Monotherapy with Intravenous Vinflunine in Patients with Advanced or Metastatic Urothelial Cancer after Failure of a Platinum-Containing Regimen: A Retrospective Analysis of German Routine Data

Axel Hegele^a Peter Goebell^b Ullrich Matz^c Thomas Neuhaus^d

^aDepartment of Urology and Pediatric Urology, University Hospital, Marburg, ^bDepartment of Urology, Friedrich Alexander University Hospital Erlangen, Erlangen, ^cMedical Urology Practice, Döbeln, and ^dDepartment of Hematology and Internal Medicine, St. Vincentius Hospital Limburg, Limburg, Germany

Key Words

Urothelial cancer · Advanced · Metastatic · Platinum failure · Vinflunine

Abstract

Objective: The objective of this retrospective study was to investigate the efficacy and safety of vinflunine monotherapy and the utility of second-line prognostic factors in patients with advanced or metastatic urothelial cancer relapsing/progressing during or after a prior platinum-containing regimen under daily routine clinical conditions in Germany.

Methods: The selection was based on the marketing authorization indication and recommendations as well as on the evaluation of second-line prognostic factors issued from prior or pivotal trials. **Results:** Eight centers across Germany provided a total of 21 patient records. Demographic and clinical characteristics were similar to the data previously reported in pivotal trials. Complete and partial response to vinflunine treatment was observed in 1 (4.8%) and 3 (14.3%) patients, respectively, resulting in an overall response rate of 19.1%. The disease control rate reached 47.7%. The median progression-free survival amounted to 4.4 months (95% CI 2.6–6.6), with a median overall survival of 6.2 months (95% CI 3.9–10.7). The observed toxicity profile was manageable and consistent with prior clinical trials: leukopenia (33.3%), neu-

tropenia (9.5%), anemia (9.5%) and hyperglycemia (4.8%). The reported satisfaction rate with the treatment was 90.5 and 61.9% among patients and physicians, respectively. **Conclusions:** This retrospective study confirms that the clinical outcomes obtained from routine medical practice in Germany with vinflunine in the treatment of advanced/metastatic urothelial cancer are in line with the data observed in prior clinical trials.

© 2013 S. Karger AG, Basel

Introduction

Bladder cancer is the fourth most frequent tumor in Europe with an incidence of 110,500 new cases per year. Furthermore, 38,200 patients die from this disease every year [1, 2]. In Germany alone, the incidence amounts to 28,000 new cases, with a mortality of approximately 5,500 deaths per year.

Untreated metastatic urothelial cancer shows a poor median survival rarely exceeding 3–6 months. Classified as a chemosensitive tumor, chemotherapy plays an important role in the treatment of advanced stages [3–6]. Usually cisplatin-containing combination chemotherapy with gemcitabine or MVAC (methotrexate, vinblastine, Adriamycin and cisplatin) is used as first-line treatment if

patients are 'fit' enough to tolerate cisplatin [4, 7–10]. Alternatively, patients unlikely to tolerate this regimen may be palliated with a carboplatin-based regimen, other single-agent regimens or best supportive care (BSC) [10–12].

A number of phase II trials investigated different second-line cytotoxics or targeted agents before vinflunine was assessed. However, these second-line data are heterogeneous, highly variable and derive from limited sample sizes [13–16]. In addition, the results may strongly depend on patient selection [17]. Moreover, the definition of 'second-line' varies between the different studies reported in the literature. In a phase III trial, a prolonged schedule of gemcitabine and paclitaxel was compared to six cycles of the same combination after failure of a cisplatin-containing chemotherapy. The study with 96 eligible patients could not show any difference between the prolonged schedule and the short-term treatment [18]. Therefore, prior to the availability of vinflunine, only empirical and 'off-label' treatment options were available. Clearly, there was a strong medical need for an evidence-based and approved treatment option.

Vinflunine is a novel microtubule inhibitor selected for its particular mechanism of action [19–22]. Vinflunine showed a high level of *in vitro* and *in vivo* antitumor activity, particularly in bladder cancer models, thus providing the rationale to investigate vinflunine in this indication [23, 24].

