Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract: an evidence-based review of safety, efficacy, and place in therapy

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Background: A systematic review and meta-analysis of the use of systemic vinflunine (VIN) in the treatment of urothelial carcinoma (UC) was performed to evaluate its efficacy based on current available clinical data.

Methods: This review was prospectively registered at the International Prospective Register of Systematic Reviews, PROSPERO (registration CRD42016049294). Electronic databases including MEDLINE®, Embase®, Cochrane Central Register of Controlled Trials, and Web of Science were searched through December 2016. We performed a meta-analysis of the published data. Primary end points were progression-free survival (PFS) and overall survival (OS). Numerous secondary clinical outcomes were analyzed including response and toxicity data.

Results: We identified 382 publications, of which 35 met inclusion criteria for this review representing 29 unique studies. A total of 2,255 patients received VIN for the treatment of UC in the included studies. OS and PFS were analyzed in a pooled Kaplan–Meier analysis. Response data were available for 1,416 VIN-treated patients with random effects proportion of complete response in 1%, partial response in 18%, and overall response rate of 21%. Toxicity analysis revealed fatigue (40.1%), nausea (33.9%), constipation (34.1%), and alopecia (26.0%) as the most prevalent overall non-hematologic adverse events (AEs). Most prevalent grade 3–4 AEs were fatigue (10.2%), abdominal pain (8.2%), myalgias (2.5%), and nausea (2.3%). Most common hematologic AEs of all grades were anemia (56.6%), neutropenia (46.0%), thrombocytopenia (25.5%), and febrile neutropenia (6.6%). Grade 3–4 hematologic AEs had the following pooled rates: neutropenia, 24.6%; anemia, 10.2%; febrile neutropenia, 5.4%; and thrombocytopenia, 3.0%.

Conclusion: VIN has been explored as a combination first-line treatment as well as a single-agent second-line, third-line, and maintenance therapy for advanced and metastatic UC. In first-line treatment of UC, either as a maintenance agent after cisplatin or as a primary combination therapy, VIN may be a promising alternative to current treatments. Further studies are needed to compare first-line combination VIN regimens to the current standard of care in order to assess long-term survival outcomes. Second- and third-line VIN monotherapy does provide a proven, although limited, survival benefit in platinum-refractory patients.

Keywords: vinflunine, urothelial carcinoma, bladder cancer, metastatic, survival, chemotherapy

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Core evidence clinical impact summary for vinflunine in advanced and metastatic urothelial carcinoma

Outcome measure	Evidence	Implication
Disease-oriented evidence	Clinical trials and retrospective analyses	Vinflunine when administered as second-line treatment for stage IV UC demonstrated modest gains in tumor response rate and survival
Patient-oriented evidence	Clinical trials and retrospective analyses	Risk of severe AEs must be weighed carefully against the modest survival benefit of VIN in advanced UC. However, most AEs are preventable or treatable
Economic evidence	Multicenter, observational, retrospective cohort study	VIN median treatment costs are €13,096 per patient, €44,789 per progression-free year gained, and €22,750 per life-year granted

Introduction

Metastatic urothelial carcinoma (UC) is an aggressive and highly lethal cancer despite many patients having an initial response to current systemic cytotoxic therapies. Current first-line treatment for advanced UC consists of platinum-based combination chemotherapy regimens. Of these, cisplatin-based combinations have demonstrated the most favorable overall survival (OS) – 12–15 months approximately – and are widely considered the standard of care.[1] Patients who are cisplatin ineligible, most often due to renal insufficiency or neurological disease, traditionally received carboplatin-based combination regimens which, although more tolerable, appear to have worse survival outcomes and are therefore considered less effective.[2] Most patients receiving platinum regimens for metastatic UC will ultimately progress, and many will be offered second-line systemic therapy. Recently, PD-L1 and PD-1 immune checkpoint inhibitors have been approved by the US Food and Drug Administration (FDA) for second-line treatment of advanced UC and for patients in first line who are cisplatin ineligible.

In 2009, the European Medical Association approved vinflunine (VIN), the newest member of the vinca alkaloid family, as a second-line therapy for advanced UC after platinum failure. This drug prevents microtubule assembly during mitosis, inducing apoptosis.[3,4] Early European Phase II trials in platinum-refractory metastatic UC examined the activity of VIN in 51 and 175 patients showing a response rate of 18% and 15%, respectively, with median progression-free survival (PFS) and OS of 3.0 and 6.6 months in the first study and 2.8 and 8.2 months in the second study.[5,6] These results led to a pivotal, multicenter Phase III randomized controlled trial by Bellmunt et al comparing VIN plus best supportive care (BSC) to BSC alone in platinum-refractory advanced UC.[7,8] This trial of 370 patients receiving second-line VIN showed a modest survival benefit of 2.3 months above BSC alone. The FDA has not approved VIN for treatment of advanced UC at this time.

JASiMA, a small 20-patient international Phase II trial, examined response data in patients with advanced UC receiving maintenance VIN immediately following gemcitabine–cisplatin first-line therapy and showed enhanced response in 5 patients (27.8%).[9] MAJA, a placebo-controlled Phase II trial, examined maintenance VIN versus BSC in a larger cohort (88) of patients with platinum-responsive advanced UC and found improved PFS of 6.5 months in the VIN arm versus 4.6 months in BSC arm (HR 0.56, 95% CI 0.34–0.93, p=0.024).[10]

The JASINT1 international Phase II trial examined first-line VIN combination therapy with either vinflunine–gemcitabine (VG) or vinflunine–carboplatin (VC) in 69 patients with advanced UC who were ineligible to receive cisplatin. This study found similar disease control rates (DCRs), overall response rates (ORRs), and OS between the 2 groups.[11] Lastly, the IMvigor211 study has been presented in abstract form and included 250 patients treated with VIN as part of a cohort patients with platinum-refractory metastatic UC receiving chemotherapy versus atezolizumab.[12]

The objective of this study was to systematically amass all relevant publications to evaluate the efficacy of VIN in adult patients with UC in terms of response and survival rates as well as toxicity and tolerability of this therapy.

