RADIONUCLIDE TREATMENT OF LIVER CANCER

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Head, Nuclear Medicine Section
International Atomic Energy Agency

SNM, Philadelphia, 2004
• One of the most common malignancies in the world
• It constitutes more than 5% of all cancers
• Annual International incidence – 1 million
• 15,000 cases in the USA
• 250,000 in China.
• 75% of primary liver cancers are HCC
• About 80% of people are male.
• One third in China
• One third in rest of South East Asia
• Rest, in the rest of the world
## REGIONAL DISTRIBUTION OF HCC IN THE WORLD

<table>
<thead>
<tr>
<th>Region/country</th>
<th>Males (no. of cases/100000)</th>
<th>Females (no. of cases/100000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. High risk areas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mozambique, Zimbabwe, China, Vietnam, Taiwan, Korea</td>
<td>30-120</td>
<td>9-3</td>
</tr>
<tr>
<td>Mongolia, Japan</td>
<td>30-120</td>
<td>9-3</td>
</tr>
<tr>
<td>South Africa, Greece, Philippines</td>
<td>10-30</td>
<td>3-9</td>
</tr>
<tr>
<td>Singapore</td>
<td>10-30</td>
<td>3-9</td>
</tr>
<tr>
<td><strong>2. Intermediate risk areas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern Europe</td>
<td>5-10</td>
<td>2-5</td>
</tr>
<tr>
<td>(Spain, Italy, France, Switzerland Argentina)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Low risk areas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Europe, USA, Canada, India</td>
<td>&lt;5</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>
HEPATOCELLULAR CARCINOMA (HCC): CURRENT SITUATION IN ASIA

<table>
<thead>
<tr>
<th>No.</th>
<th>Country</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Australia</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>02</td>
<td>China</td>
<td>30.6</td>
<td>10.7</td>
</tr>
<tr>
<td>03</td>
<td>India</td>
<td>2.4</td>
<td>0.8</td>
</tr>
<tr>
<td>04</td>
<td>Japan</td>
<td>41.5</td>
<td>9.7</td>
</tr>
<tr>
<td>05</td>
<td>Korea</td>
<td>30.5</td>
<td>7.6</td>
</tr>
<tr>
<td>06</td>
<td>Mongolia</td>
<td>39.2</td>
<td>39.2</td>
</tr>
<tr>
<td>07</td>
<td>Philippines</td>
<td>20.4</td>
<td>8</td>
</tr>
<tr>
<td>08</td>
<td>Singapore</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>09</td>
<td>Thailand</td>
<td>40.5</td>
<td>16.3</td>
</tr>
<tr>
<td>10</td>
<td>Vietnam</td>
<td>45.2</td>
<td>5.9</td>
</tr>
</tbody>
</table>
EVOLUTION OF INCIDENCES

• Rising rates of HCC in Western countries:
  – in France: 1979-94: X 3 in males and X 2 in females
  – in the UK (Scotland) and
  – in the USA: 1976-91 incidence X 1.8;
• Due to:
  – improvement of diagnostic methods,
  – better survival of cirrhotic patients +++
  – increase in the number of new etiologies: HCV++++, diabetes, obesity...
EVOLUTION OF INCIDENCES

Increase also in high incidence countries!

- Rising rates in Japan during the past 30 years:
  - despite a stable incidence of chronic hepatitis B
- Influence of undiagnosed hepatitis C
• Hepatocellular carcinoma is potentially curable by surgical resection, but surgery is the treatment of choice for only the small fraction of patients

• Prognosis depends on the degree of local tumour replacement and the extent of liver function impairment.
TREATMENT OF LIVER CANCER

- Although two-thirds of people have advanced liver disease when they seek medical help, one third of the patients have cancer that has not progressed beyond the liver. The most promising treatments apply to this latter group.
TREATMENT OF LIVER CANCER

• Radical form of Treatment:
  - Surgical resection
  - Orthotopic liver transplantation (OLT)
  - Percutaneous injection to induce coagulative necrosis of the tumor using agents like ethanol, acetic acid, hot saline, microwave and laser

• Palliative Treatment
  - Transarterial embolization (TAE)
  - Transarterial chemoembolization (TACE)
  - Transcatheter oily chemoembolization (TOCE)
  - Chemotherapeutic Agents
  - I-131 Lipiodol
TREATMENT OF LIVER CANCER: CURRENT PRACTICE

- Single nodule < 5 cm
  - Percutaneous Tt
  - Surgery: OLT

- Single nodule > 5 cm
  - Resection

- Multiple nodules
  - Chemoembolization

- Portal vein thrombosis
  - Medical support
TREATMENT OF HCC: DRAWBACKS OF CURRENT PRACTICE

- Percutaneous Tt
- Surgery: OLT
- Resection
- Chemoembolization
- Medical support/Thrombosis

Drawbacks:
- Recurrences
- Accessibility
- Tolerance
- Efficacy

SNM, Philadelphia, 2004
The understanding of pathology, pathogenesis, natural course, risk factors of HCC during the last three decades has resulted in the development of multiple therapeutic approaches with promising yet varying results.