Two phase II studies together with the international phase III registration trial formed the basis for the marketing authorization of vinflunine in Europe 2009 as monotherapy of adult patients with advanced or metastatic urothelial cancer after failure of a prior platinum-containing regimen [25–27]. The file was submitted to the European Medicines Agency only since Pierre Fabre had no partner for co-promotion in the United States at that time.

The vinflunine phase III study provides the highest level of evidence reported so far for second-line treatment in advanced or metastatic urothelial cancer (level of evidence 1b) [10]. The results favor vinflunine plus BSC versus BSC alone [overall survival of 6.9 vs. 4.3 months, $p = 0.0403$ (eligible population)]. In this study vinflunine reduced the risk of death by 23% compared to BSC (multivariate analysis adjusted for pre-specified prognostic factors, intention to treat population) without quality of life impairment while toxicities were manageable. Moreover, all the standard efficacy secondary endpoints (objective response rate, disease control rate, median progression-free survival) consistently favored vinflunine + BSC over BSC [28]. Based on these results, vinflunine is currently the first and only approved second-line treatment recom-

mended in the updated guidelines for the treatment of metastatic bladder cancer of the European Association of Urology (EAU) as well as of the European Society of Medical Oncology (ESMO) [10, 29].

In addition, data from the vinflunine research program defined and validated an array of independent adverse prognostic factors for overall survival in patients failing platinum-based chemotherapy (hemoglobin, liver metastases, performance status). These prognostic factors have to be considered for stratification in future trials and for assessing data from existing trials [17].

The rationale for this retrospective study was to investigate the efficacy and safety of vinflunine treatment in advanced or metastatic urothelial cancer progressing during or after a prior platinum-containing regimen under 'real-life' clinical conditions in Germany. A further objective was to confirm the utility of patient selection using the second-line prognostic factors (as currently featured in the EAU and ESMO guidelines) in this setting.

Methods

Patient records were eligible for inclusion into this cohort if the patients had been diagnosed to have a histologically proven, locally advanced or metastatic urothelial cancer, if they had had a documented relapse/progression after prior platinum-containing chemotherapy (platinum pretreatment could be administered with neoadjuvant, adjuvant or palliative intention) and if a treatment with vinflunine had been performed after only one regimen of platinum-based therapy. Further selection criteria included age ≥ 18 years, WHO Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 prior to vinflunine therapy, presence of not more than one negative second-line prognosis factor (WHO ECOG performance status 1, hemoglobin < 10 g/dl, liver metastases), adequate antiemetic and anticonstipation management during the vinflunine treatment phase, vinflunine therapy performed according to the prescribing information and completion of vinflunine therapy (retrospective documentation). Patient records were excluded in case of brain metastases or meningeal metastases and in case vinflunine was prescribed not in concordance with the conditions described in the marketed drug summary of product characteristic (creatinine clearance < 20 ml/min, Child-Pugh status C, prothrombin time $< 50\%$, bilirubin $> 5 \times$ upper limit of normal, transaminases $> 6 \times$ upper limit of normal, γ -glutamyl transferase $> 15 \times$ upper limit of normal, pregnant or breast-feeding women, hypersensitivity to vinflunine or other vinca alkaloids, active infections within 2 weeks of starting therapy and neutrophil counts $< 1,500/\text{mm}^3$ or platelets $< 100,000/\text{mm}^3$) [27].

Prior to the start of the project, the protocol was submitted to an independent ethics committee; the project received a positive vote on 28.02.2012. Centers with experience in vinflunine treatment were independently screened nationwide. A total of 8 centers participated in this observation, with a balance between urological and oncological departments.

