Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Review Article
Volume 23 Issue 2 - April 2023
DOI: 10.19080/CTOIJ.2023.23.556115

Cancer Ther Oncol Int J

Radio Immunotherapy (Zetotherapy) its Clinical Implications as well as its Future Prospects in India

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Submission: March 16, 2023; **Published:** April 03, 2023

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Abstract

Antibodies directed against tumor associated antigen provides a means for delivering preferentially cytotoxic radionucleotides to the tumor tissue primary as well as its metastatic sites known as Zetotherapy or Radioimmunotherapy, The factor that can influence the effectiveness of radiation in the tumor compared with its effects on radio sensitive normal tissue depends upon specificity of antibody , other factor which can influence is the distribution of target energy in the tumor and host response to the injected foreign antibody There is a continue research/studies for more specific antibodies to target against targeting antigen present on tumor , the parallel growth of Genetic Engineering are geared towards the problem of reducing antigenecity of specific antibodies and reducing the mass of cancer antigen antibodies.

Discussion

Radioimmunotherapy (RIT) got a thrust after the development of new monoclonal antibodies as part of chemotherapy / immunotherapies for cancer treatment because of three factors given below.

i. Monoclonal antibodies introduction allows more precise targeting to cancer cells (Figure 1A & 1B).

ii. The improve gamma and positrons tumor immune imaging can be obtained by the help of Monoclonal antibodies since it get concentrated in tumor tissues.

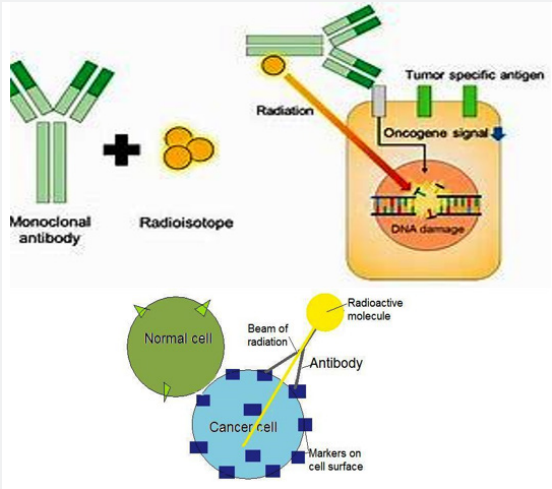

Figure 1A & B: Radioimmunotherapy.

iii. There have been number of research /studies indicating clinical response to monoclonal antibodies labeled with radionucleotides.

In view of above facts Order at el at Jhon Hopkins hospital Baltimore used Radio labeled antibodies for Hepatocellular carcinoma and Cholongiocarcinoma which included I131 labeled antiferritine and Anti carcinoembrynoic antigen (CEA), and Carrasquillo and his colleagues 1984 used murine monoclonal antibodies labeled with isotope of radioiodine against Oncofetal glycoprotein (p97) in human melanoma with definite clinical response. So, till date stage is set for this form of cancer therapies but it requires Multidisciplinary team work which includes nuclear medicine expert / Radiation oncologist /Medical Physicist [1-5].

What is targeted in Radioimmunotherapies?

The ultimate target for the administered radio labeled antibodies / polyclonal antibodies are ionizing radiation to the DNA of malignant cells.

The effect of radiations due to doubled DNA breakage (DSB). It has been found that low energy transfer LET radiations of photons/ electrons an average 200 -DSB require to kill 90% of tumor cell populations as well as high energy transfer high LET radiation α particle/ Neutrons is somewhat fewer DSB are required. One advantage that targeted radiations has over antibodies targeted cytotoxins is that a tumor cells without appropriate antigenic determinants can yet be sterilized by radiations cross fire from adjacent cells having the determinant and binding the labeled antibody the sterilizing efficiency of the crossfire effect will depends to a large degree upon the spatial arrangement of the malignant stem cells the respect of labeled carrier antibody.

It has been also found in studies that tumor biopsies that many of the McAbs (Monoclonal antibodies) directed against tumor associated membrane antigen will attack /attached to surfaces of only a portion of the malignant cells population due to Antigenic heterogeneity due this there is no doubt that many tumors it will results in uneven distribution of targeting antibody so the cross fire effect will compensate this? it is also possible that polyclonal antibodies can reduce this un even distribution of radio nucleotide carrier antibody furthermore the problem of heterogeneity of tumor cells antigen can be overcome by radioactivity were to deliver by small numbers of antibody molecules heavily laden with α and β emitters [6-12].

