


INTEGRATED ACADEMIC STUDIES OF
MEDICINE


IASM


FACULTY OF MEDICAL SCIENCES

THERAPEUTIC APPLICATION OF IONIZING RADIATION

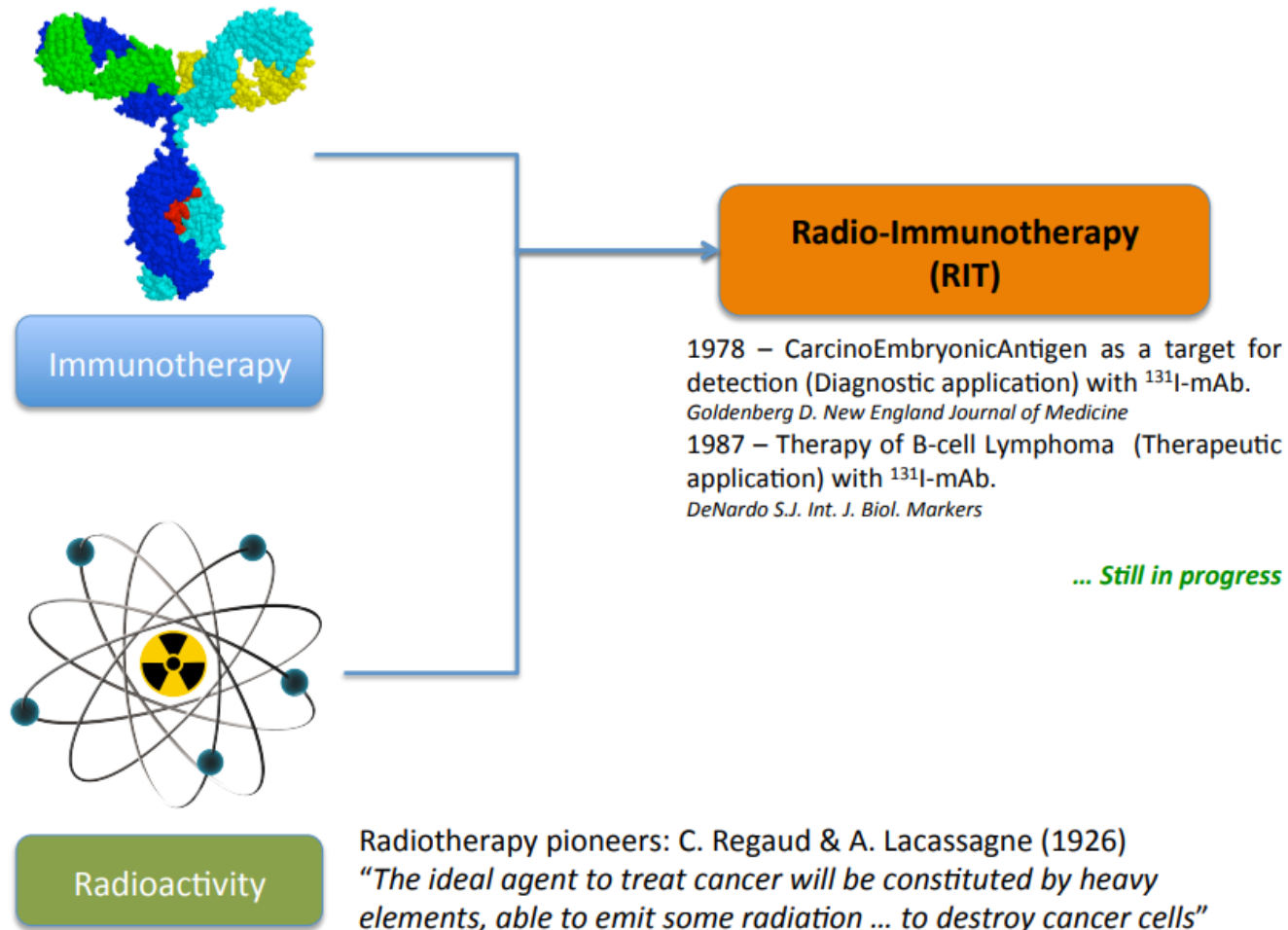
RADIONUCLIDE THERAPY

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- In RIT treatment, radioisotopes (radioactive particles) are attached to monoclonal antibodies and then infused into the body. Each time an antibody comes into contact with a cancer cell, the attached radioisotope delivers radiation directly to that cell. The major advantage of this approach is that it substantially reduces the exposure of healthy cells to radiation.