Methods

Protocol registration

Prior to the formal literature search, the protocol was prospectively registered at the International Prospective Register of Systematic Reviews, PROSPERO (registration CRD42016049294).

Study selection criteria

To be eligible, retrieved articles had to include subjects (1) aged ≥18 years, (2) with a diagnosis of UC of the bladder, ureter, urethra, or renal pelvis, and (3) who were treated with systemic VIN chemotherapy. Studies that dealt primarily with animals

or the treatment of non-urothelial malignancies were excluded. All studies, whether retrospective or prospective, whether randomized or not, were initially eligible, with the exception of single-patient case reports which were excluded. To be included in analyses, however, studies had to specifically report efficacy or toxicity outcomes for those subjects receiving VIN.

Search strategy for identification of studies

The initial literature search was designed and executed by a medical information specialist (MVN). We searched MED-LINE®, Embase®, Cochrane Central Register of Controlled Trials, and Web of Science electronic databases through December 2016. The search captured terms for VIN and urinary bladder neoplasms using subject headings and text words. The search strategies are included in the Supplementary materials, Appendix 1. Reference lists of included series were manually screened for any additional studies to minimize retrieval bias. All identified manuscripts and their citation information were imported into an electronic database.

Critical evaluation of the selected studies

All manuscripts retrieved by the search strategy had their title and abstract prescreened by 2 of the researchers. Any reference deemed to potentially meet any of the inclusion criteria was tagged for full-text screening. A third reviewer adjudicated any prescreening discrepancies occurring between the first 2 reviewers. Full-text manuscripts were retrieved (where possible) for all prescreened abstracts, and these manuscripts were reviewed in detail by 2 researchers to determine if they met inclusion/exclusion criteria for the systematic review. In some instances, conference abstracts were identified without any discernible companion manuscript and such abstracts were retained if sufficient detail was present in the abstract for later data abstraction. No studies were excluded based on perceived quality or bias. Manuscripts (and in some instances abstracts) meeting screening criteria were then subject to data abstraction.

Data abstraction

Data elements were abstracted by 2 independent reviewers from the screened manuscripts and abstracts into an electronic database. Discrepancies in abstracted data were resolved by consensus review of the manuscript. All data were extracted directly from the manuscript or calculated from the available information when necessary. Clinical data including trial details, patient-specific data (age, sex, performance status), disease-specific data (tumor stage, tumor location, location of metastases, prior treatment, associated lab abnormalities),

response data (complete response [CR], partial response [PR], stable disease, objective response rate, duration of response), survival outcomes, and toxicity outcomes were collected. The data on all trials were based on the intention-to-treat (ITT) principle whenever possible.

The primary efficacy outcomes analyzed were median PFS and OS, treatment response, and response duration. Response rates were generally reported according to RECIST criteria.[13] In this system, progressive disease is defined as the development of new lesions or growth of existing lesions ≥20%; a CR indicates the complete disappearance of tumor; a PR indicates that the tumor has shrunk by ≥30% but is still visible on imaging; the objective response rate is the sum of the CR and PR rates; and stable disease is when tumor size shrinks by <30% and grows by no more than 20%.

Safety outcome analysis included incidence, type, and (where possible) the Common Terminology Criteria for Adverse Events (CTCAE) severity of non-hematologic adverse events (AEs) (fatigue, nausea, vomiting, mucositis, abdominal pain, constipation, myalgia, neuropathy, alopecia, infusion-site reaction) and hematologic AEs (anemia, neutropenia, neutropenic fever, thrombocytopenia).[14]

Analysis and presentation of results

Abstracted data were cleaned and condensed. Trials that generated multiple publications were combined into a single consensus record per trial. This resulted in 29 total studies that contain data analyzable in our systematic review. When individual publications from the same trial had different outcome data, we selected the outcomes with 1) the longest median follow-up time and 2) the data from the publication describing the full set of subjects and toxicity outcomes (i.e., not subgroup publications) for inclusion in the consensus record.

