine, a second-generation *Vinca* alkaloid, is the first chemotherapeutic agent to be evaluated in a large UC second-line population. This review discusses the pre-clinical and clinical data published, and compares vinflunine to alternative single agents and combination regimens tested in this setting. Based on the results of the phase II and III clinical trials, there appears to be sufficient evidence to support the use of vinflunine in the second-line setting.

Keywords: vinflunine, *Vinca* alkaloid, urothelial carcinoma, transitional cell carcinoma, bladder cancer

Introduction

Bladder cancer is the ninth most common cancer worldwide, and accounted for an estimated 14,330 deaths in 2009 in the United States.[1] It affects men in the majority (77%) of cases[2] with 63% of cases occurring in the developed world. In Europe and the United States bladder cancer accounts for 5% to 10% of malignancies in men.[3] Cigarette smoking is the primary risk factor,[4–10] but other risk factors include exposure to arsenic,[11,12] aromatic amines,[13] and aniline dyes.[14] Additionally, chronic *Schistosoma haematobium* infection has been linked to the squamous cell type of bladder carcinoma, explaining the higher rates observed in parts of Africa and the Middle East.[15] Urothelial or transitional cell carcinoma (UC) accounts for 95% of bladder tumors, with the remaining cases consisting of squamous cell carcinoma and adenocarcinoma.[16]

While the majority of UC cases present as superficial disease,[17] 15% to 25% are at high risk for progression to muscle invasion.[18] For locally advanced or metastatic disease, there are two standard first-line chemotherapy regimens: MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) and gemcitabine/cisplatin. Unfortunately, the median overall survival (OS) following MVAC therapy is only 14.8 months and gemcitabine + cisplatin is associated with 7.4 months median time to progressive disease (TTP) and 13.8 months OS.[19] Although many patients are not eligible for further treatment due to poor performance status (PS), there is nonetheless an unmet clinical need for effective second-line therapy for patients having progressed on these platinum-based regimens.

Various single agents and combination regimens have been evaluated in clinical trials. Single agents having clinical activity include docetaxel,[20] paclitaxel,[21–23] pemetrexed,[24,25]

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bortezomib,[26,27] and vinblastine.[28] Combination regimens have often included taxanes combined with a second drug such as carboplatin[29–31] or gemcitabine.[32–36] Unfortunately, many of these studies have limited efficacy.

Vinflunine (VFL), a novel microtubule inhibitor, is undergoing clinical evaluation in this setting. Studies reported in the literature show encouraging results with VFL as a single agent in the treatment of refractory UC. This review discusses VFL's safety and efficacy profile in this setting, and compares it to competing single-agent and combination regimens.

Pharmacology and mechanism of action
Chemistry of vinflunine
The origins of VFL (Javlor®; Pierre Fabre Medicament Laboratories), a third-generation *Vinca* alkaloid, date back to 1958 when vinblastine was first isolated from the Madagascan periwinkle *Catharanthus roseus* (also known as *Vinca rosea*).[37] The discovery of vincristine and vinorelbine soon followed. VFL was discovered in 1988 when novel superacidic chemistry was applied to vinorelbine, allowing selective addition of two fluorine atoms at the 20' position of the catharanthine moiety to create 20',20'-difluoro-3',4'-dihydrovinorelbine, or VFL (see Figure 1). Previously, the 20' site had been inaccessible using classical synthetic chemistry.[38]

In contrast to other microtubule inhibitors, VFL is freely water-soluble. Thus, there is no risk of solvent-related hypersensitivity reactions. Phase I trials showed a mean terminal half-life of VFL to be 40 hours and a terminal half-life of 4 to 6 days for 4-*O*-deacetylvinflunine, VFL's only active metabolite. The volume of distribution is approximately 1,517 L suggesting significant tissue distribution. Excretion is both fecal (two thirds) and urinary (one third), an important consideration given that many patients with advanced bladder cancer suffer renal impairment.[39–41]

