THERAPY WITH UNSEALED RADIOPHARMACEUTICALS

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HIPPOCRATES

On EPILEPSY:

....It is not in my opinion any more divine or more sacred than other diseases, but it has a natural cause......

....It is also curable, no less than other diseases......
HISTORY OF NUCLEAR MEDICINE

DEMOCRITOS
Father of the Atomic Theory of the Matter

EPICUROS
Father of Nuclear Science and Nuclear Medicine
HISTORY OF NUCLEAR MEDICINE

Modern Atomic Theory

John Dalton

John Dalton is known for his interpretation of the experimental results of other chemists. His atomic theory helped chemists understand why many chemicals behave in certain ways.

1890

Discovery Natural and Artificial Radioactivity

Henri Becquerel

discovered mysterious “rays” from uranium.

1896

Marie Curie

named the mysterious rays “radioactivity.”

1897
ABBREVIATIONS

ORR:  Overall Response Rate

ANC:  Absolute Neutrophil Count

IPI:  International Prognostic Index

IWF GROUPS: International Working Formula A-G

ABMT:  Autologous Bone Marrow Transplant

PBSCT:  Peripheral Blood Stem Cell Transplant

CVPP:  Cyclophosphamide, Vincristine, Prednisone

AdChemo:  Adjuvant Chemotherapy (Given after surgery)

NAdChemo:  Neo-Adjuvant Chemotherapy (Given before surgery)
NUCLEAR MEDICINE

RADIOPHARMACEUTICALS:

(=Organic or Inorganic Molecules labeled with Radioactive Isotopes)

Radioactive Isotopes can be

Single Photon Emitters: $\gamma$, x rays (Planar and SPECT)

Positron Emitters: $e^+$ or positron (PET studies)

Low Energy $\gamma$ or $e^-$ Emitters: (in vitro studies)

Particle Emitters: $e^-$ electron or beta, and alpha(Therapy)
NUCLEAR MEDICINE ACTIVITIES

PATIENT IMAGING

Routine Single Photon Planar and Tomo-SPECT studies:
Use $\gamma$ or x rays; energy 80-600 keV (e.g. $^{99m}$Tc, $^{203}$TI etc)

Positron Emission Tomographic Studies:
Use positrons $e^+$ (e.g. $^{18}$F, $^{11}$C etc)

IN VITRO STUDIES

Use low energy $\gamma$ or electrons ($^{125}$I, $^3$H, $^{14}$C)

PATIENT THERAPY

Use particular radiation; electrons ($^{131}$I) or alpha particles
THERAPY WITH UNSEALED OR SYSTEMIC RADIOPHARMACEUTICALS
RADIOACTIVE ATOM and RADIATION: radioactive atoms decay and produce radiation

Radiation Emission  

Electron Capture

a) Particular radiation

b) Electromagnetic radiation

\[ e^- \rightarrow 2 \times 511\text{keV photons} \]
In a simplified way
Radioactive Decay occurs
by Three Main Processes (and others)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Type of energy</th>
<th>Characteristics</th>
<th>Representative radionuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>( \alpha )</td>
<td>Particle</td>
<td>Release of 2 protons, 2 neutrons</td>
</tr>
<tr>
<td>Beta</td>
<td>( \beta )</td>
<td>Particle</td>
<td>Release of 1 electron</td>
</tr>
<tr>
<td>Gamma</td>
<td>( \gamma )</td>
<td>Electromagnetic</td>
<td>Release of photons</td>
</tr>
</tbody>
</table>
Penetration of Particulate and Electromagnetic Radiation

Adapted from Wootton. Radiation Protection of Patients. 1993.
Environmental Radiation Safety Issues Are Less With Pure Beta Decay ($^{90}$Y)
Acrylic Syringe and Vial Shields for Pure Beta Emitters (\(^{90}\text{Y}\))

- **Syringe Shield**
  - Syringe shield conveniently holds a 12 cc syringe for infusion of \(^{90}\text{Y}\) Zevalin

- **Vial Shield**
  - Vial shield opens on one end to allow insertion of 10 cc reaction vial; other end opens to allow for drawing out of the vial

*Images of acrylic shields for syringes and vials.*
## Properties of the most usual Radioisotopes for Therapy

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Physical half-life (hrs)</th>
<th>Decay type</th>
<th>Particle energy (MeV)</th>
<th>Primary gamma energy (MeV)</th>
<th>Particle path length (mm)</th>
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</thead>
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<tr>
<td>$^{90}$Y</td>
<td>64</td>
<td>$\beta$</td>
<td>2.293</td>
<td>None</td>
<td>5.3</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>193</td>
<td>$\beta,\gamma$</td>
<td>0.606</td>
<td>0.364</td>
<td>0.8</td>
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</table>

All the properties of Yttrium are preferable for therapy.
THERAPY WITH SYSTEMIC RADIOPHARMACEUTICALS
THERAPY WITH SYSTEMIC RADIOPHARMACEUTICALS

BENIGN DISEASES

Thyrotoxicosis $^{131}$I (Grave’s Disease, Toxic Nodule, Plummer’s Disease)
Non-toxic Multinodular Goiter with $^{131}$I
Arthropathies (Hemophiliac, Rheumatoid) with intraarticular $^{32}$P
(Polycythemia Vera $^{32}$P)

MALIGNANT DISEASES

Thyroid Cancer metastases with $^{131}$I
Treatment of intractable bone pain due to blastic metastatic bone disease with $^{85}$Sr or $^{153}$Sm
Non-Hodgkin’s Lymphoma with $^{131}$I-MoAb or $^{90}$Y-MoAb
Bone Marrow Ablation with Holmium or $^{131}$I- or $^{90}$Y-MoAb
Other Experimental (neuroblastoma, multiple myeloma etc)
A) BENIGN DISEASES

Thyrotoxicosis

- Graves Disease  (10-30 mCi $^{131}$INa po)
- Toxic Adenoma  (30-150 mCi $^{131}$INa po)
- Toxic Multinodular Goiter (20-150 mCi $^{131}$INa po)
- Non Toxic Multinodular Goiter (100-300 mCi $^{131}$INa po)

Synovectomy (Hemophiliac or Rheumatoid Arthritis)

(5-10 mCi $^{32}$P Chromic Phosphate (Colloid) intraarticularly)
THYROTOXICOSIS / GOITERS

INDICATIONS

Graves Disease
Toxic Adenoma
Toxic Multinodular Goiter
Non Toxic Multinodular Goiter

METHOD

Orally 10-150mCi $^{131}$INa

RESULTS

Cure of Thyrotoxicosis
Shrinkage of Goiter
EFFECTS OF THERAPY

GRAVES DISEASE

At treatment (15 mCi $^{131}$INa po)

POST THERAPY

4 months later

Patient hypothyroid, needs T3/T4
EFFECTS OF THERAPY

TOXIC ADENOMA

At treatment (29.2 mCi $^{131}$I Na po)
suppressed

POST THERAPY

8 months later
recovered

Patient Euthyroid
HEMOPHILIC ARTHROPATHY

Management of Hemophilic arthropathy

- Surgical Synovectomy
- Arthroscopic Synovectomy
- Radioactive Synovectomy
Radiopharmaceutical Therapy of Hemophilic Arthropathy

- Hemophilic arthropathy occurs after several episodes of hemarthrosis; hemorrhage into the joint space leads to synovial hypertrophy and eventual destruction of cartilage.

- Symptoms include severe pain and decreased range of motion.

- Major goal of treatment is to reduce the frequency of joint bleeding, to decrease pain, and to increase range of motion.
NUCLEAR SYNOVECTOMY

INDICATIONS
Hemophiliac joints
Rheumatoid arthritis

METHOD
Arthrocentesis
Test with $^{99m}$Tc--SC
Instillation of 05-15 mCi of $^{32}$P-colloid

RESULTS
Improvement in motion
Relief of pain
Prevent hemorrhage
NUCLEAR SYNOVECTOMY

Radiopharmaceuticals

Phosphate-32 Colloid
- Half-life = 14.3 days
- β-emission which has shallow depth of penetration
- Inexpensive

Yttrium-90
- Half-life = 2.7 days
- β-emission which has shallow depth of penetration
- Expensive
NUCLEAR SYNOVECTOMY

Imaging at 1 week post therapy with P-32 using Bremstralung

The treated joints are visualized. They keep the activity. No leak.
NUCLEAR SYNOVECTOMY

Phosphate-32 Colloid Radiosynovectomy in Hemophilia

81 patients (125 procedures) with 2-10 year follow-up for episodes of joint bleeding and quality-of-life assessment.

74.4% of joints either had no more incidence of joint bleeding or a 75% reduction in bleeding incidence.

54% of joints had a complete cessation of bleeding.

73% of joints had improved range of motion.

79% of patients stated they had a significant improvement in quality of life.

Cost Analysis → Surgical Synovectomy $50,000 to $100,000

Radiosynovectomy (P-32) $2,000 to $5,000
Yttrium-90 Synovectomy in Hemophiliac Arthropathy

35 patients (58 joints) with 7 year follow-up for frequency of hemorrhage, pain control, and range of motion.