Statistical analysis was done using R 3.4.2 "Short Summer" on RStudio 1.1.383. For pooling proportions, the meta package was used.[15] Fixed effect (FE) and random effect (RE) models were constructed using inverse variance weighting. For variance stabilization, proportions were pooled after arcsine transformation,[16] restricted maximum likelihood estimation was used to calculate the between-study variance (τ^2) in the RE models, and pooled arcsine-transformed proportions and their 95% CIs were then back-transformed to the normal scale for presentation.[17] CIs for individual study proportions were calculated using the Clopper–Pearson method. The presence of residual heterogeneity was assessed using the I^2 statistic.[18] Forest plots were created to visually demonstrate results. To measure and plot survival times across studies, individual Kaplan–Meier plots were extracted and digitized using the digitize package for R and plotted using ggplot2.[19,20]
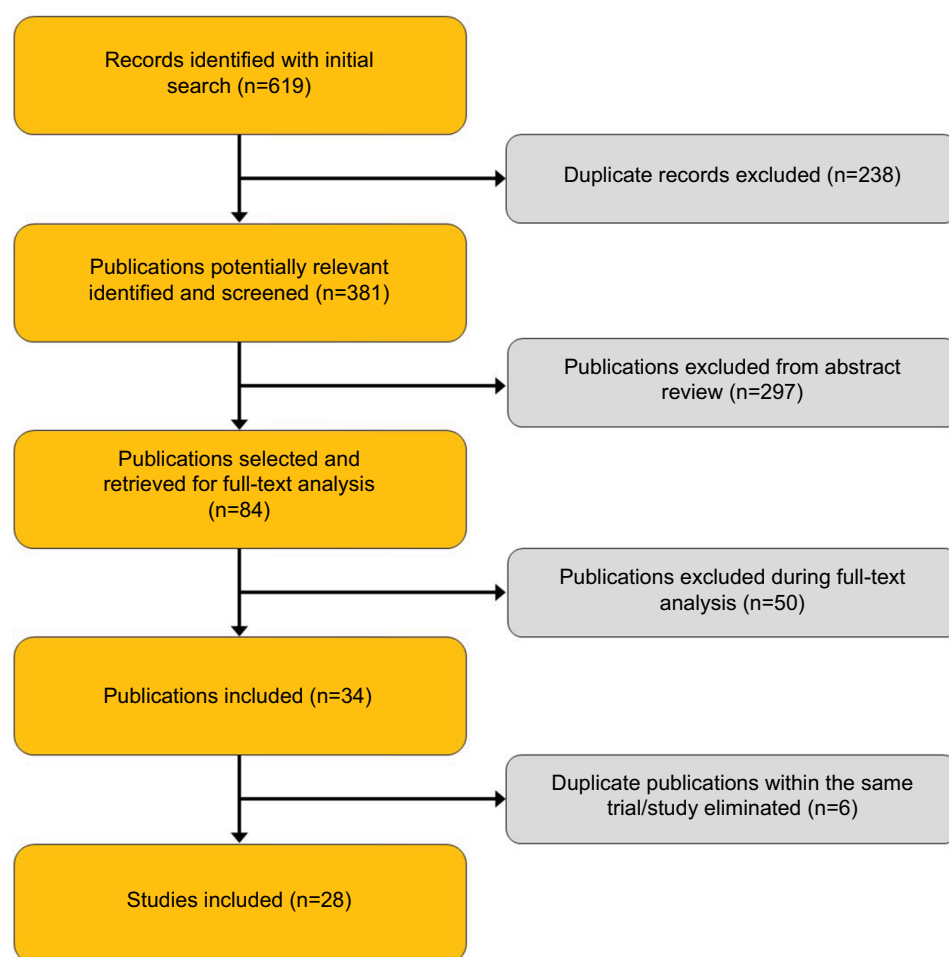
Results
Search results

Figure 1 presents the flow of identification and inclusion of articles as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[21] Our initial search resulted in 381 publications after de-duplication. After title and abstract review, 198 publications were excluded, leaving 84 studies for full-text analysis. Upon full-text analysis, 50 additional publications were excluded for various reasons (28 were duplicate data sets or articles, 16 lacked VIN data, 3 did not involve UC, 2 were not available in English, and 1 was a review article). One trial, IMvigor211, was presented in abstract form after our planned inclusion date range, but was included because it was felt to be an important study and contained a large number of VIN-treated patients. This resulted in 35 publications from which data variables were abstracted, and characteristics of these studies are shown in Table 1. The final analysis included 29 single consensus records for which data were available.

Chemotherapy with VIN

A total of 2,255 subjects received systemic therapy with VIN for the treatment of UC. All patients had the American Join Committee on Cancer stage IV cancer, though not all were metastatic as some were locally advanced nonmetastatic patients. VIN standard dose was most commonly 320 mg/m^2 every 21 days as a 20-minute infusion (reported in 17 of 28 included studies) with reduced doses of either 250 or 280 mg/m^2 with similar administration schedule. The majority of VIN administration was as second-line therapy after platinum failure; however, studies included data on third-line, maintenance, and first-line combination therapy.[9–11,22–25]

Response data

VIN chemotherapy response information was available from 17 studies, representing 1,416 patients. Forest plots for CR (Figure 2), PR (Figure 3), and overall response (Figure 4) are presented. There were few documented complete responders, and the pooled CR rate using FEs was 1% (95% CI 1–2%) and

Figure 1 Study selection flow chart.

