

RADIO-IMMUNOTHERAPY IN LYMPHOMAS



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Outline

§ What is radio-immunotherapy (RIT) ?

§ Why RIT ?

§ Clinical indications for RIT

§ Work up

§ Treatment options

§ Evidence

Non Hodgkins Lymphoma

NHL is divided into 2 general prognostic groups:

Indolent lymphomas -

- ✓ small lymphocytic lymphoma
- ✓ Marginal zone L (MALT)
- ✓ Lymphoplasmacytic lymphoma
- ✓ Follicular Lymphoma

Aggressive lymphomas -

- ✓ Diffuse large-cell Lymphoma
 - ✓ Mantle cell lymphoma
 - ✓ Burkitt's lymphoma
 - ✓ Precursor B-cell lymphoma
-

Comparison of Indolent and Aggressive NHL

| | Indolent NHL | Aggressive NHL |
|-------------|---|---|
| Proportion | 40-50% | 50-60% |
| Growth | slow | fast |
| Description | Accidental detection | symptomatic |
| Treatment | Not needed immediately due to slow growth | Treatment needed straight away |
| outcome | Responds well to Rx, but relapses common. | Responds very well to Rx, more likely to be cured |

Treatment of Relapsed or refractory LG/F/T NHL -

§No conventional chemotherapy regimen is curative

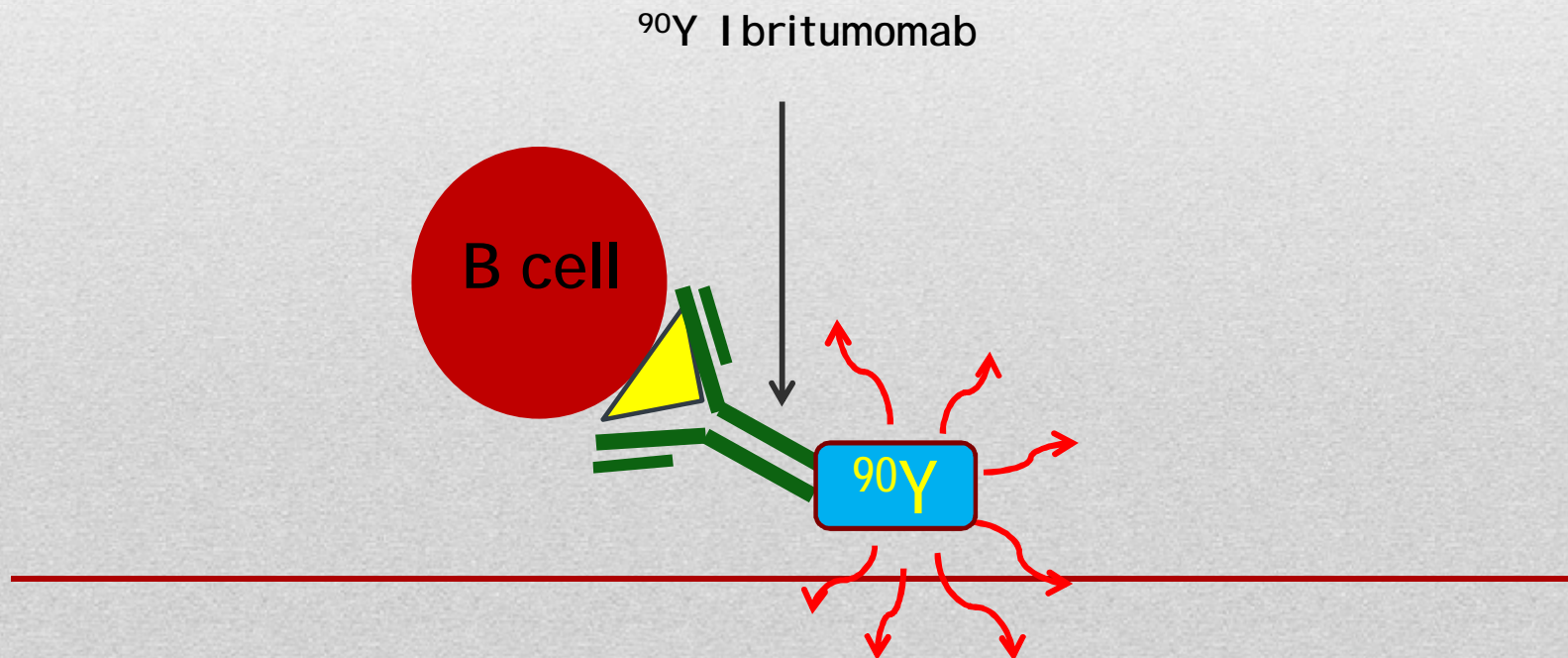
§No regimen is superior with regard to survival

§Patients need additional treatment options

§In the absence of cure or survival benefit, treatments that induce remission and prolong DFS are valuable.

