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Correlation of radiographic changes with clinical outcomes in a phase II trial of cabozantinib (XL184) in patients with urothelial carcinoma

A. Study Purpose and Rationale

The increasingly poor clinical outcome of patients with advanced bladder cancer has necessitated investigation in the development of effective screening and therapeutic interventions. Cisplatin-based chemotherapy has been the mainstay of front-line treatment for metastatic urothelial carcinoma; unfortunately the complete response rate is only approximately 30% and the median survival is approximately 15 months. Once patients have failed primary chemotherapy, the median survival is 6-9 months, with no agent demonstrating a survival benefit in this clinical state. Thus, new therapeutic approaches need to be developed for patients who fail primary chemotherapy. For those who are unresponsive to platinum based chemotherapy and who require salvage chemotherapy, agents that have been used include gemcitibine (response rate (RR)=29%) [1], ifosfamide (RR=20%) [2], and gallium nitrate (RR= 18%) [3]. In addition to single agents, trials involving treatment with combinations of two chemotherapies, such as taxanes combined with gemcitabine, do show some promise. Despite these developments in chemotherapy, the toxicities associated with these treatments limit their therapeutic effects, as the optimal dose usually exceeds the maximum tolerable dose.

A new development in targeted cancer therapy focuses on c-met, a tyrosine kinase receptor on which hepatocyte growth factor (HGF) binds, triggering a signaling cascade that promotes angiogenesis and tumor growth when bound. There was found to have higher levels of c-met expression in invasive bladder tumors compared with those at lower stages and grades. In a study conducted by Sanchez-Carbayo et al., c-met expression was inversely correlated with overall survival (P= 0.0444) [4]. A confirmatory study showed that the activation of the c-met signaling pathway is positively related to the severity of the bladder tumor stage, and that its expression is a significant predictor of metastasis and survival of those with this disease [5]. These findings may indicate that c-met is a rational target to pursue in the treatment of metastatic bladder cancer.

In phase II trials, existing data suggests that XL184 (cabozantinib), a tyrosine kinase inhibitor acting on the c-met pathway and on vascular endothelial growth factor receptor (VEGFR2), has shown clinical improvement in those with castration resistant prostate cancer, but its role in the treatment of bladder cancer has not yet been elucidated. Of particular interest has been the near complete resolution of bone scans seen in patients treated with castration resistant prostate cancer, with 19 of 20 subjects (95%) in a phase II study showing resolution [6]. Notably, 30% of patients with metastatic bladder cancer present with disease in bone and thus this would make bladder cancer a rational target to pursue with this therapeutic approach. Given this drug's good safety profile and its potential not only to decrease tumor volume but also to decrease bone metastasis, XL184 may be equally effective in the treatment of bladder carcinoma.

Hypothesis

Using data from former clinical trials of new chemotherapy agents administered to patients pre-treated with cisplatin therapy, it is hypothesized that XL184 will have a response rate (RR) of 60%, as compared to the single agent with the highest RR, gemcitabine (29%). Bone scans and CT scans will be utilized to help determine clinical response. Also, tissue from bone lesions will be obtained prior to treatment as well as during treatment to evaluate c-met expression.

B. Study Design and Statistical Analysis
This is an open-label, prospective, non-randomized, single arm phase II trial investigating the efficacy of XL184 in the treatment of patients with metastatic bladder cancer who have failed primary chemotherapy.

Endpoints
The primary endpoint of this study is response rate (RR), including both complete response (CR) and partial response (PR), which will be evaluated using the RECIST (v. 1.1) criteria:

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial Response (PR):** At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD.
- **Progression (PD):** At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum LD since the treatment started.

Secondary endpoints include resolution of bone metastasis, measured with imaging techniques outlined in section C.

Power and Statistical Analysis
The Chi square proportion test will be used to determine the sample size necessary for the trial to be powered at 80% with a 5% significance level. The number needed in the treatment arm is n=23. Clinical parameters of response (standard imaging and radiographic parameters) will be compared to changes in DWI, DCE-MRI, and FDG-PET. Correlations in these changes will be made with changes in immunohistochemical staining of tissue with MET antibodies pre and post XL184 treatment.

C. Study Procedure
Once patients are enrolled in this study, they will be evaluated with a baseline bone scan, CT scan of the abdomen and pelvis, chest X-ray, diffusion weighted image (DWI), dynamic contrast enhanced (DCE)-MRI, and ^{18}Flurodeoxyglucose positron emission spectroscopy (FDG-PET) scan. Tissue from the bone lesions will be obtained at baseline by CT-guided biopsy, and immunohistochemistry will be performed on both fresh frozen and paraffin embedded tissues. For specific epitopes on paraffin sections we will utilize antigen retrieval methods (0.01% citric acid for 15 minutes under microwave treatment) prior to incubation with primary antibodies or antiserum overnight at 4°C. Primary antibodies that will be used include mouse monoclonal antibody against c-met.