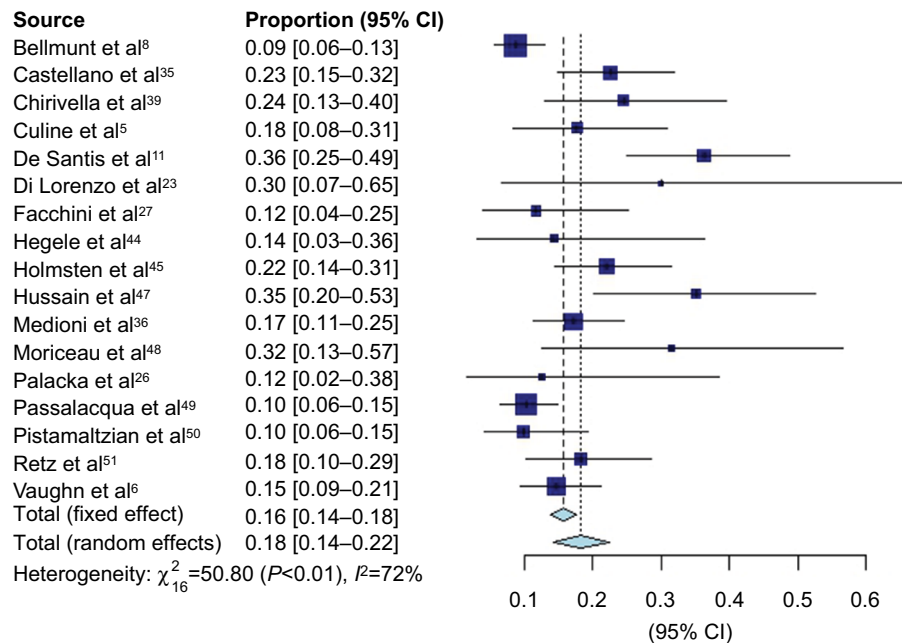| Source	Proportion (95% CI)
Bellmunt et al[8]	0.00 [0.00–0.01]
Castellano et al[35]	0.02 [0.00–0.07]
Chirivella et al[39]	0.02 [0.00–0.12]
Culine et al[5]	0.00 [0.00–0.07]
De Santis et al[11]	0.12 [0.05–0.22]
Di Lorenzo et al[23]	0.00 [0.00–0.31]
Facchini et al[27]	0.00 [0.00–0.08]
Hegele et al[44]	0.05 [0.00–0.24]
Holmsten et al[45]	0.01 [0.00–0.05]
Hussain et al[47]	0.00 [0.00–0.09]
Medioni et al[36]	0.05 [0.02–0.10]
Moriceau et al[48]	0.00 [0.00–0.18]
Palacka et al[26]	0.00 [0.00–0.21]
Passalacqua et al[49]	0.03 [0.01–0.07]
Pistamaltzian et al[50]	0.03 [0.00–0.10]
Retz et al[51]	0.05 [0.01–0.13]
Vaughn et al[6]	0.00 [0.00–0.02]
Total (fixed effect)	0.01 [0.01–0.02]
Total (random effects)	0.01 [0.00–0.03]

Heterogeneity: $\chi^2_{16}=62.84$ ($P<0.01$), $I^2=75\%$

Figure 2 Forest plot of complete response data.

Source	Proportion (95% CI)
Bellmunt et al[8]	0.09 [0.06–0.13]
Castellano et al[35]	0.23 [0.15–0.32]
Chirivella et al[39]	0.24 [0.13–0.40]
Culine et al[5]	0.18 [0.08–0.31]
De Santis et al[11]	0.36 [0.25–0.49]
Di Lorenzo et al[23]	0.30 [0.07–0.65]
Facchini et al[27]	0.12 [0.04–0.25]
Hegele et al[44]	0.14 [0.03–0.36]
Holmsten et al[45]	0.22 [0.14–0.31]
Hussain et al[47]	0.35 [0.20–0.53]
Medioni et al[36]	0.17 [0.11–0.25]
Moriceau et al[48]	0.32 [0.13–0.57]
Palacka et al[26]	0.12 [0.02–0.38]
Passalacqua et al[49]	0.10 [0.06–0.15]
Pistamaltzian et al[50]	0.10 [0.06–0.15]
Retz et al[51]	0.18 [0.10–0.29]
Vaughn et al[6]	0.15 [0.09–0.21]
Total (fixed effect)	0.16 [0.14–0.18]
Total (random effects)	0.18 [0.14–0.22]

Heterogeneity: $\chi^2_{16}=50.80$ ($P<0.01$), $I^2=72\%$

Figure 3 Forest plot of partial response data.

using REs was 1% (95% CI 1–3%), with an I^2 of 75%. The pooled PR rate was 16% (95% CI 14–18%) using FEs and 18% (95% CI 14–22%) using REs, with an I^2 of 72%. The pooled objective response rate with FEs was 18% (95% CI 16–20%) and with REs was 21% (95% CI 16–26%) with an I^2 of 79%.

Survival analysis

Kaplan–Meier curves were available for OS for 11 studies (Figure 5), and median OS ranged from 5.2 to 13.4 months.[11,26] PFS was available for 6 studies (Figure 6) and ranged from 2.2 to 6.5 months.[10,27]

