Randomized phase II study assessing the combination of Vinflunine with Gemcitabine and Vinflunine with Carboplatin in patients ineligible to cisplatin with advanced or metastatic transitional cell carcinoma of the urothelium

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Primary objective:· To determine the disease control rate as defined by RECIST assessment criteria [Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) rates] for both Vinflunine-Gemcitabine and Vinflunine-Carboplatin combinations....

Ethical review	Not approved
Status	Will not start
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON36397

Source
ToetsingOnline

Brief title
JASINT 1

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
bladder cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pierre Fabre
Source(s) of monetary or material Support: Sponsor (Pierre Fabre)

Intervention

Keyword: cisplatin, tccu, unfit, vinflunine

Outcome measures

Primary outcome

Efficacy Measures:

- Will be determined by using RECIST criteria (version 1.1). as follows:

assessment of lesions (measurable and non-measurable) at baseline and every 2

cycles.

- Progression and tumor response will be evaluated for all randomized patients

by the investigators.

- Duration of disease control and response will be evaluated for all patients

with disease control and responding patients, respectively.

- Moreover, clinical parameters as pain intensity will be performed every 2

cycles.

· Safety Measures: physical examination and vital signs, performance status,

complete blood counts, serum biochemistry, clinical safety, adverse events

using the NCI Common Toxicity Criteria (version 2.0).

Secondary outcome

To assess the safety profile of the treatment.

To evaluate other efficacy parameters: Objective Response Rate (CR + PR rates),

duration of response and duration of disease control, Time to treatment failure

(TTF), Progression free survival (PFS) and Overall survival (OS).

Study description

Background summary

There is no standard recommended treatment option in patients who cannot receive a cisplatin-based regimen as first line chemotherapy for an advanced or metastatic Transitional Cell Carcinoma of the Urothelium (TCCU), in particular those having a creatinine clearance < 60 mL/min. A carboplatin-based regimen or a single agent therapy (i.e. gemcitabine) is frequently used in practice.

Vinflunine, as single agent, provides both survival advantage over best supportive care and clinical benefits in patients with advanced or metastatic TCCU following prior failure of a platinum-based regimen. It is the only drug approved in Europe in this setting where there was no prior established standard of care [Bellmunt J et al. J Clin Oncol 2009].

Vinflunine doesn*t exhibit renal toxity. Patients with a creatinine clearance as low as 40 mL/min could receive the drug in prior clinical trials, and the drug was assessed in few patients with an even lower value (20-40 mL/min).

Based on these findings, in patients with advanced or metastatic TCCU presenting ineligibility to cisplatin, we may expect some benefits from regimen combining Vinflunine with other drugs that previously demonstrated clinical activity as single agent and/or as part of non-cisplatin containing combinations, such as gemcitabine or carboplatin.

Phase I trials assessed the dose of vinflunine that could be combined with gemcitabine or with carboplatin in patients with NSCLC.

Taking into account the frail global health status of patients with metastatic TCCU, in particular those presenting ineligibility to cisplatin, it is important to clarify the clinical benefit/risk ratio of the two most promising combination regimens including the novel therapeutic agent, vinflunine, as far as there is no clinical data on the use of vinflunine plus gemcitabine or carboplatin in TCCU, to date.

Study objective

Primary objective:
· To determine the disease control rate as defined by RECIST assessment criteria [Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) rates] for both Vinflunine-Gemcitabine and Vinflunine-Carboplatin combinations.

Secondary objectives:
· To assess the safety profile of the treatment.
· To evaluate other efficacy parameters: Objective Response Rate (CR + PR rates), duration of response and duration of disease control, Time to treatment failure (TTF), Progression free survival (PFS) and Overall survival (OS).

