3

Phase I study of a new cancer vaccine of ten mixed peptides for advanced cancer patients.

Iwasa S, Yamada Y, Heike Y, Shoji H, Honma Y, Komatsu N, Matsueda S, Yamada A, Morita M, Yamaguchi R, Tanaka N, Kawahara A, Kage M, Shichijo S, Sasada T, Itoh K

show author affiliations

Cancer Sci. 2016 May; 107(5):590-600

★★★ Exceptional

01 Jul 2016

FM John Nemunaitis

F1000 Pharmacology & Drug Discovery

Mary Crowley Medical Research Center, Dallas, TX, USA.

FOLLOW

AFM Luisa Manning

F1000 Pharmacology & Drug Discovery

Gradalis Inc, Dallas, TX, USA.

FOLLOW

DOI: 10.3410/f.726192170.793518611

This is another tool in our oncology toolbox.

Immunotherapy approaches engaged in clinical testing are highly visible as a result of the dramatic activity demonstrated with PD-L1/PD-1 inhibitors and recent FDA approved product indications {1,2}. As such, the work performed by Iwasa et al. is quite timely and relevant in the consideration of combination immunotherapy strategies. Cancer vaccines have been observed for the past several decades with limited evidence of improving clinical outcomes {3,4}. Efficient vaccine-primed cytotoxic lymphocytes may lose their responsiveness to cancer neo-antigens as a result of immunosuppressive, cytokine induced activity and involvement of T regulatory cells. Additionally, checkpoint inhibition, such as CTLA-4 (CTL-associated protein 4) or PD-1 / PD-L1 (programmed death) pathways can be pirated by cancer to mediate inhibition {5,6}.

However, recently clinical effectiveness has been shown with immune checkpoint inhibitors and durable clinical responses are described {7,8}. High response rates and increased overall outcome are associated with pre-existing immunity, detected by the presence of CD4+, CD8- cells as well as tumor-infiltrating lymphocytes (TILs). Patients with no or low levels of TIL show lower response rates and do not respond well to immunotherapies. These results suggest combination therapies of cancer vaccines may increase antigen-specific immune response with checkpoint inhibitors.

Iwasa et al. describe their experience with a new cancer vaccine, a mixture of 10 peptides, in advanced and relapsed gastrointestinal cancer patients. Their vaccine is comprised of novel CTL-epitope peptides (KRM-10) that can bind to different HLA-alleles. Compared to other conducted cancer vaccine trials that did not demonstrate evidence of appropriate dose-effect levels or predictive biomarkers, they showed correlation of both CTL and IgG response favoring vaccine activity. A majority of cancer patients express different HLA alleles, including HLA-A2, A24, A3, A11, A31, A33 or A26. Iwasa et al. selected 10 peptides, chosen in previous clinical trials for vaccination, to activate HLA-class IA CTL activity {5,9}. The frequency of protein expression, based on the selected 10 peptides for the KRM-10 vaccine, was detected in the analysis of six selected antigens identified from resected tumors of the gastrointestinal tract (esophageal, gastric, colorectal); all six of those antigens are expressed in adenocarcinomas, while 4/10 are expressed in squamous cell esophageal-carcinoma {9}. The study shows safety, with adverse effects limited to injection-side reactions, and no DTLs or delayed toxicities were observed during the use of KRM-10. Six patients had stable disease, while 15 showed progressive disease. The results of this study may suggest a potential improvement of clinical benefit with cancer vaccinations that increase immune response. However, immune tolerance or suppressive regulating activity seems to inhibit immune activation, respectively. Questions do remain whether HLA-matched peptide competition for binding the same HLA-molecule, metabolizing of peptides that bind different HLA-alleles expressed in other patients, is limiting immunogenicity.

Another, relatively small, phase 1 clinical trial shows similar data. Chianese-Bullock et al. investigated safety and efficacy of a multi-peptide cancer vaccine for patients with advanced ovarian cancer. Patients received 5 HLA-restricted peptide vaccinations, derived from ovarian-cancer associated proteins, in combination with a granulocyte-macrophage-colony-stimulating-factor (GM-CSF). GM-CSF increases the maturation and proliferation of APC and therefor enhances antigen-specific immune response {10,11}. CD8 T-cell response was observed, and selected peptides suggested

RELATED ARTICLES

Recommended | PubMed

1 gp100 peptide vaccine and interleukin-2 in patients with advanced...

2 Clinical and immunologic results of a randomized phase II trial...

3 Phase I dose escalation and pharmacokinetic study of enzastaurin...

4 Flt3 ligand as a vaccine adjuvant in association with HER-2/neu...

Relevant Sections

Gastroenterology & Hepatology
» Gastrointestinal Cancers

Pharmacology & Drug Discovery
» Cancer Therapeutics
» Immunopharmacology & Hematologic Pharmacology

Oncology
» Oncology Agents

Immunology
» Immunomodulation

immunogenicity.

