RADIATION HAZARDS AND BIOHAZARDS IN RADIOBIOCONJUGATE THERAPY

Shyam Gupta*, D. K. Hazra and M. Gupta

1. Department of Zoology, R. B. S. College, Agra (INDIA)
2. Nuclear Medicine and RIA Unit, S. N. Medical College, Agra (INDIA)

Received May 14, 2006 Accepted October 7, 2006

ABSTRACT

Currently there are three principal methods of treating cancer viz. surgery, chemotherapy and external radiation therapy. Each of these has its limitations. There is much interest today in the development of a new mode of therapy viz. the administration of radio labelled bioconjugates in nuclear medicine for the selective delivery of radiation to the cancer cells while sparing the normal cells.

Safety issues in radiobioconjugate therapy involve consideration of both radiation hazards as well as biohazards. Radiation hazards are relevant for the administration team but not for the patient who is benefiting from the therapy on the other hand Biohazards are important specially for the patient. Our center at Agra is the pioneer center for radiobioconjugate therapy in the country.

Key Words : Radiobioconjugate Therapy, Radiation hazards, Biohazards.

INTRODUCTION

At present, there are three principal methods of treating cancer viz. surgery, chemotherapy and external radiation therapy. Each of these has its limitations.1 There is much interest today in the development of a new mode of therapy viz. the administration of radio labelled bioconjugates in nuclear medicine for the selective delivery of radiation to the cancer cells while sparing the normal cells.2-3

This is analogous to radio war-head being carried by a guided missile or smart bomb (the bioconjugates) which selectively homes in the cancer cell by specific recognition of molecules on the cancer cell surface as shown in Fig. 1

The warhead for therapy should be an emitter of localized radiation such as alpha and beta radiation or Auger electrons. So far 131-Iodine has been used for this purpose but it has a disadvantage that the deiodinase enzyme in the body splits off the iodine from the antibody and causes non target irradiation.4

The other isotopes used in the West is Yttrium-90 which is a beta emitter but its disadvantage is that if it dissociates from the bioconjugate it is a bone seeker and will cause irradiation of healthy bone marrow.5-6

* Author for correspondence
Agra which is the leading centre in India for the development of this new mode of therapy has therefore been interested in alternative war-heads for therapy such as Silver, Gold and Rhenium.

Safety issues in radiobioconjugate therapy involve consideration of both radiation hazards as well as biohazards. Radiation hazards are relevant for the administration team but not for the patient who is benefiting from the therapy on the other hand biohazards are important specially for the patient. Our centre at Agra is the pioneer centre for radiobioconjugate therapy in the country.

**MATERIAL AND METHODS**

Human tumour xenografts were created in nude mice as well as swiss albino mice using cancer cell lines (HeLa).

Radionuclides $^{99}$Mo, Re-186/188, Gold 199 and $^{131}$I were also readily available from BRIT, Mumbai. $^{99m}$Tc, the daughter product of $^{99}$Mo was obtained by milking parent using $^{99}$Mo-$^{99m}$Tc generator (solvent extraction type) supplied by BRIT.

The antibodies whose labelling was studied including the following.

i. Human Immunoglobulin, polyclonal nonspecific mixture marketed as Bharglob (Bharat Serums and Vaccines Ltd., Thane).

The composition of Bharglob as following –

- Protein content : 165 mg/ml
- Stabilizer – Glycine : I.P. 0.3 M
- Preservative – Thiomersal : I.P. 0.01% w/v

ii. M3 Monoclonal antibody directed against the tissue polypeptide specific (TPS) antigen which is a pancarcinoma proliferation antigen of cytokeratin 8-18 family.

Imaging of experimental animals was performed in Orbiter-7500 Gamma Camera [SIEMENS, Germany). Counting of animal organs after sacrifice was performed using auto gamma counter (5002) obtained from PACKARD (Germany).

Radiobioconjugate therapy comprises therapy with radiolabelled biological moities, which may be antibodies, artificial antibody constructs: so called designer antibodies, peptides, antisense nucleotides, cytokines or other receptor specific molecules, or indeed combination of the two such as peptabodies. In many version of radiobioconjugate therapy there is also the option of using intermediate molecules such as avidin, biotin, chelates to enhance target / nontarget ratios, as well as agent to enhance tumour delivery such as the gamma globulin used by us for blocking...
nonspecific reticuloendothelial uptake, or the various chase agents used to clear the blood of unwanted radioactive or biological moities. In each case radiobiocjugate therapy is often preceded by radiobiocjugate administration for radiolocalisation and for confirming the delivery specificity of the therapy agent or for dosimetry. This is sometime performed with the same isotope as contemplated in therapy or a surrogate isotope.

In each case the hazard to the patient from the radionuclide moiety and from the biological molecule it self needs consideration, although of course the overriding philosophy is whether the proposed benefit in terms of tumour response overrides these hazards. Risks from the biological moiety per se are compounded by risks from contaminants such as murine or bacterial products: DNA or proteins or lipopolysaccharides such as endotoxins.

Altered methods of producing the biological moiety can reduced the risks, such as using transgenic mice with human immune systems, but do not entirely eliminate it.

Methods of minimising HAMA reactions using human antibodies, plasmapheresis and immunosuppressive regimes, and reducing the interval between scintigraphic and therapy administrations, and eschewing intradermal testing. There is of course evidence that HAMA reactions, especially the t cell component associated with it may indeed be beneficial to patients.

Modern methods of purifying the radiopharmaceutical such as multiple chromatography substantially reduce the risk of contamination wit the mouse DNA/RNA or mouse viruses. Terminal filters such as endotoxin filters advocated by our group also reduce the hazard from these although utmost care should be taken to avoid introduction of hazards during radiopharmaceutical preparation.

RESULTS AND DISCUSSION

Testing for hazards should not however be allowed to delay the development of these in cancer therapy. As Prof. Keith Briton remarked the hazard from the cancer is far greater than the infinitesimal risk of a mouse virus borne disease to the patient it should also be remembered that cytotoxic, surgical and teletherapy also carry their own risks and seeking to reduce the risks in radiobiocjugate therapy to zero or imposing mandatory expensive testing on each batch of radiopharmaceuticals is not pragmatic and in fact unwise. It should also be remembered that many of the risks attributed to immune reactions are in fact side effects of cytokine release, as using the anti EGFR Herceptin.

The potential genetic risks from introducing DNA/ RNA fragments such as antisense nucleotides are not yet fully known. Hopefully these are innocuous and incapable of replication in vivo. Utilisation of universal warhead molecules such as radiolabelled biotin should reduce the logistic and financial problems of using multiple radiobiocconstructs. Using pancarcinoma biological moieties: peptides or antibodies also reduce the risk of contamination. The existence of endogenous biotinases or allergies to avidin/streptavidin needs to be borne in mind.

CONCLUSION

It is concluded that while treating the patients one should be aware of safety profile besides the therapeutic availability of radiobiocjugate therapy.

REFERENCES