Mechanism of action
Microtubules make up the mitotic spindle required for chromosome separation and cell division, and are the target of anti-cancer agents such as *Vinca* alkaloids and taxanes. While taxanes stabilize microtubules resulting in "frozen mitosis", *Vinca* alkaloids exert their antiproliferative effect largely by preventing tubulin polymerization. This destabilizes microtubules and prevents mitotic progression.[42] At high concentrations, they depolymerize microtubules and destroy mitotic spindles; at lower concentrations, they suppress the rate and
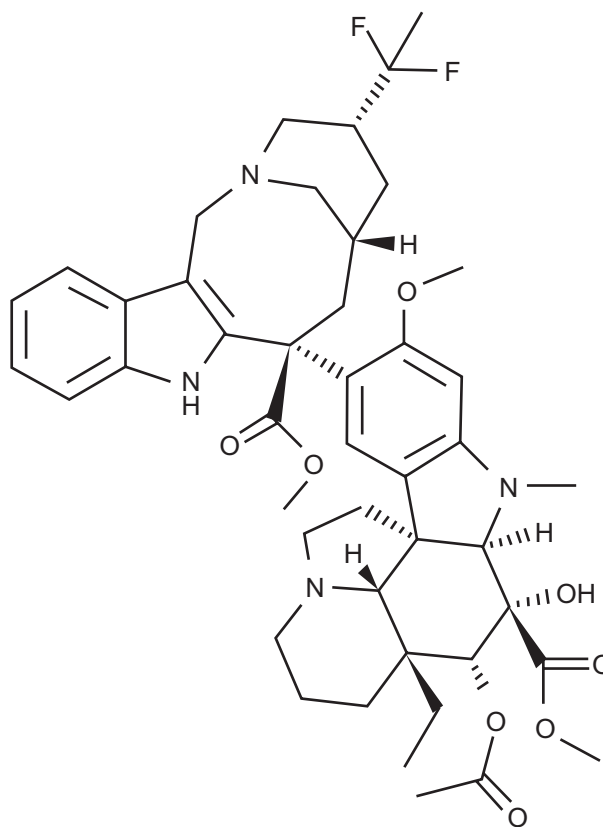

Figure 1 Structure of vinflunine.

extent of microtubule treadmilling, resulting in mitotic block and apoptotic cell death.[43,44]

Advantages relative to other *Vinca* alkaloids
VFL interacts with microtubules in a different way to other *Vinca* alkaloids. It binds to tubulin less readily, requiring 3- to 17-fold higher concentrations for similar biological effects relative to other members of its class.[45] Consequently fewer and smaller spiral polymers are induced and its interaction with tubulin is more readily reversible.[46] These different binding properties represent an advantage for VFL because they confer greater antitumor efficacy[45] and reduced neurotoxicity,[43] an important clinical consideration. The precise reason for VFL's superior antitumor efficacy is unknown, but may involve high intracellular accumulation and interaction with undefined targets.[47]

A general problem with the *Vinca* alkaloid class of drugs is the development of multidrug resistance (MDR) due to over-expression of P-glycoprotein (Pgp), a membrane efflux pump. Although VFL does induce Pgp-mediated resistance, cross-resistance to VFL occurred at a lower rate than to other *Vinca* alkaloids in human cancer cell lines including

leukemia, breast carcinoma and bladder carcinoma.[48] Additionally, mice implanted with P388 murine leukemia cells developed complete resistance to vinorelbine at 11 weeks, compared to 36 weeks for VFL.[49]

Vascular-disrupting and anti-angiogenic action

In addition to its anti-proliferative effects, studies have demonstrated that VFL has vascular-disrupting and anti-angiogenic properties *in vitro*.[50] In 2006 Kruczynski et al showed that *in vitro* VFL disrupts the network of capillary-like structures and inhibits endothelial cell migration and capacity to organize. These experiments were done at concentrations that only mildly affected endothelial cell proliferation.[50] In addition, *in vivo* studies in mice showed reduced numbers of liver metastases after intrasplenic injection of LS174T (tumor) cells. Moreover, at doses 20- to 40-fold lower than its maximal therapeutic dose (MTD), VFL inhibited bFGF-induced angiogenesis in Matrigel™ implants.[50]

Pre-clinical properties
Efficacy

VFL has shown higher *in vivo* anticancer activity than other microtubule inhibitors. In mice implanted with P388 murine leukemia cells, VFL has shown the maximum antitumor activity and survival prolongation compared to the other *Vinca* alkaloids.[51] Hill et al[52] treated nude mice implanted with a series of human tumor xenografts, and reported a 64% overall response rate with VFL compared to 27% with vinorelbine. In another important study Bonfil et al reported complete tumor eradication and 100% survival at 60 days when VFL (5–20 mg/kg) was administered intraperitoneally into mice that had had murine bladder cancer cells (MB49) implanted transurethrally.[53] The success of these studies led to the beginning of clinical trials by Bennouna et al[39] and others.

