Editorial

The emerging role of Interleukin-21 as an antineoplastic immunomodulatory treatment option

George Zarkavelis[1,2], Aristeidis Kefas[1,2], George Pentheroudakis[1,2]

[1]Department of Medical Oncology, Medical School, University of Ioannina, Ioannina, Greece; [2]Society for Research of Clonal Heterogeneity of Neoplasia (EMEKEN), Ioannina, Greece

Correspondence to: George Pentheroudakis. Department of Medical Oncology, Medical School, University of Ioannina, Ioannina, Greece. Email: gpenther@otenet.gr.

Comment on: McMichael EL, Jaime-Ramirez AC, Guenterberg KD, *et al.* IL-21 Enhances Natural Killer Cell Response to Cetuximab-Coated Pancreatic Tumor Cells. Clin Cancer Res 2017;23:489-502.

Abstract: As immunotherapy gathers momentum in the field of cancer therapeutics, a recently discovered chemokine, IL-21, has drawn attention as a promising immunomodulatory cytokine with antineoplastic effects. The aforementioned capacities of IL-21 have been investigated in phase I, II clinical trials where it has been utilized either as monotherapy or in combination with other agents. Extensive investigation and conduct of larger prospective trials are necessary for further evaluation of this promising immunotherapy modality.

Keywords: IL-21; oncology; cancer; immunotherapy; cancer therapeutics

Submitted Feb 01, 2017. Accepted for publication Feb 15, 2017.
doi: 10.21037/tcr.2017.03.36
View this article at: http://dx.doi.org/10.21037/tcr.2017.03.36

As immunotherapy gains even more attention in the field of cancer therapeutics, a recently discovered chemokine, IL-21, has drawn attention either as monotherapy modality or in a synergistic fashion combined with other cancer therapy agents due to its tumor regressive capacities. First recognized in 2000, IL-21 is a member of the cytokine family that shares identical gamma chain in their receptor (IL-21R) (1). IL-21 derives from CD4-T cells and NK cells while its receptor is mainly expressed by T, B and NK cells of the immune system. The abundancy of IL-21R on immune system cells has led to the hypothesis of immune response regulation by IL-21. The effects of IL-21/IL-21R complex on immune modulation have been investigated (2).

To date research has come to the conclusion that IL-21 conduces to B-cell apoptosis but also promotes B-cell linear proliferation, differentiation into plasma cells and upregulation of IgG1 and IgG3 both *in vivo* and *in vitro* mainly through IL-4 stimulation. Furthermore, T-cell differentiation and expansion as well as NK cell stimulation, which in turn results to high levels of INF–γ and perforin expression, enhances cellular cytotoxic activity. On the contrary, it is of notice that after IL-21 administration a decrease in the number of NK cells is observed due to redistribution into circulation rather than induced apoptosis of the specific cell line. Moreover, IL-21 has a broad immunomodulatory spectrum both on innate and adaptive immunity. It has been reported that its presence can lead to immune response suppression due to its inhibitory role on dendritic cell activation but it can also promote IL-10 an B-regulatory cells production. Furthermore, upon binding to its receptor, IL-21 activates Jak1, Jak3 and STAT3 pathways interfering with gene transcription (1,2).

The aforementioned capacities of IL-21 have been investigated in phase I, II clinical trials where it has been utilized either as monotherapy or in combination with other agents. The majority of those trials focus on melanoma and renal cell carcinoma due to response seen in these solid neoplasms after immune modulatory intervention. Davis

et al. reported complete responses (CR) in 3% and stable disease (SD) in 31% of the participants with metastatic melanoma treated with recombinant IL-21 (rIL-21) in a phase I clinical trial which further proceeded to phase IIa with encouraging results (3,4). Thompson et al reported CR in 4% of the enrolled patients and SD in 45% melanoma patients receiving rIL-21 in another phase I clinical trial. Furthermore, partial response in 4% and stable disease in 13% of the patients with renal cell carcinoma was reported by the same investigators (5).

Bhatia *et al.* tested the combination of rIL-21 with sorafenib in metastatic renal cell carcinoma in a phase I/II trial reporting partial response in 21% and stable disease in 61% of the patients (6). In addition, another phase I clinical trial conducted by Timmerman *et al.* in refractory NHL patients investigated the impact of rIL-21 in combination with rituximab reporting promising results (7). Mittal *et al.* recently reported that both in mice and humans intratumoral levels of *IL-21R* expression correlate with the antitumor effects of anti HER-2 monoclonal antibody with higher levels of *IL-21R* leading to anti-HER-2 therapy benefit (8).

Finally, to date there is one phase I clinical trial conducted in patients with metastatic colorectal cancer which investigated the combination of anti-EGFR monoclonal antibodies with rIL-21. The co-administration of cetuximab and rIL-21 *in vivo* facilitates NK activity so the potentiality of antibody-dependent cell-mediated cytotoxicity against tumor cells was investigated by Steele *et al.* The combination regime resulted in SD in 60% of the participants. However *KRAS* mutational status and epidermal growth factor receptor (EGFR) expression were not evaluated in this trial (9). In all early phase trials that have been conducted investigating the effects of IL-21 main adverse events consisted of low neutrophil count, lymphopenia, anemia, increased transaminases, hyperbilirubinemia, lethargy and diarrhea all mainly grade 2 and rare cases of grade 3 AE have been reported (3-9).

