NCT01616875

A Phase II Trial of Combination Cabazitaxel and Cisplatin Chemotherapy in the Neoadjuvant Treatment of Transitional Cell Carcinoma of the Urinary Bladder

Bristol Bladder Trial

Statistical Analysis Plan

Dated 01/03/2017

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1. Trial Summary

A phase II trial of combination cabazitaxel and cisplatin in the neoadjuvant treatment of transitional cell carcinoma of the urinary bladder
Objectives:

Primary

To evaluate the overall response rate with this chemothera-py regimen in the neoadjuvant treatment of transitional cell carcinoma of the bladder and thus determine whether this approach warrants further research (randomised Phase II/ III trial).

Secondary

To evaluate safety and tolerability;
To assess progression-free and overall survival;
To assess quality of life during treatment.

Trial Design

Non-randomised single centre trial

Type and number of patients

Patients with invasive transitional cell carcinoma of the blad-der will be eligible if they are fit to receive chemotherapy as neoadjuvant treatment and to undergo a radical cystectomy.
Approximately 26 patients will be recruited.

Treatment

Four cycles of chemotherapy using a combination regimen comprising:
Cabazitaxel 15 mg/m2 day 1 + cisplatin 70mg/ m2 day 1. The combination treatment is prescribed every 21 days.

Endpoints

Primary: The primary endpoint is overall response rate
(Complete remission rate + partial remission rate) deter-mined by histopathological staging at cystectomy.

Secondary

- Progression-free survival;
- Overall Survival;
- Acute toxicity (CTCAE v4.03) after each cycle ;
- Quality of life (assessed by EQ5D and EORTC QLQ-C30 and module BLM-30)

Associated Studies

Patients with no contraindications to MRI or gadolinium contrast may enter an optional substudy evaluating dynamic contrast enhanced MRI prior to therapy, and after one and three cycles of chemotherapy.
Patients will be offered entry into an optional pilot substudy involving measurement of circulating tumour cell (CTC) concentration prior to each cycle of chemotherapy and prior to surgery.

2. AIMS OF THE STUDY

2.1 Primary

To evaluate overall pathological response rate with a combination regimen using cabazitaxel and cisplatin in the neoadjuvant treatment of transitional cell carcinoma of the urinary bladder, thus determining whether this approach warrants further research within the context of a phase III clinical trial.

2.2 Secondary

- To evaluate safety and tolerability
- To assess progression-free and overall survival
- To assess quality of life during treatment

3. TRIAL DESIGN

This study is not randomised. This is a limited phase II study to determine the pathological response rate and tolerability of this regimen.
Patients will receive cabazitaxel 15mg/m2 with cisplatin 70mg/m2 day 1. Cycles last 21 days and a total of 4 cycles will be given to each patient, with standard workup for radical cystectomy including formal re-staging with CT imaging and cystoscopyafter 3 cycles of chemotherapy.
Patients who have no contraindications to contrast enhanced MRI will be offered entry intothe associated dynamic contrast enhanced MRI study and will undergo DCE MRI scanning prior to cycle 1 and after cycles1 and 3.
All patients will be asked to provide blood samples for circulating tumour cell (CTC) measurement prior to each cycle of chemotherapy and prior to surgery. Participation in this CTC substudy is not mandatory.

4. PATIENT SELECTION AND ELIGIBILITY

4.1 Source of patients

Patients undergoing radical treatment for bladdercancer must be managed under the auspices of a multidisciplinary team (MDT)whose core members must include a consultant oncologist, consultant urological surgeon, consultant radiologist and consultant histopathologist.
Patients will be eligible if they have histopathologicallyconfirmed muscle invasive primary transitional cell carcinoma of the urinarybladder,are fit to receive neoadjuvant combination cabazitaxeland cisplatinchemotherapy, and are fit to undergo radical cystectomy.

4.2 Number of patients

Based on previous studies in this disease, an overall response rate ofless than 35% (partial or complete remission at cystectomy) would not be sufficient to warrant further investigation of this approach. An overall response rate of 60% or higher would warrant further investigation. Using a one-sided confidence interval of 95% and 80% power, a total of 26 patients are required. It is anticipated that up to 30 patients will be required to allow for lost data and patient withdrawals.

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4.3 Inclusion Criteria

• Age ≥18 years
• Histologically confirmed primary TCC of the urinarybladder
• T2 to T4 disease, N0 M0 determined by CT imaging and biopsy or transurethral resection
• ECOG Performance status 0 or 1
• GFR≥60 mls/min. GFR to be assessed according to local practice. Recommended technique of eGFR
using the CKD-EPI formula(Appendix2).

• If the baseline eGFR is 50 -<60 mls/min patient should undergo formal testing with measurement of 51Cr-EDTA clearance.

• If the EDTA result is ≥ 60 mls/min the patient is eligible
• If the EDTA result is ≥ 55 mls/min -<60 mls/min discuss with CI
• If the EDTA result is < 55mls/min patient is excluded from the study.

