Oral Oncology 71 (2017) 99–104

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

A phase I study of cabazitaxel in combination with platinum and 5-fluorouracil (PF) in locally advanced squamous cell carcinoma of head and neck (LA-SCCHN)

Nadia Camille [a], John Rozehnal [f], Elizabeth Roy [b], Dariusz Uczkowski [c], Ashely Olson [b], Eric Genden [d], Marita Teng [d], Richard Bakst [e], Vishal Gupta [e], Marshall Posner [a], Krzysztof Misiukiewicz [a,*]

[a] Tisch Cancer Institute, Mount Sinai School of Medicine, NYC, NY 10029, United States
[b] Department of Pathology, Mount Sinai School of Medicine, NYC, NY 10029, United States
[c] University of Lodz, Lodz, Poland
[d] Department of Otolaryngology, Mount Sinai School of Medicine, NYC, NY 10029, United States
[e] Department of Radiation Oncology, Mount Sinai School of Medicine, NYC, NY 10029, United States
[f] Mount Sinai School of Medicine, NYC, NY 10029, United States

ARTICLE INFO

Article history:
Received 12 January 2017
Received in revised form 9 May 2017
Accepted 16 May 2017

Keywords:
Cabazitaxel
Induction chemotherapy
Neoadjuvant therapy
Head and neck cancer
Squamous call carcinoma of head and neck
TPF

ABSTRACT

Background: There is a clinical need to improve outcomes for patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN), especially in Human Papilloma Virus (HPV) negative and HPV positive subtypes with a significant history of tobacco use. In animal models bearing SCCHN, Cabazitaxel showed an excellent response rate compared to docetaxel and might prove useful in treatment of patients. The primary objective of this study was to determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of cabazitaxel when combined with cisplatin and 5-fluorouracil (PF) in induction chemotherapy (IC) for patients with SCCHN. Cabazitaxel-PF IC administered in 3 cycles (each 21 days) followed by concurrent chemoradiation (CRT) or surgery has been evaluated to assess overall response rate (ORR) and progression-free survival (PFS) in this population.

Methods: This phase I study employed a standard 3 + 3 design. DLT was defined as grade 4 or 5 toxicity or grade 3 toxicity lasting >7 days. Out of 40 consented patients with stage IV, curable, previously untreated, LA-SCHHN and poor prognosis, 35 (32M, 3F) were enrolled and evaluated for toxicity: 19 oropharynx, 10 larynx, 2 oral cancer, 1 nasopharynx and 3 hypopharynx. Five dose levels of cabazitaxel (10, 12.5, 15, 17.5 and 20 mg/m^2) were tested in combination with cisplatin 100 mg/m^2 and 5-fluorouracil (5-FU) 800 mg/m^2/d $\times$ 4 days. Dose escalation for cabazitaxel was terminated upon the occurrences of 2 DLTs and the establishment of MTD. Cabazitaxel was then further escalated with cisplatin 75 mg/m^2 and 5-FU 800 mg/m^2/d $\times$ 4 days in the subsequent 3 dose levels (17.5, 20 and 22.5 mg/m^2). In the expansion cohort, 9 patients were enrolled at the 22.5 mg/m^2 dose level. Following 3 cycles of IC, patients were evaluated for clinical, radiographic, and pathologic response to cabazitaxel-PF before beginning CRT or surgery.

Results: There were two DLTs (grade 4 hyperuricemia; neutropenic fever, sepsis, and grade 4 thrombocytopenia) among 2 patients in cohort 5 at the dose of 20 mg/m^2 of cabazitaxel. There were no DLTs reported with cohorts using a lower dose of cisplatin, even in the expansion cohort. The study was stopped at the dose of 22.5 mg/m^2 in accordance with the initial study design. With 33 evaluable patients for response, the Overall Response Rate (ORR) rate was 57.6%: 9.1% Complete Responses (CR) and 48.5% Partial Responses (PR) were noted.

Conclusions: The recommended phase II dose for cabazitaxel in combination with cisplatin 75 mg/m^2 and 5-FU 800 mg/m^2/d $\times$ 4 days is 22.5 mg/m^2 and for cisplatin 100 mg/m^2 and 5-FU 800 mg/m^2/d $\times$ 4 days is 17.5 mg/m^2. With a median follow-up of 39 months, PFS for the entire non-metastatic population at 3 years was approximately 58%.

* Corresponding author at: One Gustave L Levy Place, Box 1128, NYC, NY 10029, United States.
E-mail address: Krzysztof.misiukiewicz@mssm.edu (K. Misiukiewicz).

http://dx.doi.org/10.1016/j.oraloncology.2017.05.008
1368-8375/

Introduction

Squamous Cell Carcinoma of Head and Neck (SCCHN) accounts for 3% of malignancies in the United States. It is estimated that approximately 60,000 Americans develop SCCHN annually and that 12,000 die from the disease [1]. Patients with early stage or locoregionally advanced SCCHN are treated with surgery, radiotherapy alone and/or concurrent chemoradiotherapy (CRT). Unfortunately, the prognosis of patients with HPV negative and HPV positive with >10 pack-years SCCHN is poor [2,3]. After standard therapy with docetaxel-based induction chemotherapy followed by CRT, the 3-year overall survival (OS) and progression free survival (PFS) for Human Papilloma Virus (HPV) negative vs. HPV positive patients as seen in TAX 324 was 41% and 33% vs. 87% and 81%, respectively [3].

