Clinics in Oncology

Short Communication
Published: 04 May, 2017

Beyond Systemic Anti-PD-1 and CTLA-4 in Advanced Melanoma - Is Intratumoral Therapy the Answer?

*Marc Uemura[1] and Adi Diab[2]**

[1]Department of Hematology and Oncology, University of Texas-MD Anderson Cancer Center, USA

[2]Department of Melanoma Medical Oncology, University of Texas-MD Anderson Cancer Center, USA

Short Communication

Since the FDA approval of ipilimumab (Yervoy®) in 2011, systemic Checkpoint Inhibitors (CPIs) targeting Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) and programmed cell protein 1 (PD-1/PD-L1) have significantly improved the overall survival for patients with a variety of cancer types, including, but not limited to, malignant melanoma, non-small cell lung cancer, urothelial cancer, renal cell carcinoma, and squamous cell cancers of the head and neck. In malignant melanoma, for example, the response rates to these new agents are much higher what was historically achievable with chemotherapy (<10%), and is approximately 15% and 30-40%, respectively, for anti-CTLA-4 and anti-PD-1/PD-L1 agents [1-4]. Despite these advances, however, the systemic CPI therapies are not a magic bullet - long-term survival, response rates and durable remission rates, especially in the refractory patient population, remains low. To overcome these limitations, a recent strategy has focused on systemically combining CTLA-4 and PD-1 targeted therapies. This combination has resulted in even higher response rates (~55% with ipilimumab plus nivolumab in malignant melanoma); however, it is also associated with a significantly higher toxicity rate (~60% grade 3/4 adverse events) and Complete Responses (CRs) remain low (~10%) [4,5]. Thus, there remains a significant unmet need to develop new immunotherapeutic strategies that results in higher response rates and improved long term clinical benefits without causing significant immune related toxicity. Our group has recently focused on the benefit of intratumoral immunotherapy as a rational strategy to overcome the clinical limitations of systemic CPI therapy in advanced melanoma. A brief description of this strategy and its rationale follows.

Mutational Burden in Solid Tumors May Determine Sensitivity to Checkpoint Blockade

The prevalence of somatic mutations varies across different tumor types, with malignant melanoma, non-small cell lung cancer, and Microsatellite Instability (MSI) high colorectal cancers having the highest mutational loads [6]. In multiple studies, tumors expressing high somatic mutational loads also have higher numbers of Tumor Infiltrating Lymphocytes (TILs) in the microenvironment, a finding that has been associated with improved cancer prognosis [7]. Such observations may be explained by studies demonstrating that somatic mutations can give rise to neoantigens or neo-epitopes that elicit enhanced T-cell responses [8,9]. Adding to this hypothesis connecting mutational burden to the production of neo-epitopes and enhanced T-cell responses is the finding that responding patients have pre-existing endogenous, tumor-specific T-cells, which can be further potentiated by immune modulators [10,11]. Two recent studies, in fact, support this and have demonstrated a strong correlation between the frequency of mutation-induced neoantigens and the efficacy of CTLA-4 and PD-1 directed systemic immunotherapies in patients with malignant melanoma and lung cancer, respectively [12,13]. However, mutational load and neoantigen production may explain why some cancers respond to CPI therapies, this potential biomarker is far from perfect when considering the low response rates of high mutational load tumors (ie., small cell lung cancer) to systemic immunotherapy. Our group's recent focus has been improving the T-cell priming phase of the immune response using rational combinations of other immunomodulatory agents. We believe enhanced T-cell priming can improve the immunogenicity of low mutation burden tumors and poorly responsive high mutation burden tumors, resulting in improved immunogenic tumor destruction and efficacy of CPI therapies.

OPEN ACCESS

Correspondence:
Adi Diab, Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, USA, Tel: 713 745-7336; E-mail: adiab@mdanderson.org

Received Date: *13 Feb 2017*
Accepted Date: *02 May 2017*
Published Date: *04 May 2017*

Citation:
Uemura M, Diab A. Beyond Systemic Anti-PD-1 and CTLA-4 in Advanced Melanoma - Is Intratumoral Therapy the Answer?. Clin Oncol. 2017; 2: 1272.

Intratumoral Immunotherapy: Manipulating the Tumor May Be the Best "Vaccine" For T-Cell Priming

