Oral Oncology 58 (2016) 41–48

Contents lists available at ScienceDirect

Oral Oncology

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

Phase I trial of palbociclib, a selective cyclin dependent kinase 4/6 inhibitor, in combination with cetuximab in patients with recurrent/metastatic head and neck squamous cell carcinoma ☆

Loren Michel [a,b], Jessica Ley [a], Tanya M. Wildes [a,b], András Schaffer [c], Anthony Robinson [d], Se-Eun Chun [e], Wooin Lee [e], James Lewis Jr. [f], Kathryn Trinkaus [b,g], Douglas Adkins [a,b,*]

[a] Division of Medical Oncology, Washington University School of Medicine, St. Louis, MO, United States
[b] Alvin J. Siteman Cancer Center, Washington University School of Medicine, United States
[c] Department of Pathology and Immunology, Washington University School of Medicine, United States
[d] Department of Medicine, Washington University School of Medicine, United States
[e] Department of Pharmaceutical Sciences, Seoul National University College of Pharmacy, Seoul, Republic of Korea
[f] Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, United States
[g] Division of Biostatistics, Washington University School of Medicine, United States

ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form 11 May 2016
Accepted 13 May 2016
Available online 28 May 2016

Keywords:
Phase I
Palbociclib
Cetuximab
Head and neck cancer
Squamous cell carcinoma

SUMMARY

Objectives: To test the safety of the CDK4/6 inhibitor palbociclib with cetuximab in patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC).
Materials and Methods: A phase I trial using 3+3 design was performed to determine the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of palbociclib with standard dose weekly cetuximab. Palbociclib was administered orally days 1–21 every 28 days: dose level 1 (100 mg/d) and 2 (125 mg/d; approved monotherapy dose). Pharmacokinetic assessments were performed on cycle 2, day 15. Cyclin D1, $p16^{INK4a}$, and Rb protein expression were measured on pre-treatment tumor. Tumor response was assessed using RECIST1.1.
Results: Nine patients (five $p16^{INK4a}$ negative; four positive) were enrolled across dose levels 1 ($n = 3$) and 2 ($n = 6$) and none experienced a DLT. A MTD of palbociclib was not reached. Myelosuppression was the most common adverse event. Six of nine patients had cetuximab-resistant and 4/9 had platin-resistant disease. Disease control (DC) occurred in 89%, including partial response (PR) in two (22%) and stable disease in six (67%) patients. PRs occurred in $p16^{INK4a}$ negative HNSCC. Five patients (56%) had measurable decreases in tumor target lesions. In cetuximab-resistant HNSCC, best tumor response was PR in 1 and DC in 5 and median TTP was 112 days (range: 28–168). In platin-resistant HNSCC, best tumor response: PR in 1, DC in 3 and median TTP was 112 days (range: 28–112). The C_{max} and $AUC_{0\text{-}24h}$ appeared comparable in patients receiving 125 vs 100 mg dose of palbociclib.
Conclusion: This trial, the first to evaluate a CDK4/6 inhibitor in HNSCC, determined that palbociclib 125 mg/day on days 1–21 every 28 days with cetuximab was safe. Tumor responses were observed, even in cetuximab- or platin-resistant disease.

Introduction

Activation of the epidermal growth factor receptor (EGFR) is the most common event in head and neck squamous cell carcinoma (HNSCC), resulting in cellular proliferation, angiogenesis, and radiation resistance [1]. The importance of EGFR signaling was demonstrated by trials that showed improvement in overall survival (OS) when the EGFR inhibitor cetuximab was added to radiation or chemotherapy [2,3]. However, the clinical benefit of cetuximab monotherapy is surprisingly modest, with a time to progression (TTP) of 70 days in platin-resistant recurrent/metastatic (RM) disease [4].

HNSCC is a heterogeneous disease [5,6]. Based on unique gene expression signatures, at least four subgroups have been defined;

☆ Presented in abstract form at the 2015 Annual Meeting of the American Society of Clinical Oncology.

