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ASSOCIATION OF VA SURGEONS

Pancreatic Cancer Cell Lysis by Cell-Penetrating Peptide-MAGE-A3–Induced Cytotoxic T Lymphocytes

In contrast to the therapeutic advances for other malignant neoplasms, the therapeutic advances for pancreatic cancer have been slow, with the 5-year survival rate currently at less than 8% for patients with pancreatic cancer.1 Immunotherapy is a particularly appealing approach to pancreatic cancer owing to its potential for eliminating tumor cells that are often unreachable by conventional therapies and its negligible side effects. Along these lines, dendritic cells (DCs) are central to the generation of effector cytotoxic CD8+ T lymphocytes (CTLs) that recognize tumor-specific antigens (TSAs) expressed on the surface of cancer cells. MAGE-A3 (melanoma antigen family A, 3) is a TSA expressed in a significant fraction of pancreatic cancers,2 thus providing an opportunity for introducing DC-based immunotherapy. However, clinically meaningful antitumor immune responses in DC vaccine trials have been sparse owing, in part, to suboptimal intracellular bioavailability of TSA to HLA class I molecules. Various cell-penetrating peptide (CPP) domains are known to ferry covalently linked heterologous TSAs across the plasma membrane into the cytosolic compartment to access HLA class I molecules.3,4,5 We and others have previously demonstrated that CPP effectively increased the intracellular entry of TSAs.3,5 We extend this work by investigating whether DCs pulsed with MAGE-A3 linked to CPP could elicit more effective antitumor CTL responses.

During multivariable analyses, the “Previous Radiotherapy” variable was selected for inclusion only in the DSM and reoperation models at steps 10 and 7, respectively. Inclusion of the ONNCC variables increased the AIC for DSM by 0.06% (AIC of 7077.69 with; AIC of 7073.31 without), while the AIC for reoperation decreased by 0.11% (AIC of 5939.10 with; AIC of 5945.50 without) (Figure). The C statistic for every model correspondingly increased as the AIC decreased for each step.

Discussion | To accurately predict outcomes and risk adjust hospital comparisons, it is important to consider and evaluate new clinically relevant variables. We found that complex cancer-related variables were unable to improve ACS NSQIP modeling.4 Prior studies combining oncologic data from the National Cancer Data Base with ACS NSQIP data did show some ability to improve patient-level risk prediction, but there was no effect on hospital-level comparisons.5 Despite some bivariate associations being significant, we found that the new ONNCC variables did not affect patient-level comparisons and would correspondingly have no effect on hospital-level comparisons. Thus, currently abstracted ACS NSQIP variables provide sufficient adjustment for short-term outcomes of surgical patients undergoing complex cancer operations. Although the ONNCC variables represent clinical scenarios with the potential for poor postoperative outcomes, they do not provide additional statistical explanatory power to justify the added effort required to abstract them given the lack of modeling benefit. The desire for clinical specificity when building predictive models must be weighed against statistical parsimony in the face of data collection burden.5

Jason B. Liu, MD
Sharon M. Weber, MD
Julia R. Berian, MD
Shenglin Chen, PhD
Mark E. Cohen, PhD
Clifford Y. Ko, MD, MS, MSHS
Karl Y. Bilimoria, MD, MS

Author Affiliations: Division of Research and Optimal Patient Care, American College of Surgeons; Chicago, Illinois (Liu, Berian, Cohen, Ko, Bilimoria); Department of Surgery, University of Chicago Hospitals; Chicago, Illinois (Liu, Berian); Department of Surgery, University of Wisconsin Carbone Cancer Center; Madison (Weber); Department of Surgery, David Geffen School of Medicine, University of California, Los Angeles (Ko); Veterans Affairs Greater Los Angeles Healthcare System; Los Angeles, California (Ko); Department of Surgery, Surgical Outcomes and Quality Improvement Center, Feinberg School of Medicine, Northwestern University; Chicago, Illinois (Bilimoria).

Corresponding Authors: Jason B. Liu, MD, Division of Research and Optimal Patient Care, American College of Surgeons, 633 N St Clair, 22nd Floor, Chicago, IL 60611 (liub@facs.org).


Author Contributions: Dr Liu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Liu, Weber, Berian, Ko, Bilimoria.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Liu, Weber, Ko.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Liu, Berian, Chen, Cohen, Ko.

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Methods | PANC-1, an established HLA-A*0201 MAGE-A3+ human pancreatic cancer cell line, was obtained from the American Type Culture Collection and propagated at standard conditions in RPMI 1640 medium with 10% fetal bovine serum. The CPP-MAGE-A3 and MAGE-A3 (control) recombinant proteins expressed in Escherichia coli were purified as previously described using his-tag affinity chromatography.4 Dendritic cells were generated from the adherent fraction of peripheral blood mononuclear cells obtained from HLA-A*0201 donors and pulsed with 3 μmol/L of recombinant protein. Mixed lymphocyte reaction assays were conducted according to our previous method,6 to assess the effect of recombinant protein pulsing on the functional activity of DCs. MAGE-A3–specific CTLs were generated by coculturing autologous T lymphocytes with DCs pulsed with recombinant protein. We measured the resulting secretion of interleukin 4 (IL-4), IL-12p70, and IFN-γ, as well the degree of CTL-mediated killing of PANC-1 cells.6 P < .05 was considered to be statistically significant.

