Journal of
Pharmacology & Clinical Research
ISSN: 2473-5574

Juniper Publishers
key to the Researchers

Opinion
Volume 6 Issue 2 - July 2018
DOI: 10.19080/JPCR.2018.06.555682

J of Pharmacol & Clin Res
Copyright © All rights are reserved by Agnieszka Pature

IL-15 in Pancreatic Cancer

Agnieszka Pature*, Jakub Wisniewski, Vesna Erika Modrić and Zlatko Ulovec

University of Zagreb, Zagreb, Europe

Submission: July 30, 2018; **Published:** August 06, 2018

***Corresponding author:** Agnieszka Pature, University of Zagreb, Zagreb, Croatia, Europe, Tel: 8322754275; Email: agnieszkapature23@gmail.com

Introduction

Pancreatic cancer is the second most common gastrointestinal cancer in the United States with an estimated incidence of 53,070 cases in the year 2016 [1]. Survival outcomes are poor with an estimated 5year overall survival rate of less than 5%. The lack of validated prevention strategies and screening tools for early detection contribute to diagnosis of disease at more advanced stages. Radiation is used in early and locally advanced pancreatic cancer with some instances of utility in metastatic cancer as well [2]. Yet local recurrences rates are in the tune of 30-40% [3]. Currently there is increased recognition that the patient's immune system can be harnessed to improve treatment outcomes. In addition, RT has been found to have a Janus effect on immune system. It has been found to be immunostimulatory as well as immunosuppressive depending upon the dose, fraction size, tumor type and site of radiation. RT exerts its immunostimulatory effects by

a) Increased expression of Major histocompatibility antigen (MHC) on the tumor cells

b) Release of tumor associated antigens (TAA) leading to an in-situ vaccine effect

c) Enhanced expression of immunostimulatory signals like calreticulin, adenosine triphosphate (ATP), Heat shock proteins (HSP), high mobility group box proteins (HMBG)

d) Enhanced cross presentation of TAA by dendritic cells

e) Expression of concealed antigens like cancer testis antigen

f) Increases expression of Cluster of differentiation (CD) 95/Fas, intercelular adhesion molecule (ICAM) increasing sensitivity to effector T cells.

Downside to RT is that it can suppress immune system by depletion of hematopoietic progenitor cells in the lymphoid organs, upregulation of programmed death domain ligand (PDL1) and proportional increase in T regulatory cells [4,5].

In spite of advances in surgery, chemotherapy and radiation long term resistance to tumor recurrence has remained elusive. Immune system has specificity and memory which is not seen with any other therapeutic modality. RT has the potential to increase the impact of the immune system by enhancing the expression of pro immunogenic molecules and in turn the immune system also compliments the response to RT. RT and immunotherapy together mediate their anti-tumor effects by a dynamic interplay of CD8+ cytotoxic T cells, CD4+ effector T cells and T regulatory cells modulation. Among the primary lymphoid organs, RT dose to bone marrow is well known to be immunosuppressive studied in the context of medulloblastoma, total body irradiation and pelvic malignancies [6,7] Dose to the secondary lymphoid organs like spleen has been reported recently as an independent predictor of increased mortality secondary to lymphopenia in pancreatic cancer. [8] Researchers from John Hopkins have shown that lymphopenia due to RT dose to circulating lymphocytes may also be a predictor of poor overall survival in gliomas [9].

These observations point to the fact that CD4 helper T cells, CD8 effector T cells, T regulatory lymphocytes and B lymphocyte proportions might be altered. Recent studies have shown that RT dose to circulating lymphocytes reduces CD4 helper T cells, CD8 cytotoxic T lymphocytes and proportional increase in T regulatory cells. This alteration in T cell equilibrium might be responsible for reduced immunological cell death and inferior overall survival (OS). The recognition that immune system plays a vital role in tumor surveillance and the advent of immunotherapy has brought the focus on adequate number of lymphocytes in the circulation. Reduced pretreatment lymphocyte count and reduced lymphocyte infiltration in pathologically resected specimens have been associated with poor disease-free survival (DFS) and overall survival (OS) in breast, rectal, glioblastoma multiforme, non-small cell lung cancer and in a vast majority of tumors.