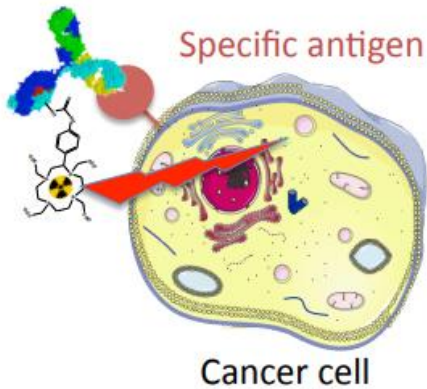
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- The targeting antibodies used for RIT should ideally have the following properties:
 - 1) low immunogenicity for repeated administration,
 - 2) optimal antigen binding,
 - 3) good tumor penetration,
 - 4) good rate of clearance from normal tissues (essential for efficient and specific tumor targeting and thus decreasing the radiation exposure to normal tissues),
 - 5) optimal tumor residence time for delivering therapeutic radiation dose
 - 6) optimal tumor accretion.

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- B-cell non-Hodgkin's lymphoma (NHL) is the most frequently diagnosed cancer of the immune system. There are numerous histologic variants of NHL, which are best classified using the WHO criteria. Approximately 80% of lymphomas are of B-cell origin, which are further classified traditionally into low grade, intermediate grade and high grade lymphomas. The Ann-Arbor system is used for staging of the patients (stage I–IV).
 - B-cell NHL patients not responding to chemotherapy and immunotherapy or who relapse after these therapies are the ideal candidates for the institution of RIT.

Historical context of Radio-Immuno Therapy (RIT)



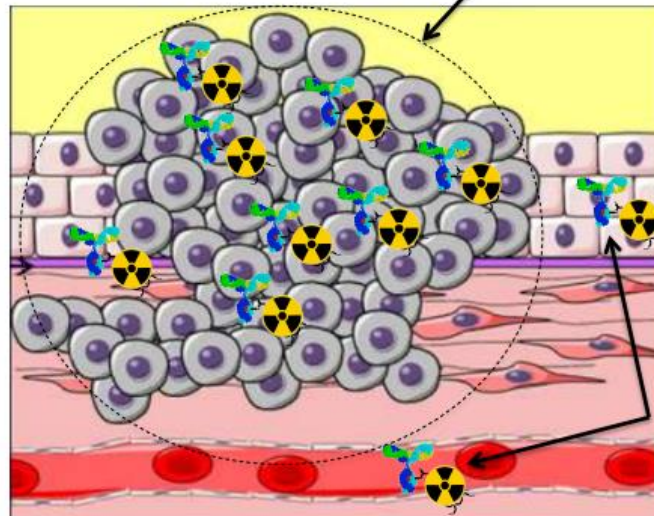
RIT principe



mAb = specific vector for cancer cell
i.e. specific irradiation of tumor cell

Specific irradiation

Specific irradiation
= goal of RIT (better effect with long accumulation time)



Non specific irradiation
= adverse event (less with
shorter circulation time and
high clearance from healthy
tissue)



Radiobiology

Typical dose rates for RIT are in the range of 10 to 20 cGy per hour.

The total dose delivered by RIT is low, in the range of 1,500 to 2,000 cGy, with an effective half-life of 24 to 72 hours.

It should be noted that these total dose ranges for RIT occur despite overall very low percent injected doses (0.1% to 10.0%) that ultimately localize in target tissue.

