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Vinflunine in the treatment of relapsed metastatic urothelial cancer: A systematic review and meta-analysis of real-world series

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ABSTRACT

Background: Vinflunine (VFL) is approved in Europe as second-line treatment of metastatic urothelial cancer after failure of platinum-containing therapy. We performed a systematic review and meta-analysis of real-world data (RWD) to assess utilization, efficacy and safety of VFL.

Methods: We performed a MEDLINE search for the period of 1/1/2000-31/8/2017. Full-length articles providing post-marketing RWD on VFL in patients failing previous chemotherapy were eligible. Interventional clinical trials were excluded.

Results: Ten studies with 797 patients were identified. According to pooled REs analysis, overall response rate was 19%, most frequent, all-grade toxicities were fatigue (41%), constipation (39%), nausea/vomiting (25%), and most prevalent Grade 3–4 toxicities were neutropenia (13%), anaemia (9%), fatigue (8%). Median OS was comparable to results reported in recent randomized studies.

Conclusion: Our findings confirm the efficacy and safety of VFL in an unselected population and support the use of VFL in the changing treatment paradigm of relapsed mUC.

1. Introduction

Urothelial carcinoma (UC) is one of the most common malignancies with an incidence of 594,393 new cases per year and a related mortality of 199,922 worldwide (Bray et al., 2018). It is more commonly found in the urinary bladder, although it can affect all sites of the urinary tract. Most UCs present as non-muscle-invasive tumours, which are best treated by surgical approaches (Burger et al., 2013). However, there is a 10–30% risk of progression to muscle-invasive disease, while about 25% of urothelial cancers are muscle-invasive at diagnosis (Abdollah et al., 2013). Muscle invasion dramatically changes prognosis, since only around 50% of patients survive 5 years following radical local therapy (most commonly radical cystectomy with lymph node dissection or radical radiotherapy) (Kamat et al., 2016). The major cause of treatment failure and death is the development of distant metastases. UC is a chemosensitive cancer and cisplatin-based chemotherapy is the current standard of care for metastatic UC (Bamias et al., 2018). However, most patients will progress after first-line chemotherapy (Clark et al., 2013; Bellmunt and Petrylak, 2012). Options for second-line treatment are limited and ultimately, the majority of patients will die of metastatic chemotherapy-resistant UC (Bellmunt and Petrylak, 2012), although a minority of patients may have long-standing responses to novel immunotherapy agents, which have been recently introduced in current practice.

Vinflunine (VFL) is a vinca alkaloid, which binds to tubulin, thus inhibiting microtubule polymerization (Kruczynski et al., 1998). This

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leads to reduction of the microtubule network of interphase cells and subsequent induction of G2/M arrest *in vitro*, resulting in apoptosis by mitotic accumulation at the metaphase/anaphase transition (Pourroy et al., 2004; Kruczynski et al., 2002). In addition, anti-angiogenic properties at sub-therapeutic doses have also been suggested (Pourroy et al., 2006). VFL binding affinity to tubulin is weaker than other vinca alkaloids, which probably explains the drug's reduced neurotoxicity (Kruczynski and Hill, 2001). Compared with other vinca alkaloids, VFL is a less-potent inductor of drug resistance *in vitro* by yet uncharacterized mechanisms (Etiévant et al., 2001). All together these characteristics suggested a possible role of VFL in the systemic treatment of UC (Bonfil et al., 2002). Accordingly, four randomized trials investigating VFL alone in second-line therapy, the combination of VFL/gemcitabine as first-line therapy and VFL as maintenance therapy after first-line showed that VFL was active in all these settings of advanced UC (Bellmunt et al., 2009; De Santis et al., 2016; Bellmunt et al., 2017a; García-Donas et al., 2017). In 2009 VFL was approved as a second-line treatment option in metastatic UC (mUC) by the European Medicines Agency (EMA). This approval was based on a 2.4-months median overall survival (OS) gain compared with best supportive care (BSC) in the per-protocol treated population of a randomized, phase III clinical trial (Bellmunt et al., 2009). As a consequence all experience with VFL outside the context of clinical trials is focused on patients with progression of mUC after first-line chemotherapy. Since the approval of VFL, real-world evidence regarding post-marketing use of VFL has been published (Castellano et al., 2014; Retz et al., 2015; Pistamaltzian et al., 2016). Expectedly, there is considerable variation in the efficacy and toxicity data in these reports, but real-world evidence is still important, since patients under study conditions may not fully reflect actual clinical practice. In order to effectively synthesize this information, we performed a systematic review of all such studies. Our aim was to investigate the available international experience on VFL as second-line therapy, and through this to evaluate the place of VFL on the developing treatment paradigm of mUC.

2. Methods

This systematic review was performed in accordance with the PRISMA guidelines (Liberati et al., 2009). Eligible articles were identified by a search of the MEDLINE bibliographical database for the period from January 1, 2000 to August 31, 2017. The search strategy included the following keywords: (urothelial AND vinflunine AND (carcinoma OR carcinomas OR cancer OR cancers OR neoplasm OR neoplasms)). Only full-length articles providing post-marketing, real-world data (RWD) on VFL administration, in patients with mUC failing previous chemotherapy, were considered eligible. Interventional clinical trials were excluded. Additional inclusion criteria were: English language; at least one of the following endpoints should have been reported: overall response rate (ORR), progression-free survival (PFS), OS, and toxicity.

Two investigators, working independently, searched the literature and extracted data from each eligible study. In addition, all the references of retrieved articles were checked, in order to identify additional potentially eligible articles. Reviews, case reports and conference abstracts were ineligible for this systematic review. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved to identify potentially additional eligible abstracts. For each of these studies, the following data were collected: first author, year of publication, country of origin, centres (multicentre *versus* single centre), number of patients treated, characteristics of patient population prior to VFL utilization, median follow-up, response rate data, median OS in months, median PFS in months, and toxicity. When multiple (overlapping) publications stemming from the same study were identified, the larger size study was included, unless the reported outcomes were mutually exclusive. In an attempt to maximize the strength of this systematic review, we contacted the authors of individual studies for clarifications, if necessary.

2.1. Statistical methodology

Lines of therapy were defined by the diagnosis of advanced disease. Therefore, patients who received VFL after either neo-adjuvant or adjuvant chemotherapy without any previous therapy for advanced disease were considered as first-line patients. ORR was the sum of complete and partial response rate (RR), while disease control rate (DCR) was defined as the sum of ORR and stable disease. Fixed effect (FE) and random effect (RE) models were constructed using inverse variance weighting. For variance stabilization, proportions were pooled after Arcsine transformation (Freeman and Tukey, 1950). Heterogeneity was quantified using the I^2 measure (Higgins et al., 2003). The confidence intervals (CIs) are based on exact binomial procedures (Newcombe, 1998). Forest plots were created to visually demonstrate results. All statistical analyses were performed using STATA/SE 15.1 software (©1985–2017; StataCorp LP, College Station, Texas, USA). For pooling proportions, the metaprop package was used.

3. Results

Search results are shown in Fig. 1. Ten studies (Castellano et al., 2014; Retz et al., 2015; Pistamaltzian et al., 2016; Médioni et al., 2016; Holmsten et al., 2016; Hussain et al., 2017; Passalacqua et al., 2017; Di Lorenzo et al., 2015; Hegele et al., 2014; Palacka et al., 2014), totalling 797 patients, were included in the analysis (Table 1): one was prospective and nine were retrospective. Publication dates ranged from 2014 to 2017. All were post-marketing studies and expectedly included patients from 10 European countries and 140 centres. Seven were collaborative studies, while three reported single-institution experience.

3.1. Patient demographics

Median age was similar across all studies ranging from 62 to 69 years. Pooled data for baseline characteristics with adequate reporting are shown in Table 2. The respective forest plots are included in Fig. S1. Most patients had Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 and a baseline haemoglobin > 10 g/dL, while 23% (95% CI 19–26) had liver metastases. The pooled baseline characteristics were numerically similar to those of the registrational study (Bellmunt et al., 2009).

3.2. Utilisation of VFL

All studies reported data on VFL administration and dosing. VFL was administered i.v. every 3 weeks, mainly as second-line therapy after platinum failure (Tables 1 and 2); however, six studies (Retz et al., 2015; Pistamaltzian et al., 2016; Médioni et al., 2016; Holmsten et al., 2016; Passalacqua et al., 2017; Di Lorenzo et al., 2015) also included 72 patients who received VFL beyond second-line, while in five studies (Retz et al., 2015; Pistamaltzian et al., 2016; Médioni et al., 2016; Holmsten et al., 2016; Hegele et al., 2014) 14 patients had received the drug as first-line therapy, following failure of perioperative chemotherapy. The impact of administering VFL as first-line or beyond second-line in this analysis was, however, minimal (Table 2).

The median number of VFL cycles was very similar across all studies (3–5). In all but one study, starting doses were 250, 280 or 320 mg/m^2, according to the summary of product characteristics (Javlor, 2019). In one study, however, all patients received a suboptimal starting dose between 200 and 250 mg/m^2 (Di Lorenzo et al., 2015). The percentage of patients starting at 320 mg/m^2 according to pooled REs analysis was 45% (95% CI 31–59), but there was considerable heterogeneity in this respect among the selected studies (Fig. 2). Although the reason for starting at a reduced dose was not specified in any of the papers, the percentage of patients with ECOG PS ≥ 1 (and history of pelvic

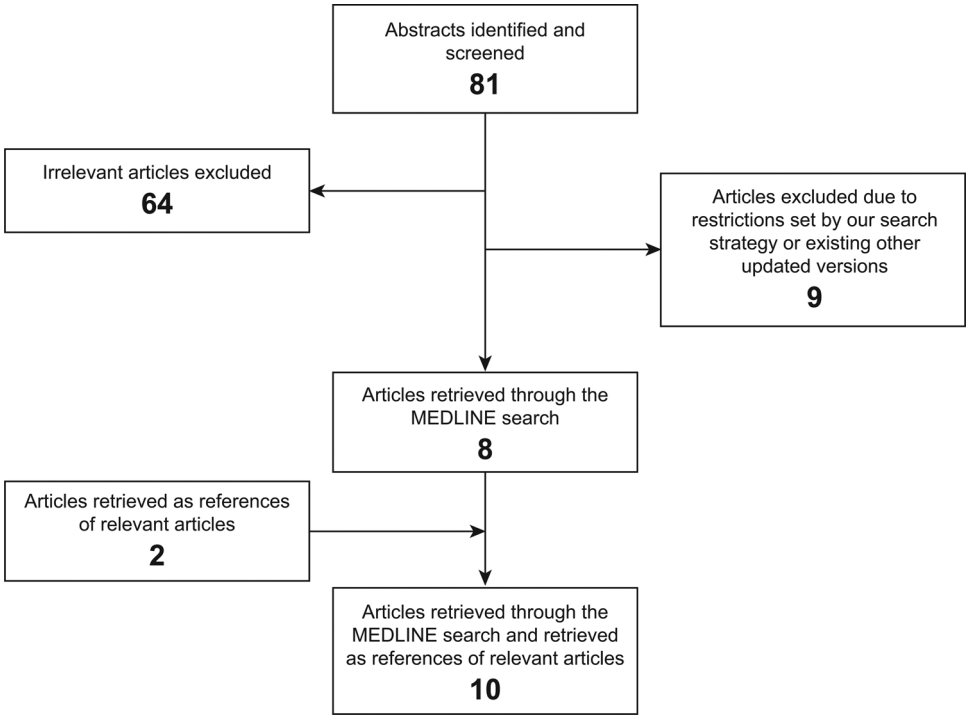

Fig. 1. Study selection flow chart.

radiation, whenever reported) was usually sufficient to account for this. Importantly, 171 patients (21%) received a starting dose of ≤ 250 mg/m^2, which may be recommended only in case of severe hepatic or renal impairment (Javlor, 2019).

3.3. Toxicity

All studies reported on Grade 3–4 toxicities but only six included information for all-grade toxicities (Castellano et al., 2014; Retz et al., 2015; Pistamaltzian et al., 2016; Médioni et al., 2016; Hussain et al., 2017; Passalacqua et al., 2017). In addition, only six publications included all Grade 3/4 (Pistamaltzian et al., 2016; Higgins et al., 2003; Newcombe, 1998; Médioni et al., 2016; Holmsten et al., 2016; Hussain et al., 2017) and only three all all-grade reported toxicities (Pistamaltzian et al., 2016; Hussain et al., 2017; Passalacqua et al., 2017), while the remaining only reported the most frequent. For this reason we only analyzed toxicities reported by at least five studies (Table 3, respective forest plots in Fig. 3). We believe that these are the most relevant, since they represent the most frequent toxicities also reported by Bellmunt et al. in the registrational study (Bellmunt et al., 2009) (included in Table 3 for descriptive purposes). Specifically for nausea/vomiting and asthenia/fatigue, when reported separately, we took into account only the most frequent of the two.

The most prevalent toxicities according to pooled REs analysis including all Common Terminology Criteria for Adverse Events (CTCAE) grades were fatigue (41%), constipation (39%), nausea/vomiting (25%), anaemia (28%) and neutropenia (25%). The most prevalent CTCAE Grade 3–4 adverse events (AEs) were neutropenia (13%), anaemia (9%), fatigue (8%) and constipation (7%). As indicated by I^2, the level of heterogeneity was higher for all-grade than for Grade 3–4 toxicities (Fig. 3).

3.4. ORR, PFS and OS

All studies reported ORR, PFS and OS. There were few complete responses (n = 23, 3%), so our analysis summed all objective responses. Since not all studies reported the number of non-evaluable patients, we performed intention-to-treat analyses, *i.e.* all patients of each study were included in the denominator. The pooled ORR with FEs was 18% (95% CI: 15–21) and with REs was 19% (95% CI 15–23) with an I^2 of 42.63%, suggesting moderate heterogeneity among the studies analyzed (Fig. 4). The pooled DCR with FEs was 49% (95% CI: 46–53) and with REs was 49% (95% CI: 42–55) with an I^2 of 66.48% (Fig. S2).

PFS and OS data from each study are shown in Table 4 and pooled

Table 1
Papers included in the analysis through MEDLINE search.

Author [ref]	Publication year	Country	Centres	No. of patients	Study type	Indication, no. patients (%)		
						First-line	Second-line	> Second-line
(Castellano et al. (2014))	2014	Spain	15	102	Retrospective		102 (100)	
(Retz et al. (2015))	2015	Germany	39	77	Prospective	9 (12)	51 (66)	17 (22)
(Pistamaltzian et al. (2016))	2016	Greece	7	71	Retrospective	2 (3)	60 (84)	9 (13)
(Médioni et al. (2016))	2016	France	22	134	Retrospective	6 (5)	93 (69)	35 (26)
(Holmsten et al. (2016))	2016	Sweden/Denmark	3	100	Retrospective	5 (5)	94 (94)	1 (1)
(Hussain et al. (2017))	2017	UK/Ireland	9	49	Retrospective		49 (100)	
(Passalacqua et al. (2017))	2017	Italy	28	217	Retrospective		167 (77)	50 (23)
(Di Lorenzo et al. (2015))	2015	Italy	4	10	Retrospective			10 (100)
(Hegele et al. (2014))	2014	Germany	8	21	Retrospective	5 (24)	16 (76)	
(Palacka et al. (2014))	2014	Slovakia	1	16	Retrospective		16 (100)	

Table 2
Baseline characteristics of 797 patients treated with vinflunine for relapsed urothelial cancer.

Characteristic	No. of patients	No. of studies	I^2, %	Fixed effect, % (95% CI)	Random effect, % (95% CI)	(Bellmunt et al. (2010)), %
Sex	669	7	73.4			
Male				85 (82–88)	83 (78–89)	79
Female				15 (12–18)	17 (11–22)	21
Previous lines of systemic therapy	791	10	95.9			NR
0				0 (0–1)	0 (0–3)	
1				95 (93–96)	90 (76–99)	
> 1				4 (3–6)	8 (1–21)	
ECOG PS	787	9	84.5			
0				35 (32–38)	38 (29–47)	32
1				63 (59–66)	61 (53–69)	68
Haemoglobin	685	8	90.8			
> 10 mg/dL				81 (78–84)	73 (63–83)	86
< 10 mg/dL				19 (16–22)	27 (17–37)	14
Liver metastases	535	6	0	23 (19–26)	23 (19–26)	29

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not reported.

data are depicted in Fig. S3. Median PFS ranged from 2.3 to 6.2 months, while median OS ranged from 5.2 to 11.9 months. Median PFS was numerically shorter than that of the registrational study in only one study, which included only 16 patients. Median OS was numerically shorter than that of the registrational study in only three studies. Two of those included only 16 and 21 patients, respectively (Hegele et al., 2014; Palacka et al., 2014).

3.5. Prognostic factors and subgroup analyses

Table 4 depicts subgroup analyses and the prognostic factors associated with OS in the five studies which included such analyses. Invariably ECOG PS was associated with prognosis. Anaemia and presence of liver metastases were the next most frequent factors described. The number of metastatic sites, visceral metastases and administration of > 6 cycles of previous chemotherapy were also found to be favourable prognostic factors in one study each. Two studies (Pistamaltzian et al., 2016; Médioni et al., 2016) stratified their patients according to the established prognostic factors for relapsed mUC, published by (Bellmunt et al. (2010)). Both confirmed the prognostic significance of this algorithm (Pistamaltzian et al., 2016; Médioni et al., 2016). Two other studies used slightly different stratification algorithms (Retz et al., 2015; Passalacqua et al., 2017). The first used all previous prognostic factors, adding time-from-previous-chemotherapy, according to (Sonpavde et al. (2013)), while the other substituted number of metastatic sites for Hb ≤ 10 g/dL (Passalacqua et al., 2017).

4. Discussion

Until recently, VFL represented the only EMA-approved agent for second-line treatment of patients with recurrent mUC following first-line platinum-based chemotherapy. The approval was based on the results of a phase III trial, which showed a survival advantage produced by VFL compared to BSC in the per-protocol-treated population, although the primary endpoint of the trial of significant advantage in the intention-to-treat population was not met (Bellmunt et al., 2009). The US Food and Drugs Association (FDA) did not approve VFL, since the median OS of 6.9 months reported in the trial was not particularly convincing with regard to the efficacy of this agent. Additionally, toxicity, especially neutropenia and constipation, could be of concern regarding the utilization of VFL in everyday practice. For this reason, generation of RWD on the efficacy and tolerability of VFL are particularly important. RWD provide insights from an environment closer to reality. It has an advantage over clinical trial data as it often represents a broader population, often over a longer timeframe, and provides information on comparators and outcomes that are not part of the clinical trial protocol. Furthermore, real-life data can aid decision makers to better manage uncertainty when making reimbursement decisions. Several European series studying the utilization of VFL in everyday practice have been published. Understandably, there is considerable

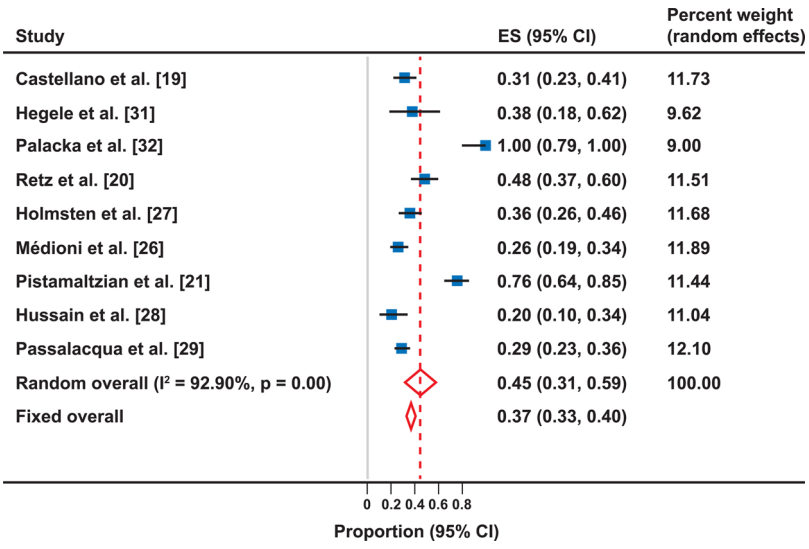

Fig. 2. Forest plot of pooled data on patients starting at 320 mg/m^2. ES, estimated size; CI, confidence interval.

Table 3
Adverse events of all CTCAE grades and Grade 3–4.

Adverse event	No. of patients	No. of studies	I^2 (%)	Fixed effect, % (95% CI)	Random effect, % (95% CI)	(Bellmunt et al. (2009)), %
Haematological (all grades)						
Neutropenia	628	6	95.5	14 (11–16)	25 (12–38)	77
Anaemia	526	5	89.4	26 (22–30)	28 (16–40)	93
Thrombocytopenia	526	5	63.0	5 (3–7)	7 (3–11)	51
Febrile infection	526	5	0	3 (1–4)	3 (1–4)	6
Non-haematological (all grades)						
Constipation	628	6	95.6	33 (29–36)	39 (21–58)	48
Asthenia/fatigue	526	5	95.3	34 (30–37)	41 (23–60)	50
Nausea/vomiting	494	5	95.6	13 (10–15)	25 (9–42)	29/29
Haematological (Grade 3–4)						
Neutropenia	775	10	87.1	6 (5–8)	13 (7–18)	50
Anaemia	673	9	77.2	7 (5–9)	9 (5–14)	19
Thrombocytopenia	673	9	0	1 (0–2)	1 (0–2)	6
Febrile infection	624	8	64.3	3(1–4)	3 (0–6)	6
Non-haematological (Grade 3–4)						
Constipation	775	10	66.3	7 (5–9)	7 (4–12)	16
Asthenia/fatigue	673	9	89.3	11 (9–14)	8 (2–17)	19
Nausea/vomiting	775	10	24.6	1 (0–3)	1 (0–3)	3/2

CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events.

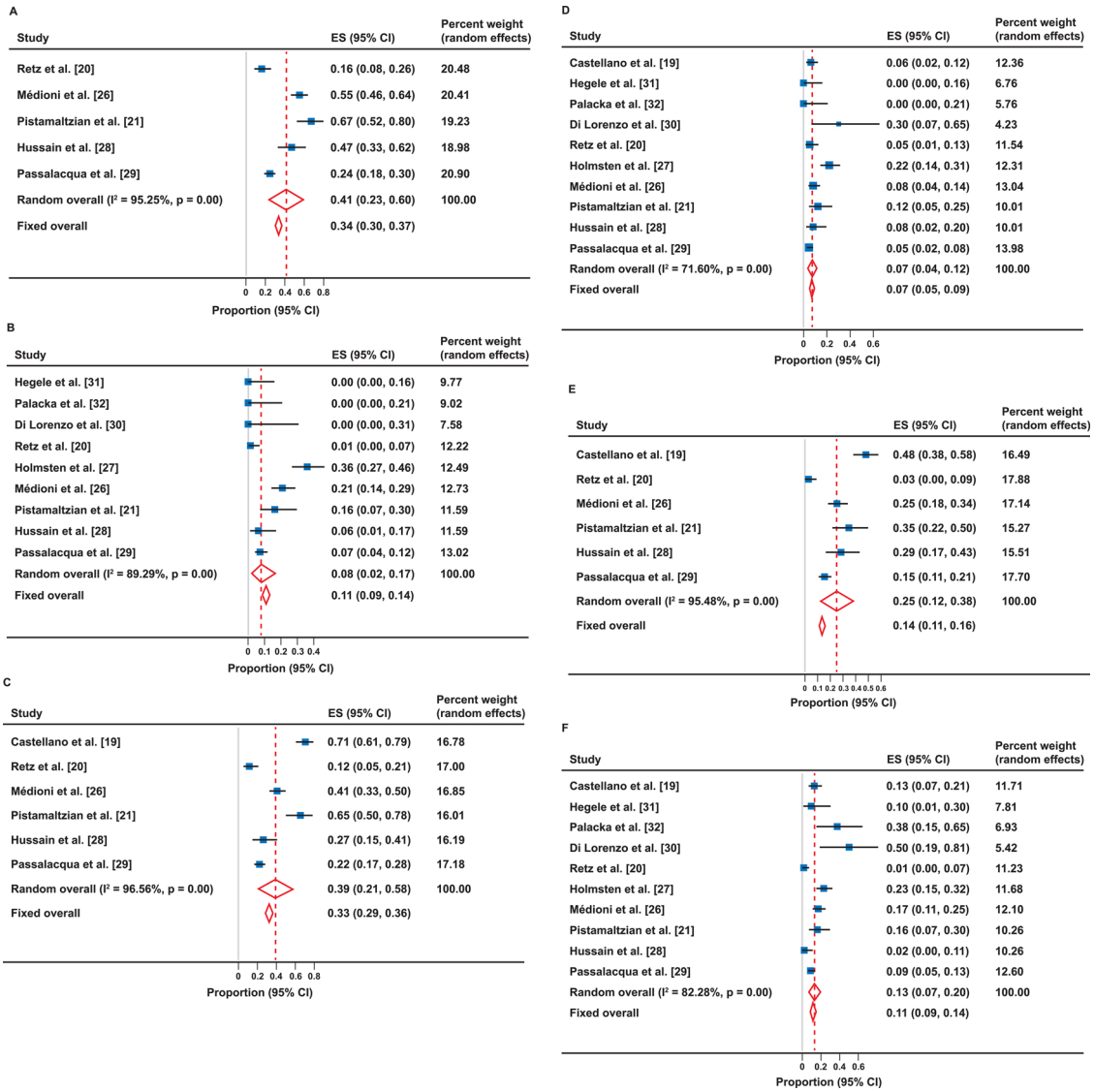

Fig. 3. Forest plots of pooled data on A) and B) fatigue; C) and D) constipation; E) and F) neutropenia. A), C) and E): all-grade toxicities; B), D) and F): Grade 3–4 toxicities. ES, estimated size; CI, confidence interval.

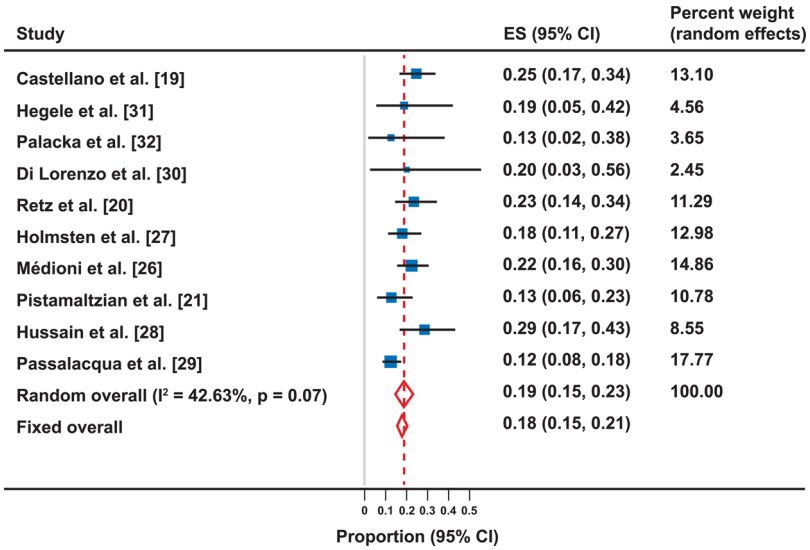

Fig. 4. Forest plot of pooled overall response rate data. ES, estimated size; CI, confidence interval.

variation in the baseline characteristics of patients included, the dosing of the agent and the outcomes reported. For this reason, a critical review of these publications is necessary to extract useful information and reliable conclusions on the everyday utilization of VFL. Recently, a meta-analysis including RWD on VFL in mUC was published (Brousell et al., 2018), however, this meta-analysis also included all published phase II and III clinical trials of VFL, thus neutralizing the important advantages of a pure RWD analysis. We therefore conducted a meta-analysis completely focused on RWD on VFL.

It is reassuring that utilization of VFL was based on the recommended dose and schedule in all but one of the included studies. Indicated reductions in starting dose were also applied, although adherence to the recommendations in this respect could not be assessed in this study. Furthermore, pooled baseline characteristics were strikingly similar to those of the registrational study, while in about 90% of cases, VFL was used as second-line therapy after failure of one platinum-based regime. Both these findings suggest that this agent was used in patients not heavily pretreated and most likely to benefit, since most patients had zero or one risk factors (Table 4). Lack of efficient alternatives at the time of the studies analyzed can certainly account to a significant extent for this pattern of practice. Importantly, the independent prognostic significance of all factors involved in the Bellmunt algorithm (Bellmunt et al., 2010) was confirmed, while the respective risk stratification was applicable in all four studies which reported such analyses, although in two of them risk criteria were slightly modified.

These pooled efficacy data must be interpreted with caution due to the lack of control over timing and type of tumour assessments. Nevertheless, it is encouraging that pooled RR was comparable to the 16% shown in the registrational study. In most studies, median OS was numerically longer than that of the randomized, phase III study of (Bellmunt et al. (2009)). Although this could be due to selection biases, frequently associated with non-comparative, retrospective series, it is in line with data derived in recent randomized trials. In these trials VFL was compared with two checkpoint inhibitors, namely pembrolizumab and atezolizumab, in patients with mUC relapsing after first-line platinum-based chemotherapy (Bellmunt et al., 2017b; Powles et al., 2018) as part of the control arm, which also included taxanes in both cases. Pembrolizumab produced an OS benefit over chemotherapy, while atezolizumab did not. Median OS for VFL was 7.4 (Petrylak et al., 2017) and 8.3 months (Powles et al., 2018), respectively, both comparing favourably with the 6.9 months reported in the first randomized trial (Bellmunt et al., 2010). It is interesting that data from the IMvigor 211 study (Powles et al., 2018) showed that the hazard ratio for atezolizumab *versus* VFL was 0.97 compared to 0.73 for atezolizumab *versus* taxanes. Although not a direct comparison between VFL and taxanes, this study shows patients deriving benefits from VFL chemotherapy. Therefore, since the approval of VFL, RWD as well as data from clinical trials confirming the efficacy of this agent in its indication have emerged.

Our review indicates a favourable toxicity profile for VFL. Toxicities reported were numerically lower than those reported in the registrational study (Bellmunt et al., 2009). This is as expected, because toxicity documentation in everyday practice is mainly clinically-driven, which also underlines the fact that most toxicities associated with VFL do not result in clinically meaningful problems for the patients. Safety data are also influenced by less frequent visit procedures compared to those of clinical trials; thus all-grade AEs might be underestimated, however, serious events are likely to be reported. This is supported by the fact that the variability reported was much higher for all-grade than for the more frequently clinically significant Grade 3–4 events, and the frequency of Grade 3–4 events is much closer to those reported in the registrational trial. Finally, the lower toxicity could be due to the fact that some patients received prophylactic treatment for neutropenia and constipation and the initial dose was often reduced based on the conditions and performance of patients.

The treatment paradigm in the treatment of mUC following failure of first-line platinum-based therapy is changing with the introduction of modern immunotherapy, using agents which inhibit the interaction between the programmed death-1 (PD-1) receptor on T lymphocytes and its ligand (PD-L1). As already mentioned, the PD-1 inhibitor pembrolizumab showed superior efficacy over chemotherapy in this setting (Bellmunt et al., 2017b). Four other checkpoint inhibitors (atezolizumab, avelumab, durvalumab and nivolumab) have also been approved for this setting. Following these developments, these agents are now considered the standard second-line therapy in mUC ((Chair) et al., 2017). Nevertheless, we believe that VFL remains a valid option in this setting. Firstly, patients with autoimmune diseases typically cannot receive immunotherapy; secondly, most patients treated with immunotherapy will not experience long-term benefit, while a small percentage will experience rapid progression (Soria et al., 2018). Although data on the efficacy of VFL after failure of immune checkpoint inhibition are lacking, this agent can be offered to these patients, since no other options are currently available in this setting. Furthermore, there are no validated clinical parameters or biomarkers that are valuable in selecting which postplatinum mUC patients will benefit mostly from VFL or immunotherapy. This represents a significant

Table 4
Efficacy results of vinflunine treatment in real-world studies in urothelial cancer.

Author [ref]	No. of patients	Median follow up, months (95% CI)	Median PFS, months (95% CI)	OS, months (95% CI)								Prognostic factors
				Total	PS		Haemoglobin		Liver		No. of risk factors (%)		
(Bellmunt et al. (2009))	253	21.5 (16.7–25.3)	3 (2.1–4.0)	6.9 (5.7–8.0)							0[**] (25) 1 (42) 2 (29) 3 (4)	14.2[&] 7.3 3.8 1.7	Liver involvement No. of organs involved Increment of one category AST Abnormal alkaline phosphatase Abnormal haemoglobin ECOG PS
(Castellano et al. (2014))	102	8.9 (NR)	3.9 (2.3–5.5)	10 (7.3–12.8)	0 ≥1	13.2 6.7			No Yes	11.7 6.1			ECOG PS Liver metastases
(Médioni et al. (2016))	134	17.6 (15.3–18.8)	4.2 (2.8–4.8)	8.2 (6.5–9.4)	0 ≥1	14.5 6.1	> 10 ≤ 10	9.6 2.4	No Yes	9.4 5.6	0[**] (23) 1 (40) 2 (27) 3 (10)	13.2 9.9 3.5 2.4	ECOG PS Anaemia Liver metastases
(Retz et al. (2015))	77	4.6 (NR)	NR	7.7 (4.1–10.4)							0[‡] (16) 1 (36) 2 (32) ≥ 3 (16)	18.5 9.5 4.1 2.8	Liver metastases
(Pistamaltzian et al. (2016))	71	11.8 (6.9–19.4)	6.2 (4.4–8.8)	11.9 (7.4–21)	0–1 ≥ 2	17.6 4.5	> 10 ≤10	17.3 4.2			0[**] (18) 1 (44) 2 (32) 3 (6)	20.5 17.3 7.4 2.4	ECOG PS Anaemia
(Holmsten et al. (2016))	100	NR	2.8 (NR)	6.3 (NR)	0–1 ≥2	7 4.6							ECOG PS Visceral metastases No. of cycles of previous chemotherapy
(Hussain et al. (2017))	49	9.1	5.1 (4.3–8.7)	9.1 (6.0–12.7)									
(Passalacqua et al. (2017))	217	NR	3.2 (2.6–3.7)	8.1 (6.3–8.9)	0	9.7			No Yes	9.5 8.6	0[$] (29) 1 (36) 2 (26) 3 (9)	11 6.3 6.2 3.1	ECOG PS No. of metastatic sites Liver metastases
(Di Lorenzo et al. (2015))	10	NR	16[*] (10–20)[†]	32[*] (31–37)[†]									
(Hegele et al. (2014))	21	NR	4.4 (2.6–6.6)	6.2 (3.9–10.7)									
(Palacka et al. (2014))	16	5.2 (0.6–16.3)	2.3 (2.1–3.2)	5.2 (3.4–8.8)									

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not reported; OS, overall survival; PFS, progression-free survival.
[*] Weeks.
[†] Interquartile range.
[**] Risk factors: ECOG PS ≥ 1, liver metastases, Hb ≤10 g/dL (Bellmunt et al., 2010).
[‡] Risk factors: ECOG PS ≥ 1, liver metastases, Hb ≤10 g/dL, time-from-prior-chemotherapy < 6 months (Brousell et al., 2018).
[$] Risk factors: ECOG PS ≥ 1, liver metastases, > 1 metastatic site.
[&] Risk stratification data from VFL-treated (n = 253) and untreated (n = 117) patients (Bellmunt et al., 2010).

unmet medical need and an area under intensive research. It is, therefore, important that new clinical trials provide information regarding the optimal use of VFL in the new treatment paradigm of mUC.

In conclusion, three randomized trials, 10 real-world series and two meta-analyses (including ours) confirm the efficacy and favourable toxicity profile of VFL in relapsed mUC. Efficacy of VFL in everyday practice is comparable to that of reported clinical trials. This supports its use in the changing treatment paradigm of this disease. The future role of VFL in mUC will be determined by future clinical research in this field.

Author contributions

All authors contributed to the conception and the critical review of the manuscript and approved the final article.

In addition to their contribution mentioned above, Aristotelis Bamias drafted the manuscript, Flora Zagouri performed the systematic review, and Kimon Tzannis performed the statistical analysis.

Conflict of interest

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Appendix A. Supplementary data

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