CEACAM6 is a candidate biomarker for pelareorep resistance in pancreatic adenocarcinoma (PDAC)

Anne M. Nosman 1, John L. Hays 1, Jacob Young 1, Ying Huang 1, Tonnis B. Bahlali-Staff 1, Ming Jiru 2, Wendy L. Frankel 1, Cynthia D. Timmers 2, Jason David 1, Colin Stela 1, Mindy Hong 3, James L. Chen 1

1Division of Medical Oncology, The James Cancer Hospital and Solove Research Institute, The Ohio State University Comprehensive Cancer Center, 2Department of Microbiology and Immunology, College of Medicine, The Ohio State University, 3Division of Hematology/Oncology, Mayo Clinic, Phoenix, Arizona.

Background: Pelareorep is a proprietary formulation of live, replication-competent, naturally occurring Reovirus. Type 3 Dearing strain. A randomized phase II trial of pelareorep in combination with carboplatin and paclitaxel in first-line treatment of metastatic PDAC (NCT01280058) was performed. Although pelareorep did not improve the primary endpoint of progression-free survival compared to carboplatin and paclitaxel alone, impressive durable responses were seen in the pelareorep arm in some patients. Further, prior studies have noted the immunomodulatory CEA cell adhesion molecule 6 (CEACAM6/CD66c) as a receptor for specific viral subtypes. We thus speculated that altered CEACAM6 levels may be predictive for pelareorep sensitivity and may serve as a biomarker.

Methods: 73 patients were enrolled on this randomized phase II trial of pelareorep in combination with carboplatin and paclitaxel (Arm A) versus carboplatin and paclitaxel alone (Arm B). Pre-treatment tissue biopsies were collected prior to enrollment for all 73 pts on study. However, mRNA expression was available for only 31 pts, 17 on Arm A and 14 on Arm B. RNA was purified from FFPE tissue and gene expression analysis was performed using SensationPlus™ (FFPE Amplification and WT labelling kit) and the Human Transcriptome Array 2.0. Differentially expressed genes were calculated at the gene and log2 transformed with the Affymetrix Expression Console. The Affymetrix Transcriptome Analysis Console 2.0 was used to perform differential gene expression analysis. Given the small data sets and the hypothesis generating nature of this analysis, the nominal p-value was used. Appropriate corrections for multiplicity were performed. Immunohistochemistry (IHC) analysis of CEACAM6 protein expression was determined by immunohistochemistry using antibody ab187829 (Abcam Inc., Cambridge, MA, USA) on a Leica Biotekautostainer. Immunohistochemical staining in luminal membrane and cytoplasmic scores were performed independent readers who were blinded to clinical outcome (CT, MJ, WF), on two occasions with discrepancies settled by discussion with the third reader (WF). Two of the readers (MJ and WF) were board certified pathologists.

Results: Low levels of CEACAM6 mRNA expression was associated with prolonged PFS in pelareorep-treated pts (p=0.05). There was no relationship between CEACAM6 mRNA levels and response in either arm (p=0.34). The luminal, but not the cytoplasmic immunohistochemistry score, was highly correlated with mRNA expression levels of CEACAM6 (p=0.007). Conclusions: Elevated levels of CEACAM6 are known to prevent entry of adenovirus into cells. CEACAM6 may be included as a candidate biomarker of resistance to pelareorep and, in theory, could inhibit viral trafficking in tumor cells.

Abstract

Background: Pelareorep is a proprietary formulation of live, replication-competent, naturally occurring Reovirus. Type 3 Dearing strain. A randomized phase II trial of pelareorep in combination with carboplatin and paclitaxel in first-line treatment of metastatic PDAC (NCT01280058) was performed. Although pelareorep did not improve the primary endpoint of progression-free survival compared to carboplatin and paclitaxel alone, impressive durable responses were seen in the pelareorep arm in some patients. Further, prior studies have noted the immunomodulatory CEA cell adhesion molecule 6 (CEACAM6/CD66c) as a receptor for specific viral subtypes. We thus speculated that altered CEACAM6 levels may be predictive for pelareorep sensitivity and may serve as a biomarker.