Pancreatic cancer is a highly malignant neoplasm with occult onset and poor prognosis despite the approved chemotherapy regimens. It is common for pancreatic adenocarcinomas to overexpress the EGFR which contributes to tumor proliferation and metastatic potential. *KRAS* mutations are also identified in the majority of pancreatic cancers resulting in activation of the Ras/Raf/MAPK and PI3k/Akt pathways (10,11). Targeting the EGFR with monoclonal antibodies is approved for the treatment of patients with metastatic colorectal cancer in whom *RAS* mutations are not identified (*RAS* wild type). Presence of either *KRAS* on *NRAS* mutations precludes the use of anti-EGFRs.

McMichael *et al.* present the results of their study where the combination of EGFR monoclonal antibody (mAb) cetuximab in combination with IL-21 was investigated for its antineoplastic properties in human pancreatic cancer cells. The team has come to the conclusion that the use of IL-21 can enhance NK cell lytic activity against both *KRAS* wild type and mutated pancreatic cancer cells after they have been coated with anti-EGFR mAb cetuximab. In addition, colorectal cancer lines were examined with same combination coming up with the finding of higher NK activity irrespective of KRAS status.

Furthermore, antibody dependent cell mediated cytotoxicity was also enhanced in the presence of IL-21 with higher rates of pancreatic cancer cetuximab-coated cell lysis observed while INF-γ levels were notably higher after IL-21 exposure with greater percentages of T cell recruitment recorded. In the same study the activation of both ERK and STAT was confirmed after the use of IL-21 inducing MAPK and Jak/STAT pathways. The antineoplastic effect of IL-21 was also tested in murine model of pancreatic cancer in co-administration with cetuximab resulting in significant reductions in tumor load. Finally, a slight improvement in tumor burden was of notice after gemcitabine was added to the EGFR positive population.

The role IL-21 in cancer immunotherapy has only been evaluated in small phase I, II clinical trials and specifically the effect on solid neoplasms and hematologic malignancies have come to promising results. However, the study of McMichael et al is , to our knowledge, the first one to be conducted on pancreatic cell lines. Apart from the enhancement in immune response induced by IL-21 administration against malignant cells, the encouraging results of effectiveness in both *KRAS* wild type and mutated cells when co- administered with cetuximab are presented.

McMichael *et al.* have provided preclinical data of improved NK activation, NK mediated ADCC, T cell activation against pancreatic cancer cells coated with anti-EGFR antibody regardless of the KRAS mutational status. Based on these results, the aspect of overcoming KRAS mutation induced resistance to anti-EGFR mAbs with the use of IL-21 is raised while new perspectives in the treatment of the aggressive pancreatic carcinomas arise with new information in cancer immunotherapy armory. Nevertheless, extensive investigation and conduction of large phase III trials are necessary for further evaluation of

this promising immunotherapy modality.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Zhen-Yu Lin (Cancer center, Union hospital, Huazhong University of Science and Technology, Wuhan, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.03.36). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sim GC, Radvanyi L. The IL-2 cytokine family in cancer immunotherapy. Cytokine Growth Factor Rev 2014;25:377-90.
2. Croce M, Rigo V, Ferrini S. et al. IL-21: a pleiotropic cytokine with potential applications in oncology. J Immunol Res 2015;2015:696578.
3. Davis ID, Skrumsager BK, Cebon J, et al. An open-label, two-arm, phase I trial of recombinant human interleukin-21 in patients with metastatic melanoma. Clin Cancer Res 2007;13:3630-6.
4. Davis ID, Brady B, Kefford RF, et al. Clinical and biological efficacy of recombinant human interleukin-21 in patients with stage IV malignant melanoma without prior treatment: a phase IIa trial. Clin Cancer Res 2009;15:2123-9.
5. Thompson JA, Curti BD, Redman BG, et al. Phase I study of recombinant interleukin-21 in patients with metastatic melanoma and renal cell carcinoma. J Clin Oncol 2008;26:2034-9.
6. Bhatia S, Curti B, Ernstoff MS, et al. Recombinant interleukin-21 plus sorafenib for metastatic renal cell carcinoma: a phase 1/2 study. J Immunother Cancer 2014;2:2.
7. Timmerman JM, Byrd JC, Andorsky DJ, et al. A phase I dose-finding trial of recombinant interleukin-21 and rituximab in relapsed and refractory low grade B-cell lymphoproliferative disorders. Clin Cancer Res 2012;18:5752-60.
8. Mittal D, Caramia F, Michiels S, et al. Improved Treatment of Breast Cancer with Anti-HER2 Therapy Requires Interleukin-21 Signaling in CD8+ T Cells. Cancer Res 2016;76:264-74.
9. Steele N, Anthony A, Saunders M, et al. A phase 1 trial of recombinant human IL-21 in combination with cetuximab in patients with metastatic colorectal cancer. Br J Cancer 2012 Feb 28;106:793-8.
10. Ying H, Dey P, Yao W, et al. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev 2016;30:355-85.
11. Eser S, Schnieke A, Schneider G, et al. Oncogenic KRAS signalling in pancreatic cancer. Br J Cancer 2014;111:817-22.

Cite this article as: Zarkavelis G, Kefas A, Pentheroudakis G. The emerging role of Interleukin-21 as an antineoplastic immunomodulatory treatment option. Transl Cancer Res 2017;6(Suppl 2):S328-S330. doi: 10.21037/tcr.2017.03.36