

Scientific Session-7 Liver Cancer & Miscellaneous

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Statistics don't lie – do people?

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Flowery phrases like 'there are lies, damn lies and statistics' or 'one can prove anything with statistics' are well known to statisticians and they usually react to them with a patronizing smile. But, while such perfunctory statements are extremely unfair to statistics, it is still true that misuse of statistics leads to wrong conclusions and that there is too much of such misuse around. Even among statisticians, for example, it is not uncommon that early analyses in testing drugs show promising results, but these findings are later not confirmed. Which is why biostatisticians say that a drug should be used immediately, while it still works. Statistics is basically a mathematical discipline, so there is no place in it for 'lies'. But in practice the mathematical base is joined with collection, editing and description of data, which are not 'covered' by mathematical theory. And on top of this comes the fact that reality does not always obey the mathematical assumptions. In all these, there is, unfortunately, space for error. Not to mention, of course, simple ignorance, or, god forbid, intentional misuse. In this lecture, I will show examples from statistical practice to illustrate some traps, which researchers should have in mind in the process, from planning a study to the analysis of data and interpretation of results. There will be no complicated statistics; the talk should be understandable to any researcher in medicine. I would like to leave the audience with two messages: 1. More statistical knowledge better statistical analysis better research. 2. It is people who 'lie' (misuse statistics). Statisticians are people.

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New Perspectives in Radiobioconjugate Targeting

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The therapy component of nuclear medicine, in fact the "medicine" in nuclear medicine as a discipline stems largely from the ability of this discipline to intervene in the treatment of cancer, one of the major challenges to human health today, initially though the happy coincidence of iodine naturally concentrating in the thyroid tissue thanks to the providential symporter pump and radioiodine being one of the easily available products of the atomic reactor in the Atomic era that dawned in the first half of the 20th century had aroused tremendous hopes in thyroidology.

The selective recognition of cancer cells remains the key to all therapy approaches: be it the deployment of force multiplier radioactive warheads or the beaming of

radiofrequency energy through nanoparticles.

This selective recognition originally came from the antibody molecule locking into the more or less tumour specific antigens on the surface of the tumour cell, many of which were expressions of the oncogenes activated in cancer cells. This was followed by an explosion of peptides targeting a diversity of cell surface receptors.

At first the intracellular elements of the cancer cell appeared to be inaccessible, but today the utilization of nuclear localizing sequences borrowed from simian viruses promises to give us gives the ability to target these as well. Carbon nano-tubules, naked DNA, RNA interference with si RNA, aptamers, antisense nucleotides, morpholino compounds are other examples of our newfound ability to target the innards of the cells.

Attention is today focused on increasing the fraction of the biological moiety concentrating in the tumour cells as contrasted to the closely similar normal mammalian cells, a far greater challenge than Paul Ehrlich's magic bullets differentiating mammalian and bacterial cells! Apart from higher specificity, designer antibody fragments and constructs also offer the advantage of the possibility of repeated administration by virtue of lessened immunogenicity, with the progressive shift from murine to chimeric to humanized to human non-immunogenic antibodies. Decreasing nonspecific reticuloendothelial trapping by getting rid of Fc moieties, blocking the reticuloendothelial system using large molecules particularly inexpensive human nonspecific Immunoglobulins is another method we have found useful in enhancing target/non-target ratios, reminiscent of the use of cold specific antibodies during the immunoglobulin therapy of lymphomas. Pre-targeting is evolving with two, three, four and five step targeting, using both the avidin biotin strong interaction, as well as the hapten chelate approach. Radiolabeled biotin is also being used to target avidin directly applied to micro-metastases field during surgery. There is hope from fusion molecules which incorporate both targeting and amplifying moieties.

Warheads continue to evolve: soft and hard betas being supplemented by alpha emitters and Auger electron emitters. The latter are particularly attractive for targeting the fine structure of the tumour cell intracellular organelles. There are problems to overcome but we feel that over the next decade radiolabeled moieties and non-labeled bio missiles against cancer will attain the ubiquity of today's antibiotics in the control of infections ! This will involve bench work and multiple centre clinical evaluations which need to be accelerated, and bureaucratic hurdles, deo gratia, overcome!