What is Radioimmunotherapy (RIT) ?

- Ø Combines the benefits of radiation therapy and immunotherapy
- Ø Utilizes Monoclonal anti-CD20 antibody to deliver β -emitting Y-90 or I-131 to the malignant B cells.



What is Radioimmunotherapy (RIT) ?

- ∅ Provides a systemic but **targeted** approach to therapy.
 - ∅ Minimizing toxicity to normal tissues.
-

Rationale for treatment with RIT in NHL

- § Over 90% of B-cell lymphomas express CD20, and it is further amplified in malignant B cells.
 - § CD20 is not present on hematopoietic stem cells, progenitor cells.
 - § When bound by anti-CD20 antibody, CD20 does not shed from the cell surface into circulation.
 - § No degradation of the radio-immunoconjugate after antibody binding.
-

Rationale for treatment with RIT in NHL

- § NHL is inherently **sensitive** to radiation.
 - § Antibodies give **targeted radiation** to the tumor cells.
(unlike the more diffuse delivery employed with conventional radiotherapy).
 - § Kills both **bound and neighboring tumor cells**, overcoming the problem of access in bulky or poorly vascularized tumor cell
(**Bystander/crossfire effect**).
-

INDICATIONS for RIT

- ✓ Relapsed/Refractory Indolent B-Cell NHL
 - ✓ Low grade FL
 - ✓ CD20+ transformed B cell NHL
 - ✓ Rituximab refractory FL
 - ✓ Indolent Lymphoma in the Front-line Setting
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Current RIT Treatment Options

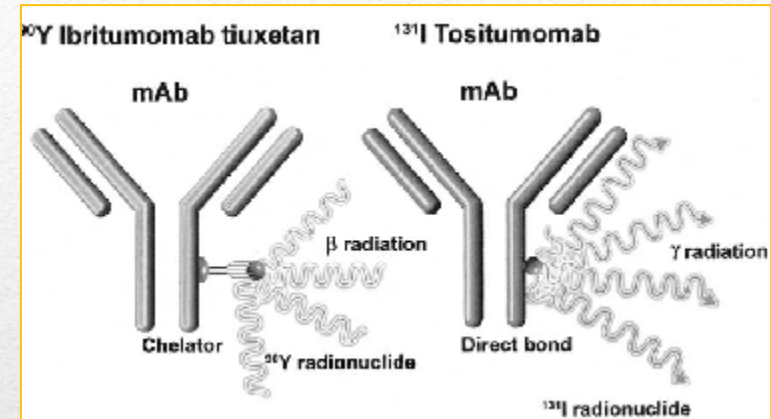
Two FDA approved Moab are available directed against CD20 antigen -

^{90}Y Ibritumomab Tiuxetan

(**Zevalin**; Spectrum Pharmaceuticals, Berlin, Germany)

^{131}I Iodine -Tositumomab

(**Bexxar**; GlaxoSmithKline, Research Triangle Park, NC)



General characteristics of RIT Moab

| Radioisotope | ⁹⁰ Y - Ibritumomab | ¹³¹ I - Tositumomab |
|--------------|--|--|
| Emission | beta | Gamma & beta |
| Range | 11.3 mm | 2.3mm |
| Energy | 2.29 MeV | 606 keV |
| Half life | 64 hours | 8 days |
| Antibody | Murine IgG - 1 | Murine IgG - 2 |
| FDA approval | ü 2002 | ü 2003 |
| Indications | Relapsed/refractory CD20+ve, Low grade NHL or PR after initial Rx | Relapsed/refractory CD20+ve Low grade NHL or transformed lymphoma |

Advantages of ^{90}Y trium -Ibritumomab -

§ Deliver radioactivity to tumors more effectively than ^{131}I and are associated with a **better therapeutic index**.

§ **Minimal risk for exposure**, because of pure beta radiation.

§ **No isolation** and can be treated in an outpatient setting.

Disadvantage -

§ For **imaging** purposes, ^{111}In , a gamma emitter, is used as a substitute for ^{90}Y .

Advantage of ^{131}I - Tositimomab-

§ Same agent can be used for **both imaging and therapeutic** purposes.

Disadvantages

§ Long half-life and the possibility of separation from the antibody can lead to **rapid excretion** or **accumulation in the thyroid**, or both.

§ Because of gamma emission and long $t_{1/2}$ - **isolation/hospitalization**, shielding, careful disposal of body fluids and are necessary.