Hemorrhage (mean): Pre-Tx = 4/month
Post-Tx = 2/year

Pain: 25/35 patients totally pain free

Range of Motion: 55 joints assessed

Improved = 9
Unchanged = 37
Worse = 7

Overall: 47/58 joints were rated by patients as improved and 11/58 joints as no difference.
B) MALIGNANT DISEASES

Treatment of *Thyroid Cancer* (150 - 300 mCi $^{131}$INa orally)

[Ablation of the Thyroid gland or Remnants (150 mCi $^{131}$INa orally)]

Treatment of *Bone Pain from Metastasis*

(4 mCi $^{89}$Sr iv or 1.2 mCi/kg $^{153}$Sm EDTMP iv)

*Bone Marrow Ablation* Holmium-166-DOTMP iv

(or $^{90}$YMoAb or $^{131}$IMoAb)

Treatment *Non-Hodgkin’s Lymphoma* ($^{131}$IMoAb or $^{90}$YMoAb)

Treatment of *Pheochromocytomas Paragangliomas and Neuroblastomas* ($^{131}$I-MIBG)
GENERAL PRINCIPLE
IN THERAPY OF MALIGNANT TUMORS

INDICATION

• Biopsy proven diagnosis

PREREQUISITES FOR THE TREATMENT

• Proof that the tumor accumulates sufficient percentage of the dose of the radiopharmaceutical (dosimetry)

• The Dose not to exceed safety limits for normal tissues (dosimetry)

• The Patient’s clinical condition and laboratory values permit
DIFFERENTIATED THYROID CANCER THERAPY with $^{131}$Ina

More Information in the Thyroid Imaging section
DIFFERENTIATED THYROID CANCER THERAPY with $^{131}$INa

GENERAL PROCESS

- Resection of Tumor and Total Thyroidectomy
- 4-6 weeks off $T_4$ = Endogenous TSH Stimulation
- Thyroid Gland Remnant Ablation (150mCi $^{131}$INa)
- Initiation of T4 Replacement/TSH Suppression
- Post Therapy Total Body Scan (day 6-10)
- Follow-up with Thyroglobulin levels
- Imaging and Retreatment (300mCi), if needed
TREATMENT of METASTATIC THYROID CANCER

15 year old boy with history of
Differentiated Thyroid Carcinoma
after thyroidectomy + remnant ablation
Now rising TGB

4th day during dosimetry
With 2 mCi of $^{131}$INa po
15 yo with METASTATIC THYROID CANCER post TREATMENT with 302 mCi of $^{131}$INa po

7 days post treatment with 302 mCi of $^{131}$INa po
THERAPY OF INTRACTABLE BONE PAIN DUE TO BLASTIC METASTATIC DISEASE
TREATMENT OF INTRACTABLE BONE PAIN FROM METASTATIC CANCERS

INDICATIONS
Deteriorating metastatic disease with intractable bone pain

REQUIREMENTS
Proof that the tumor accumulates the radiopharmaceutical
PREREQUISITE FOR METASTATIC BONE PAIN THERAPY WITH SYSTEMIC RI

- Bone pain and not nerve or fracture pain
- Pain from metastasis and not benign
- Bone scan positive and congruent with pain
- Platelet counts above 60,000/ml
- Leukocyte counts above 2,400 ml
- Discontinue any calcium therapy
PAIN ASSESSMENT

Assessment of Efficacy

- Patient daily pain diary
  Numeric pain rating score (VAS)
  Opioid pain medications

- Blinded Physicians Global Assessment (PGA)
  At Baseline and Weeks 1, 2, 3, 4, 8, 12, 16

Fig. 2.—Score systems to evaluate the efficacy of therapy.

Visual Analog Scale (VAS)

Please make a mark along the line which best represents the intensity of your pain.

Least Possible ———— | Possible Pain Worst

Fig. 3.—Assessment of the intensity of pain by Visual Analog Scale.

Physicians Global Assessment (PGA)

Worse
No Change
Slight Relief
Moderate Relief
Marked Relief
Complete Relief

Fig. 4.—Assessment of the intensity of pain by Physician Global Assessment.
Fig. 5.—Assessment of the intensity of pain using VAS and PDS score in relationship with Sm-153 EDTM injection.
TREATMENT OF INTRACTABLE BONE PAIN FROM METASTATIC CANCERS

Proof of accumulation with MDP-Bone Scan

Deteriorating metastatic disease with intractable bone pain
proof that the tumor accumulates the radiopharmaceutical
THERAPY OF INTRACTABLE BONE PAIN DUE TO BLASTIC METASTATIC DISEASE

• Phosphorous-32 (T-1/2 = 14 days)
  Dose: 5-10 mCi as Sodium Phosphate
  Efficacy: 60-90%
  Side Effects: Bone marrow suppression

• Strontium-89 (T-1/2 = 8 days)
  Dose: 4 mCi as Metastron
  Efficacy: 80% prostate, 81% breast metastasis
  Side Effects: Mild transient bone marrow suppression

• Complexes:
  1) Samarium-153-EDTMP (T-1/2 = 47 hr)
     Dose: 1.0 mCi/kg as Quadramet (\(^{153}\)Sm Lexidronam)
     Efficacy: 48-54%
     Side Effects: Bone marrow suppression
  2) Yttrium-90-DTPA-Ab (T-1/2 = 64 hr) (experimental)
STRONTIUM-89 (METASTRON)

$^{89}\text{SrCl}_2$  $T_{1/2} = 50.5$ days

Beta 1.46 MeV max

Marketing: Amersham

Dose: 4mCi (148 MBq) iv

Excreted in the urine
INDICATIONS FOR $^{89}$Sr THERAPY

- Pain from bone metastasis (prostate, breast)
- Intractable to analgesics (orchiectomy, estrogens, LHRH)
- Failed external radiotherapy (focal disease)
- Multiple metastases (wide field irradiation)
- Quality of life impaired by narcotics

- Treatment earlier in the course of the disease may become an indication
BONE PAIN THERAPY WITH $^{89}\text{Sr}$

- $^{89}\text{Sr}$ treats the bone reaction to tumor
- It has special affinity for osteoblastic tissue (>100 days)
- “Flare pain” in 20% of patients self limited
- It certainly irradiates neighboring cells
- Its effect on tumor is unknown

- 70-80% Prostatic cancer patients respond
- Onset of action after 2-3 weeks
- Median duration of response - 4 months
- Improves quality of life (sleep, activity)
- Retreatment is possible and effective
- Tumor-to-marrow absorbed dose ratio > 10:1
- Low toxicity if initial platelets above 100,000
Fig. 1.—Samarium-153 EDTM: Complex of radioactive Samarium-153 and tetrophosphonate (Ethylene Diamine Tetra Methylene-phosphonic Acid).
TREATMENT OF INTRACTABLE BONE PAIN FROM METASTATIC CANCERS

Metastatic bone tumor with intractable bone pain
Proof that the tumor accumulates the radiopharmaceutical
RESULTS


12 weeks after 30-40 uCi/kg in 100 prostate (28 breast) patients

- 10% pain free (18%)
- 29% marked decrease in pain medication (21%)
- 41% moderate (50%)
- 20% no improvement (11%)
BONE TUMOR PAIN PALLIATION
WITH RADIOISOTOPES IN CHILDREN

• 2 pts with Lung Ca and Neuroblastoma, stage IV, $^{89}$Sr:
  Mixed Results
  
  Med Pediat Oncol 26:393, 1996

• Several pts with Neuroblastoma chemo + Hpbr $O_2$ $^{131}$MIBG:
  Good Results
  
  Eur J Cancer 31A:590, 1995

• Unresectable Prim. or Recur. Osteosarcoma
  
  $^{153}$Sm-EDTMP high dose
  
TREATMENT OF OSTEOGENIC SARCOMA WITH RADIOISOTOPES IN CHILDREN

• As Neo-Adjuvant Chemotherapy, prior to surgery
• To treat osseous metastasis
• To treat calcific soft tissue metastasis
OSTEOSARCOMA

SINGLE FOCUS  MULTIFOCAL (METASTATIC)  LUNG METASTASIS
TREATMENT OF UNRESECTABLE OSTEOSARCOMA
With $^{153}$Sm-EDTMP

- 6 pts with unresectable (3) or recurrent (3) OS
- $^{153}$Sm-EDTMP (4mCi/kg) after PBSC collection
- APBSC performed on day +12 to +27
- Results: 3 pts alive and pain free
  (1 pt progression free at 36 mos)
- 3 pts died of disease at 5-20 mos
- Conclusion: May at least delay progression

*Nucl Med Dec 40:215,2001*
ROLE OF NUCLEAR MEDICINE
IN BONE MARROW TRANSPLANT THERAPY

Bone Marrow Ablation

with Holmium-166 (\textsuperscript{166}Ho- DOTMP)
Nuclear Medicine Participation in Bone Marrow Transplant

• Staging
  Gallium, FDG/PET, Other Imaging

• Evaluation prior to transplant
  MUGA

• Therapy (Bone Marrow Ablation)
  Holmium-166 ($^{166}$Ho-DOTMP)
Holmium Phase I/II

- $^{166}\text{Ho}$- DOTMP, B-emitter
- MEL 140-200 + Holmium 20-40 Gy
- Autologous PBSC transplant
- 46 evaluable for safety
- Engraftment day 10
- Non-hematological toxicity
- CR rates 44%, RR- 52%

Bensinger, Proc ASCO 2000
Holmium-166 (\(^{166}\)Ho- DOTMP)

Total Body Irradiation

Myeloablative

Immunosuppressive

Effective In all types of leukemia, lymphoma, myeloma

Limited by non-bone marrow tissue tolerance
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Late Toxicity</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>Hemorrhagic cystitis</td>
</tr>
<tr>
<td>Hepatic</td>
<td>TTP</td>
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<tr>
<td>Veno-Occlusive Disease</td>
<td>Currently on hold in studies</td>
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<tr>
<td>Hypothyroidism</td>
<td>Phase III trial ongoing</td>
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<tr>
<td>Infertility</td>
<td></td>
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<tr>
<td>GI toxicity</td>
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RADIOIMMUNOTHERAPY
INTRODUCTION
THE ANTIGENS

B-Cell Lymphomas Express Several Antigens That Can Be Targeted

DR
slg
CD19
CD20
CD22
CD23
CD40
CD80

PRODUCTION OF MONOCLONAL ANTIBODIES: against well selected ANTIGENS using either HYBRIDOMAS or BACTERIA + VIRUSES
PRODUCTION OF MoAb (MONOCLONAL ANTIBODIES)