An important limitation of many current cancer vaccination strategies is the employment of limited or even single antigens that are often 'off the shelf' and not clearly relevant to an individual patient's malignancy. In fact, evidence is growing that a large proportion of tumor 'neoantigens' are not shared between patients and that the most immunogenic and thus therapeutically effective antigens in a patient may be truly patient-unique {12-18}, thereby strongly supporting the use of autologous tumor for the antigen source. Two salient examples of this issue come from the recent literature. Rosenberg's group showed that the TH1 cell clone responsible for clinical response in a patient with metastatic cholangiocarcinoma treated on an adoptive T cell protocol was a single unique mutation in ERBB2 {19}. Schreiber's group used genomic and bioinformatic approaches to identify autologous tumor-specific mutant antigens responsible for anti-PD-1-mediated rejection of an aggressive sarcoma in a mouse model {20}. These results support the hypothesis that autologous tumor-specific neoantigens are critical targets of effective immunotherapy including checkpoint blockade therapy of the PD-1/PD-L1 axis. More directly, Karyampudi et al. {21} tested single peptide (of relevant tumor antigen) vaccine, single agent PD-1 inhibitor, multiple peptide vaccine and combination of PD-L1 inhibitor/multi-peptide vaccine in BALB/c mice with the TUBO cell line (PD-L1 negative breast cancer cell line) xenograft mouse model and eloquently demonstrated marked tumor response, growth control and survival advantage to the combination of multi-peptide vaccine and PD-1 inhibitor. None to minimal effect was observed to the singlet cohorts. Impressively, memory precursory effector cells were also significantly induced and demonstrated further protective activity after dosing completion.

There is certainly a need for additional immunomodulation combinations in the immunotherapy regimen. A focus to increase T-cell response, in combination with inhibitors, blocking the immune-suppressive pathways would appear fruitful. One of the greatest factors of immunosuppression, related to cancer cells, is TGF-β expression and its effect on immune cells {22}. TGF-β is expressed by T-regulatory and cancer cells causing apoptosis in antigen-presenting cells (APCs), and inhibiting effective CD8-cell response by blocking the synthesis of interferon-γ, granzymes A and B, and perforin. Targeted therapy of TGF-β enhances highly effective cytotoxic T-cell response against cancer cells with correlated increase of INF-γ, as a reasonable measurement for immune response {23-25}.

Another product, Vigil (previously called FANG), an autologous irradiated tumor cell immunotherapy transfected with GMCSF and bi-shRNA furin (which effectively knocks down TGFβ 1, 2 expression) plasmids, had previously demonstrated correlation of upregulated circulating activated immune effector cells via ELISPOT assay with vaccine administration in advanced cancer patients. Moreover, the upregulated number of these circulating ELISPOT responsive cells greater than or at least as great as a threshold of 10 demonstrated further correlation with survival advantage to treatment with Vigil. Iwasa et al. also demonstrated evidence of 'turn on' of circulating effector mononuclear cells in response to KRM-10 dosing.

Cancer vaccine development is headed in the right direction. These are promising results that support the start of further testing towards the development of 'another tool in our oncology toolbox' of therapeutic options for the management of cancer.

References

1. **Bladder cancer: Atezolizumab effective against advanced-stage disease.**
   Sidaway P. Nat Rev Urol. 2016 May; 13(5):238
   PMID: 27001012 DOI: 10.1038/nrurol.2016.60
2. **Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial.**
   Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Lancet. 2016 Mar 4;
   PMID: 26952546 DOI: 10.1016/S0140-6736(16)00561-4
3. **Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma.**
   Rosenberg SA, Yang JC, Schwartzentruber DJ, Hwu P, Marincola FM, Topalian SL, Restifo NP, Dudley ME, Schwarz SL, Spiess PJ, Wunderlich JR, Parkhurst MR, Kawakami Y, Seipp CA, Einhorn JH, White DE. Nat Med. 1998 Mar; 4(3):321-7
   PMID: 9500606
4. **A new era in anticancer peptide vaccines.**
   Perez SA, von Hofe E, Kallinteris NL, Gritzapis AD, Peoples GE, Papamichail M, Baxevanis CN. Cancer. 2010 May 1; 116(9):2071-80
   PMID: 20187092 DOI: 10.1002/cncr.24988
5. **Personalized peptide vaccination: a new approach for advanced cancer as therapeutic cancer vaccine.**
   Noguchi M, Sasada T, Itoh K. Cancer Immunol Immunother. 2013 May; 62(5):919-29
   PMID: 23197273 DOI: 10.1007/s00262-012-1379-1
6. **Personalized Peptide Vaccine for Treatment of Advanced Cancer.**
   Sasada T, Yamada A, Noguchi M, Itoh K. Curr Med Chem. 2014 Feb 5;
   PMID: 24524766
7. **Pembrolizumab versus Ipilimumab in Advanced Melanoma.**
   Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A, KEYNOTE-006 investigators. N Engl J Med. 2015 Jun 25; 372(26):2521-32
   PMID: 25891173 DOI: 10.1056/NEJMoa1503093
8. **Increases in absolute lymphocytes and circulating CD4+ and CD8+ T cells are associated with positive clinical outcome of melanoma patients treated with ipilimumab.**
   Martens A, Wistuba-Hamprecht K, Yuan J, Postow MA, Wong P, Capone M, Madonna G, Khammari A, Schilling B, Sucker A, Schadendorf D, Martus P, Dreno B, Ascierto PA, Wolchok JD, Pawelec G, Garbe C, Weide B. Clin Cancer Res. 2016 May 11;
   PMID: 27169993 DOI: 10.1158/1078-0432.CCR-16-0249