CL are the cells that eventually infiltrate the tumors. Hence depletion in circulating pool of lymphocytes might lead to suboptimal treatment outcomes. Radiation induced lymphopenia (RIL) has been shown to be an independent predictor of inferior overall survival in gliomas, pancreatic

cancer, lung, hepatocellular malignancies and inferior progression free survival (PFS) in head and neck cancers [8,10-14]. RIL has also been associated with poor response to therapy and higher recurrence rates in cervical and bladder cancer. Unintentional splenic irradiation in pancreatic cancer has been postulated to affect disease outcomes. Splenic Dmean of >9 Gy causes lymphopenia and this lymphopenia might lead to reduced infiltration of cytotoxic lymphocytes into the tumor leading to suboptimal tumor control [8]. It has also been found that there is a failure in the compensatory rise of IL-7 and IL-15 which are homeostatic cytokines that are responsible for optimal level of lymphocytes in circulation [15]. Hence, we propose that supplementation of IL-7 or IL-15 may overcome post radiation lymphopenia and enhance infiltration of lymphocytes into the tumor leading to better tumor control.

IL-15 is a 15,000 Dalton cytokine with structural homology with IL-2 with respect to CD 122 and gamma chain receptor. It stimulates the generation of cytotoxic CD8+ T lymphocytes, B cells and NK cells similar to IL -2. But in differs from IL -2 in not stimulating T regulatory cell production and with no capillary leak syndrome [16]. Hence it can be used an immunostimulant therapeutically. Researchers from Weil Cornell have done in vivo studies on breast cancer bearing mice and found that RT+ intratumoral IL-15 produced the greatest survival advantage compared to with either one alone. This effect correlated with increase expression of CD8+T cells, CD4 effector to T regulatory cells. In a similar experiment they also showed that NK cells in addition to CD8 T cells play a critical role in mediating tumoricidal effect of RT+IL-15. They hypothesized that NK cell are critical mediators either by direct cytotoxic effect or priming CD8+ T cells or a combination of both [17]. Mathios et al evaluated the effect of IL-15 on murine glioblastoma tumors treated with 10 Gy of RT by SRS.They found RT+IL-15 provided the most durable tumor response with increase in CD8 +T cells and NK cells. But artificial depletion of NK cells had no effect on tumor control [18]. This provides conflicting reports on role of NK cells in mediating IL-15 syngersitic effect with RT.Nerverthless, IL-15 tends to increase cytotoxic CD 8+ T lymphocytes with no effect on T regulatory cells, can be used for treating or preventing RIL. The advantage of IL-15 is that it is known to imbibe antigen memory to the T cells. The possibility of immunological cancer antigen memory in preventing long term recurrence of disease is an interesting possibility worth exploring.