Most patients with hepatoma fall into the intermediate/inoperable category, and for these, radionuclide methods to deliver high radiation doses to tumor must be considered.

It may be noted that the disease is most prevalent in those communities with maximum need and least resources.

Hence the cost and availability are of utmost importance.
RADIONUCLIDES IN THE TREATMENT OF HCC

- **I-131 Lipiodol**: Largest clinical experience in the world. Very little experience or application in the developing countries of the world, where the disease is highly prevalent. Limited experience in the treatment of HCC in Thailand, Philippines, Vietnam, Indonesia, Malaysia, China, India and Singapore.

- **Ho-166 Chitosan**: Established procedure in Korea.

- **Ho-166 Microspheres**: Phase I clinical trial in Australia.

- **Re-188 Microspheres**: may be useful.

- **Re-188 Lipiodol**: IAEA Multi-centre study.
HEPATOCELLULAR CARCINOMA: Trans-arterial injections of Lipiodol

1  BLOOD SUPPLY

Non-tumourous liver:
- Hepatic artery +
- Portal vein +++

HCC:
- Arterial supply +++
- Hypervascularization

2  LIPIODOL:
- Follows blood flow
- Goes & stays within hepatic tumors

DIAGNOSIS  TARGETED THERAPY
LIPIODOL AS THE CARRIER VEHICLE

Lungs

Tumors

Cirrhotic liver

SNM, Philadelphia, 2004
LIPIODOL AS THE CARRIER VEHICLE

Huge, diffuse tumor

THROMBOSIS
TREATMENT OF HCC WITH I-131 LIPIODOL

- Portal vein thrombosis
- Multinodular tumors
- Adjuvant treatment
  - before surgery: neoadjuvant
  - adjuvant post resection
- Curative intent
- 131-I-Lipiodol + chemotherapy
PHASE-III: LIPIOCIS Vs. CHEMOEMBOLIZATION
RESULTS: SURVIVAL

<table>
<thead>
<tr>
<th></th>
<th>6 mos</th>
<th>1 year</th>
<th>2 yrs</th>
<th>3 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPIOCIS</td>
<td>72.3%</td>
<td>44.3%</td>
<td>22.4%</td>
<td>9.9%</td>
</tr>
<tr>
<td>CE</td>
<td>65.6%</td>
<td>40.4%</td>
<td>19.5%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

Hepatology 1997; 26: 1156-61
Portal vein thrombosis is a poor prognostic factor in patients with hepatocellular carcinoma (HCC) and a contraindication for chemoembolization.

90Y- MICROSPHERES

• Resin based microspheres (30 µm)
• 90 Y (Australian radioisotope, Australia)
• Selective hepatic angiography:
  – 99mTc-MAA
    • lung shunting
    • T/NT
    • OK if: shunting < 15 % & T/NT > 2
  – injections of 0.8 to 5.0 GBq - repeated ?
• median survival = 9.4 mo
• Well tolerated: abdominal discomfort, fever


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I-131 LIPIODOL/ Y-90 MICROSPHERES

• These radiopharmaceuticals are available for several years
• Expensive
• 2000-3000 US$ per dose
• Especially from the point of view of developing countries

Need for a cost-effective radiopharmaceutical
IAEA CRP ON LIVER CANCER

Management of Liver Cancer Using Radionuclide Methods with Special Emphasis on Trans-Arterial Radionuclide Therapy and Internal Dosimetry

The Overall Objective
To improve the health care and quality of life of patients suffering from Hepato Cellular Cancer (HCC) by standardizing and making available a cost-effective radionuclide therapeutic procedure for routine clinical use.
Radioactivity distribution in rat hepatoma
\((^{188}\text{Re-N}_2\text{S}_2/\text{lipiodol})\)