Table 1 Study-level characteristics

Author	Country of Origin	Year of Publication	Journal	Centers	Blinding	Study Type
Aparicio et al[31]	Spain	2013	European Journal of Cancer	multicenter	open label	case series
Bamias et al[38]	Greece	2016	Clinical Genitourinary Cancer	multicenter	open label	case series
Bellmunt et al[28]	Spain	2010	J Clin Oncol	multicenter	open label	RCT
Bellmunt et al[7]	Spain	2013	Ann Oncol	multicenter	open label	RCT
Bellmunt et al[8]	Spain	2009	J Clin Oncol	multicenter	open label	RCT
Bellmunt et al[22]	Spain	2015	Journal	multicenter	open label	RCT
Castellano et al[35]	Spain	2014	BMC Cancer	multicenter	open label	case series
Chirivella et al[39]	Spain	2013	European Journal of Cancer	multicenter	open label	case series
Culine et al[5]	UK	2006	Br J Cancer	multicenter	open label	phase II trial
De Santis et al[11]	Austria	2016	Ann Oncol	multicenter	open label	phase II trial
De Wit et al[9]	Germany	2015	European Journal of Cancer	multicenter	open label	phase II trial
Di Lorenzo et al[23]	Italy	2015	Medicine (Baltimore)	multicenter	open label	case series
Di Palma et al[29]	France	2013	European Journal of Cancer	multicenter	open label	case series
Donini et al[40]	Italy	2015	Annals of Oncology	multicenter	open label	case series
Facchini et al[27]	Italy	2016	Front Pharmacol	single center	open label	case series
Font et al[10]	Spain	2016	Journal of Clinical Oncology	multicenter	open label	RCT
George et al[41]	USA	2007	Ejc Supplements	multicenter	open label	phase II trial
Gerullis et al[42]	Germany	2013	Anticancer Drugs	single center	open label	phase I trial
Guglieri-Lopez et al[32]	Spain	2015	Anticancer Drugs	multicenter	open label	Cohort
Harshman et al[30]	USA	2013	Br J Cancer	multicenter	open label	RCT
Hegele et al[43]	Germany	2015	Journal of Clinical Oncology	multicenter	open label	case series
Hegele et al[44]	Germany	2014	Urol Int	multicenter	open label	case series
Holmsten et al[45]	Sweden	2016	Oncol Lett	multicenter	open label	case series
Houede et al[46]	France	2016	BMC Cancer	multicenter	open label	case series
Hussain et al[47]	UK	2015	European Journal of Cancer	multicenter	open label	case series
Marongiu et al[24]	Italy	2013	European Urology, Supplements	multicenter	open label	case series
Medioni et al[36]	Italy	2016	BMC Cancer	multicenter	open label	case series
Moriceau et al[48]	France	2015	Clin Genitourin Cancer	single center	open label	case series
Palacka et al[26]	Slovak Republic	2014	Klin Onkol	single center	open label	case series
Passalacqua et al[49]	Italy	2016	Journal of Clinical Oncology	multicenter	open label	case series
Pistamaltzian et al[50]	Greece	2016	Anticancer Drugs	multicenter	open label	case series
Polo et al[25]	Spain	2014	Journal of Clinical Oncology	multicenter	open label	RCT
Powles et al[12]	UK	2017	EAS Meeting	multicenter	open label	RCT
Retz et al[51]	Germany	2015	BMC Cancer	multicenter	open label	case series
Vaughn et al[6]	USA	2009	Cancer	multicenter	open label	phase II trial

Abbreviations: RCT, randomized controlled trial; VIN, vinflunine.

Toxicity analysis

AEs (overall and grade 3–4) associated with VIN treatment are summarized in Table 2 for non-hematologic events and Table 3 for hematological events. Forest plots for these are found in the Supplementary materials, Appendix 2. The most prevalent non-hematologic AEs according to pooled REs analysis including all CTCAE grades were fatigue (40.1%), nausea (33.9%), constipation (34.1%), and alopecia (26.0%). The most prevalent CTCAE grade 3–4 non-hematologic AEs were fatigue (10.2%), abdominal pain (8.2%), myalgias (2.5%), and nausea (2.3%). The most common hematological AEs were anemia (56.6%), neutropenia (46.0%), thrombocytopenia (25.5%), and febrile neutropenia (6.6%). Grade 3–4 hematologic AE rates were 24.6% for neutropenia, 10.2% for anemia, 5.4% for febrile neutropenia, and 3.0% for thrombocytopenia.