Toxicity profile

Common toxicities of *Vinca* alkaloids include myelosuppression and neuropathy due to axonal degeneration resulting in peripheral neuropathy typically beginning as paresthesia of the fingers and toes that spreads proximally in a 'glove and stocking' distribution.[54] Compared to other *Vinca* alkaloids, VFL has a better safety profile because it binds tubulin weakly and reversibly. These characteristics may explain the smaller degree of neuropathy and noncumulative nature of VFL-related toxicities, respectively. In most cases, neuropathy resolves after drug withdrawal.[47]

Synergistic effects

In a pre-clinical study evaluating *in vitro* activity against a human non-small-cell lung cancer (NSCLC) cell line, VFL demonstrated synergistic cytotoxicity with cisplatin, mitomycin C, doxorubicin and 5-fluorouracil (5-FU). Similar results were obtained against human leukemia cells. Importantly, no antagonistic drug interactions occurred,[55] suggesting the potential for combination therapies. When these synergies were examined *in vivo* using P388 murine leukemia cells grafted intravenously, the authors found superior activity for combinations of single intraperitoneal doses of VFL with either doxorubicin, mitomycin C, cisplatin or F 11782.[56] VFL's synergistic effects with cisplatin and 5-FU were further evaluated in a transplantable murine colon adenocarcinoma model, MAC 29. While synergy was demonstrated with cisplatin, this was not shown with 5-FU.[57]

VFL may also exhibit synergy with radiotherapy. Microtubule inhibitors such as VFL synchronize cells in the mitotic phase, rendering them more sensitive to radiation.[58] Indeed, Simoens et al[59] found a concentration-dependent G2/M block and consequent radiosensitization of different tumor cell lines.

Clinical trials

Because of its broader spectrum of activity and advantages over other *Vinca* alkaloids, VFL has been evaluated as monotherapy and as combination chemotherapy in a number of different cancers, including breast cancer,[60–66] NSCLC,[67–71] small cell lung cancer (SCLC),[72,73] prostate cancer,[74] gastric cancer,[75] malignant pleural mesothelioma[76–78] and renal cell carcinoma.[79] The recommended dose for clinical studies is 320 mg/m² administered intravenously every 21 days. For patients with a lower performance status or those having received prior pelvic irradiation, the dose is reduced to 280 mg/m².[69,80] Prior pelvic irradiation is reported to exacerbate hematological toxicities.[81] In the literature, there are currently two phase II and one phase III study reported of VFL as second-line therapy in metastatic UC.

Phase I trials

On the basis of strong pre-clinical data, VFL was evaluated in several phase I trials using a variety of schedules in patients with solid tumors. Bennouna et al[39] conducted a study in 31 patients with advanced malignancy. Patients were treated with escalating doses from 30 to 400 mg/m² VFL 3-weekly, and the authors reported a maximum tolerated dose (MTD) of 400 mg/m². Adverse events reported were mucositis, constipation and neutropenia of short duration. Three partial

responses (PR) were observed. The authors recommended a dose of 350 mg/m² 3-weekly.

In 2006, Johnson et al[41] reported a similar study in 16 patients with advanced solid tumors. VFL was given 3-weekly on days 1 and 8 as a 10-minute infusion. A maximum tolerated dose (MTD) was established at 190 mg/m² based on 2 of 4 patients developing constipation and neutropenia which were dose limiting. There were no objective responses. The authors recommended a dose of 170 mg/m² on days 1 and 8 3-weekly for future studies.