The Carrier for Radio Immunotherapies

furthermore, of the carrier (Antibody) is to deliver tumor cells sufficient radioactivity to sterilized them although attention is focused on delivering high levels of radioactivity as quickly as possible to tumor cells furthermore it is equally important that retention time of radio nucleotides in the tumor cells relative to that dose limiting normal tissues should be as long as possible [13-18]. To maximize the ratio of dose to tumor cells to normal cells , ideally the physical half-life of radio nucleotide should be similar to the biological half-life of carrier (antibody) but unfortunately antibody biological half-life greatly varies tumor types to other tumor types, It seems monoclonal antibodies more avidly binds to tumor cells antigen in compare to polyclonal antibodies. Recent advancements in genetic engineering now make it possible to prepare human antibodies with high avidity to tumor tissues that reduces the chances unnecessary accumulation of radio labeled antibodies in normal tissues. After injecting radio labeled antibody immunogenic reactions happens in host and immune complex being formed these immune complexes get accumulated in host Reticuloendothelial (RES) tissues, Spleen , bone marrows. Kidneys and liver and producing harmful side effects of radiation we also know that circulatory tumor antigen is also present in host blood (LIQUID BIOPSIES) which instantly combine with injected radio nucleotide antibody and get deposited in RES, and kidneys and producing harmful effects [19-25].

Unfortunately, it remains a significant stumbling block in the treatment of Radioimmunotheripes

One can argues that high metabolic activities in tumor cell as well as high proliferative index over normal tissue will take care of RES/ KIDNEY extra radiation, but we all know that normal tissue permeability of capillaries example thyroid bone marrow renalglomeruls liver/spleen choroid plexus there is rapid passage of macromolecules so if malignancies originating from these tissues might be the ideal candidates for radioimmunotheripes.

The Choice of Radionucleotides

Tumor localization can be obtained by using specific antibodies (Monoclonal/ Polyclonal) labeled with 109 Pd, I131 (Goldenberg Et al 1982), Astatine A211 among above mention only I131 has been so far used much clinically most of the work on I131 was carried out by Order and his colleagues(1980 to 1984) they reported significant response in Hepatocellular carcinoma to I131 Labeled with Antiferritine in Hepatocellular carcimona and I131 along anti CEA antibodies used as part of complex drug/ radiation regime .Some researchers have reported added degree of response when I131 labeled with anti-epidermal growth factor receptor these researchers injected labeled McAbs either directly into tumor or artery supplying that very tumor. I131 Over many years proved its tumor destructive properties in thyroid carcinomas and it was therefore quit natural to use this radionucleotide for antibody targeted therapies knowing the fact this agent has been well studied as well as relatively cheaper to other radionucleotides.

However, some limiting factors is being noted in RIT treatment are.

i. Variation in the pattern of distribution of malignant cells within the tumor mass because of the heterogeneity factor.

ii. Variation in the size of tumor mass and their metastasis pattern.

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iii. Different retention time of different radiolabelled antibodies makes it clear that only one nucleotides will not be suitable for all different kinds of tumor.

One therapeutic approach to overcome the heterogeneity of tumor mass is to use to use a radiolabelled with high cytotoxic activities , the α emitters radionucleotides fall into this class , but the problem of with this emitter that α emitters equally efficient in killing of normal cells as well.

B emitter can be use with philosophy that allows time for the repairing of normal cells but such repairer do not happens with α emitter.

How to Protect Normal Cells & Fast-Growing Stem Cells (Bone Marrow) During Rit Treatment

THE Attention given for increase deposition of energy in tumor keeping mind that similar increase may occur in the energy deposits in bone marrow kidneys , liver like critical organs in clinical practice above problem tackled by monitoring biochemical and hematological parameters before ,during and after RIT therapy . The most common side effect found to be life threatening leucopenia and thrombocytopenia, by the help of gamma scientinography that liver and spleen (RES) accumulates large amount of radio nucleotides. It indicates that highest activities used in the therapy the dose limiting radiotoxic effect may be to those organs rather than bone marrow, in other circumstances kidney could be most affected organ because of localization of radionucleotide immune complexes of Ig fragments kidney keeping these thing in mind that estimation of local absorbed dose not simply the absorbed dose to the whole organ.