Subjects will then be treated with XL184 at a daily dose of 100 mg PO QD. Each patient will return on day 8 and 28, 6 weeks, and then every 6 weeks for re-evaluation with a bone scan, CT scan, chest X-ray, DWI, DCE-MRI, and FDG-PET. Biopsies will again be obtained 28 days after treatment. Treatment will be continued until progression of disease or unacceptable toxicity develops. The development of adverse effects will be monitored and evaluated using

the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.0), with termination of treatment if the patient develops Grade $\geq$ 2.

D. Study Drugs

XL184 (Cabozantinib)- While still an investigational drug undergoing extensive Phase II testing, its safety and efficacy have been demonstrated in Phase I trials and numerous Phase II trials, with the standard dosing determined to be 100 mg PO qd. XL184 has undergone several successful trials in the treatment of other primary tumors, thereby validating its antitumor effects. In a Phase I trial of patients with medullary thyroid carcinoma, 68% of patients had stable disease of at least 6 months or confirmed partial response [7]. It has an acceptable safety profile, but dose limiting toxicities in this study were grade 3 palmar plantar erythrodysesthesia (PPE), mucositis, and AST, ALT, and lipase elevations and grade 2 mucositis that resulted in an interruption or reduction of dosage.

E. Medical Device

N/A

F. Study Questionnaires

N/A

G. Study Subjects

Subjects must meet all inclusion and exclusion criteria below.

Inclusion Criteria

1. Subjects must understand and voluntarily sign an informed consent document.
2. Subjects must be able to adhere to the study visit schedule and other protocol requirements.
3. Patients must be $\geq$ 18 years of age.
4. Patients must have a CUMC histological confirmed diagnosis of metastatic (M1 according to NCCN guidelines) urothelial carcinoma of the bladder, and have failed primary cisplatin based chemotherapy. This includes treatment with GC (gemcitabine and cisplatin) and MVAC (methotrexate, vinblastine, adriamycin, and cisplatin).
5. Patients will be permitted to have been treated with up to 3 prior chemotherapeutic regimens.
6. Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 1
7. Laboratory values as indicated below:

Serum Creatinine	$\leq$2.0 mg/dL
Absolute Neutrophil Count	$\geq$1,500/mm^3 (or 1.5 X10^9/L)
Platelet Count	$\geq$100,000/mm^3 (or 100 x 10^9/L)
Aspartate Aminotransferase (AST/SGOT)	$\leq$ 1.5 x upper limit of normal (ULN)
Alkaline Phosphatase	< 2.5 x ULN (In the absence of liver metastasis, elevated alk phos due to bone mets is permitted)
Conjugated Bilirubin	< ULN

Exclusion Criteria

1. Chemotherapy or radiotherapy within 4 weeks prior to entering the study
2. Investigational drug use within 30 days of the first dose of XL184
3. Any serious medical condition or psychiatric illness that places the subject at an unacceptable risk for study participation or would prevent the subject from signing the informed consent.

H. Recruitment of Subjects

Patients will be recruited from the oncology clinic at CUMC. Their medical oncologist will inform them if they qualify for the study, and if interest is expressed, the patients will be contacted by research staff, who will answer any study related questions and obtain consent.

I. Confidentiality of Study Data

Any information obtained for the purposes of this study will be kept confidential in compliance with the standards set by HIPAA. Research staff at CUMC will have access to medical records related to the study. Any identifying material related to the study will be kept confidential and will not be disclosed when the results are published.

J. Potential Conflict of Interest

N/A

K. Location of the Study

This study will be conducted at the Columbia University Comprehensive Cancer Center, Herbert Irving Pavilion, 161 Fort Washington Ave., New York, NY 10032

L. Potential Risks

- Recurrence or progression of cancer during or after therapy, as the risk of taking the study treatment may not be as effective as other available experimental treatment or may produce a worse outcome compared to palliative care.

M. Potential Benefits

- Remission of cancer as a result of therapy
- You may or may not benefit as a result of your participation in this study, but your participation will help further elucidate effective treatment for future patients with metastatic bladder cancer.

N. Alternative Therapies

As there is no current standard of treatment for patients who fail primary cisplatin based chemotherapy, there are numerous non-platinum chemotherapy agents that have demonstrated some positive effects, but are limited by their toxicities. In addition to gemcitibine, ifosfamide, and gallium nitrate as potential options, other platinum free agents that are still in clinical trials include combined paclitaxel and gemcitabine doublet therapy, which in one phase II trial had a CR of 42%, but had a high level of associated pulmonary toxicity (including 1 death) [8]. Other potential doublet therapies include docetaxel and gemcitabine, which showed a RR of 30-50% in phase II trials [9-11]. Although more trials need to be conducted, platinum free doublet therapies seem to be efficacious alternatives in the treatment of patients that fail cisplatin therapy.

O. Compensation to Subjects

You will receive no compensation for your participation.

P. Costs to Subjects
There are no costs to the patients for participating in this study.

Q. Minors as Research Subjects
N/A

R. Radiation or Radioactive Substances
N/A

References

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