Table 1. Patient characteristics and pretreatments (n = 21)

Male sex, %	90.5
Median age, years (range)	63.0 (45.0–83.0)
ECOG performance status, % ^a	
0	61.9
1 ^c	38.1
Creatinine clearance, % ^a	
>60 ml/min	52.4
40–60 ml/min	28.6
20–39 ml/min	19.0
Liver function, % ^a	
Normal	76.2
Mild dysfunction	23.8
Hemoglobin, % ^a	
≥10 g/dl	95.2
<10 g/dl ^c	4.8
Location, % ^b	
Upper urinary tract	9.5
Bladder	85.7
Urethra	14.3
Grading, % ^b	
Low	14.3
High	81.0
Missing	4.8
Stage, % ^b	
Superficial (N0/x, M0/x)	4.8
Invasive (N0/x, M0/x)	33.3
N metastases (M0/x)	38.1
M metastases (N0/x)	0
N and M metastases	23.8
Tumor spreading, % ^a	
Visceral metastases	47.6
Liver metastases ^c	14.3
≥2 locations involved	57.1
Prior surgery, %	95.2
Prior radiotherapy, %	23.8
Prior systemic therapy, %	
Adjuvant	23.8
Palliative first-line	76.2
Type of prior platinum, % ^d	
Cisplatin	76.2
Carboplatin	23.8
Median number of cycles (range)	
Adjuvant (n = 5)	4 (2–6)
Palliative first-line (n = 16)	4 (2–11)
Response to palliative first-line therapy, %	n = 16
CR	6.3
ORR	31.3
SD	25.0
DCR	56.3

^a Just before vinflunine. ^b Primary diagnosis. ^c Only adverse prognostic factor allowed. ^d All patients treated with gemcitabine-cisplatin or gemcitabine-carboplatin.

CR = Complete response; ORR = objective response rate; SD = stable disease; DCR = disease control rate.

All eligible patients identified by the investigators who had been treated with vinflunine were included in the study. The following information was documented based on the patient charts for each included case: patient and disease characteristics, pretreatments, details of the vinflunine therapy, efficacy information (response information on the basis of Response Evaluation Criteria in Solid Tumors; imaging practice according to local protocol), the treating physician's and the patient's overall rating of the treatment (evaluation by the investigator), tolerability in terms of Common Terminology Criteria for Adverse Events toxicities ≥grade 3 and any follow-up treatment after the vinflunine treatment period.

The data were centrally reviewed and checked for quality and completeness prior to entry into a Microsoft Access[®] relational database. After database closure a descriptive statistical analysis was performed using SAS[®] version 9.2 (SAS Institute Inc., Cary, N.C., USA). Continuous data were summarized with the following items: frequency, mean, standard deviation, median, minimum, maximum, 25% quartile and 75% quartile, if relevant. Categorical data were presented in contingency tables with frequencies and percentages of each modality (including missing data modality); 95% CIs were calculated following the exact method.

Results

Patient Characteristics

A total of 21 patient records from the 8 participating centers were collected. These records cover an overall vinflunine treatment period from February 2010 to March 2012. The included population was predominantly male (90.5%), had a median age of 63.0 years (range 45.0–83.0) and an ECOG performance status of 0 (61.9%) to 1 (38.1%). 48 and 24% of the patients had renal or hepatic dysfunction, respectively; only 1 patient showed a pretreatment hemoglobin level of <10 g/dl. The primary tumor was predominantly located in the urinary bladder (85.7%) and had a high grading (81.0%).

All patients underwent platinum-based (76.2% cisplatin, 23.8% carboplatin) therapy before receiving vinflunine – 23.8% (n = 5) as adjuvant and 76.2% (n = 16) as palliative first-line treatment. In case of recurrence or progress after platinum-based therapy, patients received vinflunine as first- or second-line treatment. Objective response rate and disease control rate to platinum-containing palliative first-line therapy in the 16 patients with locally advanced/metastatic disease was 31.3 and 56.3%, respectively. The patient data are summarized in table 1.