* Corresponding author at: Washington University School of Medicine, Division of Medical Oncology, 660 South Euclid, Campus Box 8056, St. Louis, MO 63110, United States. Tel.: +1 314 747 8475; fax: +1 314 747 1411.
E-mail address: dadkins@dom.wustl.edu (D. Adkins).

http://dx.doi.org/10.1016/j.oraloncology.2016.05.011
1368-8375/

each with distinct signaling pathways [5–12]. Despite this heterogeneity, aberrant cell cycle regulation is a ubiquitous event. The mechanism underlying unrestrained proliferation varies depending on the tumor's transcriptionally-active human papillomavirus (HPV) status. In HPV-related HNSCC, E7 viral protein drives unrestrained proliferation by promoting Rb degradation [13]. In HPV-unrelated HNSCC, Rb inactivation occurs through hyperactivation of the Rb inhibitory complex CDK4/cyclin D. CCND1 (encoding cyclin D1, the regulatory subunit of the complex) is amplified and/or the CDK4/6 inhibitor $p16^{INK4a}$ is inactivated in nearly all of these cancers [14–16]. Alterations of CCND1 and $p16^{INK4a}$ are rare in HPV-related HNSCC. As a result, $p16^{INK4a}$ is overexpressed in HPV-related HNSCC and underexpressed in HPV-unrelated HNSCC.

The genetics of HPV-unrelated HNSCC influences the clinical course. CCND1 amplification and $p16^{INK4a}$ inactivation are poor prognostic factors in HNSCC [15,17], in part because cyclin D1 overexpression adversely affects tumor response to EGFR inhibitors and cisplatin. In HNSCC cell lines, cyclin D1 amplification and/or overexpression correlated with resistance to these drugs [18–20]. Studies in HNSCC reveal that cyclin D1 overexpression is predictive of resistance to cisplatin [21].

The essential roles of CDK4/6 and cyclin D1 in driving cell cycle progression from G1 into S phase motivated intense investigation into blocking this regulatory complex [22–24]. In pre-clinical models, CDK4/6 inhibition inhibits both Rb hyperphosphorylation and cell cycle progression [25], and the efficacy of inhibition in some models correlated with increased cyclin D1 and decreased $p16^{INK4a}$ expression [24]. Palbociclib is the first approved selective inhibitor of the CDK4/6 kinases. Palbociclib exerts potent anti-proliferative effects on Rb-positive cell lines and human breast and colon xenografts [23]. Palbociclib results in decreased Rb phosphorylation and Ki-67 expression in Rb-positive models but has no activity in Rb-negative tumor xenografts [23]. As such, phase I trials restricted the evaluation of palbociclib to patients with Rb-positive cancers [24,25]. These studies determined that the dose-limiting toxicity (DLT) of palbociclib was neutropenia and the maximum tolerated dose (MTD) was 125 mg once daily, administered for 21 days of each 28 day cycle [26,27]. The efficacy of palbociclib was demonstrated in estrogen receptor positive breast cancer [28] and in mantle cell lymphoma [29], tumors in which cyclin D contributes to their pathogenesis.

Because the genetics of HNSCC suggest a crucial role for CDK4/-cyclin D in this disease, we performed a phase I trial to determine the DLT and MTD of palbociclib combined with standard weekly doses of cetuximab in patients with RM HNSCC. We built upon the cetuximab platform because palbociclib targets a pathway associated with resistance to EGFR inhibitors [18]. We report the results of the trial along with pharmacokinetic (PK) and biomarker studies and efficacy assessments of this novel combination of targeted agents.