The first human clinical trial of IL-15 in metastatic cancer was published in 2015 and it was found to be safe. IL-15 increased serum NK cells and CD8 memory T cells. The shortcoming of IL-15 for clinical use is its short half-life and the relatively high dose required to achieve the desired effect in animal models [19]. Hence IL-15 superagonist/IL-15RaSushi-Fc fusion complex (IL-15SA/IL-15RaSu-Fc; ALT-803) has increased affinity for immune cells and has potent NK and CD8+ T cell stimulation even at lower therapeutic concentrations. ALT-803 has shown to be 5-25 times increased in vivo biological action and exhibits longer half-life [20]. This fusion complex has been studied in lymphoma, rat bladder cancer and murine glioblastoma models [21-30]. ALT-803 could be used as a protein scaffold to create IL-15-based tumor cell-specific molecules. This novel fusion protein exhibits enhanced anti-tumor activity compared to rituximab while maintaining IL-15 immunostimulant properties. Its utility in pancreatic cancer and its possible synergistic effect with radiation is an area worth exploration. We propose that IL-15 based complexes can have multi-pronged effects in terms of rescue tool for radiation induced lymphopenia, enhance the immunological effects of radiation and produce immunological memory to tumor antigens thereby producing a vaccine effect.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistic CA: a cancer journal for clinicians 66(1): 7-30.
2. Benson R, Mallick S, Prasad VB, Haresh KP, et al. (2015) Medullomyoblastoma treated with craniospinal radiation and adjuvant chemotherapy: Report of 4 cases and review of the literature. J Egypt Natl Cancer Inst 27(2): 109-111.
3. Venkatesulu BP, Pathy S, Vallonthaiel AG, Chawla B (2015) Case Report: Epithelial-myoepithelial carcinoma of lacrimal gland from an ex pleomorphic adenoma.
4. Ahmed MM, Hodge JW, Guha C, Bernhard EJ, Vikram B (2013) Harnessing the potential of radiation induced immune modulation for cancer therapy. Cancer immunology research 1(5): 280-284.
5. Weichselbaum RR, Liang H, Deng L, Fu YX (2017) Radiotherapy and immunotherapy: a beneficial liaison? Nature reviews Clinical oncology 14(6): 365-379.
6. Brown AP, Barney CL, Grosshans DR, McAleer MF (2013) Proton beam craniospinal irradiation reduces acute toxicity for adults with medulloblastoma. International journal of radiation oncology, biology, physics 86(2): 277-284.
7. Mell LK, Schomas DA, Salama JK, Devisetty K, Aydogan B, et al. (2008) Association between bone marrow dosimetric parameters and acute hematologic toxicity in anal cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. International journal of radiation oncology, biology, physics 70(5): 1431-1437.
8. Chadha AS, Liu G, Chen HC, Das P, Minsky BD, et al. (2017) Does Unintentional Splenic Radiation Predict Outcomes After Pancreatic Cancer Radiation Therapy? International journal of radiation oncology, biology, physics 97(2): 323-332.
9. Campian JL, Piotrowski AF, Ye X, Hakim FT, Rose J, et al. (2017) Serial changes in lymphocyte subsets in patients with newly diagnosed high grade astrocytomas treated with standard radiation and temozolomide. Journal of neuro-oncology.
10. Venkatesulu BP, Mallick S, Singh A, Julka PK (2015) Non-small cell carcinoma of lung with metachronous breast metastasis and cardiac tamponade: Unusual presentation of a common cancer. J Egypt Natl Cancer Inst 27(3): 165-169.
11. Venkatesulu B, Mallick S, Giridhar P, Upadhyay AD, Rath GK, et al. (2018) Pattern of care and impact of prognostic factors on the outcome of head and neck extramedullary plasmacytoma: a systematic review and individual patient data analysis of 315 cases. Eur Arch Otorhinolaryngol 275(2): 595-606.
12. Mallick S, Benson R, Venkatesulu B, Melgandi W, Rath GK, et al. (2017) Patterns of care and survival outcomes in patients with astroblastoma: an individual patient data analysis of 152 cases. Childs Nerv Syst 33(8): 1295-1302.

How to cite this article: Agnieszka Pature, Jakub Wisniewski, Vesna Erika Modrić, IL-15 in Pancreatic Cancer. J of Pharmacol & Clin Res. 2018; 6(2): 555682. DOI: 10.19080/JPCR.2018.06.555682.

13. Venkatesulu BP, Mallick S, Rath GK (2017) Patterns of care of cervical cancer in the elderly: A qualitative literature review. J Geriatr Oncol 8(2): 108-116.

14. Bhanuprasad V, Mallick S, Bhasker S, Mohanti BK (2015) Pediatric head and neck squamous cell carcinoma: report of 12 cases and illustrated review of literature. Int J Pediatr Otorhinolaryngol 79(8): 1279-1282.