Humanizing the Mouse Antibodies

Chimeric Antibodies

- **Human**
- **Murine**
- **Chimeric**
- **Humanized**

**Chimeric Antibody** (66 Percent Human)

**Humanized Antibody** (90 Percent Human)

**Fully Human Antibody**
<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>DEVELOPER/MARKETER</th>
<th>APPROVAL DATE</th>
<th>TYPE</th>
<th>TARGET</th>
<th>DISORDER</th>
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<tbody>
<tr>
<td>Orthoclone OKT3</td>
<td>Ortho Biotech/Johnson &amp; Johnson</td>
<td>1986</td>
<td>Murine</td>
<td>CD3 antigen on T lymphocytes</td>
<td>Acute rejection of transplanted kidneys, hearts and livers</td>
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<tr>
<td>(muromonab-CD3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ReoPro (abciximab)</td>
<td>Centocor/Eli Lilly &amp; Co.</td>
<td>1994</td>
<td>Chimeric</td>
<td>Clotting receptor (GP IIb/IIIa) on platelets</td>
<td>Blood clots in patients undergoing cardiac procedures such as angioplasty</td>
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<tr>
<td>Rituxan (rituximab)</td>
<td>IDEC Pharmaceuticals/Genentech/Roche</td>
<td>1997</td>
<td>Chimeric</td>
<td>CD20 receptor on B lymphocytes</td>
<td>Non-Hodgkin’s lymphoma (relapsed or refractory low-grade)</td>
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<tr>
<td>Zenapax (daclizumab)</td>
<td>Protein Design Labs/Roche</td>
<td>1997</td>
<td>Humanized</td>
<td>Interleukin-2 receptor on activated T lymphocytes</td>
<td>Acute rejection of transplanted kidneys</td>
</tr>
<tr>
<td>Herceptin (trastuzumab)</td>
<td>Genentech/Roche</td>
<td>1998</td>
<td>Humanized</td>
<td>HER2 growth factor receptor</td>
<td>Advanced breast cancers bearing HER2 receptors</td>
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<td>Remicade (infliximab)</td>
<td>Centocor/Schering-Plough</td>
<td>1998</td>
<td>Chimeric</td>
<td>Tumor necrosis factor</td>
<td>Rheumatoid arthritis and Crohn’s disease</td>
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<tr>
<td>Simulect ( basiliximab)</td>
<td>Novartis</td>
<td>1998</td>
<td>Chimeric</td>
<td>Interleukin-2 receptor on activated T lymphocytes</td>
<td>Acute rejection of transplanted kidneys</td>
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<tr>
<td>Synagis (palivizumab)</td>
<td>MedImmune</td>
<td>1998</td>
<td>Humanized</td>
<td>F protein of respiratory syncytial virus (RSV)</td>
<td>RSV infection in children</td>
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<td>Mylotarg (gemtuzumab)</td>
<td>Celltech/Wyeth-Ayerst</td>
<td>2000</td>
<td>Humanized</td>
<td>CD33 antigen on leukemia cells</td>
<td>Relapsed acute myeloid leukemia</td>
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<td>Campath (alemzumab)</td>
<td>Millennium Pharmaceuticals/Schering AG</td>
<td>2001</td>
<td>Humanized</td>
<td>CD52 antigen on B and T lymphocytes</td>
<td>B cell chronic lymphocytic leukemia</td>
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</tbody>
</table>
LIMITATIONS OF UNLABELED ANTIBODIES AND EXTERNAL BEAM RADIATION

- **All tumor cells** need to be bound by antibodies to kill them.

- Patient’s immune mechanisms may not be sufficiently intact to interact with the antibody.

- Tumor cells may be resistant to direct anti-tumor mechanisms as well as immune mechanisms of the Ab.

- There is a need to irradiate all the sites of disease which is impractical or impossible and dangerous.

ADVANTAGES OF RADIOIMMUNOTHERAPY
v/s Non-radioactive Antibodies

Monoclonal Antibody Pharmaceuticals

Non-Radioactive  Radioactive

Crossfire Effect
THERAPY WITH ANTIBODIES
ADVANTAGES OF RADIOIMMUNOTHERAPY
vs Non-radioactive Antibodies

Unlabeled “cold” Antibody

Radiolabeled Antibody

Courtesy of Andrew Zelenetz, MD.
ADVANTAGES OF RADIOIMMUNOTHERAPY vs External Beam Radiation
The need for preparing the patient with “Cold” Antibody

Purpose of Pre-dosing with Cold Antibody

- To occupy non-tumor Antigen sites (CD20 in NHL) on:
  - Circulating Normal cells (B lymphocytes in NHL)
  - Splenic or other organ cells (B splenic cells in NHL)
- To Improve Biodistribution to tumor
- To Prolong Residence Time of radiolabeled antibody
- To Add the Therapeutic Effect of unlabeled antibody
### RADIOIMMUNOTHERAPY

**Effect of Predosing on Tumor Targeting**

<table>
<thead>
<tr>
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<th>0 mg (n=15)</th>
<th>95 mg (n=14)</th>
<th>475 mg (n=28)</th>
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<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>1074 ± 776</td>
<td>1177 ± 650</td>
<td>1023 ± 711</td>
</tr>
<tr>
<td><strong>Patients with bulky disease</strong></td>
<td>526 ± 44 (n=3)</td>
<td>557 ± 226 (n=3)</td>
<td>880 ± 752 (n=13)</td>
</tr>
<tr>
<td><strong>Patients with splenomegaly</strong></td>
<td>699 ± 262 (n=3)</td>
<td>744 ± 425 (n=3)</td>
<td>946 ± 725 (n=15)</td>
</tr>
</tbody>
</table>

Data on File. Corixa Corporation.
RADIOIMMUNOTHERAPY
Effect of Predosing on Distribution

1hr post Tositumomab injection
R ANT L
No pre-dose

1hr post Tositumomab injection
R ANT L
Pre-dose

Data on File. Corixa Corporation.
RADIOIMMUNOTHERAPY

Typical pattern of patient preparation and treatment

Cold dose $\rightarrow$ Imaging dose $\rightarrow$ Cold dose $\rightarrow$ Therapeutic dose

$\uparrow$ protein (HAMA/HACA) $\rightarrow$ $\downarrow$ protein, $\downarrow$ radioactivity $\rightarrow$ $\uparrow$ protein (HAMA/HACA) $\rightarrow$ $\downarrow$ protein, $\uparrow$ radioactivity
RADIOIMMUNOTHERAPY

Potential Implications of HAMA

• Presence of HAMA may affect the results and toxicity of therapeutic agents that are produced by murine antibody technology

• HAMA positivity may affect the results of \textit{in vitro} and \textit{in vivo} diagnostic tests, as well as murine-based therapies

• Patients who have received murine proteins should be screened for HAMA
HAMA: Human Anti-Mouse Antibodies

- Complications of HAMA response
  - Anaphylactic Reactions
  - Interference with tumor targeting
  - Misleading results in immunoassays
- Screening for HAMA even in patients who have never received murine MoAb (endogenous HAMA)

Also

HAHA: Human Anti-Human Abs
HACA: Human Anti-Chimeric Abs
Radioimmunotherapy
Requires a Multidisciplinary Team

- Oncologist
- Oncology Nurse
- Nuclear Medicine or Radiation Oncology Personnel
- Radiopharmacy
- Radiation Safety Officer

PATIENT
RADIOIMMUNOTHERAPY IN NON-HODGKIN’S LYMPHOMA (NHL)
Patient 4 years after Radioantibody therapy for NHL

Quest is a publication of the UMSylvester Cancer Center
HOPE

The cancer establishment has systematically misrepresented the prospect of hope to millions of patients. Some miraculous cures had appeared….but…chemotherapy for many forms of advanced cancer turned out to be a resounding disappointment – only most patients didn’t know it….For cancer patients, this inability to predict the future becomes their sustaining hope…a deceptive force.

“The Thirty Year’s War” by Jerome Groopman 2001

Hope turns out to be something negotiated between patients and physicians…. (The) book manages to convey the perverse subtleties of these negotiations….succeeds principally because…refuses to offer a simple, easily digestible thesis.

“The Anatomy of Hope” by Jerome Groopman 2004

As analyzed by Siddhartha Mukherjee, Fellow of Dana Farber Cancer Institute/ Harvard Medical School. New York Times, Book Review, February 22 2004
RADIOIMMUNOTHERAPY FOR NHL: Summary

- NHL may have long survival but it is **incurable** by Chemotherapy or Naked (non-radioactive) Antibodies; none is superior for survival
- Radiotherapy can be curative in limited-stage NHL but limited sites can only be treated (not advanced-stage disease)
- New treatments are needed for patients with Indolent (low grade) NHL, esp. those with relapsing, refractory to chemo and naked MAb, or those transformed to high grade disease
- In the absence of cure or survival benefit, treatments that induce **remission** and prolong time off therapy are valuable
- **Radioimmunotherapy is a promising new treatment** for patients with Indolent or Follicular NHL (ORR) as many studies showed
- It is yet to be determined whether $^{131}$I or $^{90}$Y is the best radionuclide for labeling the Antibodies for therapy of NHL
Approved Antibodies by FDA for Clinical Use

“For adults with relapsed or refractory low-grade or follicular, CD20 positive, B-cell, Non-Hodgkin’s Lymphoma”

• Immunotherapy (IT)
  Rituxan® (Rituximab naked MoAb)

• Radioimmunotherapy (RIT):
  Zevalin® (Y-90-Ibritumomab)
   Bexxar® (I-131-Tositumomab)

• Investigation with Yttrium 90 Epratuzumab

• Research on RIT for Hodgkin's Lymphoma is underway with the targeted antigen being ferritin.
NON-HODGKIN’S LYMPHOMA
THE DISEASE
NON-HODGKIN’S LYMPHOMA

- Ranks 6th in cancer incidence and mortality in USA
- Incidence has risen 150% over past decades
- Incidence increases with age
- Males affected 1.5 times more than females
- 85% of all NHLs are B-cell lymphomas
- Over 90% of B-cell lymphomas are CD20+
LYMPHOMA DIAGNOSIS
Presentation: General Symptoms or Masses and their effects

Chest X-ray

CT scan

PET Scan
LYMPHOMA DIAGNOSIS

Peripheral smear examination

Bone Marrow biopsy/aspirate
LYMPHOMA STAGING
Modified Ann Arbor Staging of NHL
LYMPHOMA CLASSIFICATION

In the “good old days”

there were 4 kinds of lymphomas...

- Lymphosarcoma
- Reticulum cell sarcoma
- Follicular lymphoma
- Hodgkin’s Disease
LYMPHOMA CLASSIFICATION

REAL/WHO

Classification criteria
- Morphology
- Immunophenotype
- Genetic features
- Clinical features

Lymphoid neoplasms

B-cell neoplasms

T-cell and NK-cell neoplasms

Hodgkin's disease

NON-HODGKIN’S LYMPHOMA CLASSIFICATION

REAL/WHO Categories

Cellular origin of disease

Precursor cell
- B cell
- T cell

Mature (peripheral) cell
- B cell
  - Small lymphocytic/chronic lymphocytic
  - Plasma cell myeloma
  - Marginal zone/MALT
  - Follicular
  - Mantle cell
  - Diffuse large B cell
  - Burkitt’s
- T cell
  - Mycosis fungoides
  - Angioimmunoblastic
  - Peripheral (NOS)
  - Anaplastic large cell
## NH LYMPHOMA CLASSIFICATION
The International Working Formulation (Aggressiveness)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A–J</strong></td>
<td>A–J are all malignant lymphomas</td>
</tr>
<tr>
<td><strong>Low grade</strong></td>
<td></td>
</tr>
<tr>
<td>A.</td>
<td>Small lymphocytic</td>
</tr>
<tr>
<td>B.</td>
<td>Follicular, predominantly small cleaved cell</td>
</tr>
<tr>
<td>C.</td>
<td>Follicular, mixed, small cleaved and large cell</td>
</tr>
<tr>
<td><strong>Intermediate grade</strong></td>
<td></td>
</tr>
<tr>
<td>D.</td>
<td>Follicular, predominantly large cell</td>
</tr>
<tr>
<td>E.</td>
<td>Diffuse, small cleaved cell</td>
</tr>
<tr>
<td>F.</td>
<td>Diffuse, mixed, small and large cell</td>
</tr>
<tr>
<td>G.</td>
<td>Diffuse, large cell</td>
</tr>
<tr>
<td><strong>High grade</strong></td>
<td></td>
</tr>
<tr>
<td>H.</td>
<td>Large cell, immunoblastic</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>I.</td>
<td>Lymphoblastic</td>
</tr>
<tr>
<td>J.</td>
<td>Small noncleaved cell</td>
</tr>
<tr>
<td></td>
<td>Composite, mycosis fungoides, histiocytic, extramedullary plasmacytoma, unclassifiable, other</td>
</tr>
</tbody>
</table>

RIT: Where Does It Fit in a Treatment Plan?