EBRT typically will deliver radiation at a dose rate of 100 to 500 cGy per minute.



Radiobiology

Considering dose rate, RIT is approximately 20% less effective than HDR EBRT.

RIT, however, does appear to be relatively effective.

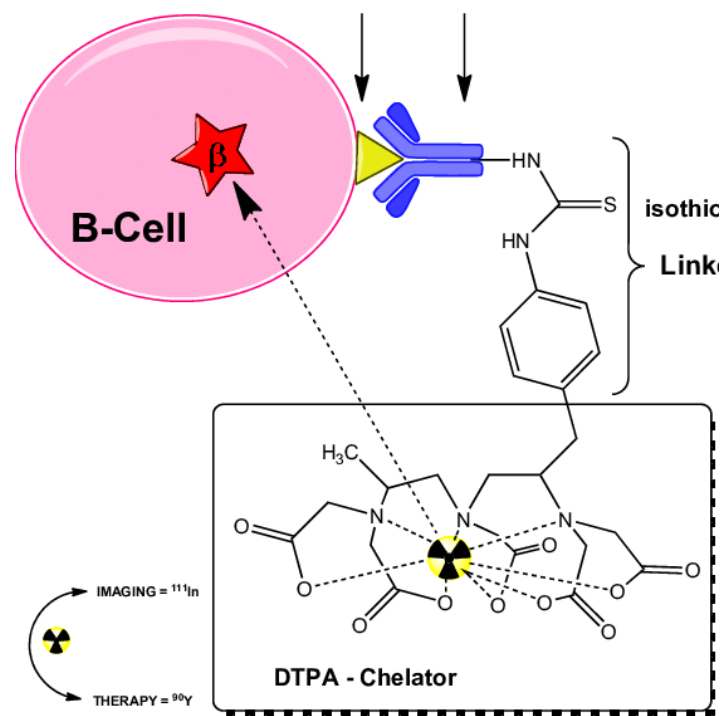
This phenomenon can be attributed to many radiobiologic processes that appear to cause greater than predicted rates of apoptosis.

These processes include low-dose/dose rate apoptosis, lowdose hyperradiosensitivity , inverse dose rate effect (G2 synchronization), radiation-induced biologic bystander effect, and the crossfire effect.

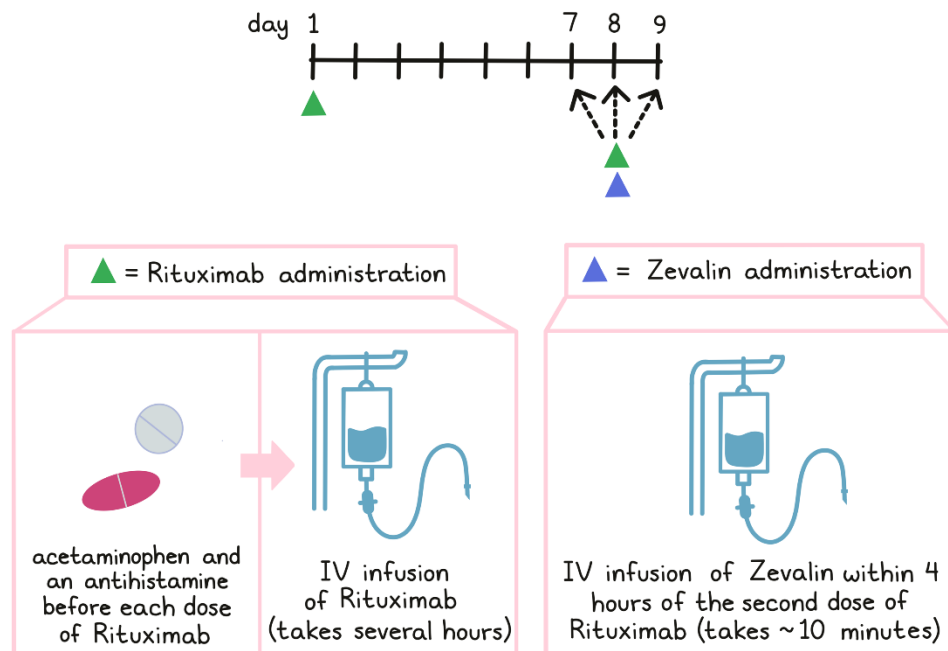
Ibritumomab Tiuxetan (Zevalin)

