Gynecologic Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Phase 1b safety study of farletuzumab, carboplatin and pegylated liposomal doxorubicin in patients with platinum-sensitive epithelial ovarian cancer☆,☆☆,★

Kenneth H. Kim [a], Danijela Jelovac [b], Deborah K. Armstrong [b], Benjamin Schwartz [c], Susan C. Weil [d], Charles Schweizer [d], Ronald D. Alvarez [e,*]

[a] University of North Carolina Health Care, Division of Gynecology Oncology, Chapel Hill, NC, United States
[b] Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, United States
[c] Island Gynecologic Oncology, PLLC, Brightwaters, NY, United States
[d] Morphotek, Inc., Exton, PA, United States
[e] University of Alabama at Birmingham, AL, United States

HIGHLIGHTS

- Farletuzumab (FAR), a monoclonal antibody to folate receptor alpha, which is expressed in epithelial ovarian cancer (EOC).
- FAR has shown activity against EOC in platinum-sensitive relapse when combined with carboplatin and a taxane.
- Carboplatin in combination with pegylated liposomal doxorubicin (PLD) is a frequently used alterative regimen.
- This safety study assessed the addition of FAR to carboplatin/PLD, with a view toward future larger studies.
- This combination was generally well tolerated; adverse event profile was similar to that of carboplatin/PLD alone.

ARTICLE INFO

Article history:
Received 8 September 2015
Received in revised form 25 November 2015
Accepted 27 November 2015
Available online xxxx

Keywords:
Ovarian cancer
Platinum-sensitive relapse
Pegylated liposomal doxorubicin
Farletuzumab
Monoclonal antibody therapy

ABSTRACT

Objective. Farletuzumab is a humanized monoclonal antibody that binds to folate receptor alpha, over-expressed in epithelial ovarian cancer (EOC) but largely absent in normal tissue. Previously, carboplatin plus pegylated liposomal doxorubicin showed superior progression-free survival and an improved therapeutic index compared with carboplatin/paclitaxel in relapsed platinum-sensitive EOC. This study assessed safety of farletuzumab/carboplatin/pegylated liposomal doxorubicin in women with platinum-sensitive recurrent EOC.

Methods. This multicenter, single-arm study enrolled patients with platinum-sensitive EOC in first or second relapse for treatment with weekly farletuzumab 2.5 mg/kg plus carboplatin $AUC_{5\text{-}6}$ and pegylated liposomal doxorubicin 30 mg/m^2 every 4 weeks for 6 cycles. Subsequently, maintenance with single-agent farletuzumab 2.5 mg/kg once weekly or farletuzumab 7.5 mg/kg once every three weeks continued until progression. The primary objective was to assess the safety of farletuzumab/carboplatin/pegylated liposomal doxorubicin.

Results. Fifteen patients received a median of 12.0 cycles (range, 3–26) of farletuzumab as combination therapy or maintenance, for a median of 45.0 weeks (range 9–95). Farletuzumab/carboplatin/pegylated liposomal doxorubicin was generally well tolerated, with no farletuzumab-related grades 3–4 adverse events. The most commonly reported adverse events were associated with combination chemotherapy: fatigue (73.3%), nausea (46.7%), and neutropenia (40%). Ten patients had grade ≥3 adverse events, most frequently neutropenia and fatigue. No cardiac toxicity was seen. Best overall responses (RECIST) were a complete response for one patient, partial responses for 10 patients, and stable disease for four patients.

Conclusions. Farletuzumab plus carboplatin/pegylated liposomal doxorubicin in women with platinum-sensitive EOC demonstrated a safety profile consistent with that of carboplatin plus pegylated liposomal doxorubicin.