Treatment plans differ with
- Patient’s clinical status
- Patient’s medical history
- Histologic type
- Presence of bulky disease
NH LYMPHOMA CLASSIFICATIONS
Low-Grade or Indolent vs. Follicular Lymphoma

**International Working Formulation**

- **A** Small lymphocytic
- **B** Follicular, small cleaved
- **C** Follicular, mixed
- **D** Follicular, large cell
- **E** Diffuse, small cleaved
- **F** Diffuse, mixed
- **G** Diffuse, large cell

**WHO/REAL Classification**

- **Small lymphocytic** (+lymphoplasmacytoid)
- **Follicular lymphoma** BEXXAR (Mantle cell lymphoma)
- **Diffuse, large B cell**

**ZEVALIN**

**Intermediate-Grade**

- **D** Follicular, large cell
- **E** Diffuse, small cleaved
- **F** Diffuse, mixed
- **G** Diffuse, large cell

**High-Grade**

- **H** Large cell, immunoblastic
- **I** Lymphoblastic
- **J** Small non-cleaved
NON-HODGKIN’S LYMPHOAMA
Indolent and Aggressive Types

**Indolent NHL**
- Follicular NHL
- Marginal zone B-cell NHL, MALT type
- Marginal zone B-cell NHL, nodal type
- Small lymphocytic NHL
- Lymphoplasmacytic NHL

**Aggressive NHL**
- Diffuse large B-cell NHL
- Mantle cell NHL
- Peripheral T-cell NHL
- Primary mediastinal large B-cell NHL
- Anaplastic large cell NHL
- Lymphoblastic NHL
- Burkitt-like NHL
- Burkitt’s NHL

**ZEVALIN**
**BEXXAR**
Frequency of NHL Subtypes in Adults

- Indolent (35%)
- Diffuse large B-cell (31%)
- Mantle cell (6%)
- Peripheral T-cell (6%)
- Other subtypes with a frequency ≤2% (9%)
- Composite lymphomas (13%)

NON-HODGKIN’S LYMPHOMA PROGNOSIS

Low-Grade or Indolent NHL

Approximately 30% of all NHL is low-grade\(^{(1)}\) and incurable disease:

- Median survival from diagnosis\(^{(2)}\): 8–10 years
- Often transforms to more aggressive histology with median survival time of less than one year\(^{(2)}\)

\(^{(1)}\) ASH Educational Book. 2002.
NON-HODGKIN’S LYMPHOMA PROGNOSIS

Low-Grade or Indolent NHL

Overall Survival Has Not Been Improved Over the Past Four Decades

1987 to 1996 (N = 668)
1976 to 1987 (N = 513)
1960 to 1976 (N = 195)

Courtesy of Sandra J. Horning, MD.
Indolent NHL Responds to Repeated Chemotherapy With Shorter Durations of Response

Responding patients (n = 110) in remission through 4 treatments

<table>
<thead>
<tr>
<th>CR</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.0</td>
</tr>
<tr>
<td>2</td>
<td>11.2</td>
</tr>
<tr>
<td>3</td>
<td>9.6</td>
</tr>
<tr>
<td>4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

MANAGEMENT OPTIONS
for Indolent or Low Grade NHL

**Early stage**
- XRT
- XRT + chemotherapy

**Advanced stage**
- Watchful waiting
- External beam radiation
- Chemotherapy
- High-dose chemotherapy with transplantation support
- Monoclonal antibody therapy
  - Rituximab
- Radioimmunotherapy
  - $^{90}$Y ibritumomab tiuxetan
  - $^{131}$I tositumomab
- Investigational therapies
  - $^{90}$Y epratuzumab
TREATMENT OF INDOLENT NHL

- Conventional Chemotherapy is not curative
- No regimen is superior in terms of survival
- Additional treatment options are needed
- In the absence of cure or survival benefit,
  treatments that induce remission
  and prolong time off therapy are valuable
- Radioimmunotherapy is a promising new treatment for patients
  with indolent NHL
Radioimmunotherapy in NHL: Summary

• New treatments are needed for patients with indolent NHL, especially those with relapsing, refractory, and transformed disease

• Radioimmunotherapy is a promising new treatment for patients with indolent NHL

• The successful delivery of Radioimmunotherapy requires a collaborative effort among multiple healthcare specialties
LYMPHOMA PROGNOSIS

Follicular NHL

• 2\textsuperscript{nd} most common subtype of NHL\textsuperscript{1}

• Accounts for 25 - 40\% of all adult lymphomas\textsuperscript{1}
  – Common in elderly population\textsuperscript{1}

• Involves low grade and intermediate grade subtypes of IWF classifications of NHL

LYMPHOMA PROGNOSIS

Follicular Lymphoma

Duration of Chemotherapy-Induced Remissions

 MANAGEMENT OPTIONS for Follicular Lymphoma

**Initial Therapy**
- **Stage I, II**
  - RT ± Chemo
  - Ext field RT or Observe

**Stage II***
- Clinical trial or RT or Chemotherapy or Rituximab ± chemotherapy

**Stage III, IV**
- Clinical trial or RT or Chemotherapy or Rituximab ± chemotherapy

**Additional Therapy**

**Without transformation**
- Clinical trial or Chemotherapy or Antibody-based therapy (including RIT) or RT

**Transformed to DLBCL**
- Clinical trial or RIT or Palliative or BSC

* Bulky, abdominal disease.

RADIOIMMUNOTHERAPY IN NON-HODGKIN’S LYMPHOMA (NHL)
TREATMENT OF NHL WITH ANTIBODIES
THE ANTIGENS, CD20

B-Cell Lymphomas Express Several Antigens That Can Be Targeted

Structure of CD20 Antigen

297 amino acids
4 transmembrane domains

Intracellular phosphorylation consensus sequences for serine/threonine kinases

- Protein kinase C (orange)
- Calmodulin/calcium kinase (green)
- Casein kinase II (yellow)

B-Cell Life Cycle and CD20 Expression

CD20 Is Not Expressed on Stem Cells or Plasma Cells

Pluripotent stem cell → Lymphoid stem cell → Pre-B cell → B cell → Activated B cell → Plasma cell

TREATMENT OF NHL WITH ANTIBODIES: THE ANTIBODIES

- Rituximab CD20 (Rituxan)
- Ibritumomab CD20 (Zevalin)
- Tositumomab CD20 (Bexxar)
- Epratuzumab CD22
- Campath-1H CD52
- T101 CD5
- cMT412 CD4
RITUXAN (Rituximab=Murine anti C-20 MoAb)
First MoAb FDA approved for NHL

- FDA approved Indication: Relapsed or refractory low- grade or follicular, CD20+, B-cell NHL
- Chimeric MoAb to CD20
- Dose: 375 mg/m² wk × 4 or 8
- Response rate total was 48% (follicular subtype 60%, small lymphocytic 13%, \( P < .01 \))
- Median duration 11.2 months

Summary of Safety

Infusion-related events most common toxicity (grade 3/4 in<10% of patients)
Severe tumor lysis syndrome, which can be fatal, occurs rarely (<0.1%),

Rituxan® (Rituximab) [prescribing information]. South San Francisco, Ca: Genentech, Inc. 1997.
RITUXAN Results in Cell Death by Several Mechanisms

- Complement-dependent cytolysis (CDC)
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Apoptosis
RADIOIMMUNOTHERAPY IN NON-HODGKIN’S LYMPHOMA (NHL)

Yttrium 90 ibritumomab tiuxetan (ZEVALIN®)
  – Anti-CD20
  – Approved for commercial use in the United States, February 2002

Iodine 131 tositumomab (BEXXAR®)
  – Anti-CD20
  – Approved for commercial use in the United States, June 2003 but longer experience than Zevalin

Yttrium 90 epratuzumab (Investigational)
  – Anti-CD22
ZEVALIN-\textsuperscript{90}Y (Ibritumomab=Murine anti C-20 MAb) 
First Radiolabeled MoAb FDA approved for NHL

- FDA approved Indication: Relapsed or refractory low-grade or follicular, CD20+, B-cell NHL
- Chimeric MoAb to CD20
- Dose: 0.3-0.4mCi/kg max 32mCi
- OA Response rate total was 80% (follicular subtype 82 % Rituxan refractory 74 %)
- Median duration 6.8 months Survivors > 3 years

- Tiuxetan (chelator)
  - Conjugated to antibody, forms strong urea-type bond
  - Stable retention \textsuperscript{90}Y

- Chelator

- Monoclonal antibody

- \textsuperscript{90}Yttrium

- Beta radiation
Tyrosine residue bond conjugates antibody with radionuclide

**BEXXAR-^{131}I (Tositumomab=Murine anti C-20 MAb)**
Second Radiolabeled MoAb FDA approved for NHL

- FDA approved Indication: Relapsed or refractory to chemo and Rituxan follicular, CD20+, B-cell NHL, with or without transformation

- Murine IgG2 alpha MAb

- It is not indicated for the initial treatment of Patients with NHL

- Dose: 65-75 cGy

- Response rate total was 68% (Rituxan naïve Chemo refractory OOR: 47-64)

- Median duration 26 months
BEXXAR-$^{131}$I (Tositumomab = Murine anti C-20 MAb)
Second Radiolabeled MoAb FDA approved for NHL

Indication:
relapsed/refractory to chemotherapy and Rituxan follicular, CD20 positive B-cell NHL

Iodine-131 radioisotope
Cytotoxic beta emission
Physical half-life of 8 days
Short path length
Gamma emission allows dosimetry
# PROPERTIES OF RADIOISOTOPES COMMONLY USED FOR THERAPY