Autoradiography

H&E

Normal liver tissue

Hepatoma

1 hr

24 hr

Seoul National University, Seoul, Korea

SNM, Philadelphia, 2004

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# IAEA CRP ON LIVER CANCER

## RC Holders:
- China
- Colombia
- India
- Korea
- Mongolia
- Philippines
- Singapore
- Thailand
- Vietnam

## RA Holders:
- Australia
- Austria
- France
- India
- Korea
- Slovenia
- United Kingdom
- United States of America (2)

<table>
<thead>
<tr>
<th>15 Countries</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>

*SM, Philadelphia, 2004*
PREPARATION OF Re-188 HDD LIPIODOL

188Re-perrhenate & buffer

188Re-perrhenate & buffer

HDD, SnCl₂·2H₂O, Weak chelator

Add lipiodol

Heating 1 hr

Venting needle

188Re-HDD / Lipiodol

Centrifuge 3000 rpm, 10 min

SnM, Philadelphia, 2004

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DOSIMETRY PROTOCOL

- A specially designed Spreadsheet was used to determine maximum tolerated activity (MTA), defined as the amount of radioactivity calculated to deliver no more than:
  - 12 Gray (Gy) to lungs
  - 30 Gy to liver
  - 1.5 Gy to bone marrow
## Absorbed Doses

<table>
<thead>
<tr>
<th>Target Region, ( r_k )</th>
<th>Source Region ( r_h )</th>
<th>Liver Radiation</th>
<th>Liver Non-Penetrating</th>
<th>Lung Radiation</th>
<th>Lung Non-Penetrating</th>
<th>Total Radiation</th>
<th>Total Non-Penetrating</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td></td>
<td>1.40E-02</td>
<td>3.91E-01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.405</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>3.52E-04</td>
<td>7.23E-02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07262</td>
</tr>
<tr>
<td>Red Marrow</td>
<td></td>
<td>1.87E-04</td>
<td>0.00E+00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.000187</td>
</tr>
</tbody>
</table>

*NO blood sample-Red Marrow dose does NOT include self-irradiation*

## Therapy Administered Activity

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Maximum Tolerated Absorbed Dose (cGy)</th>
<th>Administered Activity Absorbed Dose (MBq)</th>
<th>Therapy Administered Activity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>3,000</td>
<td>7,415</td>
<td>7,415 MBq</td>
</tr>
<tr>
<td>Lung</td>
<td>1,200</td>
<td>16,523</td>
<td>= 200 mCi</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>150</td>
<td>801,514</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>No of Patients with scout dose and treatment</th>
<th>Amount of Scout dose mean (range)</th>
<th>Treatment dose mean (range)</th>
<th>MTD Limiting organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>200 MBq (141 to 289 MBq)</td>
<td>4 GBq (1.8 to 7.5 GBq)</td>
<td>Lung = 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liver = 13</td>
</tr>
</tbody>
</table>
Prothrombine

Seconds

Basal 1 s 2 s 4 s

Therapy 1 2 3 4 5 6 7 8 9 10 11

SNM, Philadelphia, 2004
Bilirubins

Normal

Basal 1 s 2 s 4 s

Therapy 1 2 3 4 5 6 7 8 9 10 11

SNM, Philadelphia, 2004

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### ADVERSE EFFECTS

- Nausea : 03
- Vomiting : 01
- Low Grade Fever : 01
- Rt. Hypo. Pain : 03

**NO HAEMATOLOGICAL TOXICITY**
Rhenium-188 lipiodol is an easily available radio-conjugate for trans-arterial treatment of HCC.

The right quantity of the radioconjugate can be delivered after 'scout' dose dosimetry studies have been done, to spare normal liver and lung from excess radiation dose.

The Phase-I study has shown Re-188 Lipiodol treatment to be safe with minimal side-effects, at a dose up to about 220 mCi.

Although there appears to be some response to treatment, (and a few patients have had re-treatment) the efficacy of this new agent for the treatment of HCC has to be confirmed in a larger multi-centre Phase-2 study.
## Phase-2: Interim Results

- **Total No. of Patients Treated so far as per the protocol:**
  - Colombia : 11
  - Mongolia : 30
  - Thailand : 5
  - India : 18
  - Singapore : 14
  - China : 15
  - Vietnam : 63
  - Philippines : 8
  - Total (Dec, 2003) : 164
## Data Analyses available in 75 Patients

<table>
<thead>
<tr>
<th>No of Doses/ Pts (N=75)</th>
<th>Cumulative Activity</th>
<th>MTA Limiting Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>Calculated Activity: 63-618 mCi</td>
<td>Lung = 32</td>
</tr>
<tr>
<td>Two</td>
<td>Median: 252 mCi Administered Activity: 35-229 mCi</td>
<td>Liver = 43</td>
</tr>
<tr>
<td>Three</td>
<td>Median: 78 mCi</td>
<td></td>
</tr>
</tbody>
</table>