Discussion

VIN has been evaluated in multiple trials as a first-line, second-line, third-line, and maintenance chemotherapeutic agent in the treatment of advanced and metastatic UC. The largest multinational study to date looking at VIN plus BSC versus BSC alone showed that VIN treatment as a second-line agent in platinum-refractory patients provides a 2.3-month improvement in median OS. With >40 months of follow-up, this difference was not statistically significant in the ITT population (p=0.2613); however, analysis of the eligible population as well as a multivariate analysis showed a significant survival benefit. Importantly, in post hoc analyses of these data, a prognostic model was created which was validated in several other studies.[28–30] This treatment response model classifies patients into 4 risk categories based on the presence of 0, 1, 2, or 3 of the
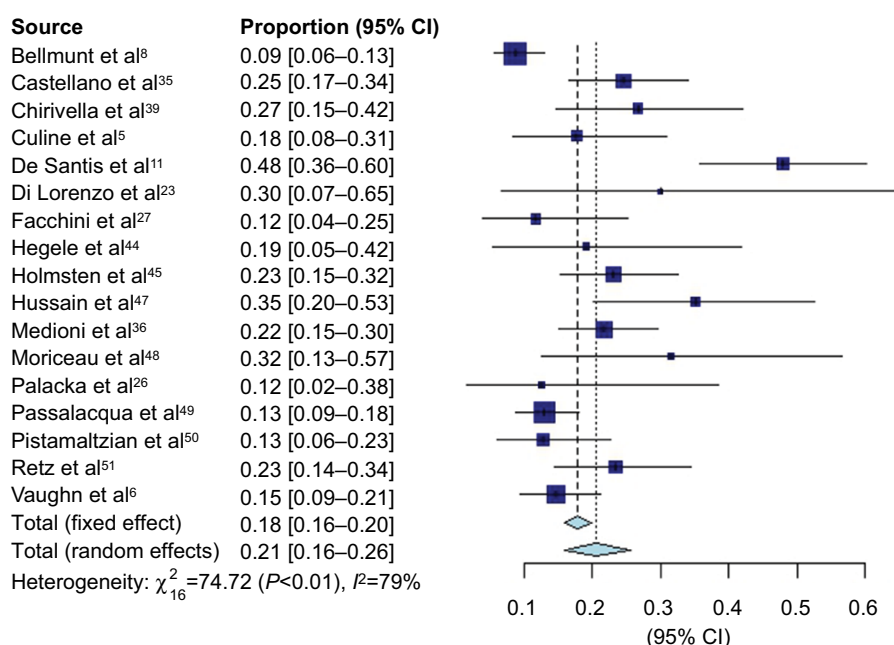
Sampling Frame	Study Start Date	Study End Date	Trial ID	No. Patients Vinflunine	Median Age	Male	Female	No. Patients Stage IV	Median Follow-up (months)
Retrospective				10				10	10.5
Retrospective	1/1/2011	12/31/2013	HGUCG	36	68	31	5	36	16.8
Prospective	5/15/2003	8/15/2006	L00070 IN 302	253	64	292	78	370	
Prospective	5/15/2003	8/15/2006	L00070 IN 302	253	64				42.9
Prospective	5/15/2003	8/15/2006	L00070 IN 302	253	64				
Prospective	4/15/2012	1/15/2015	MAJA	33	63				7.2
Retrospective	12/15/2009	6/15/2013		102	67			102	8.9
Retrospective	4/15/2010	12/15/2012		45	68				
Prospective	11/15/2000	9/15/2002		51	63	41	17	58	
Prospective	2/15/2011	8/15/2012	JASINT1	69	70			69	25.9
Prospective	2/15/2012	7/15/2013	JASiMA	19					9
Retrospective	1/15/2010	1/15/2015		10				52	
Retrospective	11/15/2012	2/15/2013	CURVE	134					
Retrospective	2/15/2011	6/15/2014	MOVIE	84	72	71	13	84	
Retrospective	2/15/2012	3/15/2015		43	63.5	40	3	43	24
Prospective	4/15/2012	1/15/2015	MAJA	45	64			88	12.2
Prospective				114	66	88	26		
Prospective	5/15/2011	12/15/2011	NCT01265940	5	72	5	0	5	
Retrospective	3/15/2010	11/15/2013		37	67	36	1		37
Prospective	5/15/2003	8/15/2006	L00070 IN 302	253	64	279	91	370	45.4
Prospective				77					
Retrospective	2/15/2010	3/15/2012		21	63	19	2	21	
Retrospective	2/15/2010	7/15/2013		100	68	72	28	100	
Ambispective	4/15/2013	4/15/2014		72	68	183	35		
Retrospective				37	64	24	13	37	
Retrosective	1/1/2001	12/31/2013		40	67			40	
Retrosective	1/1/2011	12/31/2011		134	65.3	119	15	134	17.6
Retrospective	5/15/2010	3/15/2014		19	66	18	1	19	
Prospective	4/15/2011	6/15/2014		16	62	13	3	16	5.2
Retrospective	2/15/2011	6/15/2014	MOVIE	217	69	182	35	217	
Retrospective	7/15/2005	7/15/2014		71	66.8	65	6		11.8
Prospective	4/15/2012	9/15/2013	MAJA	20	65.6			46	
Prospective	1/13/2015	3/13/2017	IMvigor211	250	67	195	55	233	17.3
Prospective	8/15/2010	9/15/2011	NCT01103544	77	67	63	14	77	4.6
Prospective				151	66	121	30	151	11.9

following risk factors: ECOG performance status (0 versus 1), liver metastases (present versus absent), and hemoglobin (<10 versus ≥10 g/dl). In this study, median OS varied from 14.2 to 1.7 months depending on these risk factors, stressing the importance of patient selection in VIN as second-line therapy.
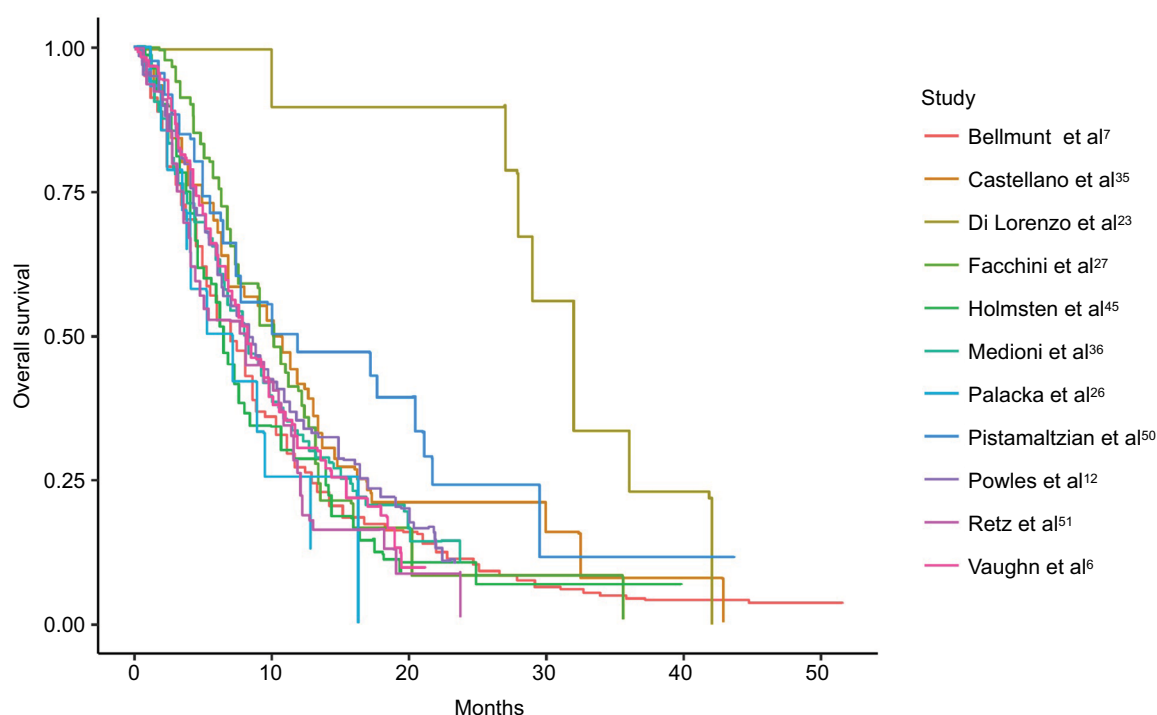
JASINT1 was the first study to examine first-line therapy doublets containing VIN in patients with good ECOG performance status (0/1) and impaired renal function making them ineligible for cisplatin. Significantly less grade 3–4 hematologic AEs were reported with VG versus VC with similar DCR, ORR, and OS.[11] To date, there have been no efficacy comparison studies of VIN combinations to current standard of first-line alternatives to cisplatin-containing regimens. We suggest a comparison study with carboplatin combinations as a logical next step in assessing this treatment as we are unable to assess comparative survival statistics at this time.