## Iodine-131 vs. Yttrium-90

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Physical half-life</th>
<th>Decay type</th>
<th>Particle energy (MeV)</th>
<th>Primary gamma energy (MeV)</th>
<th>Particle path length (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iodine-131</strong></td>
<td>8 days</td>
<td>β,γ</td>
<td>0.6</td>
<td>0.364</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Yttrium-90</strong></td>
<td>2.7 days</td>
<td>β</td>
<td>2.3</td>
<td>None</td>
<td>5.3</td>
</tr>
</tbody>
</table>
ZEVALIN

CLINICAL DEVELOPMENT
AND RECOMMENDATIONS
ZEVALIN-$^{90}$Y (Ibritumomab = Murine anti C-20 MoAb)
First Radiolabeled MoAb FDA approved for NHL

- FDA approved Indication: Relapsed or refractory low-grade or follicular, CD20+, B-cell NHL

Tiuxetan (chelator)
- Conjugated to antibody, forms strong urea-type bond
- Stable retention $^{90}$Y

Beta radiation

Monoclonal antibody

$^{90}$Yttrium radionuclide
ZEVALIN Therapeutic Regimen
Treatment Schedule

**Imaging dose**

- **Rituxan 250 mg/m²**
- Followed by
  - $^{111}$In Zevalin
  - 5 mCi

**Therapeutic dose**

- **Rituxan 250 mg/m²**
- Followed by
  - $^{90}$Y Zevalin
  - (0.4 or 0.3 mCi/kg*; max dose 32 mCi)

- or
- or

**Day**

1. 2
2. 3
3. 4
4. 5
5. 6
6. 7
7. 8
8. 9

**Scans**

- 2–24 hours
- 48–72 hours
- 90–120 hours *(optional)*

*0.4 mCi/kg in patients with a platelet count ≥150,000 cells/µL or 0.3 mCi/kg with a platelet count 100,000–149,000 cells/µL. Maximum dose is 32.0 mCi.
ZEVALIN
Patient Selection

- **Clinical indication:** For patients with *relapsed or refractory low-grade, follicular, or transformed B-cell NHL*, including *Rituxan-refractory follicular NHL*

- Impaired bone marrow correlates with hematologic toxicity

- **Strict adherence is required to**
  - Patient selection criteria
  - Approved regimen
  - Standard mCi/kg dosing
ZEVALIN Clinical Trial Experience Confirms Safety and Efficacy of mCi/kg Dosing

More than 700 patients (2002) treated safely and effectively in 7 clinical trials:

- 2 Phase I trials
- Phase I/II dose-finding trial
- Phase II trial of 0.3 mCi/kg in mild thrombocytopenia
- Phase III trial of 0.4 mCi/kg in Rituxan-refractory cases
- Phase III comparative trial with Rituxan immunotherapy
- Expanded access open-label trial
ZEVALIN Efficacy: Conclusions

• High overall response rates compare favorably to current therapeutic options
  – 74% in patients with follicular lymphoma who were refractory to Rituxan, with 15% complete responses
  – 80% in patients with indolent lymphoma who had relapsed after chemotherapy, with 30% complete responses

• Active even in patients with unfavorable prognostic characteristics, ie, bulky disease, bone marrow involvement, or extranodal sites
Response Rates in ZEVALIN Trials

ZEVALIN in Rituxan-Refractory Trial (N = 54): Response and Time to Progression

<table>
<thead>
<tr>
<th>Overall response</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>Response rate</td>
</tr>
<tr>
<td></td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Months</td>
<td>Median time to progression</td>
</tr>
<tr>
<td></td>
<td>6.8 (1.1–25.9+)</td>
</tr>
</tbody>
</table>

**ZEVALIN and Rituxan Randomized Trial: Response**

**Zevalin (n = 73) ORR**
- ORR = 80%
- CR = 30%

**Rituxan (n = 70) ORR**
- ORR = 56%
- CR = 16%

*P = .002*

*P = .04*

90Y-ZEVALIN: Radiation Dose of Therapy

- Radiolabeling begins with 40 mCi 90Y

- Typical patient dose range is 21–30 mCi
  - Therapeutic dose is determined by body weight and platelet count
  - Maximum dose is 32 mCi

- Once administered, calculated potential for exposure to others at maximum dose is <1 mrem

**90Y-ZEVALIN: Pharmacokinetics: Dose of Therapy**

- Unique characteristics of Zevalin allow by-weight (mCi/kg) dosing
- 0.4 mCi/kg (32 mCi maximum) determined to be maximum tolerated dose (non-myeloablative)
- With standard mCi/kg dosing of Zevalin, radiation absorbed doses are well within predefined tolerances for both solid organs and bone marrow
- Heavily pretreated patients with relapsed and refractory disease were treated safely, with manageable toxicity and effectively, with response rates as high as 80%
- $^{111}$In-labeled Zevalin imaging is performed as an additional safety measure to confirm the expected biodistribution
In-111-ZEVALIN Dosimetry:
Estimated Radiation Dose to Organs is Acceptable

Mean total absorbed dose (cGy)

- Tumor: 1484 cGy (N = 72)
- Spleen: 848 cGy
- Liver: 532 cGy
- Lungs: 215 cGy
- Bladder wall: 95 cGy
- Red marrow: 71 cGy
- Other organs*: 65 cGy
- Kidneys: 15 cGy

*Some patients have had significant doses to the testes.
ZEVALIN Hematologic Toxicity (Neutrophil/Platelet Nadir) does not Correlate* with Dosimetry

*All $P = NS$

**111 In-ZEVALIN Imaging**

- **Purpose:** in approved indication with mCi/kg dosing, 
  
  111\text{In}-labeled Zevalin imaging is performed as an additional safety measure to confirm the expected biodistribution

- **Biodistribution** should be assessed by visual examination of whole body planar view anterior and posterior images at
  
  - 2–24 hours
  
  - 48–72 hours
  
  - If necessary, 90–120 hours to resolve ambiguities
**In-ZEVALIN Imaging: Expected Biodistribution**

- Radioactivity in the **blood pool** on 1st image, less on 2nd image
- High uptake in normal liver and spleen
- Low uptake in kidneys, urinary bladder, and bowel
- **Tumor uptake** visualized as areas of increased intensity
### 111 In-ZEVALIN Expected Biodistribution

<table>
<thead>
<tr>
<th></th>
<th>Scan 2–24 h</th>
<th>Scan 48–72 h</th>
<th>Scan 90–120 h (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pool</td>
<td>Present</td>
<td>Decreases</td>
<td>Decreases</td>
</tr>
<tr>
<td>Normal liver</td>
<td>Moderately high to high</td>
<td>Moderately high to high</td>
<td>Moderately high to high</td>
</tr>
<tr>
<td>and spleen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal kidneys,</td>
<td>Moderately low to very low</td>
<td>Moderately low to very low</td>
<td>Moderately low to very low</td>
</tr>
<tr>
<td>bladder, bowel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Activity should decrease with time (includes large vessels).
Tumor visualization not required to assess biodistribution.
Note: Normal = uninvolved by tumor.
$^{111}$ In-ZEVALIN Imaging: Expected Biodistribution

Scan 1

Scan 2

Scan 3
## ¹¹¹ In-ZEVALIN
Possible Altered Biodistribution

<table>
<thead>
<tr>
<th>Blood pool</th>
<th>Scan 2–24 h</th>
<th>Scan 48–72 h</th>
<th>Scan 90–120 h (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not visualized</td>
<td>Not visualized</td>
<td>Not visualized</td>
<td></td>
</tr>
<tr>
<td>Diffuse uptake</td>
<td>&gt;Cardiac blood pool</td>
<td>&gt;Liver</td>
<td>&gt;Liver</td>
</tr>
<tr>
<td>Normal lungs</td>
<td>_____</td>
<td>&gt;Liver in posterior view</td>
<td>&gt;Liver in posterior view</td>
</tr>
<tr>
<td>Normal kidneys</td>
<td>_____</td>
<td>&gt;Liver</td>
<td>&gt;Liver</td>
</tr>
<tr>
<td>Normal bowel</td>
<td>_____</td>
<td>&gt;Liver</td>
<td>&gt;Liver</td>
</tr>
</tbody>
</table>
111 In-ZEVALIN: Possible Altered Biodistribution

- Blood pool not visualized on first image
- Lung uptake more intense than liver uptake on 2nd image
- Kidney uptake greater than liver on 2nd image
- Diffuse intense uptake in bowel comparable to liver on second image
$^{111}$In-ZEVALIN Imaging:
Altered Biodistribution

4 hours  
Anterior  Posterior

67 hours  
Anterior  Posterior

Abnormal
Bone marrow uptake widespread with high intensity

- We need to know what images of patients with >25% bone marrow tumor involvement look like; perhaps, an equivalent of a “normal file” for patients with <25% tumor involvement for comparison may be helpful. Semi quantitative analysis for evaluating bone marrow dosimetry, and a method to assess bone marrow reserve would enhance the value of the imaging to identify risk from radiation to normal organs.

*With current protocol qualitative bone marrow assessment has been sufficient*
Levels of Radiation Exposure

- Chest X-ray ~20 mrem
- Average person in the United States 360 mrem/year
- Average hospital radiation worker in USA +150 (510) mrem/year
- Radiation sickness from single dose >100 rem
- Immune system, vascular damage >300 rem
- Calculated potential for exposure to others with ⁹⁰Y ibritumomab tiuxetan at maximum dose <1 mrem
**90Y-ZEVALIN: Radiation Safety Conclusions**

- **90Y ibritumomab tiuxetan is a pure beta emitter**
- Acrylic shielding protects staff members
- Administration can be in an outpatient setting with no restrictions
- **After treatment**
  - Patients pose no radiation exposure risk to healthcare professionals and others
  - Minimal disruption to patients’ daily routines
- **90Y Ibritumomab Tiuxetan Precautions = Universal Precautions**

ZEVALIN: $^{90}\text{Y}$- is a Pure Beta Emitter

Acrylic Syringe and Vial Shields for Dose

Syringe shield conveniently holds a 12 cc syringe for infusion of $^{90}\text{Y}$ Zevalin

Vial shield opens on one end to allow insertion of 10 cc reaction vial; other end opens to allow for drawing out of the vial
90Y-ZEVALIN: Risk of Radiation Exposure to Others Is Minimal

• 90Y is a pure beta emitter
  – Acrylic shielding protects staff
  – Isolation room not required
  – Risk of exposure to staff from treated patients is minimal

• Outpatient administration without restrictions
  – No need to determine activity limits or dose rate limits prior to patient release
  – Patients can be released immediately after treatment