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Targeted Liver Tumor Therapy with Radioembolization

Prof. G. Wiseman, Mayo Clinic, USA

Abstract not available

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A perspective on WRPTC: We may not change the world, but we can make a small difference

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World Radiopharmaceutical Therapy Council (WRPTC) is an International Scientific Organization with stake holders from all fields of nuclear medicine and several allied clinical specialties, e.g., nuclear medicine physicians, radiologists, internists, endocrinologists, radiation oncologists, radio-chemists, physicists, medical oncologists, rheumatologists, etc who share research commitments to, and clinical practice in, therapeutic nuclear medicine. The major objective of the WRPTC includes setting standards for provision of radiopharmaceutical therapy; particularly in the development of uniform protocols for clinical practice of therapeutic nuclear medicine worldwide. To-day radiopharmaceutical therapy is the fastest growing branch of nuclear medicine. However, its practice in developing countries is limited by the prohibitive cost of radiopharmaceuticals. Many of the radionuclides are not easily available on site; have to be imported from far off places – there by making them still more expensive. Besides, stringent regulatory processes make our life still more difficult and impossible to use in some countries. It is important to understand that innovative ideas, simplified procedures, use of local expertise in the developing countries and in-house preparation of some of the therapeutic radiopharmaceuticals may enable the nuclear medicine community in the developing world to use a number of therapeutic procedures in nuclear medicine successfully and effectively at a very very reasonable cost. These are some of the issues which the WRPTC would like to address, which may enable the needy and deserving patients to receive more and more of such types of treatments than the case at present.

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Evaluación de la eficacia terapéutica de un complejo mixto $^{188}\text{Re(V)}$ -oxo como potencial agente para terapia de melanomaS. Fernández¹, J. Giglio¹, M. Terán¹, M. Incerti², C. Agorio³, A. Chabalgoity³, A. Rey¹¹ Cátedra de Radioquímica, Facultad de Química;² Cátedra de Química Farmacéutica, Facultad de Química;³ Laboratorio de Vacunas Recombinantes, Instituto de Higiene, Facultad de Medicina.

El melanoma es un tumor cuya incidencia ha ido en aumento dado que no existen tratamientos realmente eficaces en estadios avanzados de la enfermedad, siendo entonces fundamental el desarrollo de nuevas opciones

terapéuticas.

Nuestro grupo ha desarrollado una familia de oxocomplejos mixtos “3+1” diseñada mediante un concepto “integrado” que aprovecha la similitud química con la N-(2-dietilaminoetil)-4-iodobenzamida, de alta afinidad por melanoma. Algunos de estos compuestos mostraron una alta captación en animales portadores de melanoma murino inducido por lo que se decidió estudiar su eficacia terapéutica.

La marcación con ^{188}Re fue realizada por coordinación simultánea del ligando tridentado N-(2-mercaptoetil)-N',N'-dietiletilendiamina con el tiol monodentado p-I-tiofenol utilizando oxalato de sodio como expansor de la esfera de coordinación. El rendimiento de marcación calculado en base al porcentaje de extracción en diclorometano fue de 42 - 44% y la pureza radioquímica determinada por HPLC superior al 90%.

La evaluación “in vivo” fue realizada mediante biodistribución en animales portadores de melanomas inducidos por inoculación subcutánea de 2×10^5 células de B16-F1, a los que se inyectó el producto en la zona peritumoral, debido a que la vía de administración sistémica mostró una elevada captación hepato-biliar. Los resultados muestran una importante captación y retención en el tumor así como una elevada depuración sanguínea y tejidos blandos.

La evaluación dosimétrica realizada mediante metodología MIRD y código Olinda estima una dosis de 54.4 Gy/mCi para un tumor esférico de 1g con un margen de seguridad elevado ya que la dosis en médula ósea es de 5.1 mGy/mCi y en riñón de 0.014 mGy/mCi.

Los estudios de eficacia terapéutica fueron diseñados sobre el mismo modelo animal portador de melanoma murino previamente descrito. 3 grupos de animales (5 animales por grupo) fueron tratados con una única dosis de 300 μCi del radiomarcado, 600 μCi o 2 dosis de 300 μCi (con una semana entre ellas) en la zona peritumoral. Un grupo de animales no tratados también se incluyó en el estudio. El tamaño del tumor fue determinado cada 2-3 días mediante la medida de su largo, ancho y profundidad y se calculó su volumen utilizando la siguiente fórmula: (largo x ancho x profundidad) x $\pi/6$.

Los estudios de los efectos sobre el crecimiento del tumor revelaron tamaños relativos promedio significativamente menores en todos los grupos tratados en comparación con el grupo no tratado, siendo más importante la diferencia para los que recibieron la dosis única de 600 μCi y 300 μCi . El efecto sobre la sobrevida de los animales se evaluó mediante la construcción de curvas de supervivencia Kaplan-Meier, resultando en una mayor probabilidad de supervivencia para el grupo que recibió una única dosis de 300 μCi .

Como conclusión se puede señalar que estos primeros estudios de eficacia terapéutica resultaron muy auspiciosos, demostrando efectos positivos sobre el tratamiento de melanoma murino en todos los casos evaluados. Esto permite enfocarnos a futuro en la profundización de estudios terapéuticos para este tipo de oxocomplejos mixtos “3+1”.