Methods: 73 patients were enrolled on this randomized phase II trial of pelareorep in combination with carboplatin and paclitaxel (Arm A) versus carboplatin and paclitaxel alone (Arm B). Pre-treatment tissue biopsies were collected prior to enrollment for all 73 pts on study. However, mRNA expression was available for only 31 pts, 17 on Arm A and 14 on Arm B. RNA was purified from FFPE tissue and gene expression analysis was performed using SensationPlus™ (FFPE Amplification and WT labelling kit) and the Human Transcriptome Array 2.0. Differentially expressed genes were calculated at the gene and log2 transformed with the Affymetrix Expression Console. The Affymetrix Transcriptome Analysis Console 2.0 was used to perform differential gene expression analysis. Given the small data sets and the hypothesis generating nature of this analysis, the nominal p-value was used. Appropriate corrections for multiplicity were performed. Immunohistochemistry (IHC) analysis of CEACAM6 protein expression was determined by immunohistochemistry using antibody ab187829 (Abcam Inc., Cambridge, MA, USA) on a Leica Biotekautostainer. Immunohistochemical staining in luminal membrane and cytoplasmic scores were performed independent readers who were blinded to clinical outcome (CT, MJ, WF), on two occasions with discrepancies settled by discussion with the third reader (WF). Two of the readers (MJ and WF) were board certified pathologists.

Results: Low levels of CEACAM6 mRNA expression was associated with prolonged PFS in pelareorep-treated pts (p=0.05). There was no relationship between CEACAM6 mRNA levels and response in either arm (p=0.34). The luminal, but not the cytoplasmic immunohistochemistry score, was highly correlated with mRNA expression levels of CEACAM6 (p=0.007). Conclusions: Elevated levels of CEACAM6 are known to prevent entry of adenovirus into cells. CEACAM6 may be included as a candidate biomarker of resistance to pelareorep and, in theory, could inhibit viral trafficking in tumor cells.

Abstract

Background: Pelareorep is a proprietary formulation of live, replication-competent, naturally occurring Reovirus. Type 3 Dearing strain. A randomized phase II trial of pelareorep in combination with carboplatin and paclitaxel in first-line treatment of metastatic PDAC (NCT01280058) was performed. Although pelareorep did not improve the primary endpoint of progression-free survival compared to carboplatin and paclitaxel alone, impressive durable responses were seen in the pelareorep arm in some patients. Further, prior studies have noted the immunomodulatory CEA cell adhesion molecule 6 (CEACAM6/CD66c) as a receptor for specific viral subtypes. We thus speculated that altered CEACAM6 levels may be predictive for pelareorep sensitivity and may serve as a biomarker.

Methods: 73 patients were enrolled on this randomized phase II trial of pelareorep in combination with carboplatin and paclitaxel (Arm A) versus carboplatin and paclitaxel alone (Arm B). Pre-treatment tissue biopsies were collected prior to enrollment for all 73 pts on study. However, mRNA expression was available for only 31 pts, 17 on Arm A and 14 on Arm B. RNA was purified from FFPE tissue and gene expression analysis was performed using SensationPlus™ (FFPE Amplification and WT labelling kit) and the Human Transcriptome Array 2.0. Differentially expressed genes were calculated at the gene and log2 transformed with the Affymetrix Expression Console. The Affymetrix Transcriptome Analysis Console 2.0 was used to perform differential gene expression analysis. Given the small data sets and the hypothesis generating nature of this analysis, the nominal p-value was used. Appropriate corrections for multiplicity were performed. Immunohistochemistry (IHC) analysis of CEACAM6 protein expression was determined by immunohistochemistry using antibody ab187829 (Abcam Inc., Cambridge, MA, USA) on a Leica Biotekautostainer. Immunohistochemical staining in luminal membrane and cytoplasmic scores were performed independent readers who were blinded to clinical outcome (CT, MJ, WF), on two occasions with discrepancies settled by discussion with the third reader (WF). Two of the readers (MJ and WF) were board certified pathologists.

Results: Low levels of CEACAM6 mRNA expression was associated with prolonged PFS in pelareorep-treated pts (p=0.05). There was no relationship between CEACAM6 mRNA levels and response in either arm (p=0.34). The luminal, but not the cytoplasmic immunohistochemistry score, was highly correlated with mRNA expression levels of CEACAM6 (p=0.007). Conclusions: Elevated levels of CEACAM6 are known to prevent entry of adenovirus into cells. CEACAM6 may be included as a candidate biomarker of resistance to pelareorep and, in theory, could inhibit viral trafficking in tumor cells.