Study design

Two-arm, open-label, randomized, multinational phase II trial

Study scheme:
1 cycle is 3 weeks
* Arm A:
+ Day 1: Vinflunine 280 or 250 mg/m² (20 min IV infusion) + Gemcitabine 1000 or 750 mg/m² (30 min IV infusion)
+ Day 8: Gemcitabine 1000 or 750 mg/m² (30 min IV infusion)
* Arm B:
+ Day 1: Vinflunine 280 or 250 mg/m² (20 min IV infusion) + Carboplatin AUC 4,5 (60 min IV infusion)
Response assessment every 2 cycles (1 Cycle = 3 weeks)
Starting dose of drugs depends on baseline creatinine clearance.

In case of significant haematological or non-haematological toxicity, dose of drugs might be reduced for subsequent cycles. The dose of gemcitabine will be escalated to 1000 mg/m2 during the subsequent cycles if no toxicity requiring dose reduction occurs in cycle 1.

Randomisation will be stratified on (minimization procedure):
- Study site
- *Prior neoadjuvant/ adjuvant chemotherapy* received by the patient for the treatment of TCCU versus *no prior chemotherapy*
- PS 0 versus PS1
- Calculated creatinine clearance value (Cockroft-Gault formula) at baseline: > or equal to 60 mL/min Vs 40-60 mL/min Vs 30-40 mL/min measured within 7 days of 1st drug administration.

At study entry, the complete history of malignant and non malignant disease will be collected with a full physical examination including vital signs, weight, BP, BSA, PS, ECG, audiogram. Baseline serum biochemistry assessments and a complete blood cell counts (CBCC) will be performed before randomization, before each administration of the cytotoxic(s), at D8 of each cycle and in the event of fever or infection .

Patients who discontinue chemotherapy without evidence of Progressive Disease (PD) will continue to be monitored until progression. All patients will be followed-up until death or study closure.

Intervention

* Arm A:
+ Day 1: Vinflunine 280 or 250 mg/m² (20 min IV infusion) + Gemcitabine 1000 or 750 mg/m² (30 min IV infusion)
+ Day 8: Gemcitabine 1000 or 750 mg/m² (30 min IV infusion)

* Arm B:
+ Day 1: Vinflunine 280 or 250 mg/m² (20 min IV infusion) + Carboplatin AUC 4,5 (60 min IV infusion)

Response assessment every 2 cycles (1 Cycle = 3 weeks)
Starting dose of drugs depends on baseline creatinine clearance.

Study burden and risks

There is no standard recommended treatment option in the patients population targeted by this trial who cannot receive a cisplatin-based regimen as first line chemotherapy for an advanced or metastatic Transitional Cell Carcinoma of the Urothelium (TCCU), in particular those having a creatinine clearance < 60 mL/min. Median survival for this type of population is arund 8.5 months with a rapidly progressive disease. A carboplatin-based regimen or a single agent therapy (i.e. gemcitabine) is frequently used in practice.We propose to combine each of the above mentionned agents to a drug which has been recently approved in a later stage of the disease with limited toxicity, expecting to improve outcomes.
The number of blood test and imaging will depend on the treatment duration for each patient as discribed in the study flow chart table of the protocol but all tests are standard tests performed in the follow-up of this type of disease: one or two blood tests every 3 weeks, imaging (CT scans and or MRI) every 6 weeks, a standard physical examination with Weight / BSA / BP /Vital Signs / ECOG Performance Status assessment every 3 weeks. Only bone scintigraphy is an examination (to assess bone lesions) which is not always prescribed when disease extension is assessed; this may vary according to centres habits: it is required at baseline and only in some cases (i.e. progression suspiscion) once again thenafter.
The burden is limited, only being considered as a close follow-up and the possible risks are related to the disease itself and the treatment combination administered. Nevertheless all drugs are already marketed in TCCU and both combinations have already been tested in a more limited sample size of patients having another type of cancer. On the other hand, we may expect some benefits in efficacy and outcomes for the patients from the combination of drugs, each

having shown to be active in this type of cancer, justifying this trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Man or woman aged > or equal to 18 years and < 80 years
- Signed written informed consent
- Histologically confirmed diagnosis of locally advanced or metastatic predominantly transitional cell carcinoma of the urothelium (TCCU) [urinary bladder, kidney, renal pelvis, or ureter]
- With the following disease conditions : Ineligibility for cisplatin-based therapy because of at least one of the following two medical conditions:
+ Calculated creatinine clearance (Cockroft-Gault formula) < 60 mL/min
+ New York Heart Association Classification Stage II-III Congestive Heart Failure (documented