Results | MAGE-A3, CPP-MAGE-A3, and mock-treated DCs all demonstrated similar degrees of cell proliferation in mixed lymphocyte reaction assays, indicating retention of DC functionality after pulsing with recombinant protein (Figure 1A). Coculture of autologous T lymphocytes with DCs treated with CPP-MAGE-A3 demonstrated significantly higher IFN-γ secretion but a similar degree of IL-4 and IL-12p70 release when compared with MAGE-A3 alone (Figure 1B). In addition, overall levels of the cytokines stimulating CD8+ T cells and the HLA class I pathway (IFN-γ and IL-12p70) were significantly higher than levels of IL-4, a cytokine promoting the CD4+ HLA class II pathway. Finally, we found that a significantly higher level of PANC-1 target cell lysis was observed following treatment of CTL with CPP-MAGE-A3 compared with MAGE-A3 alone (81.5% vs 60%; P < .05) (Figure 2).

Discussion | In this study, we demonstrate that the addition of a CPP to MAGE-A3 enhances IFN-γ secretion and pancreatic cancer cell killing without altering DC functionality, potentially improving the potency of existing MAGE-A3 protein and peptide vaccines. Although the addition of the CPP did not enhance the secretion levels of IL-12p70, we did observe a significant enhancement in the release of IFN-γ that is more directly responsible for tumor cell lysis. Our demonstration of more potent cell-mediated immune responses and enhanced tumor cell lysis of the PANC-1 cell line indicate that the CPP could be a crucial factor in enhancing the killing activity of MAGE-A3+ pancreatic tumors and could also be linked to TSAs targeting other malignant neoplasms. This form of DC immunotherapy, either alone or more likely in combination with other immune-enhancing protocols, may prove useful in the clinical setting for the management of pancreatic cancer.

Ramesh B. Batchu, PhD
Oksana V. Gruzdyn, BS
Aamer M. Qazi, PhD
Ebrahim M. Mahmud, BS
Gamal Mostafa, MD
Donald W. Weaver, MD
Scott A. Gruber, MD, PhD, MBA

Author Affiliations: Wayne State University School of Medicine, Detroit, Michigan (Batchu, Gruzdyn, Qazi, Mahmud, Mostafa, Weaver, Gruber); John D. Dingell VA Medical Center, Detroit, Michigan (Batchu, Gruzdyn, Qazi, Mostafa, Gruber).

Corresponding Author: Ramesh B. Batchu, PhD, John D. Dingell VA Medical Center, 4640 John R St, Detroit, MI 48201 (rbatchu@med.wayne.edu).
Ten-Year Retrospective Review of Cubital Tunnel Surgery at the Malcom Randall Veterans Affairs Medical Center, 2005 to 2014

Compression of the ulnar nerve at the level of the elbow is the second most common nerve compression after carpal tunnel syndrome.7 There are multiple surgical options for treating this problem with favorable outcomes and low morbidity. The objective of this study was to determine whether a particular method of decompression performed at our facility or a perioperative risk factor carried a greater risk of postoperative local complications.

Methods | This study was approved by the institutional review boards of the University of Florida and the North Florida/South Georgia Veterans Health Service Research and Development Committee. It was a retrospective medical record review of all cubital tunnel decompressions by the Malcom Randall VA plastic surgery service over a 10-year period (2005-2014). Informed consent was waived because of the nature of the study (retrospective medical record review). The methods of decompression (in situ, subcutaneous, transmuscular, submuscular, and alloderm sling) and local complications (neurapraxia, infection, seroma, hematoma, and dehiscence) over a 6-month postoperative period were recorded. Perioperative risk factors studied were tobacco use, diabetes status, tourniquet time, perioperative antibiotics, and body mass index. A Fisher exact test was used to determine whether a specific type of decompression or a perioperative risk factor had a statistically significant higher rate of postoperative complications. A P value of less than .05 was used to determine statistical significance.

Results | A total of 387 patients had their ulnar nerve decompressed at the elbow. Twelve plastic surgeons performed 5 different types of decompression. Various methods of transposition (n = 375; submuscular, subcutaneous, transmuscular, and alloderm sling) (Figure, A) were favored over the open in situ technique (n = 12) (Figure, B). There were 66 patients (17%) who were noted to have an objective local complication. Two complications (0.5%) required surgical intervention (1 subluxation and 1 hematoma). A Fischer exact test did not find a statistically significant increased rate of complications with any of the 5 different nerve decompressions (Table 1). Current smokers were found to have a statistically significant complication risk (risk ratio, 0.8; 95% CI, 0.47-1.36; P = .03) (Table 2). Local

Figure. Ulnar Nerve Decompression at Elbow

A. Transmuscular transposition (black arrowhead indicates ulnar nerve; white arrowhead indicates fascial slip). B. In situ release (black arrowhead indicates ulnar nerve).