Efficacy

Complete and partial response to vinflunine treatment was observed in 1 (4.8%) and 3 (14.3%) out of the 21 included patients, resulting in an objective response rate of 19.1%. Stable disease was reported in 6 patients (28.6%),

Table 2. Response to vinflunine treatment (n = 21)

Complete response (CR), %	4.8
Partial response (PR), %	14.3
Stable disease (SD), %	28.6
Progressive disease, %	42.9
Not evaluable, %	9.5
Overall response rate (CR + PR), %	19.1
Disease control rate (CR + PR + SD), %	47.7

for a disease control rate of 47.7%. The remaining 9 and 2 patients showed progressive disease or were not evaluable, respectively. Details of the response data are shown in table 2. The median progression-free survival under vinflunine amounted to 4.4 months (n = 20; 95% CI 2.6–6.6), the median overall survival was 6.2 months (95% CI 3.9–10.7).

Tolerability

The 21 patients included in this observation received a total of 111 vinflunine cycles, with a median number of 4.0 cycles per patient (range 2.0–27.0). This number of cycles reflects two types of treatment schedules: some physicians predetermined a fixed number of cycles (usually 4–6) when vinflunine treatment was first administered, others offered vinflunine up to progression or unacceptable toxicity according to the prior clinical trials. The starting doses ranged from 250 to 320 mg/m² with 38.1, 47.6 and 14.3% of the patients receiving 300–320, 280 or 250 mg/m², respectively. Dose increase was observed in 19.0% and dose reduction in 9.5% of the patients. The main reasons for treatment discontinuation were progression (42.8%), planned number of cycles reached (28.6%), worsening of performance status (14.3%) and patient decision (9.5%); only 1 patient (4.8%) discontinued treatment due to reasons associated with toxicity. All patients received antiemetic prophylaxis and 90.5% also laxative prophylaxis during the vinflunine treatment.

The percentage of patients experiencing any toxicity (Common Toxicity Criteria grade ≥3) amounted to 42.9%. The frequency of hematologic and nonhematologic events was 38.1 and 4.8%, respectively. The reported events were leukopenia (33.3%), neutropenia (9.5%), anemia (9.5%) and hyperglycemia (4.8%).

The reported overall satisfaction rate with the treatment was 90.5 and 61.9% among patients and physicians, respectively (moderately satisfied or satisfied). Satisfaction rated by physicians was higher considering tolerability, assessed as adequate to good in the majority (95.2%) of patients, with only 4.8% deemed poor.

A total of 33.3% of the patients receive further antitumor treatment after vinflunine: gemcitabine-paclitaxel 14.3%, gemcitabine-carboplatin 4.8%, paclitaxel-carboplatin 4.8%, gemcitabine-monotherapy 4.8% and radiation 9.5%.

Discussion

Palliative second-line treatment of urothelial cancer is a challenging indication as the considered patients are frequently older than those managed for other tumors, have a limited performance status, suffer from multiple comorbidities and have already been treated with platinum-containing combination chemotherapy. Before the registration of vinflunine, this indication represented an unmet medical need [30]. The vinflunine pivotal studies provided the grounds for an evidence-based and registered treatment option [10, 27]. Interventional clinical studies, however, fail to adequately reflect the ‘real-life’ situation in clinical routine. This retrospective study provides initial information about the patients that were actually treated with vinflunine and the associated effectiveness and toxicity profile. The sample of 21 current patient records (years 2010–2012) was collected from urological/oncological clinics and one medical practice; the selection of centers is consistent with the treatment situation for these patients in Germany. The observation was started very early after the registration of vinflunine in Europe, which explains the low number of recruited patients at that time: the centers were not used to this treatment as a standard of care for patients after failure of platinum-containing therapy. In addition, many of the patients were in very bad condition and not eligible for any further chemotherapy.