Phase II trials in urothelial carcinoma

Based on the safety data reported in phase I trials and the complete tumor eradication reported in a murine bladder carcinoma model,[53] phase II trials of vinflunine in UC were begun. Culine et al[82] conducted an open-label, multicenter, noncomparative phase II study in 51 patients from 16 European centers with advanced UC who failed first-line platinum-based regimens. Patients were treated with 320 mg/m² VFL. The primary endpoint was efficacy as measured by tumor response rate; secondary objectives were duration of response, progression-free survival (PFS), OS, and treatment-related toxicity. Eligible patients were aged ≥18 years with a Karnofsky performance status (KPS) ≥80. Tumor response was assessed after the initial 2 cycles. Nine patients (18%; 95% CI: 8.4%–30.9%) achieved PR and 25 achieved stable disease (SD) for an overall disease control rate of (PR + SD) of 67% (95% CI: 52.1%–79.3%). Additionally, objective response was seen in 8 of 34 patients (24%) previously treated for metastatic disease and in 1 of 17 (6%) patients previously treated in the neoadjuvant or adjuvant setting. The median duration of response was 9.1 months (95% CI: 4.2–15.0) and median PFS was 3.0 months (95% CI: 2.4–3.8). Median OS was 6.6 months (95% CI: 4.8–7.6). Significant toxicities included grade 3–4 leukopenia in 45% patients and grade 3–4 neutropenia in 67% patients. Five patients (10%) experienced febrile neutropenia, 2 of whom died of drug related toxicity. Importantly, grade 3–4 sensory neuropathy was not observed, nor was grade 3–4 renal function impairment.

In 2009, Vaughn et al[83] reported results of a similar study done in the United States evaluating the safety and efficacy of VFL in patients having progressed within 12 months after platinum-based chemotherapy. Eligibility criteria were similar to the Culine et al trial,[82] and patients were treated with 320 mg/m² VFL unless they had impaired renal function, KPS ≥ 80, prior pelvic irradiation, or were aged ≥75 years. These patients received an initial

dose of 280 mg/m², which was escalated to 320 mg/m² in cycle 2 if well tolerated. Of 175 patients enrolled, 151 received at least one dose of VFL. The primary objective was response rate as defined by an independent response review committee (IRRC); secondary endpoints included duration of response, time to response, disease control rate, PFS, OS, and toxicity. Twenty-two of 151 subjects achieved PR (15%; 95% CI: 9%–21%) and 64 achieved SD (42%), for an overall response rate (ORR) of 14.6% (95% CI: 9.4%–21.2%). The median duration of response was 6.0 months (95% CI: 5.4–9.5 months), and the median duration of disease stabilization was 4.0 months (95% CI: 3.5–4.7 months). Median PFS was 2.8 months, and median OS was 8.2 months. The main toxicity of VFL was hematologic: grade 3 or 4 neutropenia was reported in 58% patients, leucopoenia in 49%, and anemia in 16%. Grade 3–4 febrile neutropenia was seen in 10 patients (7%). Grade 3–4 non-hematologic toxicities included constipation (17%), fatigue (13%), ileus (5%), and abdominal pain (5%). Patients with renal impairment had a similar safety profile, and VFL did not damage renal function.

Phase III trials in urothelial carcinoma

On the basis of the two phase II trials, Bellmunt et al[81] conducted a randomized, multinational, phase III trial of VFL and best supportive care (BSC) as second-line treatment in patients progressing after platinum-containing chemotherapy. Three hundred and seventy patients were recruited: 253 were randomized to the VFL + BSC arm, and 117 to the BSC only arm. Eligibility criteria were similar to the phase II trials. Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 were given 320 mg/m² VFL, while patients with ECOG PS 0 and prior pelvic irradiation or ECOG PS 1 were given 280 mg/m² VFL. The primary objective was obtaining a median 2-month survival advantage favoring the VFL + BSC group. This was achieved (6.9 versus 4.6 months) in both the intent-to-treat and eligible population, but the difference in OS was only significant ($P = 0.040$) in the eligible population. The intent-to-treat population was the randomly assigned population, and the eligible population excluded 13 patients with at least one major protocol violation at baseline. Secondary endpoints were ORR, disease control rate and duration, and median PFS. Sixteen (8.6%) patients achieved PR with a 7.4 months (95% CI: 4.5–17.0) median duration of response, and 86 (46.5%) achieved SD. Significant (grade 3–4) toxicities

were primarily hematologic, including neutropenia (50%), febrile neutropenia (6%) and anemia (19%).