VIN maintenance therapy after first-line cisplatin-based treatment was shown in the JASiMA trial as well as by Aparicio et al to have an acceptable toxicity profile.[9,31] Neutropenia, the most common AE, was reversible and non-cumulative. The MAJA trial has shown favorable outcomes comparing VIN maintenance with BSC with 59% disease progression and 43% patient death in the treatment arm versus 81% and 62%, respectively, in the BSC control arm.[10] Survival analysis in this trial is pending; however, this response benefit was demonstrated in the context of favorable tolerability.

Di Lorenzo et al evaluated third-line therapies including cyclophosphamide, platinum-containing regimens, paclitaxel, docetaxel, gemcitabine, and VIN in a total of 52 patients.[23] In this setting, VIN showed inferior PFS and OS outcomes to cyclophosphamide as well as 18.75% higher absolute incidence of grade 3 and above AEs. Although a

Source	Proportion (95% CI)
Bellmunt et al[8]	0.09 [0.06–0.13]
Castellano et al[35]	0.25 [0.17–0.34]
Chirivella et al[39]	0.27 [0.15–0.42]
Culine et al[5]	0.18 [0.08–0.31]
De Santis et al[11]	0.48 [0.36–0.60]
Di Lorenzo et al[23]	0.30 [0.07–0.65]
Facchini et al[27]	0.12 [0.04–0.25]
Hegele et al[44]	0.19 [0.05–0.42]
Holmsten et al[45]	0.23 [0.15–0.32]
Hussain et al[47]	0.35 [0.20–0.53]
Medioni et al[36]	0.22 [0.15–0.30]
Moriceau et al[48]	0.32 [0.13–0.57]
Palacka et al[26]	0.12 [0.02–0.38]
Passalacqua et al[49]	0.13 [0.09–0.18]
Pistamaltzian et al[50]	0.13 [0.06–0.23]
Retz et al[51]	0.23 [0.14–0.34]
Vaughn et al[6]	0.15 [0.09–0.21]
Total (fixed effect)	0.18 [0.16–0.20]
Total (random effects)	0.21 [0.16–0.26]

Heterogeneity: $\chi^2_{16}=74.72$ ($P<0.01$), $I^2=79\%$

**Figure 4** Forest plot of overall response rate data.

Figure 5 Pooled Kaplan–Meier estimate plots of overall survival.

better powered study would be beneficial, it does seem from this preliminary data that VIN does not seem active as a third-line choice.

It is exceedingly important to consider the cost to the health care system with the introduction of any new treatment.

Guglieri-Lopez et al performed an economic analysis of VIN, finding a median treatment cost of €8,524 per patient, a €44,789 per progression-free year gained, and €22,750 per life-year granted.[32] We know that bladder cancer is the most expensive among cancer diagnoses per patient lifetime
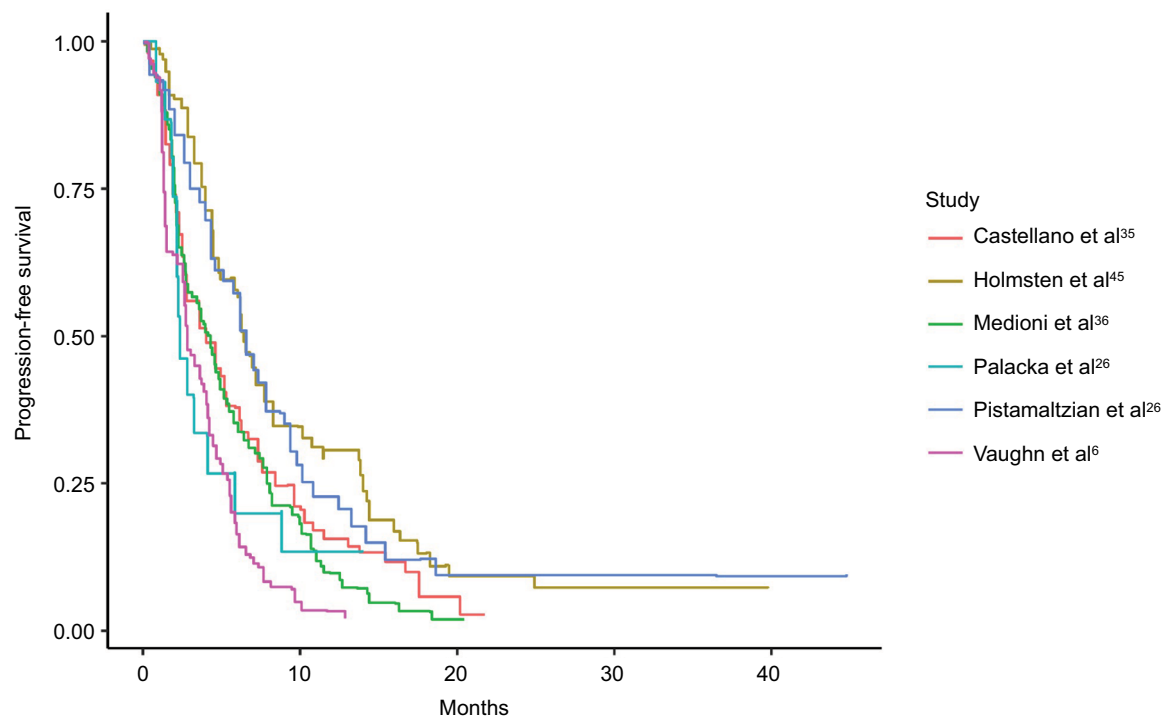
Figure 6 Pooled Kaplan–Meier estimate plots of progression-free survival.