One of the secondary aims of our investigation was to assess the influence of second-line prognostic factors as established from the vinflunine phase II and III trials (performance status, liver metastases and hemoglobin) [17]. Despite the selection of patients with a maximum of one risk factor (risk factor for clinical trial stratification), the baseline data obtained in our observation showed that an unfavorable prognosis group was selected in this routine practice sample. This was evidenced by the limited objective response rate (31.3%) and disease control rate (56.3%) obtained during prior platinum-based first-line treatment as compared to the literature [8, 12, 31, 32]. In this context, it would have been interesting to further investigate patient profiles in terms of concomitant diseases and toxicities from first-line treatment. However, due to the retrospective character of this observation, such in-

Table 3. Overview of efficacy data from clinical trials and retrospective documentation

	Culine et al., 2006 [25]	Vaughn et al., 2009 [26]	Bellmunt et al., 2009 [28]	Present study
ORR, %	17.6	14.6	8.6	19.1
DCR, %	66.7	56.9	41.1	47.7
Median PFS, months	3.0	2.8	3.0	4.4
Median OS, months	6.6	8.2	6.9	6.2

ORR = Objective response rate; DCR = disease control rate; PFS = progression-free survival; OS = overall survival.

formation was not collected. Overall, these results as well as newly reported evaluations [33–36] suggest that – besides the known second-line prognostic factors – additional factors such as prior response to first-line treatment, progression-free survival after first-line treatment and time between prior treatment and initiation of second-line treatment could be relevant with regard to the assessment of the patient’s risk profile and for patient selection in future clinical trials.

In summary, the patient cohort in this retrospective observation is representative of patients with advanced or metastasized urothelial carcinoma eligible for vinflunine treatment and thus reflects daily practice. Regarding efficacy, in all of the pivotal trials investigating vinflunine monotherapy in platinum-pretreated patients, objective response rates of 8.6–17.6%, disease control rates of 41.1–66.7%, median progression-free survival times of 2.8–3.0 months and median overall survival times of 6.6–8.2 months were reported [25, 26, 28]. In our investigation, we were able to confirm previously published data with an objective response rate of 19.1%, a disease control rate of 47.7%, a median progression-free survival of 4.4 months and a median overall survival of 6.2 months (table 3). Apart from the limitations of the cohort sample size, it should be clarified that the reason of death was not reported in the present work, impeding further detailed analysis of the survival parameter. The observed tolerability was adequate and toxicities were consistent with the known safety profile. This was also reflected in an adequate exposure to vinflunine, with a median number of 4 cycles and a maximum of 27 cycles, 80.9% of patients receiving the standard starting doses of 280/320 mg/m², a very low rate of dose reductions (9.5%) and toxicity-related treatment discontinuations (4.8%). These results led to a high satisfaction rate of 90.5 and 61.9% on the side of the patients and the physicians, respectively.

Conclusions

For patients with progressive disease after treatment with platinum-containing chemotherapy, vinflunine is currently the only registered option, with clinical results at the highest evidence level available so far (level of evidence 1b). This retrospective study confirms that the clinical outcomes obtained from routine medical practice in Germany are in line with the data observed in clinical trials. Due to the limited sample size and the retrospective character of our observation, our results require further confirmation from prospective studies aimed to evaluate the impact of prognosis factors. However, as a result of this analysis, additional factors such as prior response to first-line treatment, progression-free survival after first-line treatment and time between prior treatment and initiation of second-line should be implemented in the assessment of the patient’s risk profile and for patient selection in these future clinical trials.

Acknowledgements

The authors wish to thank the following physicians and institutes for contributing cases to this observation: Dr. C. Bolling, Department of Internal Medicine, Markus Hospital Frankfurt/Main; Dr. M. Fuchs, Department of Gastroenterology, Hepatology and Gastroenterological Oncology, Hospital Munich-Bogenhausen; Dr. F. Rehkugler, Department of Urology, Marienhospital Marl; Prof. Dr. H. Sperling, Department of Urology, Hospital Maria Hilf Mönchengladbach.

Disclosure Statement

The project was conducted on behalf of Pierre Fabre Pharma GmbH. Prof. Dr. Hegele worked as a consultant for Pierre Fabre Pharma GmbH within the scope of this project.