The VINCENT (vinflunine in cisplatin-ineligible patients) phase III clinical trial is currently ongoing. It compares gemcitabine plus VFL versus gemcitabine plus placebo in chemotherapy-naïve patients. The target accrual is 450 patients.[84]

Safety and tolerability

In all phase II and III trials evaluating VFL in UC the drug was reported to have an acceptable safety profile. The main grade 3–4 toxicities were hematologic (see Table 1). Common non-hematologic adverse effects were fatigue and constipation. Importantly, the dose-limiting neurotoxicity seen in other *Vinca* alkaloids was not observed in VFL, and toxicities were non-cumulative. In general, the safety profile of VFL compared relatively favorably to that of other single agents (see Table 2).

The potential role of vinflunine in the management of urothelial carcinoma

The wide variety of single agents (see Table 2) and combination of agents (see Table 3) studied in the second-line setting of metastatic UC begs the question: is there sufficient evidence to recommend a standard second-line treatment in metastatic cisplatin-resistant UC?

Single agents

Second-line single agents, mainly studied in phase II trials, have not demonstrated impressive response rates (0%–27.7%), median TTP, or OS. Molecularly targeted agents in particular have generally fared poorly, as exemplified by the trials of bortezomib[26,27] and lapatinib.[85] In addition, many studies enrolled relatively few patients, making it difficult to draw conclusions about efficacy. VFL has been the only drug evaluated in a randomized controlled phase III trial that has demonstrated moderate activity and a good safety profile.

Combination regimens

Combination regimens generally offer the compromise of higher response rates and longer OS in exchange for more severe toxicities. In assessing the potential role of VFL it is important to consider combinations for which there is most evidence. Gemcitabine/paclitaxel has been one of the more extensively studied regimens recently, particularly in Japan. Different doses and schedules have been tried, with response rates ranging from 30% to 70% and median OS of 10.3 to 14.4 months. Reported grade 3–4 toxicities have been mainly hematological, but also include peripheral neuropathy and allergic reactions to paclitaxel. Kanai et al[35] observed grade 3–4 neutropenia in 6 patients (30%), anemia in 3 patients (15%), and thrombocytopenia in 1 patient (5%). No instances of grade 3–4 peripheral neuropathy were reported. Matsumoto et al[34] also observed

Table 1 Grade 3–4 adverse events in patients with advanced or metastatic urothelial carcinoma treated with vinflunine

Trial description	Vinflunine, phase II	Vinflunine, phase II	VFL + BSC vs BSC, phase III
Investigators	Culine[82]	Vaughn[83]	Bellmunt[81]
Dose and schedule	320 mg/m² IV every 21 days	Dose escalation of 280 to 320 mg/m² IV every 21 days	Two arms with 280 or 320 mg/m² IV every 21 days
Hematologic	No patients (%)	No patients (%)	No patients (%)
Anemia	7 (14)	23 (15.5)	47 (19.1)
Leukopenia	23 (45)	73 (49.3)	NR
Neutropenia	34 (67)	86 (58.1)	123 (50.0)
Thrombocytopenia	3 (6)	5 (3.4)	14 (5.7)
Febrile neutropenia	5 (10)	10 (6.6)	15 (6.0)
Neutropenia with infection	3 (6)	3 (2.0)	NR
Nonhematologic toxicities			
Nausea	2 (4)	5 (3.3)	6 (2.4)
Vomiting	3 (6)	3 (2.0)	7 (2.8)
Constipation	4 (8)	25 (16.6)	40 (16.1)
Stomatitis/mucositis	3 (6)	5 (3.3)	4 (1.6)
Asthenia/fatigue	5 (10)	19 (12.6)	48 (19.3)
Abdominal pain	4 (8)	7 (4.6)	10 (4.0)
Peripheral sensory neuropathy	0	1 (0.7)	3 (1.2)
Injection site reactions	0	1 (0.7)	1 (0.4)
Myalgia	2 (4)	4 (2.6)	8 (3.2)

Abbreviation: NR, not reported.