SNM, Philadelphia, 2004
Measure of Efficacy:
Tumour Size

1. Positive tumour reduction: 64%
2. New Liver Metastases: 04%
3. Distant Metastases: 04%
Tumour Response

AFP status was evaluated by the clinicians as follows:

- complete response: 16%
- partial response: 16%
- stable disease: 48%
- progression: 20% of the cases

Similarly encouraging results were obtained regarding tumour response:

- complete response: 3%
- partial response: 16%
- Stable disease: 64%
- progression: 16% of the cases
The Kaplan-Meier estimate of the survival curve is presented below (crosses indicate patients still alive at their last observation; the lower part of the curve should not be trusted due to small number of patients under observation):

The median follow-up time was 448 days. Estimated one-year survival was 52%, while at the time of the analysis (which is almost two years after the start of the study for some patients) the survival rate is 40%.
IAEA Multi-centre study-Re-188 Lipiodol

Estimated one-year survival: 52%

I-131 Lipiodol

I-131 Lipiodol
January, 2002

April

AFP=1200

March

July, 2002

AFP=04

Patient still living – April, 2004

Dra. Patricia Bernal, Bogota, Colombia

SNM, Philadelphia, 2004

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Hepatocellular Carcinoma

SNM, Philadelphia, 2004

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Second Dose: Tumor disappeared
Current Status: On FU
Publications so far.....


6. Padhy AK, Bernal P. A CD Rom on the preparation of Re-188 Lipiodol (Perth, Australia, April, 2001)

Biological Dosimetry

Of
Re-188 Lipiodol
Vs.
I-131 Lipiodol
In HCC

Re-188 Lipiodol therapy yields a significantly lower cytotoxicity effect and lower radiation exposure for an expected higher tumour killing effect.

Ruyck KD et al. Journal of Nuclear Medicine 2004; 45: 612-618

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CONCLUSIONS

• It is one of the world’s most common malignancies, causing almost one million deaths annually
• Patients with HCC have an extremely poor prognosis with a five year survival rate of less than 5%
• The understanding of pathology, pathogenesis, natural course, risk factors of HCC during the last three decades has resulted in the development of multiple therapeutic approaches with promising yet varying results.
• Most patients with hepatoma fall into the intermediate/inoperable category, and for these, radionuclide methods to deliver high radiation doses to tumor must be considered
• Various radio-conjugates have been used in the treatment of HCC with variable results
• The commercially available radiopharmaceutical- Re-188 Lipiodol is expensive and is not practical for use on a day to day basis in the developing countries
CONCLUSIONS

- Re-188 Lipiodol is an excellent radiopharmaceutical for Internal Radiation Therapy of HCC
- Re-188 allows higher administered dose
- Reduces radiation protection problems
- Improves the Quality of life by shortening hospitalization
- MTD can be given without any toxicity or adverse effects
- Efficacy has been shown in terms of tumour regression and increased survival even in the group of patients treated in our series so far, where most of the patients treated presented with extensive disease
- Adjuvant to Surgical treatment
- Cyto-reduction
- Cost-effective
COST-EFFECTIVENESS OF Re-188 LIPIODOL

- One Rhenium Generator costs: US$ 9000
- A single 1 Curie generator would last 6 months
- One can use it virtually every day
- Multi-modality use of Re-188
- Intracoronary therapy, Radiosynovectomy, metastatic bone disease etc.
- Work-horse of therapeutic nuclear medicine
IAEA’s small step in meeting the challenges of Liver cancer in developing countries: A Truly Global Effort

**IAEA: NAHU-NMS**
- Coordination of The entire Research & Developmental activities.
- Protocols
- Multi-centre Studies

**IAEA: TC**
- Transfer of Technology
- HRD Fellowship
- Group Training
- Expert Missions
- Supply of Radiopharmaceuticals

**MSKCC, New York**
- (Internal Dosimetry)

**Seoul National University Hospital**
- (Radiopharmacy)

**Department of Energy, USA:** Re-188 generators at subsidized price to IAEA (US$ 7800 instead of 14,000)
- Expert Advise, Fabrication of accessories etc.

- Centre Eugene Marquis, Rue de la Bataille Frandres-Dunkerque, Rennes-Cedex, France – For Clinical Protocols

- Singapore General Hospital, Core Centre For the Clinical Studies

- 10 Centres from 10 developing countries, 6 centres from 5 developed countries
- And 9 Universities from 9 developing countries
Participating Countries
Spirit of Vietnam