References

- 1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM: Estimates of world-wide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–2917.
- 2 Boyle P, Ferlay J: Cancer incidence and mortality in Europe, 2004. *Ann Oncol* 2005;16: 481–488.
- 3 Donat M, Herr H: Transitional cell carcinoma of the renal pelvis and ureter: diagnosis, staging, management, and prognosis; in Osterling JE, Richie JP (eds): *Urologic Oncology*. Philadelphia, WB Saunders Harcourt Brace & Co, 1997.

- 4 Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, Sogani PC, Vaughan ED Jr, Bander N, Weiselberg LR, et al: M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988;139:461–469.
- 5 Sternberg CN: Second-line treatment of advanced transitional cell carcinoma of the urothelial tract. *Curr Opin Urol* 2001;11:523–529.
- 6 Zeegers MP, Goldbohm RA, van den Brandt PA: A prospective study on active and environmental tobacco smoking and bladder cancer risk (The Netherlands). *Cancer Causes Control* 2002;13:83–90.
- 7 von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, Moore MJ, Zimmermann A, Arning M: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602–4608.
- 8 von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kerbrat P, Sanchez Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Gruel CM, Conte PF: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000;18:3068–3077.
- 9 Cohen MH, Rothmann M: Gemcitabine and cisplatin for advanced, metastatic bladder cancer. *J Clin Oncol* 2001;19:1229–1231.
- 10 Stenzl A, Witjes JA, Compérat E, Cowan NC, De Santis M, Kuczyk MA, Lebrecht T, Ribal MJ, Sherif A: The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. <http://www.uroweb.org/guidelines/online-guidelines/> (accessed October 17, 2012).
- 11 Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, Dreicer R, Vogelzang N, Sternberg CN, Bajorin DF, Bellmunt J: Treatment of patients with metastatic urothelial cancer ‘unfit’ for cisplatin-based chemotherapy. *J Clin Oncol* 2011;29:2432–2438.
- 12 De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, Skoneczna I, Marreaud S, de Wit R, Sylvester R: Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer ‘unfit’ for cisplatin-based chemotherapy: phase II – results of EORTC study 30986. *J Clin Oncol* 2009;27:5634–5639.
- 13 Lorusso V, Pollera CF, Antimi M, Luporini G, Gridelli C, Frassinetti GL, Oliva C, Pacini M, De Lena M: A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. *Italian Co-operative Group on Bladder Cancer. Eur J Cancer* 1998;34:1208–1212.
- 14 Costantini C, Millard F: Update on chemotherapy in the treatment of urothelial carcinoma. *Sci World J* 2011;11:1981–1994.
- 15 Lei AQ, Cheng L, Pan CX: Current treatment of metastatic bladder cancer and future directions. *Expert Rev Anticancer Ther* 2011;11:1851–1862.
- 16 Serrano C, Morales R, Suarez C, Nunez I, Valverde C, Rodon J, Humbert J, Padros O, Carles J: Emerging therapies for urothelial cancer. *Cancer Treat Rev* 2012;38:311–317.
- 17 Bellmunt J, Choueiri TK, Fougeray R, Schutz FA, Salhi Y, Winquist E, Culine S, von der Maase H, Vaughn DJ, Rosenberg JE: Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol* 2010;28:1850–1855.
- 18 Albers P, Park SI, Niegisch G, Fechner G, Steiner U, Lehmann J, Heimbach D, Heidenreich A, Fimmers R, Siener R; AUO Bladder Cancer Group: Randomized phase III trial of 2nd line gemcitabine and paclitaxel chemotherapy in patients with advanced bladder cancer: short-term versus prolonged treatment [German Association of Urological Oncology (AUO) trial AB 20/99]. *Ann Oncol* 2011;22:288–294.