by medical history)
- *Measurable* disease with at least one uni-dimensional lesion according to RECIST guideline (version 1.1)
- ECOG performance status of 0 or 1
- Estimated life expectancy of at least 12 weeks
- Patient without prior systemic anticancer therapy unless if it had been administered as neoadjuvant or adjuvant CT for TCCU and if the patient has documented relapse > or equal to 6 months after the last dose of CT (prior intravesical CT allowed)
- Adequate bone marrow and hepatic functions as evidenced by:
+ Absolute Neutrophil Count > or equal to 2,000/mm3 (> or equal to 2.0 x 109/L)
+ Haemoglobin > or equal to 10 g/dL
+ Platelet count > or equal to 100,000/mm3
+ Serum total bilirubin > or equal to 1.5 x upper limit of normal (ULN)
+ Transaminases < or equal to 2.5 x ULN [< or equal to 5 x ULN only in case of liver metastasis]
- Absence of psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; these conditions should be assessed with the patient before registration in the trial
- Patient access to social insurance if applicable in the local regulations
- Women of childbearing potential must be using a medically accepted method of contraception to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and for up to 3 months after the last dose of study treatment; women of childbearing
potential must have a negative serum or urine pregnancy test within 72 hours prior to the start of study treatment
- Fertile men must be using an effective method of birth control during the study and up to 6 months after the last dose of study treatment if their partners are women of childbearing potential

Exclusion criteria

- ECOG performance status > or equal to 2
- Woman if pregnant or lactating or with positive pregnancy test at inclusion; woman of child-bearing potential who did not use or is unwilling or unable to use an acceptable method to avoid pregnancy during the 2 months preceding the start of study treatment, for the entire study period and for up to 3 months after the last dose of study treatment; sexually active fertile man not using effective birth control during the study and up to 6 months after the last dose of study treatment if his partner is a woman of childbearing potential
- Known brain metastasis or leptomeningeal involvement. (Computed Tomography (CT)-scans are not required to rule this out unless there is clinical suspicion of central nervous system (CNS) disease)
- Peripheral neuropathy Grade > or equal to 2 by NCI CTC [National Cancer Institute Common Terminology Criteria]
- Prior radiation to > or equal to 30% of the bone marrow or completed < 30 days ago or without full recovery of toxicities

- Other serious illness or medical condition including:
+ Infection requiring systemic anti-infective therapy
+ Any medical condition that might not be controlled, for instance patients with unstable angina, patients with myocardial infarction within 6 months or uncontrolled diabetes
- Prior systemic chemotherapy for advanced or metastatic disease or neoadjuvant/adjuvant chemotherapy that was completed < 6 months before documented progression
- Patient who had received any other investigational drug or anti-cancer therapy within 30 days before randomisation
- Other malignancies except adequately treated basal carcinoma of the skin, in-situ cervix carcinoma or any other tumor with a disease free interval > or equal to 5 years
- Inadequate renal function defined by a serum creatinine clearance < 30 mL/min (Cockcroft-Gault formula)
- Known hypersensitivity to the study drugs or to drugs with similar chemical structures
- Patients who require treatment with ketoconazole, itraconazole, ritonavir, amprenavir, indinavir, rifampicine (any potent CYP3A4 inhibitor or inducer) or phenytoine
- Any concurrent chronic system immune therapy or previous organ allograft
- Electrocardiogram (ECG) with significant modifications suggesting a high risk of occurrence of an acute clinical event (such as signs of angina pectoris or high risk arrhythmia*)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-03-2011
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	GEMZAR
Generic name:	Gemcitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	JAVLOR
Generic name:	Vinflunine
Registration:	Yes - NL outside intended use

Ethics review

Not approved

Date:	28-03-2011
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-020620-22-NL
CCMO	NL34225.094.11