☆ Financial support: Funding for this study was provided by Morphotek, Inc., Exton, PA.
☆☆ Neither this manuscript nor any similar manuscript, in whole or in part, other than the abstract listed below, is under consideration, in press, published, or reported elsewhere.
★ The results presented in this manuscript were previously presented at the ASCO 2011 Annual Meeting: Jelovac D. et al. Phase 1 safety study of Farletuzumab, Carboplatin and Pegylated Liposomal Doxorubicin (PLD) in subjects with platinum-sensitive epithelial ovarian cancer (EOC). J Clin Oncol 2011;29(suppl):abstr 5056.
* Corresponding author at: University of Alabama at Birmingham, 1700 6th Avenue South, Birmingham, AL 35233, United States.
E-mail address: ralvarez@uabmc.edu (R.D. Alvarez).

http://dx.doi.org/10.1016/j.ygyno.2015.11.031

1. Introduction

Farletuzumab (FAR) is a humanized monoclonal antibody that binds to folate receptor alpha, known to be overexpressed in epithelial ovarian cancer (EOC) but largely absent in normal tissue [1–4]. In preclinical studies, FAR has exhibited immune-effector mediated effects via antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity, and single-agent anti-tumor activity in xenograft models of ovarian cancer, as well as synergistic effects with chemotherapeutic agents [5,6]. The combination of carboplatin and paclitaxel has long been utilized as a preferred treatment regimen for platinum-sensitive EOC. This regimen was used in a Phase 2 study of FAR in patients with EOC who had experienced first relapse, with the combination of carboplatin/paclitaxel/FAR found to be active as well as well tolerated [7]. Recent studies have shown that FAR enhances type 2 cell death in tumor cells and that the combination of combination of these immune-effector cellular signaling pathway most likely result in tumor growth suppression and toxicity [8].

Recent studies have suggested that the combination of carboplatin and pegylated liposomal doxorubicin (PLD) may be the preferred regimen than carboplatin/paclitaxel for platinum-sensitive recurrent EOC [9–11]. In a randomized Phase 3 noninferiority study [9] of carboplatin plus PLD versus carboplatin plus paclitaxel in relapsed platinum-sensitive ovarian cancer, the carboplatin/PLD combination demonstrated noninferiority with the comparator in terms of progression-free survival (PFS) (11.3 months versus 9.4 months; $P = 0.005$) and lower rates of severe and long-lasting neuropathy. The benefit of carboplatin/PLD over carboplatin/paclitaxel was noted to persist in analysis of patients who relapsed between 6 and 12 and 6–24 months [11,12]. Toxicities were more common with carboplatin/paclitaxel and included neutropenia, neuropathy, and hypersensitivity reactions. Interestingly, carboplatin/PLD was associated with a substantially reduced incidence of platinum-associated hypersensitivity reactions in this study. It should be noted that the safety profile of FAR consists of infrequent and mild drug hypersensitivity adverse events (AEs) and rare interstitial pulmonary changes. No adverse interaction with chemotherapy was expected.

In view of a recent increase in the use of carboplatin plus PLD in patients with platinum-sensitive EOC, a Phase 1b study of FAR plus carboplatin and PLD was undertaken to assess the safety of this triple-agent combination in this disease context.

2. Methods

2.1. Study population

Each participant provided written informed consent before initiating study procedures. All enrolled patients were greater than 18 years old and had histologically- or cytologically-confirmed, platinum-sensitive EOC (including primary peritoneal or fallopian tube malignancies) with relapse as defined by Gynecologic Cancer InterGroup (GCIG) CA-125 criteria or protocol-specific modified (to reflect current practices in the medical oncology community and nuances specific to ovarian cancer) Response Evaluation Criteria in Solid Tumors (RECIST) v.1.0 for 6 months or longer after completion of first- or second-line platinum chemotherapy. All had a Karnofsky Performance Status at least 70%. Patients were required to have the following laboratory and clinical results within two weeks prior to study day 1: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ cells/L; platelet count $\geq 100 \times 10^9$ cells/L; hemoglobin ≥9 g/dL; creatinine ≤1.5 × upper limit of normal (ULN); bilirubin ≤1.5 × ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALK-P) <2.5 × ULN.