9. **Phase II study of personalized peptide vaccination for previously treated advanced colorectal cancer.**
Kibe S, Yutani S, Motoyama S, Nomura T, Tanaka N, Kawahara A, Yamaguchi T, Matsueda S, Komatsu N, Miura M, Hinai Y, Hattori S, Yamada A, Kage M, Itoh K, Akagi Y, Sasada T. Cancer Immunol Res. 2014 Dec; 2(12):1154-62
PMID: 25351849 DOI: 10.1158/2326-6066.CIR-14-0035

10. **GVAX (GMCSF gene modified tumor vaccine) in advanced stage non small cell lung cancer.**
Nemunaitis J. J Control Release. 2003 Aug 28; 91(1-2):225-31
PMID: 12932654

11. **Granulocyte-macrophage colony-stimulating factor (GM-CSF) and T-cell responses: what we do and don't know.**
Shi Y, Liu CH, Roberts AI, Das J, Xu G, Ren G, Zhang Y, Zhang L, Yuan ZR, Tan HS, Das G, Devadas S. Cell Res. 2006 Feb; 16(2):126-33
PMID: 16474424 DOI: 10.1038/sj.cr.7310017

12. **The response of autologous T cells to a human melanoma is dominated by mutated neoantigens.**
Lennerz V, Fatho M, Gentilini C, Frye RA, Lifke A, Ferel D, Wölfel C, Huber C, Wölfel T. Proc Natl Acad Sci U S A. 2005 Nov 1; 102(44):16013-8
PMID: 16247014 DOI: 10.1073/pnas.0500090102

13. **Exploiting the mutanome for tumor vaccination.**
Castle JC, Kreiter S, Diekmann J, Löwer M, van de Roemer N, de Graaf J, Selmi A, Diken M, Boegel S, Paret C, Koslowski M, Kuhn AN, Britten CM, Huber C, Türeci O, Sahin U. Cancer Res. 2012 Mar 1; 72(5):1081-91
PMID: 22237626 DOI: 10.1158/0008-5472.CAN-11-3722

14. **Cancer exome analysis reveals a T-cell-dependent mechanism of cancer immunoediting.**
Matsushita H, Vesely MD, Koboldt DC, Rickert CG, Uppaluri R, Magrini VJ, Arthur CD, White JM, Chen YS, Shea LK, Hundal J, Wendl MC, Demeter R, Wylie T, Allison JP, Smyth MJ, Old LJ, Mardis ER, Schreiber RD. Nature. 2012 Feb 16; 482(7385):400-4
PMID: 22318521 DOI: 10.1038/nature10755

15. **Targeting the tumor mutanome for personalized vaccination therapy.**
Kreiter S, Castle JC, Türeci O, Sahin U. Oncoimmunology. 2012 Aug 1; 1(5):768-769
PMID: 22934277 DOI: 10.4161/onci.19727

16. **Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma.**
van Rooij N, van Buuren MM, Philips D, Velds A, Toebes M, Heemskerk B, van Dijk LJ, Behjati S, Hilkmann H, El Atmioui D, Nieuwland M, Stratton MR, Kerkhoven RM, Kesmir C, Haanen JB, Kvistborg P, Schumacher TN. J Clin Oncol. 2013 Nov 10; 31(32):e439-42
PMID: 24043743 DOI: 10.1200/JCO.2012.47.7521

17. **Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.**
Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA. Science. 2015 Apr 3; 348(6230):124-8
PMID: 25765070 DOI: 10.1126/science.aaa1348

18. **Genetic basis for clinical response to CTLA-4 blockade.**
Snyder A, Wolchok JD, Chan TA. N Engl J Med. 2015 Feb 19; 372(8):783
PMID: 25693024 DOI: 10.1056/NEJMc1415938