To date, most therapeutic vaccine studies in patients with advanced melanoma have utilized non-mutated, differentiation antigens, such as gp100, which have shown real but modest clinical benefit [14]. One strategy to improve vaccine therapy in melanoma utilizes the patient's own tumor as a "vaccine site" through Direct Intratumoral (IT) immune modulation. Through activation of antigen-presenting Dendritic Cells (DCs) with optimal neoantigen presentation and subsequent up regulation of tumor-specific T-cells, IT modulation empowers the immune system to elicit strong T-cell responses against tumor-associated antigens, which are most immunogenic [15]. In combination with CPI therapy, IT-immune modulation may lead to specific, durable antitumor immune responses with subsequent improvement in clinical responses without higher toxicity. As proof of concept, we previously reported that IT directed cryoablation combined with systemic ipilimumab in a cohort of early-stage breast cancer patients resulted in tumor necrosis, peripheral activation of T-cells in blood, and a significantly increased ratio of tumor CD8+KI67+T-cells to T-regulatory cells (Treg) [16]. More recently, we evaluated the safety and efficacy of IT cryoablation in combination with systemic CPI therapy (ipilimumab or pembrolizumab) in patients with metastatic melanoma. The results from this small pilot study are promising and suggest that this strategy is well-tolerated and can potentially lead to enhanced CPI antitumor activity [17]. Despite these encouraging data, we recognize that IT ablation alone may be insufficient for full DC activation to effectively promote expiation of a fully committed and long-lasting T-cell response.

IT Therapy with TLR9 Agonist And CD40L

Given the therapeutic potential for IT therapy combined with systemic CPI, our group has recently opened clinical trials investigating two IT-directed agents in combination with systemic CPI therapy in patients with refractory, advanced melanoma: TLR9 agonist, IMO-2125 (Idera Pharmaceuticals, Inc.), and CD40 agonist, APX005M (Apexigen, Inc.). IMO-2125 is a synthetic phosphorothioate oligonucleotide toll like receptor 9 (TLR9) agonist that stimulates both the innate and adaptive immune response by increasing endogenous cytokine production and B cell proliferation. In preclinical models, we have shown that IT directed TLR9 agonists lead to enhanced infiltration of $CD8^+$ T cells at injected and non-injected tumors [18]. In addition, IT IMO-2125 resulted in decreased tumor volume when administered in a dose-dependent manner and synergized with anti-CTLA-4 therapy. APX005M is a humanized monoclonal antibody that binds CD40, which is expressed on all antigen presenting cells. Its ligation results in full activation and maturation of dendritic cells with subsequent up regulation of co-stimulatory immune molecules (CD80, CD86 and CD70) as well as other TNF super family members, such as 4-1BBL, OX40L, and CTIRL. Our preclinical studies have shown that IT directed rAdCD40L, a recombinant adenovirus expressing CD40 ligand, in mice harboring B16 melanoma tumors resulted in strong expansion of tumor infiltrating $CD8^+$ T-cells and up regulation of PD-1 as compared to injection of an empty vector. Like that seen for IT IMO-2125, IT rAdCD40L resulted in suppression or tumors at both injected and distant, non-injected tumor sites.

Conclusion

Systemic immunotherapies have radically changed the therapeutic landscape for patients with advanced melanoma. Novel strategies are needed to improve the response rates, durable remission rates, and immunotoxicity of these agents. Our group is studying the clinical benefit of IT directed immune agonists in combination with CPI therapies, and is leading multiple clinical trials testing these agents.

References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.
2. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375-84.
3. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol. 2015;16(8):908-18.
4. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(1):23-34.
5. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006-17.
6. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-21.
7. Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer. 2011;105(1):93-103.
8. Segal NH, Parsons DW, Peggs KS, Velculescu V, Kinzler KW, Vogelstein B, et al. Epitope landscape in breast and colorectal cancer. Cancer Res. 2008;68(3):889-92.
9. Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, et al. Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting. Nature. 2012;482(7385):400-4.
10. van Rooij N, van Buuren MM, Philips D, Velds A, Toebes M, Heemskerk B, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol. 2013;31(32):e439-42.
11. Overwijk WW, Wang E, Marincola FM, Rammensee HG, Restifo NP. Mining the mutanome: developing highly personalized Immunotherapies based on mutational analysis of tumors. J Immunother Cancer. 2013;1:11.
12. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014;371(23):2189-99.
13. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348(6230):124-8.
14. Schwartzentruber DJ, Lawson DH, Richards JM, Conry RM, Miller DM, Treisman J, et al. gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma. N Engl J Med. 2011;364(22):2119-27.
15. Singh M, Overwijk WW. Intratumoral immunotherapy for melanoma. Cancer Immunol Immunother. 2015;64(7):911-21.
16. McArthur HL, Diab A, Page DB, Yuan J, Solomon SB, Sacchini V, et al. A

Pilot Study of Preoperative Single-Dose Ipilimumab and/or Cryoablation in Women with Early-Stage Breast Cancer with Comprehensive Immune Profiling. Clin Cancer Res. 2016;22(23):5729-5737.

17. Kim DW HC, McQuail N. Pilot study of intratumoral (IT) cryoablation (cryo) in combination with systemic checkpoint blockade in patients with metastatic melanoma (MM). J Immunother Cancer. 2015;3: P137.

18. Wang D YD ASIioI. A novel Toll-like receptor 9 agonist, with ipilimumab induces a systemic tumor-specific immune response [abstract]. American Association for Cancer Research (AACR) Meeting - Tumor Immunology and Immunotherapy. 2014.