Zetotherapy prospects

Cancer treatment with targeted radionucleotide treatment also known as Zetotherapy (Zeto means therapy by seeking out tumor cells) is area of radiotherapy with considerable potential , this potential is to realize problems as well associated with this form of therapy need to be sorted out clinically and must be realized and addressed upon .given below points must be clarified and resolved.

Antigenic heterogeneity

The irregular distribution of binding sites throughout the tumor cell population is likely to produce a similar irregular deposition of energy for that an approach must be addressed to get an uniform distribution of radiation energy among tumor cell population, McAbs (monoclonal antibodies) supposed to less heterogeneously distributed and more specific to tumor cells.

Specificity of Antibody (Carrier)

Many of the presently available antibodies are localized in the area other than tumor. It's important that search must made for most appropriate antibodies as carrier that preferentially localized in primary tumor or its secondaries only.

Fractions of Radiations

With external irradiation EBRT fractionations dose is given in such way that normal tissue gets time to repairer the same principle will apply with β emitters but not with α emitters. The difficulty with fractionations of dose with Zetotherapy is the major problem due to antigenicity of given radiolabel antibodies the most pragmatic and successful to this problem were tried to resolve by Order and his collogues by using multiple sessions of giving polyclonal antibodies each time of using different species of to develop antibodies other most practical salutation appears to me that we deployed Genetic engineering dept to develop carrier antibodies molecule with minimum antigenicity to host.

Access of antibody to target antigen

Science estimation of radioactivity deposition at microscopic level in tumor mass cannot be done even by Gamma Scintigraphy or by PET scanning [26-35]. ***Actually Specking This Represents a Major Problem in Our Present Knowledge***

Conclusion

In India parallel development of Genetic engineering, Radiation oncology along nuclear medicine branch as well as medical physicist will surely give boon to this form of therapies, our aim should be therefore addressing the problems associated with Zetotherapy as discussed above as well as try to identify tumors as quickly as possible those are most suitable for this kind of therapies in cancer treatment.

References

1. R W Wissler, P A Barker, M H Flax, D W Talmage (1956) A study of the preparation, localization, and effects of antitumor antibodies labeled with I131. Cancer Research 16(8): 761–773.
2. O A Gansow, M W Brechbiel, S Mirzadeh, D Colcher, M Roselli, et al. (1990) Chelates and antibodies: current methods and new directions. Cancer Treatment and Research 51: 153–171.
3. M K Moi, S J DeNardo, C F Meares (1990) Stable bifunctional chelates of metals used in radiotherapy. Cancer Res 50(3): S789–S793.
4. D M Goldenberg, R M Sharkey (2006) Advances in cancer therapy with radiolabeled monoclonal antibodies. Q J Nucl Med Mol Imaging 50(4): 248–264.
5. K M Prise, J M O'Sullivan (2009) Radiation-induced bystander signaling in cancer therapy. Nature Reviews Cancer 9(5): 351–360.
6. J A Bertout, S A Patel, M C Simon (2008) The impact of O_2 availability on human cancer. Nat Rev Cancer 8(12): 967-975.
7. P Vaupel, A Mayer (2007) Hypoxia in cancer: significance and impact on clinical outcome. Cancer and Metastasis Reviews vol 26(2): 225–239.
8. G Kroemer, L Galluzzi, C Brenner (2007) Mitochondrial membrane permeabilization in cell death. Physiological Reviews 87(1): 99–163.
9. L Cabon, P Galan-Malo, A Bouharrour, L Delavallée, M-N Brunelle-Navas, et al. (2012) BID regulates ´AIF-mediated caspase-independent necroptosis by promoting BAX activation. Cell Death and Differentiation 19(2): 245–256.
10. R Ganss, E Ryschich, E Klar, B Arnold, G J Hammerling (2002) Combination of T-cell therapy and trigger of inflammation induces

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remodeling of the vasculature and tumor eradication. Cancer Research 62(5): 1462–1470.

11. E Tartour, H Pere, B Maillere, M Terme, N Merillon, et al. (2011) Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. Cancer and Metastasis Reviews vol 30(1): 83–95.

12. R W Howell (2008) Auger processes in the 21st century. International Journal of Radiation Biology 84(12): 959–975.

13. M J Mattes (2002) Radionuclide-antibody conjugates for single-cell cytotoxicity. Cancer 94(4): 1215-1223.

14. G L Ong, S E Elsamra, D M Goldenberg, M Jules Mattes (2001) Single-cell cytotoxicity with radiolabeled antibodies. Clinical Cancer Research 7(1): 192–201.