- Ibritumomab tiuxetan (Zevalin) was the first RIT approved by the U.S. Food and Drug Administration (FDA). This RIT contains a radioisotope called yttrium-90 (Y90) that kills cancer cells. Ibritumomab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of malignant B cells. Tiuxetan is a chelator (connector) that links the Y90 molecule to the ibritumomab molecule.

Ibritumomab tiuxetan has been approved for the treatment of patients with relapsed (disease returns after treatment) or refractory (disease does not respond to treatment) low-grade or follicular B-cell non-Hodgkin lymphoma (NHL). It is also approved for use in previously untreated patients with follicular NHL who achieve partial or complete responses to first-line chemotherapy.





- Patients being treated with ibritumomab tiuxetan (Zevalin) first receive two infusions of rituximab (Rituxan), another monoclonal antibody that also targets CD20 but does not carry any radioisotope, followed by a one-time infusion of ibritumomab tiuxetan. On day one, the patient receives premedication with acetaminophen (Tylenol) and diphenhydramine (Benadryl) followed by an IV infusion of rituximab that takes up to six hours. Seven to nine days later, the patient returns for a second infusion of rituximab followed by ibritumomab tiuxetan four hours later. Dosing is based on the patient's weight and platelet count.




Iodine-131 [¹³¹I]-tositumomab (Bexxar®)

- is another CD20-binding agent composed of tositumomab, a murine anti-CD20 mAb radiolabelled with ¹³¹I. In patients with chemotherapy-refractory or transformed low-grade NHL, [¹³¹I]-tositumomab resulted in significantly better overall response rates and complete responses as compared to the last chemotherapy regimens. Also, as a first-line treatment for advanced follicular lymphoma, ¹³¹I-tositumomab showed promising activity with an ORR and CR of 95% and 75%, respectively, resulting in a median PFS of 6.1 years.

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- Compared with conventional cytotoxic chemotherapy, nonhematologic toxicities from either ⁹⁰Y-ibritumomab tiuxetan or ¹³¹I-tositumomab are generally quite mild. Most of these side effects relate to minor allergic responses to the protein components of the cold antibody. The likelihood of an infusion reaction is somewhat greater for patients treated with rituximab compared with tositumomab.
 - The most significant second malignancy risk that has been studied for lymphoma RIT involves treatment-related myelodysplastic syndrome and leukemia. This marrow syndrome is a well-recognized late problem in patients with a diagnosis of B-cell NHL no matter how they are treated.

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- Given the predictive and prognostic value of HER2, in particular, in breast and gastric cancers, and the heterogeneity of expression of HER2 in some tumors, accurate determination of HER2 status is critical. Numerous preclinical studies have shown high receptor saturation and tumor uptake of radiolabeled pertuzumab and trastuzumab, using a variety of radionuclides, including zirconium-89, copper-64, iodine-131, lutetium-177, and indium-111

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- Ovarian Cancer RIT in ovarian cancer is typically administered intraperitoneally rather than by intravenous administration. Responses typically correlate to tumor volume, with higher responses observed in patients with minimal residual disease or with low disease burden.
 - MUC1, a member of the mucin family, is a glycosylated protein that is overexpressed in a variety of epithelial cancers. MUC1 plays a crucial role in tumorigenesis, cancer progression, and treatment resistance. In a phase II trial, patients with ovarian cancer in remission after chemotherapy treated with 90Y labeled anti-MUC1 antibody, HMFG-1, had a significant improvement in five-year survival compared to the controls (80% vs. 55%, respectively)