Dosing schedule for ^{90}Y trium -Ibritumomab

Imaging dose

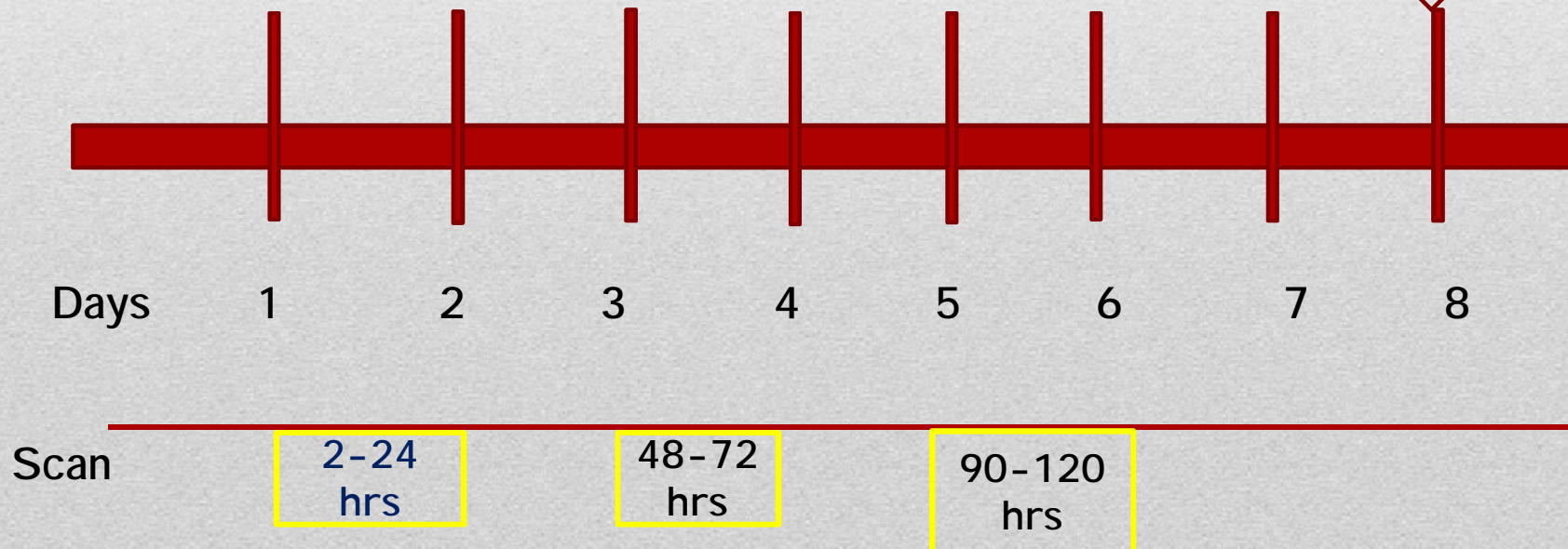
Rituximab 250mg/m²

Followed by (4 hrs) ^{111}In
Ibritumomab 5mCi
(1.6mg)

Therapeutic dose

Rituximab 250mg/m²

Followed by ^{90}Y
Ibritumomab
0.4 or 0.3 mCi/kg
(max dose 32mCi)



Premedication

§ 650-mg oral acetaminophen (NSAID) and 50-mg oral diphenhydramine (Antihistamine)

✓ helps to decrease potential side effects from the infusion of rituximab.

§ 250-mg/m² rituximab IV at a rate of 50 mg/h

✓ to clear the peripheral blood of B cells, increasing the uptake of the radiolabeled antibody to the tumor cells.