Women with known central nervous system (CNS) tumor involvement, other active malignancy, clinically significant cardiac disease, active serious systemic disease or infection, evidence of immune or allergic reaction or documented antidrug antibodies (ADAs) after prior monoclonal antibody therapy were excluded from participation.

2.2. Study design and treatment

This was a multicenter, open-label Phase 1b study with 2.5 mg/kg intravenous (IV) FAR in combination with carboplatin and PLD to assess the safety of this drug regimen in patients with platinum-sensitive EOC. The primary objective of this study was to assess the safety of FAR/carboplatin/PLD in this patient population. Hematology, clinical chemistries, urine, and left ventricular ejection fraction (LVEF) were monitored on Day 1, Week 1 of every 4-week cycle. Tumor assessment (using RECIST v.1.0) was performed every other cycle. Secondary objectives included assessment of response and PFS and the pharmacokinetic effect of FAR on chemotherapy (not reported here).

Study patients received carboplatin AUC_{5-6} IV and PLD 30 mg/m^2 IV on Day 1 of an every 4-week combination treatment cycle. An ANC of 1.5×10^9 cells/L was required for retreatment with chemotherapy. If toxicity due to carboplatin or PLD occurred, doses could be reduced or delayed according to institutional guidelines. If chemotherapy was discontinued without disease progression, the investigator could elect to continue the patient on single-agent FAR until disease progression. Following completion of approximately 6 cycles with FAR/carboplatin/PLD therapy, patients who had not progressed began maintenance treatment with single-agent FAR 2.5 mg/kg once weekly in 4-week cycles until disease progression. A protocol amendment based on new pharmacokinetic data subsequently changed the maintenance therapy administration to single-agent FAR 7.5 mg/kg once every three weeks. Disease response and progression free survival was assessed utilizing modified RECIST v1.0 based upon computed tomography (CT) scan or magnetic resonance imaging (MRI) findings and by CA-125 levels (i.e., CA-125 ≥ 2 × upper limit of normal documented on 2 occasions).

All patients were premedicated prior to FAR infusion with acetaminophen 650 mg by mouth and, optionally, diphenhydramine 25 mg to 50 mg IV or equivalent per clinic routine. In the event of a drug hypersensitivity reaction believed to be associated with FAR, patients were premedicated for subsequent infusions with antipyretic and histamine receptor blocking medications per clinic routine. Prophylactic antiemetics were used for carboplatin and PLD according to usual practice at each site.

All documents pertaining to study design, informed consent, and patient information received Institutional Review Board approval in accordance with the Declaration of Helsinki before the study began.

2.3. Safety and efficacy evaluations

Safety assessments consisted of monitoring and recording all AEs and serious AEs; performance of history and physical examinations; regular monitoring of hematology, blood chemistry, and urine laboratory values (prior to treatment on Day 1, Week 1 of cycle 1); and monitoring with ECHO or MUGA at baseline and every third cycle during combination therapy, then every fourth cycle during maintenance therapy.

Efficacy evaluations by modified RECIST v1.0 were performed at screening, every second cycle during combination treatment, every third cycle during maintenance, and at the study exit visit. Patients who discontinued prior to disease progression for any other reason (e.g., intolerable AE) were followed radiographically until documented disease progression or initiation of a new anticancer treatment occurred. As feasible, follow-up scans were obtained every 3 months; CT or MRI scans were read locally.

2.4. Anti-drug antibodies

Patients were monitored for the presence of ADA at screening, Day 1 of each combination treatment cycle, Day 1 of every third once-weekly

Please cite this article as: K.H. Kim, et al., Phase 1b safety study of farletuzumab, carboplatin and pegylated liposomal doxorubicin in patients with platinum-sensitive epithel..., Gynecol Oncol (2015), http://dx.doi.org/10.1016/j.ygyno.2015.11.031