**90Y-ZEVALIN: Risk of Radiation Exposure to Others Is Minimal**

- Prospective study in 13 family members of patients treated with 90Y ibritumomab tiuxetan
  - Family members with closest contact wore DoseGUARD Plus personal dosimeter for 7 days
  - Family was instructed to avoid body wastes, but no other precautions were given
  - Median deep dose equivalent over 7 days = 3.5 mrem (range, 1.4–7.9 mrem)
- Conclusion: exposure to others is negligible, in the range of background radiation

\textbf{90Y-ZEVALIN: Risk of Radiation Exposure to Others Is Minimal}

- Most activity retained; urinary excretion = 7.3\% ± 3.2/7 days

- Assuming maximum 32-mCi dose and excretion of 7\% over a week, total urinary excretion over a week = 2.3 mCi
  - Activity per urination = microcuries

- Ordinary amounts of blood (eg, menstruation, bad cuts, hemorrhoids) will not contain appreciable levels of radioactivity
  - \textbf{\textit{90Y Ibritumomab Tiuxetan Precautions = Universal Precautions}}

For 3 days after treatment

- Clean up spilled urine and dispose of body-fluid-contaminated material so that others will not inadvertently handle it (ie, flush down toilet or place in plastic bag in household trash)
- Wash hands thoroughly after using the toilet

For 1 week after treatment

- Use condoms for sexual relations

ZEVALIN Integrated Safety (N = 349):
Adverse Event Summary

- Well tolerated
- Adverse Events primarily hematologic and reversible
- Grade 3/4 toxicity is delayed 7–9 wks (chemo 1–2 weeks) and correlates with pretreatment status of the patient
  - Bone marrow impairment (low pretreatment platelets, etc.)
  - Bone marrow involvement by lymphoma
  - Number of prior therapies/purine analogues
- Nonhematologic AEs are primarily grade 1 or 2 (as Rituxan)
  (not hair loss, severe mucositis, nausea/vomiting as chemo)
- Low incidence of HAMA/HACA: 1.4% (N = 211)
- Rare cases of Myelodysplasias (MDS), within expected rate for heavily pretreated population
ZEVALIN Integrated Safety (N = 349): Median Blood Counts After Treatment

<table>
<thead>
<tr>
<th>Hemoglobin (g/dL)</th>
<th>ANC (10^3/µL)</th>
<th>Platelets (10^3/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
<td>50,000</td>
</tr>
</tbody>
</table>

Study week: 0 2 4 6 8 10 12 14
ZEVALIN: Integrated Safety (N = 349): Hematologic Toxicity

Myelosuppression profile in patients with grade 3 or 4 toxicity (time to nadir, 7–9 weeks)

<table>
<thead>
<tr>
<th></th>
<th>Nadir (median)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>800/µL</td>
<td>28  30</td>
</tr>
<tr>
<td>(ANC &lt;1000/µL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>41,000/µL</td>
<td>52  10</td>
</tr>
<tr>
<td>(platelets &lt;50,000/µL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>10.5 g/dL</td>
<td>14  3</td>
</tr>
<tr>
<td>(hemoglobin &lt;8.0 g/dL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No difference in hematologic toxicity between patients <65 and ≥65 years of age.

**ZEVALIN: Integrated Safety (N = 349): Clinical Impact of Hematologic Toxicity**

**Hematopoietic support (n = 211)**
- Growth factors 18% of patients
  - G-CSF 13%
  - Erythropoietin 8%
- Red blood cell transfusion 20%
- Platelet transfusion 22%

**Incidence of infection**
- Any grade 29%
- Grade 3 or 4 5%
- Febrile neutropenia 2%

**Incidence of severe bleeding**
- Grade 3 or 4 2%
CHOP CHEMOTHERAPY: Most Common Nonhematologic Adverse Events (N = 202)

- Alopecia: 97% (Grades 1, 2), 3% (Grades 3, 4)
- Fever: 59% (Grades 1, 2), 41% (Grades 3, 4)
- Neurologic toxicity: 54% (Grades 1, 2), 46% (Grades 3, 4)
- Nausea or vomiting: 48% (Grades 1, 2), 52% (Grades 3, 4)
- Liver toxicity: 46% (Grades 1, 2), 54% (Grades 3, 4)
- Constipation: 41% (Grades 1, 2), 59% (Grades 3, 4)
- Cardiac toxicity: 35% (Grades 1, 2), 65% (Grades 3, 4)
- Mucositis: 31% (Grades 1, 2), 69% (Grades 3, 4)
- Lung toxicity: 30% (Grades 1, 2), 70% (Grades 3, 4)
- Renal toxicity: 14% (Grades 1, 2), 86% (Grades 3, 4)

ZEVALIN Integrated Safety (N = 349):
Most Common Nonhematologic AEs (Incidence ≥10%)

- Asthenia: 43 patients
- Nausea: 31 patients
- Infection: 29 patients
- Chills: 24 patients
- Fever: 17 patients
- Abdominal pain: 16 patients
- Dyspnea: 14 patients
- Pain: 13 patients
- Headache: 12 patients
- Vomiting: 12 patients
- Increased cough: 10 patients
- Dizziness: 10 patients
- Throat irritation: 10 patients

ZEVALIN and Rituxan Randomized Trial: Nonhematologic Adverse Events* (N = 143)

Grades 3 and 4

- Angioedema
- Pruritus
- Dyspnea
- Dizziness
- Increased cough
- Headache
- Throat irritation
- Vomiting
- Abdominal pain
- Fever
- Nausea
- Asthenia

Grades 1 and 2

- Pain
- Chills
- Fever
- Abdominal pain
- Vomiting
- Throat irritation
- Headache
- Increased cough
- Dizziness
- Dyspnea
- Pruritus
- Angioedema

*Incidence ≥15%.
**Conclusions**

- A novel immunotherapeutic that combines a monoclonal antibody with radioactive yttrium
  - High overall and complete response rates in relapsed or refractory indolent, follicular, or transformed NHL, including Rituxan-refractory NHL
  - Well tolerated
  - Treatment course is completed in 7–9 days

- **Pure beta emitter**
  - Allows for routine outpatient administration, with no or minimal disruption to patients’ routines
  - Zevalin precautions = universal precautions
Among the lymphomas that occur in children, diffuse large-cell lymphoma and Burkitt lymphoma both express high levels of CD20.

A pediatric phase I study sponsored by the National Cancer Institute will study the use of Zevalin(Y-90-Ibritumomab) in children with recurrent B-cell lymphomas. The study is set to begin accruing patients in the second half of 2002.
BEXXAR-$^{131}$I (Tositumomab = Murine anti C-20 MAb)
Second Radiolabeled MoAb approved for NHL

- FDA approved Indication: Relapsed or refractory to chemo and Rituxan follicular, CD20+, B-cell NHL, with or without transformation

- Murine IgG2 alpha MAb
- It is not indicated for the initial treatment of Patients with NHL
- Dose: 65-75 cGy
- Response rate total was 68% (Rituxan naïve Chemo refractory OOR: 47-64)
- Median duration 26 months

Tyrosine residue bond conjugates antibody with radionuclide
BEXXAR-^{131}I (Tositumomab=Murine anti C-20 MAb)
Second Radiolabeled MAb FDA approved for NHL

Tositumomab
Murine IgG2a anti-CD20 Mab B-cell specific
Induction of apoptosis
Complement-dependent cytotoxicity (CDC)
Antibody-dependent cellular cytotoxicity (ADCC)

• **BEXXAR-^{131}I** FDA approved Indication:
  Relapsed or refractory to chemo and
  Rituxan follicular, CD20+, B-cell
  NHL, with or without transformation

• **Iodine-131 radioisotope**
  • Cytotoxic beta emission
  • Physical half-life of 8 days
  • Short path length
  • Gamma emission allows dosimetry
**BEXXAR Patient Selection**

- **Clinical indication:**
  For patients with CD20 positive, **follicular**, non-Hodgkin’s lymphoma, with and without transformation, whose disease is **refractory to Rituximab** and has relapsed following chemotherapy. It is not indicated for initial therapy of NHL

- **Impaired bone marrow correlates with hematologic toxicity**

- **Strict adherence is required to**
  - Patient selection criteria
  - Approved regimen
  - **DOSIMETRY**
**BEXXAR Therapeutic Regimen**

**Treatment Schedule**

**Dosimetric Step**

- **Day 1:** 450 mg of Tositumomab
  1-hour infusion

- **Day 2:** 35 mg of Tositumomab with 5 mCi Iodine-131
  20-minute infusion

**Therapeutic Step**

- **Day 3:** 450 mg of Tositumomab
  1-hour infusion

- **Day 4:** 35 mg of Tositumomab with Iodine-131 to give 75 cGy total body dose
  20-minute infusion

- **Day 5:** Calculation of Individualized dose of radioactivity

**Scans**

- **Scan #1:** Day 1, 4-8 hrs
- **Scan #2:** Day 5
- **Scan #3:** Day 7, or Day 8, or Day 14

**Thyroprotection:** Day -1 continuing through 14 days post-therapeutic step administer daily SSKI (2 drops po tid)

*65 cGy in patients with a platelet count 100,000-150,000 cells/µL Maximum dose is 32.0 mCi.
BEXXAR EFFICACY: CONCLUSIONS

Rituximab-Refractory or Relapsed NHL

ORR 68% in follicular treated with Rituximab and chemotherapy
Effective in patients with Rituximab-refractory or relapsed disease
with a median duration of response 25 months
The median duration of complete response has not been reached at a median follow up of 26 months

Rituximab-Naïve, Chemotherapy-Refractory Follicular NHL

Durable responses in four clinical studies with Rituximab-naïve, chemotherapy-relapsed or refractory follicular NHL

- ORR: 47%-64% Median TTP: 13 months - Not reached
- Complete Responses: 20%-38% Median TTP: 29 months - Not reached

ORR=Overall Response; TTP=
### BEXXAR in Rituximab-Refractory or Relapsed NHL

**Response in NHL Previously Treated With Rituximab (N=40)**

<table>
<thead>
<tr>
<th></th>
<th>Response Rate (%) (95% CI*)</th>
<th>Median Duration of Response (Mos) (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response</strong></td>
<td>68% (51%- 81%)</td>
<td>16 (1+ - 35+)</td>
</tr>
<tr>
<td><strong>Complete Response†</strong></td>
<td>33% (19%- 49%)</td>
<td>NR† (4- 35+)</td>
</tr>
<tr>
<td><strong>Median duration of follow-up</strong></td>
<td>26 months</td>
<td></td>
</tr>
</tbody>
</table>

* CI = Confidence Interval.
† Complete response rate = Pathologic and clinical complete responses.
‡ NR = Not reached.