Imaging findings

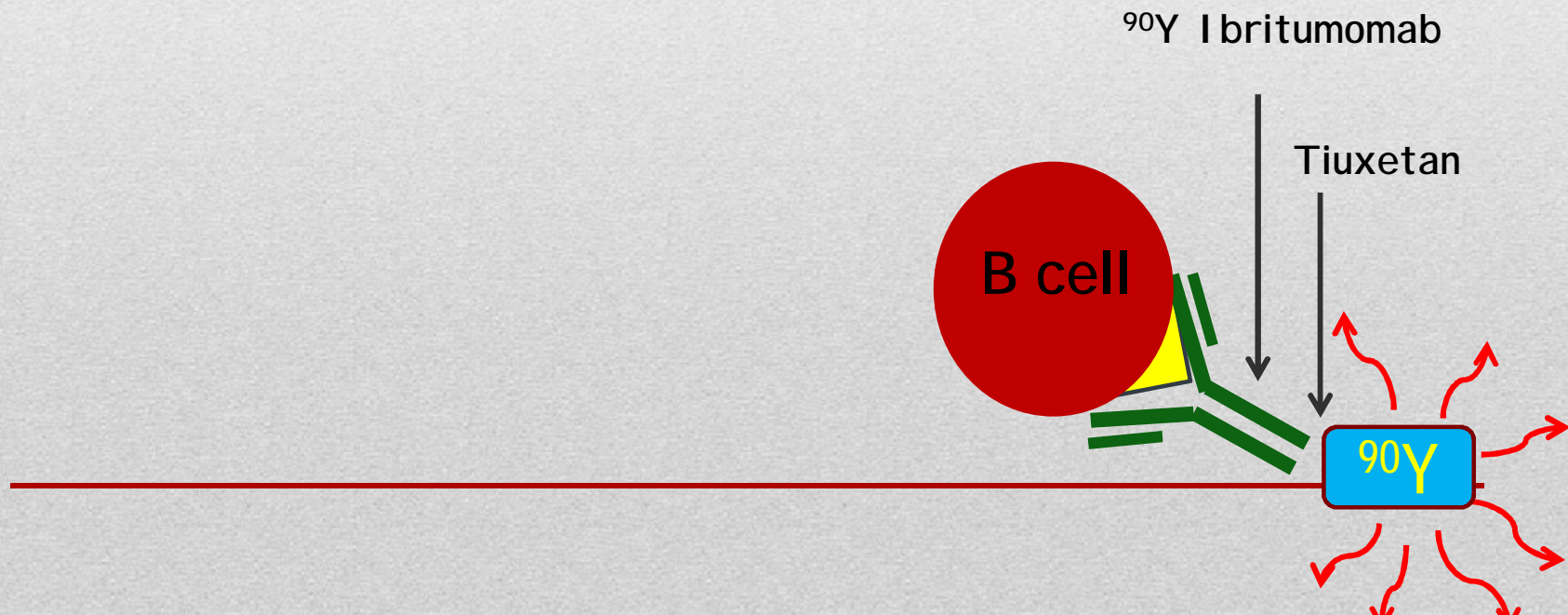
- § In the first scan (2-24 hrs) blood pool areas will be visualized, this will become less in later images.
 - § Low uptake is expected in the lungs, kidneys, and urinary bladder, with higher uptake expected in the normal liver and spleen.
 - § Visualization of the tumor is not a criterion for proceeding to the active therapy.
 - § If altered biodistribution is seen, the patient will not receive the therapeutic dose.
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Imaging findings