Table 2 Trials of single agents in second-line treatment of advanced or metastatic urothelial carcinoma

Agent	No of evaluable patients	ORR: patients responding (%)	Median TTP (months)	Median OS (months)	Main grade 3–4 toxicities: no patients (%)	Reference
Vinflunine	51	9 (18%)	3.0	6.6	34 (67%) neutropenia; 23 (45%) leukopenia; 7 (14%) anemia	Culine[82]
Vinflunine	151	22 (15%)	2.8	8.2	86 (58.1%) neutropenia; 73 (49%) leukopenia; 23 (16%) anemia	Vaughn[83]
Vinflunine	370	16 (8.6%)	3.0	6.9	123 (50%) neutropenia; 47 (19%) anemia	Bellmunt[81]
Vinblastine	28	5 (18%)	N/A	N/A	N/A	Blumenreich[28]
Paclitaxel	14	1 (7.1%)	N/A	N/A	Hematological toxicities in 23 of 42 courses; 2 (14%) with other grade 3–4 toxicities	Papamichael[21]
Paclitaxel	31	3 (10%)	2.2	7.2	4 (13%) anemia; 2 (7%) asthenia	Vaughn[22]
Paclitaxel	45	4 (9%)	3	7	N/A	Joly[23]
Docetaxel	30	4 (13.3%)	N/A	9	18 (60%)	McCaffrey[20]
Ifosfamide	20	1 (5%)	6.0	8.0	2 (10%)	Pronzato[87]
Ifosfamide	56	11 (20%)	2.2	5.1	N/A	Witte[88]
Topotecan	44	4 (9.1%)	1.4	6.3	34 (77%) leukopenia; 27 (61%) anemia; 19 (43%) thrombocytopenia	Witte[89]
Pyrazoloacridine	14	0	N/A	9 months	8 (57%) neutropenia; 2 (14%) thrombocytopenia	Dodd[90]
Piritrexim	27	2 (7%)	2.1	7.0	4 (15%) thrombocytopenia; 3 (11%) anemia; 5 (19%) neuropathy; 2 (7%) hepatotoxicity; 2 (7%) nausea	Roth[91]
Piritrexim	22	0	N/A	N/A	6 (27%)	Lassiter[92]
Oxaliplatin	20	1 (5%)	N/A	N/A	11 (55%)	Winquist[93]
Pemetrexed	47	13 (27.7%)	2.9	9.6	4 (9%) thrombocytopenia; 4 (9%) neutropenia; 2 (4%) anemia; 3 (6%) fatigue; 2 (4%) diarrhea	Sweeney[24]
Pemetrexed	12	1 (8%)	N/A	N/A	3 (23%) anemia; 3 (23%) neutropenia; 3 (23%) thrombocytopenia	Galsky[25]
Bortezomib	21	0	1.9	3.5	15 (71%)	Gomez-Abuin[26]
Bortezomib	25	0	1.4	5.7	5 (21%) hematological toxicity	Rosenberg[27]
Gemcitabine	44	11 (25%)	3.1	12.6	21 (48%) neutropenia; 4 (9%) anorexia	Akaza[94]
Epothilone B analog BMS-247550 (ixabepilone)	45	5 (11.9%)	2.7	8.0	16 (36%) granulocytopenia; 5 (11%) thrombocytopenia; 3 (7%) sensory neuropathy; 5 (11%) fatigue; 4 (9%) dehydration	Dreicer[95]
Irinotecan	40	2 (5%)	2.1	5.4	N/A	Beer[96]
Lapatinib	59	1 (1.7%)	2.0	4.1	4 (7%) vomiting; 2 (3%) diarrhea; 2 (3%) dehydration; 2 (3%) hyponatremia	Wulfing[85]

Abbreviations: N/A, not available or not reported; ORR, overall response rate; OS, overall survival; TTP, time to progression.

mainly hematologic toxicities as well as hypersensitivity reactions to paclitaxel. Of the 10 patients in the study, 5 developed grade 3 neutropenia and 1 experienced grade 4 thrombocytopenia. Seven patients experienced minor (lower than grade 3) hypersensitivity reactions to paclitaxel, suggesting that allergic reactions are a major limitation of this regimen. Sternberg et al[32] reported grade 3–4 neutropenia in 13 patients (32%) and febrile neutropenia in 3 patients (7%). Granulocyte colony-stimulating factor was given to 10 patients (24%). Suyama et al[36] reported 15 patients