• Written, informed consent

4.4 Exclusion Criteria

• ECOG Performance Status ≥ 2
• Lymph node involvement or metastatic disease
• Prior surgery (except transurethral resection of bladder tumour), radiation, chemotherapy, or other anti-cancer therapy within 4 weeks prior to enrolment
• Active Grade ≥2 peripheral neuropathy
• Active secondary cancers
• History of severe hypersensitivity reaction (≥Grade 3) to polysorbate 80 containing drugs
• Other concurrent serious illness or medical conditions
• Inadequate organ function as evidenced by the following peripheral blood countsand serum biochemistry at enrolment:
• Neutrophils ≤1.5 x 109/L
• Haemoglobin ≤10 g/dL
• Platelets ≤100 x 109/L
• Total bilirubin > 1.5 X upper limit of normal (ULN)
• Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)≥1.5 x ULN
• Alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT)≥1.5 x ULN
• Electrocardiogram (ECG) evidence of uncontrolledcardiac arrhythmias, angina pectoris, and/or hypertension, history of congestive heart failure, or myocardial infarction within last 6 months.
• Uncontrolled diabetes mellitus.
• Active uncontrolled gastro-oesophageal reflux disease (GORD).
• Active infection requiring systemic antibiotic or anti-fungal medication
• Participation in another clinical trial with any investigational drug within 30 days prior to study enrolment
• Concurrent or planned treatment with strong inhibitors of cytochrome P450 3A4/5. A 1-week washout
period is necessary for patients who are already on these treatments.
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• Contraindications to cisplatin.
• Patient with reproductive potential not implementing an accepted and effective method of contraception.
• Concurrent yellow fever vaccine

5. ENDPOINTS

5.1 Primary

The primary endpoint is the overall response rate (complete remission rate + partial remission rate).

5.2 Secondary

- Progression free survival
- Overall survival
- Acute toxicity (defined by CTCAE v4.03) after each cycle
- Quality of life during treatment using questionnaire EORTC QLQ C-30 and sup-porting module BLM-30
- Quality adjusted life years assessed by EQ-5D

6. STATISTICAL CONSIDERATIONS

To determine the activity of cabazitaxel and cisplatin in invasive bladder cancer (transitional cell carcinoma) patients, the principal endpoint for the study will be **the overall response rate** (complete remission + partial remission) determined by patho-logic staging at radical cystectomy.

Sample size calculations

- It is assumed that a response rate of less than 35% is not sufficiently large enough to warrant further investigation in an expanded phase II or phase III setting, but that a rate of 60% or higher would warrant further investigation.

- Using an exact test for a single proportion, p_0 =0.35 and p_1 =0.60, setting α =0.05 (onesided) and power = 80%, 26 patients are required.

- In order to recruit 26 patients evaluable for the primary endpoint, recruitment will be extended to replace patients deemed not evaluable. It is anticipated that a total of approximately 30 patients will need to be recruited

7. Methods of Analysis

7.1 Primary endpoint

Response will be evaluated according to pathologic T staging at radical cystectomy using the AJCC TNM system (39). The objective response rate for this study is de-fined as the proportion of patients having achieved partial or complete remission according to their pathologic stage at cystectomy compared with pathologic T stage at diagnosis. For the purposes of the trial, pathology must be viewed by a multidis-ciplinary team (MDT) specialising in the management of urological malignancies. Analysis will include tabulation of baseline characteristics of recruited patients. Intention to treat analysis will be used. Baseline characteristics for those patients not completing trial treatment will be tabulated for comparison with treated patients, to ensure generalisability of results. Baseline characteristics will include (but are not limited to) demographic data, tumour stage and grade.

Secondary endpoints

Progression-free survival

- Progression free survival will be calculated from the date of study entry until a progression occurs. Progression events are defined as clinical, pathologic or radiologically documented

disease progression, or death from any cause, Patients free from a progression event will be censored on the date of last follow up.

- A progression-free survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. Median PFS rate will be reported with 95% CIs.
- Duration of response as measured by Kaplan-Meier at each follow-up, or until progression, will be reported.

Overall survival

- An overall survival curve will be generated using the methods of Kaplan and Meier. All patients registered in the study will be included. The median overall survival will be reported with 95% CI.

Toxicity

- The proportion of patients experiencing grade 3 or 4 toxicity as measured by NCI-CTCAE v4.03 at trial visits or until progression and the number of SAEs will be reported.

Quality of Life

- Quality of Life is assessed using questionnaires EORTC QLQ C-30 (with sup-porting module BLM-30) and EQ-5D at each trial visit. Quality of life data will be reported for each time point and in terms of quality-adjusted life years (QALYs) using EQ-5D.
- A repeated measure analysis of variance will be used to assess quality of life changes during the course of the study.

Missing Data

- In the event that data for an individual patient has not been collected, after the response, assessment has taken place but in the absence of an event, a percentage of missing data will be calculated and will establish if the missing data imputation is a suitable method to use.

Scoring the EORTC QLQ-C30 version 3.0

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.
All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a high score for a functional scale represents a high / healthy level of functioning,
a high score for the global health status / QoL represents a high QoL,
but a high score for a symptom scale / item represents a high level of symptomatology / problems.
The principle for scoring these scales is the same in all cases:
1. Estimate the average of the items that contribute to the scale; this is the raw score.
2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.
Coding of the scoring procedure for SPSS will be used here. Technical Summary
In practical terms, if items *I1, I2, ... In* are included in a scale, the procedure is as follows:
Raw score
Calculate the raw score
RawScore = RS =(I1+I2+……In) / n
Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

$$\text{Functional scales: } S = 1 - \frac{(RS - 1)}{range} \times 100$$

Symptom scales / items: $S = \{(RS - 1) / range\} * 100$

Global health status / QoL: $S = \{(RS - 1) / range\} * 100$

Symptom scales / items: S = {(RS −1) range}×100
Global health status / QoL: S = {(RS −1) range}×100
Range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have $range = 1$.