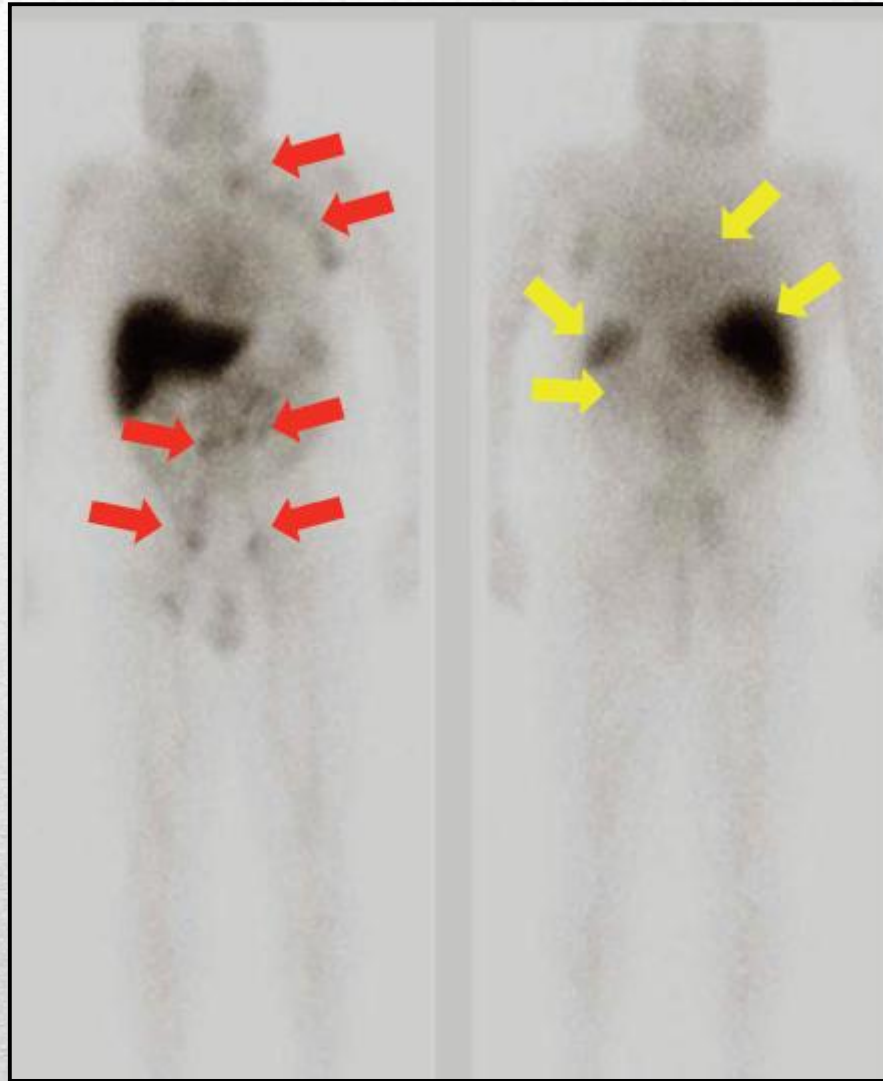
Altered biodistribution -

§failure to visualize the blood pool on the first image, which possibly indicates rapid clearance of the radionuclide, or

§diffuse uptake in the normal lungs or kidneys becoming more intense in the liver on the second or third image.



^{111}In Zevalin biodistribution scan



Dosing schedule for ^{131}I - Tositumomab

Concomitant Medications

✓ Oral thyroid blocking agents:

Ø To decrease the risk of hypothyroidism

Ø Starting at least 24 hours prior to the dosimetric dose and continuing for 14 days after receiving the therapeutic dose.

§ SSKI - 4 drops orally 3 times/day

§ Lugol's solution - 20 drops orally 3 times/day

§ Potassium iodide tablets - 130 mg orally once/day

✓ Oral Acetaminophen 650 mg and diphenhydramine 50 mg: To reduce infusion-related events - 30 min prior to administration of each of the Tositumomab doses.

Thyroid protection - 1 day prior to 14 days post therapeutic dose

Dosimetric step

450 mg Tositumomab
(1hr infusion)

5mCi ¹³¹I Tositumomab
(35mg) (20min)