Four major approaches have been investigated for treatment of locally advanced SCCHN: (i) concomitant chemotherapy and radiotherapy (CRT); (ii) induction chemotherapy (IC) before surgery and/or radiotherapy (RT); (iii) sequential CRT consisting of IC and CRT; or (iv) surgery followed by radiotherapy with or without chemotherapy in operable patients. The role of IC followed by CRT versus CRT alone, as assessed in DeCIDE and Paradigm trials, remains controversial due to underpowered studies and conflicting results [4,5]. Ghi et al. presented results of a randomized trial comparing CRT to sequential therapy at the 2014 American Society of Clinical Oncology (ASCO) meeting suggesting favorable outcomes of induction chemotherapy [6]. In their phase II/III trial, patients treated with IC followed by CRT had significantly improved overall survival (OS) compared with CRT alone at a median follow-up of 41 months. Full publication of this adequately powered cooperative group trial is eagerly awaited as the most definitive study providing insight into the outcomes after treatment with IC.

A recent study by Ang et al. demonstrated that tumor HPV status and tobacco smoking (>10 pack-years) were the two strongest independent determinants of survival for patients with oropharyngeal cancer treated by CRT [2]. Subsequent retrospective analysis of two major RTOG clinical trials, RTOG 9003 and RTOG 0129, confirmed those results [7]. Alcohol consumption was associated with an increased risk of SCCHN but only when alcohol was consumed at high frequency, additionally it is difficult to separate the effects of smoking and alcohol [8]. There is a need and an opportunity to find therapies that improve survival in the high risk populations defined in this study as HPV negative and HPV positive with >10 pack-years smoking history.

Cabazitaxel is a semisynthetic taxane (T) that was selected for development on the basis of its poor affinity for P-glycoprotein compared with docetaxel and paclitaxel [9]. In head-to-head comparison of cabazitaxel and docetaxel in mice bearing docetaxel-sensitive advanced human head and neck tumors, CR was achieved in 6 of 6 animals in the cabazitaxel arm and 1 of 6 in the docetaxel arm. Cabazitaxel showed significant activity, not only in tumor models poorly or not sensitive to docetaxel, but also in models with acquired resistance to docetaxel and models innately resistant to docetaxel [10]. In two separate phase II studies for metastatic breast cancer, cabazitaxel given alone or in combination with capecitabine showed responses in tumors resistant to docetaxel [11,12]. Due to the above pharmacologic properties of cabazitaxel and preclinical and clinical data, we hypothesized that cabazitaxel might improve the efficacy of docetaxel given in combination with platinum and fluorouracil (TPF) IC by replacing docetaxel in the treatment of HPV negative and HPV positive with >10 pack-years smoking history patients, a sub-population where improvements in treatment efficacy are desperately needed.

Patients and methods

Study design

The primary objectives of the study were to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and recommended phase II dose of cabazitaxel given in combination with platinum and 5-fluorouracil (Ca-PF) as induction therapy for patients with stage IV, previously untreated and curable LA-high risk SCCHN. Secondary objectives of the study were to evaluate toxicity, Progression-Free Survival (PFS) and the Overall Response Rate (ORR). After signing IRB-approved consent forms, subjects were assessed for eligibility, registered and assigned to the appropriate treatment dose level in the escalation cohort. An additional 9 patients were enrolled into a planned expansion cohort with an identical treatment regimen in order to improve the accuracy of our assessment of the probability of toxicity and response. Ca-PF IC was given every 21 days starting on days 1, 22 and 43 (±2 days). After the completion of three cycles of Ca-PF, all study subjects were assessed for clinical, radiologic and pathologic evidence of response before beginning 6–7 weeks of standard CRT. Patients with progressive disease after induction chemotherapy were treated with salvage surgery. After the completion of CRT or salvage surgery, patients were followed for survival and relapse (assessed by a physical exam, endoscopy and standard radiologic scans) at 3 months, 12 months and 24 months after the last dose of CRT or surgery.

Patient eligibility

Eligible patients with histologically confirmed stage IV SCC of the oral cavity, oropharynx, nasopharynx, larynx, hypopharynx and unknown primary were enrolled into the escalation cohort regardless of HPV status. HPV positive patients with SCC of the oropharynx or unknown primary were allowed in the expansion cohort if they were current smokers, where current smoking was defined as either active smoking within the past 20 years with a cumulative pack-year history of >20 pack-years, or active smoking (>1 cigarette per day) within the last 5 years. HPV status was determined before enrollment by p16 immunohistochemistry (IHC) with confirmatory HPV testing by PCR. Patients with metastatic SCCHN (except for symptomatic, unstable brain metastases) were allowed in the escalation cohort, but not in the expansion cohort. Patients had measurable disease of the primary tumor, lymph nodes or both by clinical and radiographic methods per Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. No prior therapy or any other investigational agents were allowed. ECOG performance status of 0 or 1 and normal hepatic, renal and bone marrow function were required. Exclusion criteria included grade 2 or greater peripheral neuropathy by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 3.0, other serious comorbid illness, and involuntary weight loss of more than 20% of body weight in the 3 months preceding study entry.

Dose escalation and stopping rules

This phase I study employed a standard 3 + 3 design and DLT, defined as grade 4 or 5 toxicity or grade 3 toxicity lasting >7 days, was the basis for determining the MTD. Five dose levels of cabazitaxel were tested in combination with cisplatin 100 mg/m^2 and 5-FU 800 mg/m^2/d × 4 days (Table 3). Treatment cohorts were dosed in escalating order until MTD was established. Dose escalation for the subsequent cohort was permitted only after all patients in the