15. A K Claesson, B Stenerlow, L Jacobsson, K Elmroth (2007) Relative biological effectiveness of the α-particle emitter 211At for double-strand break induction in human fibroblasts. Radiation Research 167(3): 312–318.

16. E J Hall, A J Giaccia (2007) Radiology for the Radiologist, Lippincott Williams & Wilkins, Pa, 7th edn, Philadelphia, USA.

17. M R McDevitt, G Sgouros, R D Finn, J L Humm, J G Jurcic, et al. (1998) Radioimmunotherapy with α-emitting nuclides. Eur J Nucl Med 25(9): 1341–1351.

18. M Cherel, S Gouard, J Gaschet, Catherine Sai-Maurel, Frank Bruchertseifer, et al. (2013) 213Bi radioimmunotherapy with an anti-mCD138 monoclonal antibody in a murine model of multiple myeloma. J Nucl Med 54(9): 1597-1604.

19. G Vaidyanathan, M R Zalutsky (2008) Astatine radiopharmaceuticals: prospects and problems," Curr Radiopharm 1(3): 177–196.

20. M Miederer, D A Scheinberg, M R McDevitt (2008) Realizing the potential of the Actinium-225 radionuclide generator in targeted alpha particle therapy applications. Advanced Drug Delivery Reviews 60(12): 1371–1382.

21. M L Sautter-Bihl, G Herbold, H Bihl (1996) Minimal residual disease: a target for radioimmunotherapy with 131Ilabeled monoclonal antibodies? Some dosimetric considerations," Recent Results in Cancer Research 141: 67–75.

22. K Chen, X Chen (2010) Design and development of molecular imaging probes. Curr Top Med Chem 10(12): 1227–1236.

23. K Chen, P S Conti (2010) Target-specific delivery of peptidebased probes for PET imaging. Advanced Drug Delivery Reviews 62(11): 1005–1022.

24. G Kohler, C Milstein (1975) Continuous cultures of fused cells ¨ secreting antibody of predefined specificity. Nature 256(5517): 495-497.

25. J L Murray, M G Rosenblum, L Lamki, H J Glenn, Z Krizan, et al. (1987) Clinical parameters related to optimal tumor localization of indium-111- labeled mouse antimelanoma monoclonal antibody ZME-018. The J Nucl Med 28(1): 25–33.

26. S F Rosebrough, Z D Grossman, J G McAfee, B J Kudryk, G Subramanian, et al. (1988) Thrombus imaging with Indium-111 and Iodine-131-labeled fibrin-specific monoclonal antibody and its F(ab')2 and Fab fragments. J Nucl Med 29(7): 1212–1222.

27. A M Wu, P D Senter (2005) Arming antibodies: prospects and challenges for immunoconjugates. Nature Biotechnology 23(9): 1137–1146.

28. L A Maleki, B Baradaran, J Majidi (2013) Future prospects of monoclonal antibodies as magic bullets in immunotherapy. Human Antibodies 22(1-2): 9-13.

29. G Sgouros, S Squeri, A M Ballangrud, Katherine S Kolbert, Jerrold B Teitcher, et al. (2003) Patient-specific, 3-dimensional dosimetry in non-Hodgkin's lymphoma patients treated with 131I-anti-B1 antibody: assessment of tumor doseresponse. J Nucl Med 44(2): 260–268.

30. R M Sharkey, A Brenner, J Burton, George Hajjar, Stephen P Toder, et al. (2003) Radioimmunotherapy of non-Hodgkin's lymphoma with 90Y-DOTA humanized anti-CD22 IgG (90Y-Epratuzumab): do tumor targeting and dosimetry predict therapeutic response? J Nucl Med 44(12): 2000-2018.

31. S J Goldsmith (2010) Radioimmunotherapy of lymphoma: bexxar and zevalin. Seminars in Nuclear Medicine 40(2): 122–135.

32. M S Kaminski, M Tuck, J Estes, Arne Kolstad, Charles W Ross, et al. (2005) 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 352(5): 441–449.

33. M F Leahy, J H Turner (2011) Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood vol 117(1): 45–52.

34. J H Turner, A A Martindale, J Boucek, P G Claringbold, M F Leahy (2003) 131I-anti CD20 radioimmunotherapy of relapsed or refractory non-Hodgkins lymphoma: a phase II clinical trial of a nonmyeloablative dose regimen of chimeric rituximab radiolabeled in a hospital. Cancer Biotherapy & Radiopharmaceuticals 18(4): 513–524.

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