15. Bhasker S, Mallick S, Benson R, Bhanuprasad V, Sharma A, Thakar A (2017) A multimodality approach to sinonasal undifferentiated carcinoma: a single institute experience. J Laryngol Otol 131(1): 19-25.

16. Waldmann TA (2006) The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design. Nature reviews Immunology 6(8): 595-601.

17. Martinez EG, Pilones K A, Aryankalayil J, Formenti S, Demaria S (2017) Therapeutic effect of local Interleukin-15 with radiotherapy in breast cancer. ASCO Chiacgo: J Clin Oncol.

18. Mathios D, Park CK, Marcus WD, Alter S, Rhode PR, et al. (2016) Therapeutic administration of IL-15 superagonist complex ALT-803 leads to long-term survival and durable antitumor immune response in a murine glioblastoma model. International journal of cancer 138(1): 187-194.

19. Conlon KC, Lugli E, Welles HC, Rosenberg SA, Fojo AT, et al. (2015) Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 33(1): 74-82.

20. Bailey CP, Budak-Alpdogan T, Sauter CT, Panis MM, Buyukgoz C, et al. (2017) New interleukin-15 superagonist (IL-15SA) significantly enhances graft-versus-tumor activity. Oncotarget. 8(27): 44366-44378.

21. Venkatesulu BP, Mallick S, Lin SH, Krishnan S (2018) A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. Crit Rev Oncol Hematol 123: 42-51.

22. Ko K, Wang Y, Kotla S, Fujii Y, Vu HT, et al. (2018) Developing a reliable Mouse Model for cancer Therapy-induced cardiovascular Toxicity in cancer Patients and survivors. Front Cardiovasc Med 5: 26.

23. Mahadevan LS, Zhong J, Venkatesulu B, Kaur H, Bhide S, et al. (2018) Imaging predictors of treatment outcomes in rectal cancer: an overview. Crit Rev Oncol Hematol.

24. Prasad VB, Mallick S, Upadhyay AD, Rath GK (2017) Systematic review and individual patient data analysis of pediatric head and neck squamous cell carcinoma: an analysis of 217 cases. Int J Pediatr Otorhinolaryngol 92: 75-81.

25. Bolotin E, Smogorzewska M, Smith S, Widmer M, Weinberg K (1996) Enhancement of thymopoiesis after bone marrow transplant by in vivo interleukin-7. Blood 88: 1887-1894.

26. Geiselhart LA (2001) IL-7 administration alters the CD4: CD8 ratio, increases T cell numbers, and increases T cell function in the absence of activation. J. Immunol. Baltim. Md 1950 166, 3019-3027.

27. Fry TJ, Christensen BL, Komschlies KL, Gress RE, Mackall CL (2001) Interleukin-7 restores immunity in athymic T-cell-depleted hosts. Blood 97 pp. 1525-1533.

28. Damia G, Komschlies KL, Faltynek CR, Ruscetti FW , Wiltrout RH (1992) Administration of recombinant human interleukin-7 alters the frequency and number of myeloid progenitor cells in the bone marrow and spleen of mice. Blood 79: 1121-1129.

29. Faltynek CR (1992) Administration of human recombinant IL-7 to normal and irradiated mice increases the numbers of lymphocytes and some immature cells of the myeloid lineage. J Immunol 149(4): 1276-1282.

30. (2017) IL-7 in Increasing Low CD4 Counts After Concurrent Radiation and Temozolomide Treatment in Patients With High Grade Gliomas. Clinical Trials gov.

This work is licensed under Creative Commons Attribution 4.0 License
DOI: 10.19080/JPCR.2018.06.555682

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats
  (Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
https://juniperpublishers.com/online-submission.php

How to cite this article: Agnieszka Pature, Jakub Wisniewski, Vesna Erika Modrić, IL-15 in Pancreatic Cancer. J of Pharmacol & Clin Res. 2018; 6(2): 555682. DOI: 10.19080/JPCR.2018.06.555682.