19. **Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.**
Tran E, Turcotte S, Gros A, Robbins PF, Lu YC, Dudley ME, Wunderlich JR, Somerville RP, Hogan K, Hinrichs CS, Parkhurst MR, Yang JC, Rosenberg SA. Science. 2014 May 9; 344(6184):641-5
PMID: 24812403 DOI: 10.1126/science.1251102

20. **Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens.**
Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, Ivanova Y, Hundal J, Arthur CD, Krebber WJ, Mulder GE, Toebes M, Vesely MD, Lam SS, Korman AJ, Allison JP, Freeman GJ, Sharpe AH, Pearce EL, Schumacher TN, Aebersold R, Rammensee HG, Melief CJ, Mardis ER, Gillanders WE, Artyomov MN, Schreiber RD. Nature. 2014 Nov 27; 515(7528):577-81
PMID: 25428507 DOI: 10.1038/nature13988

21. **Accumulation of Memory Precursor CD8 T Cells in Regressing Tumors Following Combination Therapy with Vaccine and Anti-PD-1 Antibody.**
Karyampudi L, Lamichhane P, Scheid AD, Kalli KR, Shreeder B, Krempski JW, Behrens MD, Knutson KL. Cancer Res. 2014 Apr 11;
PMID: 24728077 DOI: 10.1158/0008-5472.CAN-13-2564

22. **TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance.**
Thomas DA, Massagué J. Cancer Cell. 2005 Nov; 8(5):369-80
PMID: 16286245 DOI: 10.1016/j.ccr.2005.10.012

23. **A phase I trial of GMCSF gene-TGFbeta antisense gene autologous tumor cell (TAG) vaccine in advanced cancer.**
Nemunaitis J. et al. Mol Therapy. 2009; 17(Suppl 1):S206.

24. **Phase I trial of TGF-beta 2 antisense GM-CSF gene-modified autologous tumor cell (TAG) vaccine.**
Olivares J, Kumar P, Yu Y, Maples PB, Senzer N, Bedell C, Barve M, Tong A, Pappen BO, Kuhn J, Magee M, Wallraven G, Nemunaitis J. Clin Cancer Res. 2011 Jan 1; 17(1):183-92
PMID: 21208907 DOI: 10.1158/1078-0432.CCR-10-2195

25. **Phase I trial of "bi-shRNAi(furin)/GMCSF DNA/autologous tumor cell" vaccine (FANG) in advanced cancer.**
Senzer N, Barve M, Kuhn J, Melnyk A, Beitsch P, Lazar M, Lifshitz S, Magee M, Oh J, Mill SW, Bedell C, Higgs C, Kumar P, Yu Y, Norvell F, Phalon C, Taquet N, Rao DD, Wang Z, Jay CM, Pappen BO, Wallraven G, Brunicardi FC, Shanahan DM, Maples PB, Nemunaitis J. Mol Ther. 2012 Mar; 20(3):679-86
PMID: 22186789 DOI: 10.1038/mt.2011.269

Disclosures

John Nemunaitis has stock interest in Gradalis, Inc., and Strike, Inc.

Add a comment

Cite this Recommendation

ABSTRACT

A phase I study of a new cancer vaccine (KRM-10), consisting of a mixture of 10 different short peptides, was conducted for patients with advanced gastrointestinal cancers. Primary or secondary endpoints included the dose-limiting toxicity (DLT), or safety and immune responses, respectively. Peptide-specific cytotoxic T lymphocytes (CTL) and immunoglobulin G (IgG), together with soluble inflammatory factors, were measured before and after vaccination. Twenty-one patients were vaccinated with KRM-10 at dose levels of 10 (n = 6), 20 (n... more »

DOI: 10.1111/cas.12919
PMID: 26920496

COMMENTS add a comment

Cite this page

F1000 Faculty Reviews are comprehensive, open access, topical reviews written by members of the prestigious F1000 Faculty. These peer reviewed articles provide context on emerging themes in biology and medicine.

view all

Bioinformatics & Computational Biology | Biotechnology | Genomics & Genetics | Molecular Medicine | Cell Biology | Cancer Biology

Emerging technologies for the genomic analysis of cancer

F1000 Biology Reports 2009 1:(35) *(08 May 2009)*

Full text | PDF | Abstract on PubMed

Bioinformatics & Computational Biology | Biotechnology | Genomics & Genetics | Molecular Medicine | Neuroscience | Cell Biology | Chemical Biology | Immunology | Physiology | Pharmacology & Drug Discovery

The search for novel analgesics: targets and mechanisms

Tony L. Yaksh, Sarah A. Woller, Roshni Ramachandran, Linda S. Sorkin
F1000Prime Reports 2015 7:(56) *(26 May 2015)*

Full text | PDF | Abstract on PubMed