- 19 Jordan MA, Horwitz SB, Lobert S, Correia JJ: Exploring the mechanisms of action of the novel microtubule inhibitor vinflunine. *Semin Oncol* 2008;35(suppl 3):S6–S12.
- 20 Kruczynski A, Hill BT: Vinflunine, the latest vinca alkaloid in clinical development. A review of its preclinical anticancer properties. *Crit Rev Oncol Hematol* 2001;40:159–173.
- 21 Kruczynski A, Etievant C, Perrin D, Chansard N, Duflos A, Hill BT: Characterization of cell death induced by vinflunine, the most recent vinca alkaloid in clinical development. *Br J Cancer* 2002;86:143–150.
- 22 Kruczynski A, Barret JM, Etievant C, Colpaert F, Fahy J, Hill BT: Antimitotic and tubulin-interacting properties of vinflunine, a novel fluorinated vinca alkaloid. *Biochem Pharmacol* 1998;55:635–648.
- 23 Bonfil RD, Russo DM, Binda MM, Delgado FM, Vincenti M: Higher antitumor activity of vinflunine than vinorelbine against an orthotopic murine model of transitional cell carcinoma of the bladder. *Urol Oncol* 2002;7:159–166.
- 24 Hill BT, Fiebig HH, Waud WR, Poupon MF, Colpaert F, Kruczynski A: Superior in vivo experimental antitumor activity of vinflunine, relative to vinorelbine, in a panel of human tumour xenografts. *Eur J Cancer* 1999;35:512–520.
- 25 Culine S, Theodore C, De Santis M, Bui B, Demkow T, Lorenz J, Rolland F, Delgado FM, Longerey B, James N: A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer* 2006;94:1395–1401.
- 26 Vaughn DJ, Srinivas S, Stadler WM, Pili R, Petrylak D, Sternberg CN, Smith DC, Ringuette S, de Wit E, Pautret V, George C: Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma – results of a large phase 2 study. *Cancer* 2009;115:4110–4117.
- 27 Médicament PF: Javlor® summary of product characteristics. June 2012.
- 28 Bellmunt J, Theodore C, Demkov T, Komysakov B, Sengelov L, Daugaard G, Caty A, Carles J, Jagiello-Gruszfeld A, Karyakin O, Delgado FM, Hurteloup P, Winquist E, Morsli N, Salhi Y, Culine S, von der Maase H: Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454–4461.
- 29 Bellmunt J, Orsola A, Wiegel T, Guix M, De Santis M, Kataja V: Bladder cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;22:vi45–vi49.
- 30 Otto T: Drug Report Vinflunin. Stuttgart, Thieme, 2010.
- 31 Bamias A, Moulouopoulos LA, Koutras A, Aravantinos G, Fountzilias G, Pectasides D, Kastritis E, Gika D, Skarlos D, Linardou H, Kalofonos HP, Dimopoulos MA: The combination of gemcitabine and carboplatin as first-line treatment in patients with advanced urothelial carcinoma. A phase II study of the Hellenic Cooperative Oncology Group. *Cancer* 2006;106:297–303.
- 32 Bellmunt J, de Wit R, Albanell J, Baselga J: A feasibility study of carboplatin with fixed dose of gemcitabine in ‘unfit’ patients with advanced bladder cancer. *Eur J Cancer* 2001;37:2212–2215.
- 33 Biswas B, Sahoo R, Kumar L, Mohanti B, Seth A: Muscle invasive urinary bladder cancer: response to neoadjuvant chemotherapy is predictor of improved progression free survival. *Ann Oncol* 2012;23(suppl 9):ix264.
- 34 Maughan B, Boucher K, Agarwal N: Correlation of progression-free survival at 6 months (PFS6) with overall survival at 12 months (OS12) in an analysis of 10 trials of second-line therapy for advanced urothelial carcinoma (UC). *J Clin Oncol* 2012;30:Abstr 4525.
- 35 Pond R, Sonpavde G, Choueiri T: Time from prior chemotherapy (TFPC) as a prognostic factor in advanced urothelial carcinoma (UC) receiving second-line systemic therapy. *J Clin Oncol* 2012;30:Abstr 4522.
- 36 Sonpavde G, Pond G, Choueiri T: Prognostic stratification of advanced urothelial carcinoma (UC) receiving second-line systemic therapy including time from prior chemotherapy (TFPC) as a prognostic factor. *Ann Oncol* 2012;23(suppl 9):ix265.