Materials and methods

Patient inclusion and exclusion criteria

Eligibility required RM HNSCC, defined as distant metastases or unresectable, previously irradiated local/regional recurrence. Prior cetuximab or platin for RM disease was allowed. Prior cytotoxic chemotherapy for RM disease was not required because some patients are poor candidates for or decline such therapy. Patients were $\geqslant$18 years, had Eastern Cooperative Oncology Group performance status of $\leqslant$2, adequate marrow/organ function (absolute neutrophil count $\geqslant$1500/mm^3, platelet count $\geqslant$100,000/mm^3, creatinine and bilirubin <1.5$\times$ upper limits of normal [ULN], and aspartate transaminase, alanine transaminase, and alkaline phosphatase <2.5$\times$ ULN), and QTc < 480 ms. Patient selection based on $p16^{INK4a}$, cyclinD1, or Rb status was not performed because this was a phase I trial. Exclusion criteria included inability to swallow and concurrent use of CYP3A4 inhibitors/inducers.

The protocol was approved by the Institutional Review Board. All patients provided signed consent to participate (NCI-2014-01079).

Study design

Palbociclib was administered orally with food on days 1–21 of each 28 day cycle. Palbociclib doses were level 1 (100 mg/d), level 2 (125 mg/d; the approved monotherapy dose), and level −1 (75 mg/d, if de-escalation needed). Intra-patient dose escalation was not permitted. Cetuximab 400 mg/m^2 was given intravenously on cycle 1 day 1, then 250 mg/m^2 weekly.

A 3+3 design was employed. Three patients were enrolled per dose level, expanded to 6 if 1 of 3 developed a DLT. If 0 of 3 patients within a dose level developed a DLT, the dose was escalated; if $\geqslant$2 of 6 within a dose level developed a DLT, the dose below was considered the MTD. DLT and MTD were assessed during cycle one. If a MTD was not established at the maximum dose level, the latter was the recommended phase II dose of palbociclib. Six patients were enrolled at the recommended phase II palbociclib dose.

Hematologic DLT was defined as: grade 4 neutropenia, grade 4 infection with grade 3/4 neutropenia or grade 4 thrombocytopenia with bleeding. Non-hematologic DLT was defined as palbociclib-related grade 3/4 toxicity except: sub-optimally treated nausea/vomiting/diarrhea or grade 3 metabolic abnormalities.

Criteria to initiate subsequent cycles included an absolute neutrophil count (ANC) $\geqslant$ 1000/mcL, platelets $\geqslant$ 50,000/mcL, and non-hematologic toxicities $\leqslant$ grade 1. If not met, palbociclib was delayed one week; however, cetuximab was continued. After a 2 week delay, palbociclib was discontinued.

Dose modifications

Adverse events (AE) were monitored weekly during cycle 1, and then monthly. AEs were graded using NCI-CTCAE version 4.0.

Palbociclib dose was adjusted for selected AEs. A dose decrease by 25 mg/d was recommended for: grade 4 neutropenia/thrombocytopenia, grade 3 neutropenia with infection/fever, grade $\geqslant$3 non-hematologic toxicity, or treatment delay >1 week due to persisting AE if recovery occurs within 2 weeks. Patients who required more than two dose reductions were treated with cetuximab alone. The lowest dose permitted was 75 mg/d. Doses omitted for AEs were not replaced within the same cycle.

Tumor response assessments

Tumor response assessments were performed every two cycles with neck/chest CT scans using RECIST criteria1.1. Treatment was continued until: disease progression, death, severe AE, or patient withdrawal.

Best overall tumor response was recorded from the start of treatment until disease progression. Disease control was defined as complete response (CR), partial response (PR), stable disease. Efficacy was measured by overall tumor response rate (CR + PR) and time-to-progression (TTP) measured from start of initiation of treatment until progression. OS was defined as the time from start of treatment to death.

Biomarker assessment performed on archived tumor tissue

Archival tumor tissue obtained at diagnosis (n = 4) or recurrence (n = 5) were used to assess $p16^{INK4a}$, cyclin D1, and p-Rb expression in tumor, determined by immunohistochemistry (IHC) [15,30,31]. Anti-cyclin D1 antibody (clone SP4-R) and anti-p16