Whole body
scans x 3

Day 0

Day 2, 3, or 4

Day 6 or 7

Whole body count
&
Biodistribution



Therapeutic step

450 mg Tositumomab

---mCi ¹³¹I Tositumomab
(35mg) to deliver the
desired cGy TBD

Based on the WBS, patient Specific
Dose of activity is calculated

Platelet count $>150 \times 10^9/L$

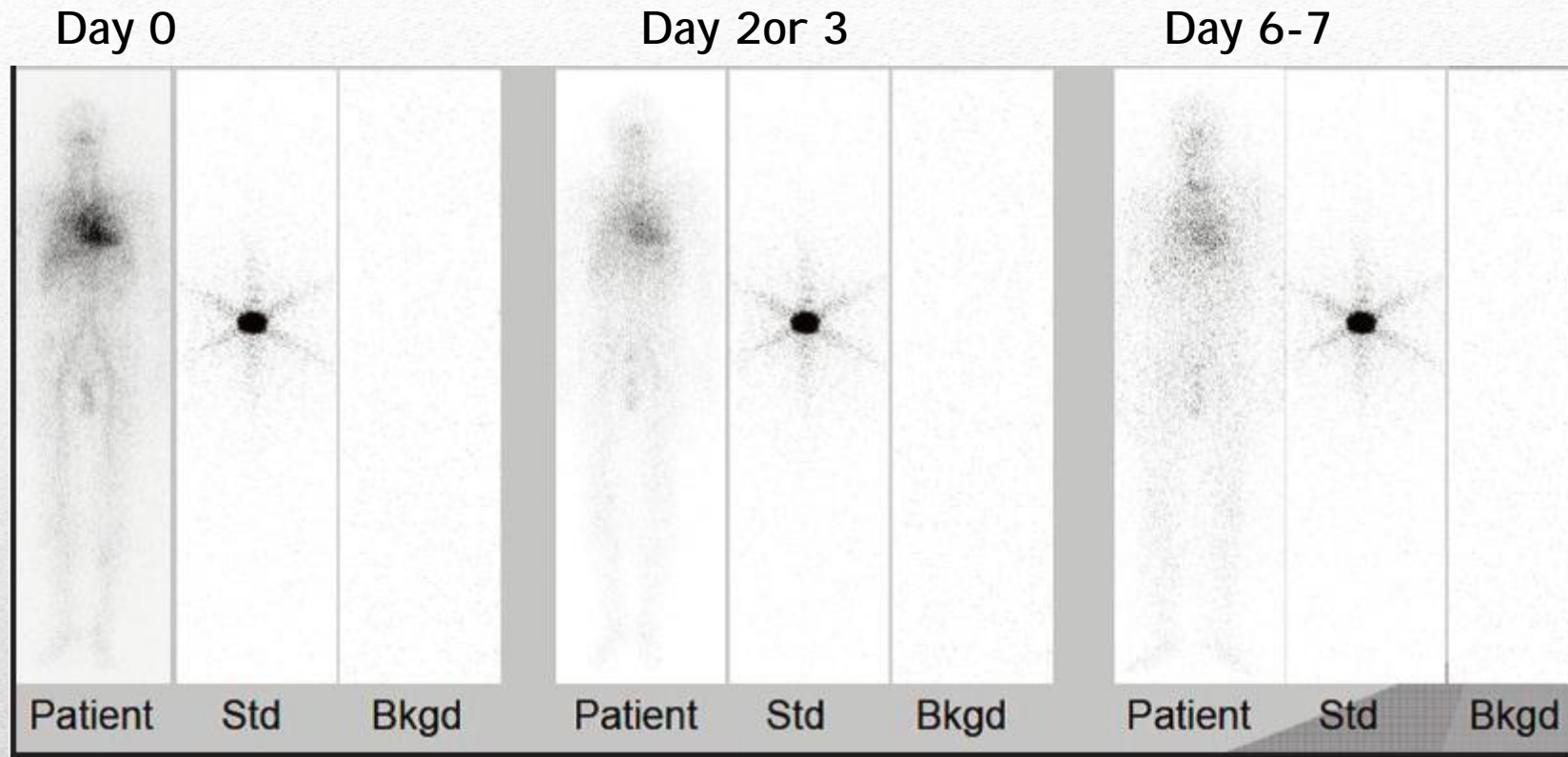
75cGy TBD

Platelet count $<150 \times 10^9/L$

65cGy TBD

Day 7 upto Day 14
therapeutic dose

¹³¹I Bexxar biodistribution & dosimetric scan



Bkgd - dose calculation

Std - quality control

Dose calculation - Total body counts, residence time (50-150 hrs)

Chamarthy MR etal. Yale J biol Med 2011

SELECTING PATIENTS FOR RIT

Contraindications -

§Prior hypersensitivities to murine antibodies.

§Prior bone marrow transplants.

§>25% of BM involvement.

§Bone marrow exhibits hypocellularity (<15%).

§Platelet count <100,000/microl

§Neutrophil count <1.5x10³/microl

§ Elevated HAMA titres

RIT for Relapsed/Refractory LG/F/T B-Cell NHL

RCT - Witzig et al, 2002 . 90Y-ibritumomab vs rituximab

N - 143 patients

| | 90Y- ibritumomab | Rituximab |
|-----------------------------|---------------------|-------------|
| Overall Response Rate (OR) | 80% | 56% |
| Complete Response rate (CR) | 30% | 16% |
| Time to progression | 24.7 months | 13.7 months |

Witzig TE, et al. J Clin Oncol 2002;20: 2453-2463.

§ Use of 90Y-ibritumomab earlier rather than later in relapsed or refractory disease also is important.

§ Evidence suggests superior responses and PFS for patients treated in first relapse rather than later in the course of the disease.

Emmanouilides et al, in 2006, have reported -

N = 211

| | 1 st relapse | 2 nd relapse |
|---------------------|-------------------------|-------------------------|
| CR rate | 51% | 28% |
| Time to progression | 15.4 months | 9.2 months |

Emmanouilides C, et al. Leuk Lymphoma. 2006 Apr;47(4):629-36.

Clinical Efficacy of ¹³¹I Tositumomab

In five clinical trials in 190 patients with follicular NHL,

§OR (overall response rates) ranged from 47% to 64%

§median durations of response ranged from 12 to 18 months.

Vose JM, et al. J Clin Oncol 2000;18:1316-1323.

Vose JM, et al. Blood 1999;94:89a

Kaminski MS, et al. Blood 2000;96:1259-1266.

RIT for Indolent Lymphoma in Front-line Setting


RCT (FIT trial) - Morschhauser et al, 2008,

§Comparing 90Y-ibritumomab vs no further therapy in patients who obtained a CR or a PR to standard front-line chemotherapy regimens.

§Investigators were allowed to utilize their first-line regimen of choice.

§Subjects were restaged upon completion of chemotherapy, and those achieving a CR or a PR were then randomized between the control and the 90Y-ibritumomab arms. N= 414 patients (consolidation = 208; control = 206)

| PFS | RIT arm | Control arm |
|---------------------|------------|-------------|
| Partial responders | 30 months | 6 months |
| Complete responders | 92+ months | 32 months |

- 
- § Patients randomized to receive 90Y-ibritumomab exhibited a prolonged median PFS compared to controls.
 - § Conversion of 77% of partial responders to CR.
 - § No differences in OS were noted in follow-up to this point, given the indolent nature of follicular lymphoma.

Complications of RIT

Ø The primary and dose-limiting side effect from RIT is

§ **hematologic toxicity** - anemia, thrombocytopenia and neutropenia.