---

BEXXAR PI.
### Response in Rituximab-Refractory Patients (N=35)

<table>
<thead>
<tr>
<th></th>
<th>Response Rate (%) (95% CI*)</th>
<th>Median Duration of Response (Mos) (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>63% (45%- 79%)</td>
<td>25 (4+ - 35+)</td>
</tr>
<tr>
<td>Complete Response†</td>
<td>29% (15%- 46%)</td>
<td>NR† (4 - 35+)</td>
</tr>
<tr>
<td>Median duration of follow-up</td>
<td></td>
<td>26 months</td>
</tr>
</tbody>
</table>

* CI = Confidence Interval.
† Complete response rate = Pathologic and clinical complete responses.
‡ NR = Not reached.

BEXXAR PI.
BEXXAR in Rituximab-Refractory or Relapsed NHL

Duration of Response in Rituximab-Refractory Patients by Responders (N=35)

Data on File. Corixa Corporation.
# BEXXAR in Other Clinical Studies

## Durable Remissions in Low-Grade, or Follicular NHL

<table>
<thead>
<tr>
<th>Study Description/Name</th>
<th>Overall Response (%)</th>
<th>Median TTP (mos) (range)</th>
<th>Complete Response (%)</th>
<th>Median TTP (mos) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Refractory (RIT-II-004)</td>
<td>47%</td>
<td>13.2 (3.2 - 48.7)</td>
<td>20%</td>
<td>48.7 (10.5 - 48.7)</td>
</tr>
<tr>
<td>Chemotherapy–Relapsed or Refractory (RIT-II-002*)</td>
<td>59%</td>
<td>NRb (3.2 - 58.9+)</td>
<td>36%</td>
<td>NR† (6.3 - 58.9+)</td>
</tr>
<tr>
<td>Chemotherapy–Relapsed or Refractory LG NHL (RIT-II-001)</td>
<td>49%</td>
<td>14.4 (3.0+ - 62.1+)</td>
<td>26%</td>
<td>60.1 (11.6 - 62.1+)</td>
</tr>
<tr>
<td>Chemotherapy–Relapsed or Refractory (RIT-I-000‡)</td>
<td>64%</td>
<td>15.2 (3.7 - 95.8+)</td>
<td>38%</td>
<td>29.1 (3.7 - 95.8+)</td>
</tr>
</tbody>
</table>

* Excludes patients who only received unlabeled Tositumomab (Arm B); † NR = Not reached; ‡ Excludes 17 patients with intermediate- and high-grade lymphoma.

The BEXXAR therapeutic regimen is not indicated for chemotherapy-refractory, low-grade, or follicular NHL.

Data on File. Corixa Corporation.
**BEXXAR Pivotal Trial in Relapsed NHL: Study Design**

**Objective:** Compare efficacy of BEXXAR and patients’ last qualifying chemotherapy

---

**Dosimetric Step**
- 450 mg of Tositumomab
  - 1-hour infusion
- **•35 mg of Tositumomab**
  - with 5 mCi Iodine-131
  - 20-minute infusion

---

**Therapeutic Step**
- 450 mg of Tositumomab
  - 1-hour infusion
- **35 mg of Tositumomab**
  - with Iodine-131 to give 75* cGy total body dose
  - 20-minute infusion

---

**Day**
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 14

**Scans**
- Scan #1
  - 4-8 hrs
- Scan #2
- Scan #3
- Calculation of Individualized dose of radioactivity

---

**Thyroprotection:** Day -1 continuing through 14 days post-therapeutic step
administer daily SSKI (2 drops po tid)

*65 cGy in patients with a platelet count 100,000-150,000 cells/µL Maximum dose is 32.0 mCi.*
**BEXXAR** Pivotal Trial in Relapsed NHL: Inclusion Criteria

- Low-grade or transformed low-grade CD20+ B-cell NHL
- Chemotherapy-refractory
  - Two or more previous regimens
  - No response to or duration of response
  - Less than 6 months with last regimen
- Adequate Karnofsky Performance Status
- ANC >1500/µL
- Platelet count >100,000/µL
- ≤25% involvement on bilateral bone marrow biopsy

**BEXXAR** Pivotal Trial in Relapsed NHL: Exclusion Criteria

1) Patients with $\geq 25\%$ lymphoma marrow involvement and/or impaired bone marrow reserves, as indicated by
   - Prior myeloablative therapies with ABM/PBSC transplantation
   - Platelet count $<100,000/\mu L$ or ANC $<1500/\mu L$
   - Hypocellular bone marrow ($\leq 15\%$ cellularity; marked reduction in bone marrow precursors of one or more cell lines)
   - History of failed stem cell collection
   - Prior external beam radiation to $>25\%$ active marrow

2) Renal Insufficiency, Pregnancy and Breast-Feeding

*BEXXAR* is not indicated for the initial treatment of Patients with NHL
**BEXXAR Pivotal Trial in Relapsed NHL: Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Last qualifying chemotherapy</th>
<th>BEXXAR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td>17/60 (28%)</td>
<td>39/60 (65%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Median (95% CI)</strong></td>
<td>3.4 (2.5–4.7)</td>
<td>6.5 (3.1–11.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Complete Response</strong></td>
<td>2/60 (3%)</td>
<td>12/60 (20%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Median (95% CI)</strong></td>
<td>6.3 (5.4–8.1)</td>
<td>8.4 (5.1–12.9)</td>
<td></td>
</tr>
</tbody>
</table>

Duration of response (mo)

Duration of Progression-Free Survival (mo)

Median follow-up, 10 mo; range, 6–20 mo.

Elimination of Iodine-131 occurs by decay and urine excretion

Total body residence time or clearance rate depends on tumor size, splenomegaly, bone marrow involvement, predosing

Targeted total body radiation dose (T-TB-RaD) is

75cGy for patients with platelets 150,000/mm³ or
65cGy for patients with platelets 100,000 - 150,000/mm³

It is not possible to achieve the targeted T-TB-RaD without individualizing the dose to each patient by dosimetry

Dosimetry study is necessary for each individual patient
**BEXXAR**: Not possible to achieve Targeted Total Body Radiation Dose without individualizing the dose to each patient by dosimetry.

Impact of Fixed Dosing (mCi/kg) on Total Body Radiation Dose

**LEGEND:**
- **Green** - Below Target Range by ≥ 10%
- **Blue** - Within 10% of Target Range
- **Red** - Above Target Range by ≥ 10%

*Total Body Dose With Fixed 1.1 mCi/kg Dosing (N = 634)*

**BEXXAR**: Not possible to achieve T-TB-RaD without individualizing the dose to each patient by dosimetry

Dose in mCi to deliver T-TB-RaD varies among patients

*Targeted total body radiation dose 75cGy for patients with platelets 150,000/mm³ or 65cGy for patients with platelet counts between 100,000 and 150,000/mm³.*

BEXXAR: EFFECT of CLEARANCE on Radiation Exposure

Individuals with a rapid clearance rate require a higher dose of radiation (in mCi)

Individuals with a slow clearance rate require a lower dose of radiation (in mCi)

Rapid Clearance

Slow Clearance

Days

Days

Treatment dose, mCi

Treatment dose, mCi

75 cGy

75 cGy

1 2 3

1 2 3 4 5

50

50
BEXXAR: PREDOSING improves CLEARANCE
Systemic Pharmacokinetics of Iodine I 131 Tositumomab Following 0, 95, and 475 mg Predose of Unlabeled Tositumomab

475 mg of unlabeled Tositumomab was established as the predosing amount

Data on File. Corixa Corporation.
BEXXAR: PREDOSING improves CLEARANCE

Effect of Unlabeled Antibody Pre-Dose on Distribution

Data on File. Corixa Corporation.
BEXXAR:
CALCULATION OF THE THERAPEUTIC DOSE

1. **Determine Activity Hours to deliver a 75 cGy TBD**

<table>
<thead>
<tr>
<th>Mass</th>
<th>Activity Hours</th>
<th>Mass</th>
<th>Activity Hours</th>
<th>Mass</th>
<th>Activity Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.0</td>
<td>9633</td>
<td>94.5</td>
<td>10068</td>
<td>99.0</td>
<td>10500</td>
</tr>
<tr>
<td>90.5</td>
<td>9682</td>
<td>95.0</td>
<td>10117</td>
<td>99.5</td>
<td>10548</td>
</tr>
<tr>
<td>91.0</td>
<td>9730</td>
<td>95.5</td>
<td>10165</td>
<td>100.0</td>
<td>10595</td>
</tr>
<tr>
<td>91.5</td>
<td>9779</td>
<td>96.0</td>
<td>10213</td>
<td>100.5</td>
<td>10643</td>
</tr>
<tr>
<td>92.0</td>
<td>9827</td>
<td>96.5</td>
<td>10261</td>
<td>101.0</td>
<td>10690</td>
</tr>
<tr>
<td>92.5</td>
<td>9875</td>
<td>97.0</td>
<td>10309</td>
<td>101.5</td>
<td>10738</td>
</tr>
<tr>
<td>93.0</td>
<td>9924</td>
<td>97.5</td>
<td>10357</td>
<td>102.0</td>
<td>10785</td>
</tr>
<tr>
<td>93.5</td>
<td>9972</td>
<td>98.0</td>
<td>10404</td>
<td>102.5</td>
<td>10833</td>
</tr>
<tr>
<td>94.0</td>
<td>10020</td>
<td>98.5</td>
<td>10452</td>
<td>103.0</td>
<td>10880</td>
</tr>
</tbody>
</table>

Activity Hours to Deliver 75 cGy TBD
BEXXAR:
CALCULATION OF THE THERAPEUTIC DOSE

2. Determine total body residence time (clearance rate)

Graphic Estimate of Total Body Residence Time

Residence time = 82 hours
BEXXAR:
CALCULATION OF THE THERAPEUTIC DOSE
3. Determine Therapeutic Dose for 75 (65) cGy TB-RaD

Therapeutic dose (mCi) =

\[
\text{Activity Hours (mCi hr)} \times \frac{\text{Desired TBD (cGy)}}{\text{Residence Time (hr)}} \times \frac{75 \text{ cGy}}{}
\]

The Equation Used to Calculate the Therapeutic Dose
BEXXAR Safety: Conclusions

• Nonhematologic AEs predominantly Grade 1 and 2

• Hematologic AEs - Dose Limiting
  – Primarily Grade 3 or 4 thrombocytopenia (53%) and Grade 3 or 4 neutropenia (63%)
  – Delayed time to nadir: 4 to 7 weeks
  – Limited need for supportive care
  – Low incidence of serious infection: 8%

• Delayed AEs
  – MDS/AML: 3.2%
  – HAMA: 10%
  – Hypothyroidism: 9%
BEXXAR: Adverse Reactions