Table 2 Non-hematologic adverse events of all CTCAE grades and grade 3–4

Non-hematologic adverse events	Number of subjects (N)	Number of studies (k)	I^2	Fixed effect	95% CI	Random effect	95% CI
Adverse event (overall)							
Fatigue	1,000	10	93.9	0.426	0.395–0.456	0.401	0.276–0.533
Nausea	715	7	82.1	0.357	0.323–0.393	0.339	0.252–0.432
Constipation	1,112	12	96.7	0.31	0.283–0.337	0.341	0.207–0.489
Alopecia	416	4	71.5	0.273	0.232–0.317	0.26	0.163–0.371
Infusion-site reaction	508	5	95.6	0.257	0.220–0.296	0.34	0.023–0.789
Vomiting	854	9	90.4	0.249	0.220–0.278	0.219	0.128–0.326
Mucositis	644	6	87.3	0.212	0.181–0.244	0.184	0.099–0.289
Abdominal pain	917	9	84.1	0.178	0.154–0.203	0.168	0.101–0.247
Myalgias	567	5	8.8	0.154	0.125–0.185	0.154	0.125–0.185
Neuropathy	805	7	92.5	0.151	0.127–0.177	0.157	0.071–0.271
Adverse event (grade 3–4)							
Fatigue	1,381	14	91.3	0.113	0.097–0.131	0.102	0.053–0.164
Constipation	1,631	19	76.9	0.086	0.073–0.100	0.082	0.056–0.113
Abdominal pain	1,025	10	56.9	0.047	0.035–0.061	0.046	0.028–0.070
Myalgias	667	6	4.7	0.025	0.015–0.038	0.025	0.015–0.038
Nausea	870	10	42.4	0.023	0.014–0.034	0.023	0.011–0.038
Vomiting	972	11	40.1	0.023	0.014–0.033	0.022	0.012–0.036
Mucositis	773	9	56.2	0.02	0.011–0.031	0.02	0.006–0.041
Neuropathy	974	10	81.7	0.015	0.008–0.024	0.018	0.002–0.048
Infusion-site reaction	598	5	64	0.007	0.002–0.016	0.007	0.000–0.025

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

and carries annual costs of $3.98 billion in the US.[33,34] Although we are unable to directly compare this study to the cost-effectiveness data of other UC therapies, the high cost associated with VIN makes patient selection an extremely important factor, specifically when considering the modest survival benefit to patients in higher-risk categories.

As far as toxicity is concerned, VIN was associated with considerable rates of high-grade anemia and neutropenia.

Table 3 Hematologic adverse events of all CTCAE grades and grade 3–4

Hematologic adverse events	Number of subjects (N)	Number of studies (k)	I^2	Fixed effect	95% CI	Random effect	95% CI
Adverse event (overall)							
Anemia	1,058	12	98.4	0.653	0.624–0.681	0.546	0.299–0.782
Neutropenia	1,058	12	97.6	0.513	0.483–0.543	0.46	0.273–0.654
Thrombocytopenia	1,037	11	96.8	0.298	0.271–0.326	0.255	0.125–0.412
Febrile neutropenia	815	8	70.4	0.06	0.045–0.078	0.066	0.033–0.110
Adverse event (grade 3–4)							
Neutropenia	1,521	18	94.3	0.264	0.242–0.286	0.246	0.165–0.338
Anemia	1,222	15	86.5	0.115	0.098–0.133	0.102	0.059–0.154
Febrile neutropenia	995	12	38.6	0.055	0.042–0.070	0.054	0.035–0.076
Thrombocytopenia	1,073	11	69.6	0.032	0.022–0.043	0.03	0.013–0.054

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

While these conditions can come at the cost of the need for dose reduction and even treatment termination, it is important to consider that these AEs are often preventable with appropriate prophylaxis, or are treatable and reversible.[35,36] Data suggest that overall AEs may be correlated with increased efficacy of treatment.[37]

Conclusion

VIN has been explored as a combination first-line treatment as well as a single-agent second-line, third-line, and maintenance therapy in advanced and metastatic UC. In first-line treatment of UC, either as a maintenance agent after cisplatin or as a primary combination therapy, VIN may be a promising alternative to current treatments. Further studies are needed to compare first-line combination VIN regimens to the current standard of care in order to assess long-term survival outcomes. Second- and third-line VIN monotherapy does provide a proven, although limited, survival benefit in platinum-refractory patients.

Disclosure

The authors report no conflicts of interest in this work.

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