§ Seen in 22 - 75% - within days to weeks, recovers by 13 - 14 weeks.

| | Zevalin | Bexxar |
|--------------------------------|----------|-------------|
| Myelodysplastic Syndrome (MDS) | 1.4-5.2% | 10% |
| HAMA | 2% | 20% or more |
| Hypothyroidism | -- | ++ |

HAMA- usually resolves spontaneously. Alters the biodistribution of the Ab-
contraindication for future therapies.

Concerns

§ Effective treatment but still under-utilized.

§ Not available in India as of now but VERY SOON SHOULD BE AVAILABLE

§ Cost ??

§ Newer Rps - ^{177}Lu rituximab, ^{131}I rituximab.

To sum up.....

- § RIT combines the effects of immunotherapy (Apoptosis, ADCC, CDC) and radiation therapy - thus **more effective**.
 - § Usually **one-time therapy**.
 - § Lesser side-effects - **less toxic**
 - § Even ag-negative non-targeted cells can be irradiated due to **Bystander effect**.
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Team -work

Medical oncologist

Radiation oncologist

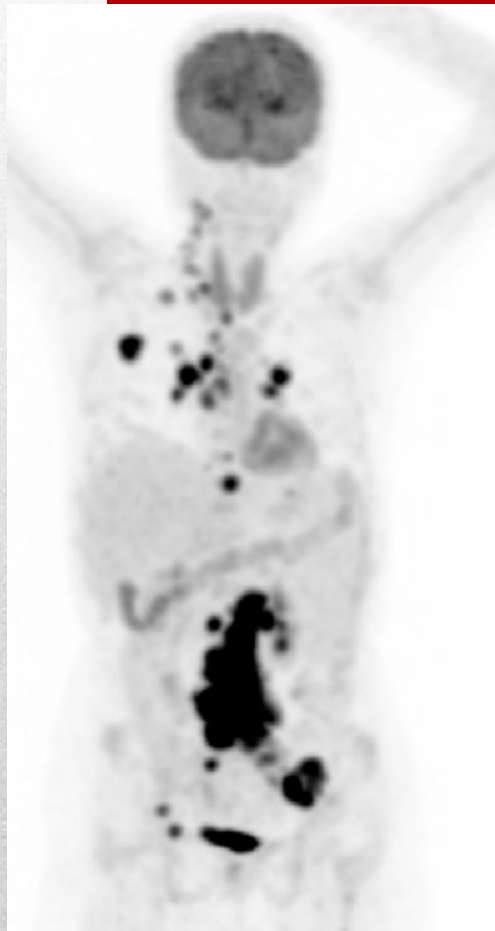


Pharmacist & technologist

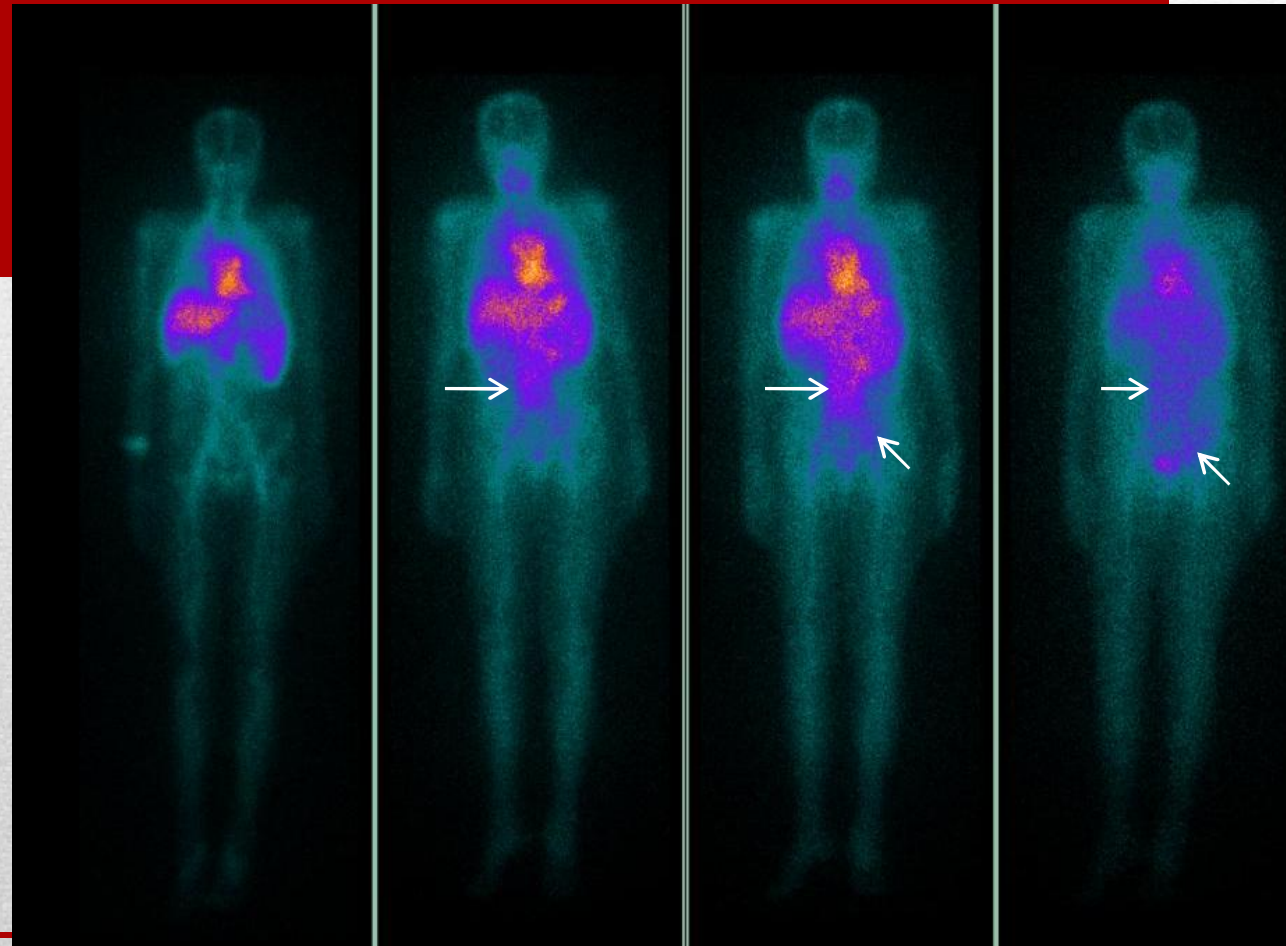
NM physician



Retention time= 167.54 hrs, Calculated therapeutic activity= 30.45mCi



FDG PET/CT




¹³¹I-Rituximab D0

D1

D2

D7



Nucl Med Commun. 2016 Jul;37(7):735-42. doi: 10.1097/MNM.0000000000000501.

Dosimetric analysis of ¹⁷⁷Lu-DOTA-rituximab in patients with relapsed/refractory non-Hodgkin's lymphoma.

Yadav MP¹, Singla S, Thakral P, Ballal S, Bal C.

10 patients

There may be considerable interindividual differences in absorbed doses of organs and generalization or extrapolation of doses in the clinical setting at present is not feasible with Lu-DOTA-rituximab in non-Hodgkin's lymphoma patients. Patient-specific dosimetry is thus recommended to eliminate the variations and reduce the possibility of dose-limiting toxicity.

Curr Radiopharm. 2016;9(2):160-8.

Preliminary Experience with Yttrium-90-labelled Rituximab (Chimeric Anti CD-20 Antibody) in Patients with Relapsed and Refractory B Cell Non-Hodgkins Lymphoma.

Thakral P1, Singla S, Vashist A, Yadav MP, Gupta SK, Tyagi JS, Sharma A, Bal CS, Snehlata EY, Malhotra A.

All the patients received rituximab 250 mg/m² on days 1 and 8, and either 14 MBq/kg (0.4 mCi/kg) or 11 MBq/kg (0.3 mCi/kg) of Y-90 Rituximab on day 8 (maximum dose, 32 mCi) depending upon their platelet count. The patients were observed for systemic toxicity and response for at least 12 weeks after therapy.

90Y-Rituximab therapy is safe and well tolerated in high risk extensively pretreated NHL patients. Toxicity is primarily hematologic, transient and reversible.

RIT in Leukemias

pre BMT

Rhenium 188-labeled anti-CD66 (a, b, c, e) monoclonal antibody to intensify the conditioning regimen prior to stem cell transplantation for patients with high-risk acute myeloid leukemia or myelodysplastic syndrome: results of a phase I - II study. *Blood*. 2001;98:565-572.

Radioimmunotherapy with **[188Re]-labelled anti-CD66** antibody in the conditioning for allogeneic stem cell transplantation for high-risk acute myeloid leukemia. *Int J Hematol*. 2008;87:414-421.

188Re anti-CD66 radioimmunotherapy combined with reduced-intensity conditioning and in-vivo T cell depletion in elderly patients undergoing allogeneic haematopoietic cell transplantation. *Br J Haematol*. 2010;148:910-917.

131I -anti-CD45 antibody plus busulfan and cyclophosphamide before allogeneic hematopoietic cell transplantation for treatment of acute myeloid leukemia in first remission. *Blood*. 2006;107:2184-2191.