Table 3 Trials of combination chemotherapy in second-line treatment of advanced or metastatic urothelial carcinoma

Agents	No of evaluable patients	ORR: patients responding (%)	Median TTP (months)	Median OS (months)	Reference
Paclitaxel, cisplatin, methotrexate	25	10 (40%)	NR	3.7	Tu[97]
5-Fluorouracil, cisplatin, interferon-alpha	40	5 (12.5%)	2.3	4.8	De Mulder[98]
Docetaxel, ifosfamide	20	4 (25%)	NR	4.0	Krege[99]
Gemcitabine, paclitaxel	40	24 (60%)	6.4	14.4	Sternberg[32]
Gemcitabine, paclitaxel	27	12 (44%)	11.0	13.0	Fechner[33]
Gemcitabine, paclitaxel	10	7 (70%)	4.1	10.3	Matsumoto[34]
Gemcitabine, paclitaxel	20	6 (30%)	4.5	11.5	Kanai[35]
Gemcitabine, paclitaxel	30	10 (33.3%)	5.5	11.3	Suyama[36]
Gemcitabine, ifosfamide	34	7 (21%)	4.0	9.0	Pectasides[100]
Cisplatin, gemcitabine, ifosfamide	49	20 (40.8%)	NR	9.5	Pagliaro[101]
Gemcitabine, docetaxel	29	5 (17%)	NR	7.7	Dreicer[102]
Oxaliplatin, fluorouracil, folinic acid (FOLFOX-4)	16	3 (19%)	NR	4.0	Di Lorenzo[103]
Paclitaxel, carboplatin	44	7 (16%)	4.0	6.0	Vaishampayan[29]
Paclitaxel, carboplatin	31	10 (32.3%)	3.7	7.9	Kouno[30]
Paclitaxel, carboplatin	18	6 (33%)	4.0	11.0	Soga[31]
Paclitaxel, ifosfamide, nedaplatin	32	24 (75%)	8.0	22.0	Shinohara[104]
Paclitaxel, cisplatin	28	10 (36%)	6.2	10.3	Uhm[105]
Gemcitabine, ifosfamide	23	5 (22%)	NR	4.8	Lin[106]
Methotrexate, vinblastine, doxorubicin, cisplatin	30	9 (30%)	5.3	10.9	Han[107]

Abbreviations: NR, not reported; ORR, overall response rate; OS, overall survival; TTP, time to progression.

(45%) experiencing grade 3–4 neutropenia, all of whom responded well to granulocyte colony-stimulating factor. Peripheral neuropathy occurred in 19 patients: 2 cases (6%) were grade 3 and 17 (52%) were grade 2.

The paclitaxel/carboplatin combination has also yielded good response rates, but fared the worst in terms of OS in the largest study.[29] Toxicities were also significant: 28 patients (64%) experienced grade 3–4 hematologic toxicities, and 11 patients (25%) experienced neurologic toxicities.

Given the relatively large number of patients enrolled in phase II and III clinical trials in UC and clinical efficacy and safety data available, there appears to be sufficient evidence to support the use of VFL in the second-line setting. Randomized trials comparing VFL with combinations most commonly used, such as Gemcitabine/paclitaxel and paclitaxel/carboplatin, would establish the clinical utility of VFL. However, such trials would necessarily be large in order to prove superiority of one regimen to another.

Conclusion

There is currently no standard second-line treatment for managing cisplatin-resistant metastatic UC. Most single agents have yielded unimpressive results, and combination regimens have shown improved response rates and OS, but also greater toxicity. Previous studies have shown the importance of prognostic factors such as chemosensitivity to first-line therapy[86] or the presence of visceral metastasis,[32]

making comparisons among smaller trials difficult given their necessarily more heterogeneous patient populations.

VFL is the first chemotherapeutic agent to be evaluated in a large UC second-line population: the phase II and III trials included a total of 572 patients. In these studies, VFL has demonstrated relevant clinical activity and, perhaps more importantly, an acceptable and manageable toxicity profile in advanced and refractory disease. Approval of VFL in this setting would provide a safe and moderately effective standard of care against which other single agents or combination regimens could be compared.

Disclosure

The authors report no conflicts of interest.

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