Infusional Toxicity

• All patients in the clinical studies received pretreatment with acetaminophen and an antihistamine

• 67 (29%) patients reported fever, rigors/chills, or sweating within 14 days following the dosimetric dose

• Adjustment of the rate of infusion to control adverse reactions occurred in only 16 (7%) patients
BEXXAR: Adverse Reactions
Non-Hematologic Adverse Experiences Occurring in >5% Patients (N=230)

* Grade 3/4 <1%. BEXXAR PI.
BEXXAR: Adverse Reactions
Non-Hematologic Adverse Experiences Occurring in >5% Patients (N=230)

Endocrine System
Hypothyroidism
Peripheral edema
Weight Loss*
Musculoskeletal
Myalgia*
Arthralgia
Nervous System
Dizziness
Somnolence
Cough
Respiratory System
Pharyngitis
Dyspnea
Rhinitis
Pneumonia
Skin & Appendages
Rash*
Pruritus
Sweating*

* Grade 3/4 <1%
BEXXAR PI.
**BEXXAR: Adverse Reactions**

**Hematologic Toxicity (N=230)**

<table>
<thead>
<tr>
<th></th>
<th>Platelets</th>
<th>ANC</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4*</td>
<td>53%</td>
<td>63%</td>
<td>29%</td>
</tr>
<tr>
<td>Median duration of Grade 3/4</td>
<td>32 days</td>
<td>31 days</td>
<td>23 days</td>
</tr>
<tr>
<td>Grade 4†</td>
<td>21%</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Median duration of Grade 4</td>
<td>28 days</td>
<td>16 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Median Nadir</td>
<td>43,000 /mm$^3$</td>
<td>690 cells/mm$^3$</td>
<td>10 gm/dL</td>
</tr>
<tr>
<td>Median time to Nadir</td>
<td>34 days</td>
<td>43 days</td>
<td>47 days</td>
</tr>
</tbody>
</table>

*Definition of Grade 3/4: Platelets <50,000 /mm$^3$; ANC <1,000 cells/mm$^3$; Hemoglobin <8 gm/dL.
†Definition of Grade 4: Platelets <25,000 /mm$^3$; ANC <500 cells/mm$^3$; Hemoglobin <6.5 mg/dL.

Data on File. Corixa Corporation; BEXXAR PI.
BEXXAR: Adverse Reactions
Infectious and Hematologic Events

• 104 (45%) pts had one/more adverse events related to infection
  – 19 (8%) patients serious infection that needed hospitalization
• 28 (12%) patients experienced hemorrhagic events
  – Majority were mild to moderate
• 63 (27%) pts received one/more hematologic supportive care:
  – G-CSF, 12%; Epoetin alfa, 7%; platelet transfusion, 15%; RBC transfusion, 16%

Thyroid Function

• 9% of pts developed hypothyroidism as determined by elevated TSH with a median observation period of 18 months
• The cumulative incidence of hypothyroidism was 9.1% and 17.4% at 2 and 4 years, respectively
### BEXXAR: Adverse Reactions

#### Myelodysplasia/Acute Leukemia

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Investigator-Reported New Cases (crude incidence)</th>
<th>Cumulative Incidence</th>
<th>Median Follow-up (months)</th>
<th>Median time to development of MDS/Acute Leukemia (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Studies</strong></td>
<td>229*</td>
<td>19 (8.3%)</td>
<td>4.2% at 2 yrs 10.7% at 4 yrs</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td><strong>Expanded Access Program</strong></td>
<td>765</td>
<td>13 (1.7%)</td>
<td>1.4% at 2 yrs 4.8% at 4 yrs</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>994*</td>
<td>32 (3.2%)</td>
<td></td>
<td>21</td>
<td>27</td>
</tr>
</tbody>
</table>

* Excluded one patient in the clinical studies who was determined by the investigator to have MDS prior to treatment.

BEXXAR PI.
**BEXXAR: Pivotal Trial in Relapsed Lymphoma: Secondary Malignancies**

<table>
<thead>
<tr>
<th></th>
<th>$^{131}$I tositumomab (8-year cumulative)</th>
<th>Autologous stem cell transplantation (5-year cumulative)</th>
<th>Alkylating agents (9-year cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary hematologic malignancies</td>
<td>8.5% (5/59)</td>
<td>12%–18%</td>
<td>8%</td>
</tr>
<tr>
<td>Subsequent solid tumors</td>
<td>5.1% (3/59)</td>
<td>9%</td>
<td>NA</td>
</tr>
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BEXXAR: Adverse Reactions

Human Anti-Mouse Antibody (HAMA)

- 10% of patients became HAMA positive with a median observation period of 6 months

- The median time to HAMA development was 148 days
  - Most of the patients became HAMA positive within 6 months
  - No patients became HAMA positive more than 30 months after administration of the BEXXAR therapeutic regimen
BEXXAR: Safety
Healthcare Workers and Patient Release

According to Nuclear Regulatory Commission (NRC) Guidelines, patient is releasable if total effective dose equivalent to other individuals “is not likely to exceed” 500 mrem

Study: 20 healthcare workers and 26 family members of the 22 patients were provided with monitoring devices (for 2 to 17 days). Patients received BEXXAR TBD 30-75 cGy (25-129 mCi)

Results: The additional radiation exposure per month per healthcare worker was 5.8 mrem (mean). In family members the measured dose values ranged from 17 to 409 mrem

Conclusion: Pts can be treated with little or no risk to healthcare professionals and released immediately with confidence that doses to other individuals should be below the 500 mrem limit.

BEXXAR: Instructions to Patients for 1-2 weeks

Drink plenty of liquids
Sleep in a separate bed (≥6 feet apart)
Do not take long trips (4 hours or more) sitting near others
Avoid contact with children or pregnant women
Stay at least 6 feet away from other people when possible
Have sole use of bathroom; urinate sitting flush X3 lid down
Wash hands frequently; shower daily
Keep dishes/utensils separate from household; wash separately
Use separate toothbrush, towels and washcloths
Wash laundry separately after 1 week
Bag and throw out trash separately
For a short time, do not have sex
Menstruating women should use tampons that can be flushed down the toilet
Radiolabeled Antibody Therapy in Pediatrics
Lymphoma

Pediatrics

Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma

- Lymphoblastic
- Small Non-Cleaved Cell (Burkitt’s and non-Burkitt’s)
- Large Cell
Lymphoma

Radioimmunotherapy (RIT) is currently available for adults with relapsed or refractory low-grade or follicular, CD20+, B-cell NHL.

→ Zevalin (Y-90-Ibritumomab)

Research of RIT with Hodgkin's Lymphoma is underway with the targeted antigen being ferritin.
Among the lymphomas that occur in children, diffuse large-cell lymphoma and Burkitt lymphoma both express high levels of CD20.

A pediatric phase I study sponsored by the National Cancer Institute will study the use of Zevalin (Y-90-Ibritumomab) in children with recurrent B-cell lymphomas.

The study is set to begin accruing patients in the second half of 2002.
TREATMENT OF NEUROBLASTOMA WITH RADIOISOTOPES IN CHILDREN
Neuroblastoma

Neuroblastoma arises from neural crest cells that are progenitors of the adrenal medulla and the sympathetic nervous system.

Most common extracranial solid tumor of childhood.

Most common neoplasm diagnosed in the first year of life.

Unlike other solid tumors, 60% of neuroblastoma’s are already metastatic at the time of diagnosis.
TREATMENT OF NEUROBLASTOMA WITH RADIOISOTOPES IN CHILDREN

Radiopharmaceutical Therapy

1) Metabolic( I-131 MIBG)

2) Receptor Binding(Peptides)

3) Immunological(Antibodies)
Neuroblastoma

1) **Metabolic**

Iodine-131-MIBG is a guanethidine analog, structurally similar to norepinephrine. It is selectively concentrated in neurosecretory storage granules of chromaffin cells in neural crest tumors.

2) **Receptor Binding(Peptides)**

Indium-111-Octreotide, concentrates in neuroendocrine and some non-neuroendocrine tumors containing somatostatin receptors.

3) **Immunological(Antibodies)**

Targeted radioimmunotherapy, exploits the specificity of antibodies to deliver a radioisotope directly to tumor cells.
Neuroblastoma

I-131-MIBG

*Indications for use in Stage III or IV Disease:*
Recurrent or progressive metastatic disease after all other treatment modalities utilized.
Pre-Operatively to reduce initially inoperable tumors.
In combination with hyperbaric oxygen therapy in patients with recurrent disease.

*Contraindications:*
Severe Myelosuppression
Renal Failure
Unstable patient which would prohibit isolation
Neuroblastoma

I-131-MIBG

Recurrent or progressive metastatic disease after all other treatment modalities utilized

Netherlands Cancer Institute (53 patients followed for 38 months)

7 patients (13%) with complete remission
23 patients (43%) with partial remission
10 patients (19%) with progressive disease arrested

Troncone et al. (47 patients)

21 patients (47%) with complete or partial remission

Multicenter (273 patients)

95 patients (35%) with complete or partial remission

The conclusion from these and others studies is that I-131-MIBG after conventional therapy is the best palliative treatment with pain relief in days.
Neuroblastoma

I-131-MIBG

*Pre-Operatively to reduce initially inoperable tumors.*
→ reduces tumor volume for surgery, less toxicity than chemotherapy, and avoids early drug resistance

Hoefnagel et al. (31 patients)
70% had were able to have complete or greater than 95% of the primary tumor resected.

Hoefnagel et al. (49 patients Stage III & IV)
1 Year Survival = 65%
2 Year Survival = 45%
3 Year Survival = 40%
4 Year Survival = 38%

The study concluded that pre-op I-131-MIBG is at least as effective as combination chemotherapy, but with considerably less toxicity.
Neuroblastoma

Somatostatin Receptor Therapy

No literature on use in children with neuroblastoma.

Has been used in some trials in patients with other neuroendocrine tumors.

Indium-111-Octreotide has been shown to have an objective response in some of these patients.

But for better therapeutic responses, somatostatins will most likely have to be radiolabeled with $\beta$ or $\alpha$-emittors.
Neuroblastoma

Future Therapy

I-131-3F8(Radiolabeled Antibody)

This antibody targets the glycolipid antigen, ganglioside GD2, which is abundantly expressed on neuroblastoma cells.

Current trials underway by Cheung at Sloan-Kettering
THERAPY WITH UNSEALED RADIOPHARMACEUTICALS

George N. Sfakianakis MD
Professor of Radiology and Pediatrics
Director, Division of Nuclear Medicine