I Labeled Lipiodol Injection: A Cost Effective Alternative for Liver Cancer Treatment

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Global incidence of Hepatocellular carcinoma (HCC) is reported to be more than 1 million patients per year. In Asia and Africa, it is the most frequent cause of cancer-induced deaths. Due to the late appearance of symptoms and poor patient prognosis, more than 95% of patients do not survive five years past the initial diagnosis. Resective surgery, systemic chemotherapy and external beam radiotherapy have proven singularly ineffective for treatment of the disease in terms of survival benefit.

Trans-arterial chemo-embolization (TACE) using drugs like cisplatin, doxorubicin, methotrexate, paclitaxel has been employed in conjunction with Lipiodol for locoregional therapy. TACE involves administration of drugs intra-arterially for preferential localization in regions of tumor as majority of normal hepatic blood supply is via the portal vein and neo-angiogenic vessels are primarily connected to the hepatic artery as shown in Fig 1.

In TACE, Lipiodol serves as both drug carrier and embolizing agent. Intra-vascular retention of Lipiodol leads to starvation of tumor cells of nutrient and oxygen supply and deliver high doses of the drug(s) loco-regionally, which provides greater chemotherapeutic effect than by the systemic route. Embolization in conjunction with a radiotherapy agent, is called radio-embolization. There are two main categories of radio-embolic agents approved for clinical use. First category is based on micron-range particulates that encapsulate or adsorb therapeutic radionuclides, like 90Y-bearing glass spheres (Therasphere®) and polymeric selective internal radiation spheres (SIR-spheres®).

Although Therasphere and SIR-spheres are being used worldwide, their exorbitant cost is a major limitation for their wider use in developing countries like India. Second category is Lipiodol or related embolic substances tagged with therapeutic radionuclide.

Lipiodol or Ethiodised oil is a naturally iodinated fatty acid ethyl ester of poppy seed oil (37% w/w of iodine). It is employed as a magnetic resonance imaging (MRI) contrast agent for the liver and has also been labeled with therapeutic radionuclides such as $^{131}$I and $^{188}$Re for HCC treatment. Isotopic exchange is used to label iodine rich Lipiodol with $^{131}$I to prepare radioiodinated Lipiodol, while $^{188}$Re-labeled 4-hexadecyl-1,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD) is dispersed in Lipiodol for preparation of $^{188}$Re-labeled radioembolizing agent.

$^{131}$I, radioisotope is indigenously available in sufficient quantities at a very low cost due to its reactor production route and dry distillation processing method as compared to generator produced $^{90}$Y and $^{188}$Re. $^{131}$I labeled Lipiodol can be

![Fig 1.: Schematic representation of transarterial radioembolization (TARE) procedure](image)

### Table 1: Comparison of Radiopharmaceuticals for Transarterial radioembolization

<table>
<thead>
<tr>
<th>Radiopharmaceuticals</th>
<th>$^{90}$Y Glass spheres (Therasphere®)</th>
<th>$^{90}$Y Polymeric SIR-spheres®</th>
<th>$^{188}$Re-HDD-Lipiodol</th>
<th>$^{131}$I-labeled Lipiodol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radioisotope</strong></td>
<td>$^{90}$Y</td>
<td>$^{90}$Y</td>
<td>$^{188}$Re</td>
<td>$^{131}$I</td>
</tr>
<tr>
<td><strong>Nuclear Emissions</strong></td>
<td>$E_{p_{max}}$: 2.28MeV</td>
<td>$E_{p_{max}}$: 2.28MeV</td>
<td>$E_{p_{max}}$: 2.12 MeV, 1.97 MeV</td>
<td>$E_{p_{max}}$: 610 KeV</td>
</tr>
<tr>
<td></td>
<td>$E_{p_{max}}$: 2.28MeV</td>
<td></td>
<td>$E_{p_{max}}$: 155 keV</td>
<td>$E_{p_{max}}$: 364 KeV</td>
</tr>
<tr>
<td><strong>Half Life</strong></td>
<td>64.1h</td>
<td>64.1h</td>
<td>17 h</td>
<td>8 days</td>
</tr>
<tr>
<td><strong>Production of isotope</strong></td>
<td>$^{90}$Sr/$^{90}$Y Generator</td>
<td>$^{90}$Sr/$^{90}$Y Generator</td>
<td>$^{188}$W/$^{188}$Re Generator</td>
<td>Reactor</td>
</tr>
<tr>
<td><strong>Material</strong></td>
<td>Glass</td>
<td>Resin</td>
<td>Oil</td>
<td>Oil</td>
</tr>
<tr>
<td><strong>Cost per patient dose</strong></td>
<td>~ 5 lakhs</td>
<td>~ 5 lakhs</td>
<td>~ 2 lakhs</td>
<td>40,000/-</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>Imported</td>
<td>Imported</td>
<td>Imported</td>
<td>BARC/ BRIT product</td>
</tr>
</tbody>
</table>
easily prepared and supplied from a centralized radiopharmacy owing to suitable half-life of $^{131}$I, allowing convenient logistics of production and quality control checks prior to patient administration.

