Randomized phase II study of maintenance vinflunine versus best supportive care after first line chemotherapy in patients with advanced urothelial carcinoma: The MAJA study (SOGUG 2011/02)

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ABSTRACT

BACKGROUND: The purpose of this trial was to evaluate if maintenance vinflunine (VFL), a microtubule inhibitor approved by EMA as treatment after failure to platinum-containing regimen, delays progression following disease control with first-line platinum based chemotherapy (CT).

METHODS: Open-label, randomised study in which patients from 21 Spanish hospitals with locally advanced/metastatic transitional cell carcinoma of the urothelial tract and adequate organ function, with radiological response or stabilization after 4-6 cycles of a cisplatin-gemcitabine (CG) chemotherapy (carboplatin was allowed after cycle 4) were randomized 1:1 by block randomization and stratified based on three factors: initial dose of VFL, liver metastases and number of prior CG cycles. Patients were centrally assigned and treatment allocation was not masked. Patients received intravenous VFL 320 mg/m^2 (or 280 mg/m^2 in case of ECOG performance status 1, age ≥ 75 years, prior pelvic radiotherapy or creatinine clearance < 60ml/min) every 21 days or best supportive care (BSC), until disease progression. Primary endpoint was progression free survival (PFS) in the intention-to-treat population (NCT01529411).

FINDINGS: 88 patients were randomized from April 2012 to January 2015, to the VFL arm (n=45) and to the BSC arm (n=43). After a median follow-up of all population of 15·8 months (range 0·5-48·7), 29 (65·9%) patients had progressed and 24 (54·5%) had died in the VFL arm, compared to 35 (83·3%) and 31 (73·8%) in the BSC arm respectively. Median PFS was 6·53 months (range 2·02-11·05) in the VFL arm and 4·20 months (range 1·77-6·64) in the BSC arm (Hazard Ratio 0·600, 95%CI 0·37-0·98, p=0·037). Most common G3/4 adverse events in the VFL arm were neutropenia (n=8; 18·2%), fatigue (n=7; 15·9%) and constipation (n=6; 13·6%). Treatment discontinuation due to drug-related adverse events occurred in 3 patients (6·7%) in the VFL arm. After progression, 16 (36·4%) patients received treatment at the VFL arm and 25 (59·5%) at the BSC arm.

INTERPRETATION: Maintenance therapy with VFL in patients with disease control after first line cisplatin-based chemotherapy provides a significant improvement in PFS with a reduction of 40% in the risk of progression, and with an acceptable tolerability profile.

FUNDING: Pierre-Fabre Médicament.

Keywords: maintenance therapy, vinflunine, advanced or metastatic transitional cell carcinoma of urothelial tract

INTRODUCTION

Transitional cell carcinoma of the urothelial tract (TCCU) is the fifth most common type of cancer in western countries[1].

TCCU is considered a relatively chemosensitive tumour, and high objective response rates (ORR) are obtained with first line treatment with platinum-based regimens, varying from 40 to 70%[2-4]. Nevertheless the duration of response is limited and when progression occurs the prognosis of these patients is generally poor[5].

In 2000, cisplatin-gemcitabine (CG) demonstrated similar efficacy to the MVAC scheme with less toxicity, becoming the most used combination in first-line treatment[6]. Median overall survival (OS) in these patients is about 14 months and ORR is 49%.

In order to improve global results, several regimens have been tested in the recurrent setting, including single agents[7] and combinations[8-10], but all of them showed modest activity, often associated with significant toxicity. Even though gemcitabine-paclitaxel doublet demonstrated activity in two phase II trials[11,12], a standard second line treatment was inexistent before 2009.

Vinflunine (VFL) is an antineoplastic agent of the vinca alkaloids family, with higher inhibition of microtubules dynamics than other antimicrotubule drugs, exposing patients to a minor risk of neurotoxicity[13,14]. Efficacy of VFL after failure of platinum-based chemotherapy was proved in two phase II trials[15,16]. Afterwards, a phase III trial comparing VFL vs. best supportive care (BSC) after prior platinum-based chemotherapy was conducted[17]. Bellmunt et al. demonstrated that VFL significantly improved PFS (3 vs. 1·5 months, P = 0·0012), ORR (16 vs. 0%, P = 0·0063) and DCR (41·1 vs. 24·8%, P = 0·0063). An improvement in the primary endpoint of OS was achieved (6·9 vs. 4·6; p = 0·29) in the intention to treat population (ITT) (n = 365), and was statistically significant (6·9 vs. 4·3; p = 0·04) in the eligible population (n = 357). These data were confirmed after a long-term follow-up of more than 3·5 years[18]. Because of these results, VFL received the approval from the European Medicine Agency (EMA) for treatment of TCCU patients after progression to a prior platinum-based regimen in September 2009[19].

Recent results prove activity of immunecheckpoint inhibitors in patients that have progressed to platinum-based regimens[20,21], and have led to accelerated approval of atezolizumab, an anti-PDL1 antibody[22]. In a phase III trial[20], Pembrolizumab, an anti-PD1 antibody, has demonstrated compared to CT an improvement in OS (10·3 vs 7·4 months; p = 0·0022) and ORR (21·1 vs 11·4 %; p = 0·0011), without improvement in PFS. In this scenario of limited progress, optimizing the use of currently available chemotherapy could clearly improve the outcomes of disease.

Thus, an attractive approach could be to introduce maintenance therapy following first-line

treatment in patients who obtain disease control, as has been done in other tumours, such as non-small cell lung cancer[23]. VFL is an attractive agent to explore in this setting since it has a favourable toxicity profile without cumulative toxic effects.

Therefore, we designed a randomized phase II study with the primary objective of improving progression-free survival (PFS) with VFL used as maintenance monotherapy in patients with advanced TCCU who have reached an objective response or stabilization disease after completing a minimum of 4 cycles of CG in first line.

METHODS

Study design

This was an open-label, 1:1, randomized phase II trial, performed at 21 institutions members of the Spanish Oncology Genitourinary Group (SOGUG) in Spain. The Spanish Agency for Drugs and Sanitary Products (AEMPS) and the Ethical committees approved the protocol in all participating hospitals. The study was conducted according to the Declaration of Helsinki and was registered in ClinicalTrials.gov (NCT01529411).

Patients

Patients were enrolled after completion of first line chemotherapy with 6 cycles of CG (carboplatin was allowed after cycle 4), only if they had radiological response or stabilization according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Once recruitment had started, the protocol was ammended to allow to include patients that had received a minimum of 4 cycles of CG. Patients provided written informed consent before inclusion in the study and for those already recruited, also after the amendment.

Enrolment should occur no later than 6 weeks from the last dose of the first line treatment. Inclusion criteria included age between 18 and 80 years; life expectancy ≥12 weeks; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; at least one measurable or evaluable lesion prior to first line treatment with CG; confirmed advanced surgically unresectable or metastatic TCCU; adequate bone marrow and organ function, with a creatinine clearance (CrCl) ≥40 ml/min, according to Cockcroft-Gault formula; neutrophil count ≥1·5 x 10^9/L; haemoglobin ≥10 g/dl; platelet count ≥10^{12}/L; bilirubin ≤1·5 x upper limit of the normal range (ULN); aspartate transaminase and alanine aminotransferase ≤2·5 x ULN; alkaline phosphatase ≤5 x ULN. Neoadjuvant or adjuvant chemotherapy based on cisplatin was allowed, provided it had been administered more than six months before the beginning of first line chemotherapy for advanced or metastatic disease.

Key exclusion criteria were peripheral neuropathy grade ≥2, ≥30% prior bone marrow radiotherapy, brain metastases and serious cardiac disease.

Randomisation and masking

Patients were randomly assigned 1:1 to receive VFL plus BSC vs BSC until disease progression, using the method of block randomization. Each block was composed of 6 patients. Randomisation was stratified based on three factors: initial dose of VFL (320 vs 280 mg/m^2), liver metastases (yes/no) and, after the amendment, number of prior CT cycles (4 vs 5/6). Thus, eight randomization lists were created in which the different blocks were randomized using the program SPSS version 15. Patients were centrally assigned. Treatment allocation was not masked.

Procedures

Patients in the BSC arm received supportive therapy only. In the VFL arm, patients received a 20 min intravenous infusion of VFL 320 mg/m^2 every 21 days, until disease progression, unacceptable toxicity, patient withdrawal or investigator decision, except for patients with PS 1, age ≥ 75 years, prior pelvic radiotherapy, or CrCl < 60ml/min, in which the dose was 280 mg/m^2.

When neutrophil count was <1·5 x 10^9/L, platelet count was <0·75 x 10^{12}/L or there was a grade 2 toxicity other than asthenia, a dose delay of a maximum of two weeks was allowed. In the event of toxicity (neutropenia G4 >7 days, febrile neutropenia, thrombocytopenia G 3/4, non-haematological toxicities G ≥3, except for vomiting, nausea, asthenia G3) dose was reduced from 320 to 280 mg/m^2 after the first episode and to 250 mg/m^2 after the second. For patients with initial dose of 280 mg/m^2 dose was reduced only once, to 250 mg/m^2. If a new dose reduction was required, discontinuation treatment would follow in both cases. Patients who required a dose reduction continued to receive a reduced dose for the remainder of the study. Granulocyte-colony stimulating factor was recommended in case of neutropenia G4 > 7 days or febrile neutropenia.

Antiemetic prophylaxis, supplementary laxative and dietetic measures were indicated in every cycle according to standard clinical practice of each institution.

Tumour volume was assessed at baseline by CT scan or magnetic resonance obtained 28 days before randomization. In case of bone metastasis, a bone scan was required. Tumour histology was also documented. Follow-up visits were scheduled every nine weeks for patients who had not progressed. Assessments included a complete physical examination, the reporting of adverse events and use of concomitant medication, and the evaluation of lesions according to

RECIST version 1·1. Patients who had progressed were evaluated every three months. Adverse events were recorded according to the Common Terminology Criteria for Adverse Events NCI CTCAE version 4.0.

Outcomes

The primary objective of this study was PFS, and the secondary objectives were OS, ORR, disease control rate (DCR), median duration of response (MDR), median duration of disease control (MDDC), time to response (TTR) and safety assessment of patients treated with VFL plus BSC vs those treated only with BSC.

PFS was measured from the date of randomization, after completion of induction therapy, to RECIST-defined progression or death from any cause, incorporating all randomly assigned patients on an intention-to-treat basis.

ORR was defined as the percentage of patients who achieved a complete response (CR) and partial response (PR) according to RECIST version 1.1. DCR was defined as the percentage of patients who achieved CR, PR and stable disease (SD) according to RECIST version 1.1. Duration of response was measured from the first documentation of tumour response to disease progression according RECIST version 1.1 or death from any cause. Duration of disease control was measured from the date of randomization to RECIST-defined disease progression or death from any cause. TTR was measured as the time from the date of randomization to the first response according RECIST version 1.1.

Safety was assessed in the treated population, including all patients who received at least one dose of assigned treatment.

Statistical analysis

Considering an unacceptable median PFS of 4 months and an acceptable one of 6·5 months for the experimental arm, 39 eligible patients in each arm were required to guarantee an α-error not greater than 0·05 (one-tail test). This value was increased in 10% to account for the possible inclusion of non-evaluable patients. Thus, a total of 43 patients had to be recruited in each arm. The study had a power of 90% and was carried out after a median follow up of more than 12 months since inclusion of the last patient. Continuous variables were represented by mean, standard deviation, median and range, and qualitative variables by absolute and relative frequencies (%) and the corresponding 95% confidence interval (CI). Qualitative variables were compared by Chi square test or Fisher exact test. The Kaplan-Meier method was used to estimate MDR, TTR, MDDC, and PFS. In case of Kaplan-Meier curves of PFS, alive patients without evidence of progression and those that were lost to follow up were censored during

the last assessment; in case of Kaplan-Meier curves of OS, alive patients and those that were lost to follow up were censored in the last visit (time of last known survival); in case of Kaplan-Meier curves of MDR and MDDC, patients without an assessment after response detection or stabilization were censored during the last radiological assessment. The log rank test was used to compare survival curves. Cox regression models were used to estimate and test hazard ratios (HR). Computation for the statistical tests was performed with SPSS version 15. Statistical analyses were performed at significance level of 0·05.

Role of the funding source

The funder of the study (Pierre Fabre Médicament) did not participate in study design, data collection, data analysis, data interpretation, and writing of the report. The Spanish Oncology Genito Urinary Group (SOGUG) was the sponsor of the study. All authors had the opportunity to review, final study data and are responsible for data interpretation and preparation of the report. All authors had access to data base. All authors attest the accuracy of the data and data analysis, and all were responsible for the final decision to submit for publication.

RESULTS

Overall, 88 patients were enrolled from April 12th, 2012 to January 29th, 2015 in 21 Spanish hospitals. Median age was 64 years [range 42-84]; 44·3% (n=39) of them had a PS 1; 29·5% (n=26) of them had CrCl <60 mg/min; and 20·5% (n=18) had liver metastases at the moment of randomization. Most patients were male (n=77; 87·5%), had metastatic disease (n=70; 79·5%) with bladder cancer as primary site (n=73; 83·0%), and had had 6 cycles of prior platinum-gemcitabine (n=62; 70·5%). Patients were randomly assigned to the VFL arm (n=45) or to the BSC arm (n=43). All baseline characteristics were well balanced between both arms (Tables 1-3), with the exception of the presence of liver metastases, which was less frequent in the VFL arm (n=5; 11·1%) than in the BSC arm (n=13; 30·2%). However, distribution of prognostic factors among patients in both arms was well balanced (Table 1). In the VFL arm, 15·6% of patients (n=7) had a CR and 62·2% (n=28) had a PR to the prior CG regimen whereas these values were 16·3% (n=7) and 53·5% (n=23) respectively in the control arm (Table 3). One patient from the VFL arm did not receive treatment, and another one from the BSC arm was found not eligible due to an excess of time between the last dose of cisplatin and the inclusion in the study (Figure 1). As of April 30th, 2016 (data cut-off date) 7 patients (15·6%) continued on VFL.

The initial dose of VFL in the VFL arm was of 320 mg/m^2 for 15 patients and of 280 mg/m^2 for 30 patients (Table 2). The median number of maintenance cycles delivered was 6·0 (range 1–

49) in the VFL arm and 5·5 (1–50) in the BSC arm, with a total number of cycles of 569 and 470, respectively. The mean weekly dose intensity of VFL for patients receiving a dose of 280 mg/m^2 was 84·7 mg (SD 9·2; 90·8% of the planned mean dose) and that of patients administered with 320 mg/m^2 was 92·7 mg (SD 16·8; 86·9% of the planned mean dose).

After a median follow-up for all patients of 15·8 months [0·5-48·7] and a median follow-up for alive patients of 27·6 months [14·9-48·7], 65·9% of patients have progressed (n=29) and 54·5% of patients (n=24) have died in the VFL arm as compared with 83·3% (n=35) and 73·8% (n=31) respectively in the BSC arm. The median PFS was 6·53 months (95% CI 2·02-11·05) in the VFL arm and 4·20 months (95% CI 1·77-6·64) in the BSC arm (HR 0·600, 95% CI 0·37-0·98, log rank p=0·037) (Figure 2A). Immature median OS was 16·7 months (95% CI 3·1-30·3) in the VFL arm and 13·2 months (95% CI 6·7-19.7) in the BSC arm, although this variable will be analysed again after a follow greater than 24 months according to the protocol.

The ORR was 20·5% in the VFL arm vs 7·3% in the BSC arm (p=0·087). There were 3 responses in the BSC arm at the first evaluation after randomization, and investigators indicated that they were late responses to the CG treatment. The DCR was 79·5% (n=31) in the VFL arm vs 56·1% (n=23) in the control arm (p=0·026). MDR was not reached in any of the arms. TTR was 3 months (95% CI 1·4-14·9) in the VFL arm and 2·7 months (95% CI 2·5-4·2) in the BSC arm (Table 4). MDDC was not reached in the VFL arm and was of 12·4 months (95% CI 1·6-23·2) in the control arm (HR 0·589, 95% CI 0·29-1·19; log rank p=0·137) (Table 4 and Figure 2B).

43·2% of patients (n=16) received further treatment after progression treatment in the VFL arm as compared with 71·4% (n=25) at BSC arm (p=0·016) (Table 5).

Most common haematological G3/4 AEs in the VFL arm were neutropenia (n=8; 18·2% G3/4), anaemia (n=2; 4·5% G3) and febrile neutropenia (n=1; 2·3% G3). Most common non haematological G3/4 AEs were constipation (n=6; 13·6% G3/4), fatigue (n=7; 15·9% G3), in the VFL arm, and pneumonia (n=2; 4·7%) in the control arm (Table 6).

Treatment discontinuation due to progressive disease (PD) occurred in 20 patients (44·4%) in the VFL arm and in 33 patients (76·7%) in the BSC arm. There were 2 deaths (4·4%) in the VFL arm, due to dyspnoea and pneumonia respectively, versus 2 (4·7%) in the BSC arm due to respiratory failure and progression. The pneumonia on the VFL arm was deemed by the investigator as treatment related. Treatment discontinuation due to drug-related adverse events occurred in 3 patients (6·7%) in the VFL arm: one with ischemic colitis and incarcerated hernia, another one with fatigue, nausea/vomiting and constipation, and the third one with constipation. Eight patients (17·8%) decided to discontinue treatment in the VFL arm (Table 7).

DISCUSSION

To our knowledge, this is the first clinical trial evaluating the role of VFL as maintenance therapy for TCCU patients who present disease control after first line treatment with GC chemotherapy. Findings from this randomized study have shown a significant PFS benefit with a tolerable safety profile for maintenance treatment with VFL.

Maintenance therapy represents a valuable alternative in the metastatic setting, and can be applied over a prolonged period of time. Theoretical benefits are prevention of symptom deterioration, preservation of PS and tumour reduction with low toxicity. This immediate therapy is feasible both for patients that may not be eligible for second line treatment, yet for whom clinical benefit can still be obtained; and for those that are eligible, but who might otherwise rapidly progress thus becoming ineligible for the second-line treatment[24,25].

Exploration of the feasibility of maintenance therapy in TCCU is still limited[26]. There are currently no effective agents approved for maintenance treatment[27]. Indeed, apart from the present study, no positive phase II/III studies have been reported. A case report gave expectations that maintenance gemcitabine in advanced urothelial carcinoma could provide good outcomes[28]. A retrospective analysis reported better OS but no change in PFS with gemcitabine[29] whereas another one reported significantly better disease-specific survival[30]. A distinct retrospective study in low-dose maintenance gemcitabine-carboplatin chemotherapy indicated that this combination could also represent an alternative[31]. Likewise, a very small study of 5 patients with bevacizumab maintenance therapy after a regimen of bevacizumab, gemcitabine and platinum showed good survival outcomes[32] and hence, a phase III study with this combination is ongoing (NCT00942331). On the other hand, phase II trials conducted with maintenance sunitinib[33], lapatinib[34] or gefitinib[35] have shown no improvement in PFS.

In this context, our results are encouraging since they show a significant improvement in PFS in the VFL group.

Recently, the encouraging results achieved by atezolizumab in the second line setting have prompted its approval by the FDA[21,22]. Though several other checkpoint inhibitors are under clinical development in bladder cancer, benefits seem to be restricted to a subset of cases. Thus maximizing benefits from every approach, immunotherapy and chemotherapy, could be the best option in order to impact the overall outcome of patients. Maintenance trials with the new checkpoint inhibitors, such as avelumab are now ongoing (NCT02603432).

The initial dose intensity of VFL was maintained throughout the study with low incidence of drug-related AEs and discontinuations, and with one drug-related death. As expected, VFL-treated patients presented more toxicities than the BSC group, but grade 3–4 neutropenia, fatigue, and constipation were the only AE occurring in over 5% of patients, and they were all manageable. Our results suggest that maintenance VFL could lead to an improved tolerance

profile than second line treatment. For example in our study, the frequency of G3/4 neutropenia and anaemia was of 27% and 5% respectively, as compared with 50% and 19% in the phase III study of VFL[17,18]. These results might be explained by the differences in PS between both populations (51% of PS 0 in this study vs 28% in the registration trial) that entails lesser disease burden for the MAJA population.

Among limitations of this work is the use of PFS as a primary endpoint instead of OS. Although PFS has been proposed as a subrogate marker of OS this has not yet been properly established. Other limitations are: the presence of an important percentage of patients with locoregional disease, the unbalance in the percentage of patients with liver metastasis between arms and the fact that VFL dose was not uniform; however both doses 320 mg/m^2 and 280 mg/m^2 are often used in clinical practice, with no clear superiority of one over the other. Indeed, a previous study demonstrated that initial dose did not correlate with clinical results[36]. Also, the study population was restricted to patients who had not progressed to first line. Nevertheless, the randomization process likely avoided favouring one arm as compared to the other. Finally, the trial included only patients with good performance status (PS 0/1) and it remains to be seen whether maintenance therapy would be also beneficial for patients with worse general condition.

In conclusion, despite a phase III study should be done to confirm these results, our study shows that maintenance VFL in patients with disease control after first line cisplatin-based chemotherapy significantly improves PFS with an acceptable tolerability profile. Trial is maturing to assess the impact of maintenance VFL in survival. Further studies are warranted to better establish the role of maintenance VFL, including combinations with checkpoint inhibitors.

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Declaration of interest

There are no relevant conflicts of interest to disclose.

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Figure legends

Figure 1. Trial profile.

Figure 2. Log rank test comparing Kaplan Meier curves between VFL arm and BSC arm. (A) Progression free survival. (B) Duration of disease control.