There is a demand from Nuclear medicine fraternity for $^{131}$I labeled Lipiodol if supplied as a cost effective, ready-to-use radiopharmaceutical. The patient dose preparation of $^{131}$I labeled Lipiodol requires high amounts of initial activity (>3.7GBq) of $^{131}$I. The high energy gamma radiations (637 KeV, ~7% abundance & $E_{\text{max}}$: 610 KeV) of $^{131}$I pose considerable safety related limitations for radiolabeling. Hence, a semi-automated modular system was designed and fabricated to ensure operator safety as well as pharmaceutical purity and safety of the product.

**Design**

Photograph of semi-automated module for production of patient dose of $^{131}$I-Lipiodol and control panel is depicted in Fig 2. The module holds two lead pots of 30mm thickness. The lead pot containing Na$^{131}$I can easily slide on the base plate of the module and the radioactivity vial gets firmly held with the help of a precisely designed bottle guard plate for safe operations. The reaction vessel assembly is enclosed in a silicon glycerin bath, fitted at rear end of the base plate of the module.

Precise addition of reagents to vials as well as all transfers of reagents are carried out remotely. Inert nitrogen gas of high purity is used for pressurizing vessels. Tefzel tubings compatible with organic solvents are used for transfer of reagents which are connected to solenoid valves mounted on plate and connected to junction box. Heating of reaction vessel is carried out using thermocouple with display of temperature.

The module is placed inside locally designed and fabricated shielded facility similar to commercially available mini hot cell with adequate lead shielding having negative pressure and charcoal filters fitted at release duct. For external surface sterilization of this set up ultraviolet light is installed and kept on for minimum three hours prior to synthesis. Electrical valve operations and heating controls are placed separately on control panel, which are operated manually by simple on/off switch away from module. Valve operation sequence was standardized based on optimized reaction parameters.

Radiation field, air activity and activity released through charcoal trap were monitored during all operations. Several batches of $^{131}$I labeled Lipiodol were prepared using standardized operating protocol.$^{5}$

**Radiosynthesis**

Isotope exchange reaction between organic iodine of Lipiodol with ionic $^{131}$I was carried out with slight modifications in the reported procedure. Radioactive assay of the product was carried out using Ion chamber and yield of the product is calculated. The reaction is monitored for $^{131}$I activity measurement at all the stages of production. Quality control

| Table 2: Specifications of $^{131}$I labeled Lipiodol and QC acceptance criteria |
|---------------------------------|----------------------|
| **Product Code** | IOM-40 |
| **Description** | $^{131}$I labeled Lipiodol is ready to use sterile, pyrogen free injectable formulation. The formulation contains $^{131}$I iodinated ethyl esters of fatty acids of poppy seed oil ($^{131}$I labeled Lipiodol) |
| **Appearance** | Clear yellow to light brown liquid |
| **Radionuclide Identification** | Principal Energy peaks 364 & 637 keV (+5keV) |
| **Radionuclide Purity** | >99.9% |
| **Radiochemical purity** | >95% |
| **Radioactive concentration** | 15-20 mCi /mL |
| **Storage** | Stored between 10 to 25°C in dark with adequate shielding |
| **Expiry** | Seven days from the date of reference |
analysis by physicochemical test is done immediately after preparation for all the batches of $^{131}$I labeled Lipiodol while biological tests as per Indian Pharmacopoeia are done after decay of activity. Table 2 depicts specifications of the product, $^{131}$I labeled Lipiodol injection.

Pre Clinical Evaluation

Animal biodistribution studies were done in normal Wistar rats using viable surgery protocol to study liver retention and kinetics over a period of 5 days post injection of $^{131}$I Lipiodol. Fig 3a depicts a typical procedure used for preclinical evaluation in orthotropic model and Fig 3b depict the biodistribution pattern confirming retention of >90% injected $^{131}$I activity in liver 24h post injection.

Regulatory Approval

Dossier containing detailed production procedures, quality control monographs and data of consecutive batch production and QC was submitted and approval was obtained from DAE-Radiopharmaceutical committee on March 2017 for manufacture and supply of $^{131}$I Lipiodol Injection for clinical use.

Clinical evaluation

Clinical evaluation of $^{131}$I labeled Lipiodol in HCC patients started from April 2017. Production and QC of nine batches of patient dose of $^{131}$I labeled Lipiodol was carried out till Dec 2017. Initial clinical results are promising with major retention of activity in liver upto 72h post injection for therapeutic response. Fig 4 depicts representative image of patient injected with $^{131}$I labeled Lipiodol.

Conclusion

Radiopharmaceutical Division has successfully carried out indigenous development of therapeutic radiopharmaceutical $^{131}$I labeled Lipiodol Injection and deployment of safe and pure product for clinical use as IOM-40 from BRIT (patient dose of 75mCi activity at a cost of Rs. 40,000). Initial results are very satisfying and requests from various nuclear medicine centres are being received for the product. $^{131}$I labeled Lipiodol injection is a cost effective alternative for treatment of Hepatocellular carcinoma.

References: