

Radionuclide Therapy of Hepatocellular Carcinoma

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Abstract

Introduction: Hepatocellular carcinoma (HCC) is a common malignancy worldwide. Surgical resection is generally accepted as the first choice treatment of HCC. Many non-surgical techniques have been developed and used for the treatment of inoperable HCC, with limited efficacy. This paper studies the role of radionuclide therapy in the treatment of inoperable HCC and in an adjuvant setting following curative resection of HCC. **Materials and Methods:** Relevant articles published between 1980 and 2002 were reviewed. Articles were identified through a Medline search using the key words hepatocellular carcinoma, iodine-131 (I-131), lipiodol, yttrium-90 (Y-90), rhenium-188 (Re-188), monoclonal antibodies and anti-ferritin. **Results:** The objective response rate of patients with HCC treated with intra-arterial I-131 lipiodol was 40% to 70% and the median survival was between 6 and 9 months. The efficacy of I-131 lipiodol was similar to transarterial chemo-embolisation, but appears to be better tolerated by patients. A median survival of 9.4 months to 54 weeks was achieved using intra-arterial Y-90 microspheres for the treatment of HCC. Tumours in 4 patients became resectable after treatment. Re-188 lipiodol is a relatively new radiopharmaceutical used for the treatment of HCC. The results of a pilot study have shown Re-188 lipiodol to be a safe and cost-effective radiopharmaceutical for the treatment of HCC via the intra-arterial route. Its efficacy should be subjected to further evaluation. The use of radio-labelled monoclonal antibodies, such as anticarcinoembryonic antigen and antiferritin, for the treatment of HCC has yielded encouraging results but these forms of treatment are largely experimental and limited to a few centres. Intra-arterial treatment using I-131 lipiodol in an adjuvant setting for patients following curative resection of HCC has resulted in improved disease-free and overall survival. The 3-year survival for the treatment and control groups were 86.4% and 46.3%, respectively. **Conclusion:** Radionuclide therapy presents another interesting option for the treatment of HCC amidst the wide array of non-surgical modalities available.

Ann Acad Med Singapore 2003; 32:518-24

Key words: Antiferritin, Hepatocellular carcinoma, Iodine-131, Lipiodol, Monoclonal antibodies, Rhenium-188, Yttrium-90

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. It is a major cause of death from cancer in East Asia, especially China, Japan, Korea, Taiwan and Singapore, and sub-Saharan Africa, particularly Zimbabwe, Ethiopia and Mozambique.¹ The age-standardised incidence rate of HCC in Singapore is 18.9 per 100,000 a year.²

Surgical resection is generally accepted as the first choice treatment for HCC. However, only about 20% of all patients have resectable HCC at initial presentation due to its multifocal nature and frequent association with cirrhosis.^{3,4} Treatment of inoperable HCC is mainly palliative. Many non-surgical treatment modalities have been developed and used for the treatment of HCC. These include percutaneous ethanol injection (PEI), cryotherapy, radiofrequency ablation (RFA), systemic chemotherapy, transarterial chemoembolisation (TACE), hormonal therapy, immunotherapy, external radiotherapy and radionuclide therapy.

PEI and RFA techniques have shown some success in the treatment of small HCCs.⁵⁻¹¹ Some authors have reported that the results of patients who have received PEI are similar to those of patients who had surgical resection of HCC.^{6,8} However, treatment of larger HCCs using PEI and RFA appears to be less efficacious in causing complete necrosis of the tumour when compared with the smaller lesions.^{12,13} There is also a significant rate of tumour recurrence.^{6,14} The use of cryotherapy, systemic chemotherapy, hormonal therapy, immunotherapy and external beam radiotherapy for the treatment of HCC are either ineffective or have met with limited success.¹⁵⁻³¹

Despite many reports on the effectiveness of TACE in the treatment of HCC,³²⁻⁴⁹ there are very few randomised controlled trials to validate its efficacy. Arterial blood flow can be obstructed by the injection of gelfoam or by placing metallic coils. Flow obstruction can be combined with injection of a mixture of lipiodol and chemotherapy drugs, also known as TACE. There is no evidence that TACE is more effective than embolisation (TAE) alone.⁴⁰ TACE is

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widely used for the treatment of HCC. In a French randomised controlled trial, where patients with unresectable HCCs were randomised to receive TACE or no treatment, the survival of patients was not significantly improved by TACE although there was a trend favouring the treated group.⁴¹ Given the limited efficacy of available modalities for the treatment of HCC, is there a role for radionuclide therapy? Radionuclide therapy has been utilised for palliative treatment of inoperable HCC and for adjuvant therapy following curative resection of HCC.

Palliative Radionuclide Therapy for Inoperable HCC

The radionuclide is usually delivered via the hepatic intra-arterial approach. Iodine-131 (I-131) lipiodol, Yttrium-90 (Y-90) microspheres and Rhenium-188 (Re-188) lipiodol are some of the radiopharmaceuticals that have been utilised. Monoclonal antibodies, such as anticarcinoembryonic antigen and antiferritin labelled with Y-90 and I-131, have also been utilised and are usually given parenterally. Other approaches, such as ultrasound-guided percutaneous intra-tumoral injection of Y-90 microspheres, have been used. Tian et al⁵⁰ have treated 27 patients with HCC, and 6 patients with liver metastases using this approach and have shown encouraging results. In their study, most of the patients have failed other treatment modalities. Twenty-seven patients were still alive 12 to 32 months after treatment, with 90.6% of the tumour foci becoming smaller. The serum α -fetoprotein (AFP) levels normalised in 10 of 13 patients. Doses of up to 282 Gy to 757 Gy were delivered to the tumours.

I-131 lipiodol

I-131 emits both β and γ rays. The average energy of the β rays emitted by I-131 is 181 keV and that of γ rays is 364 keV. It is, therefore, suitable for both therapeutic and imaging purposes. The physical half-life of I-131 is 8.05 days. Lipiodol is an iodised ethyl ester of the fatty acids of poppy seed oil containing 38% of iodine by weight. It is known to selectively localise in HCC following intra-arterial hepatic administration.

Many studies have reported encouraging results with the use of I-131 lipiodol for the treatment of unresectable HCC.⁵¹⁻⁶³ The activity of I-131 lipiodol administered ranges from 740 MBq to 6220 MBq, either in single or multiple treatments.⁵¹⁻⁶³ Where the hepatic tumours are large, fractionated doses of I-131 lipiodol were given at 4-day intervals.⁶⁰ Repeat treatment can be given at intervals of 8 to 12 weeks. The objective response rates, in terms of radiological regression of tumour and/or reduction in serum α -fetoprotein levels, range from 40% to 70%.^{55,59,60} Overall, the response of HCC to intra-arterial I-131 lipiodol appears to be dependent on the size of the tumour and the magnitude of the treatment dose delivered transarterially. The response

was poorer with increasing size of tumour and lower administered treatment dose. This is to be expected from basic radiation dosimetry principles, which relate cell death to radiation absorbed dose by tumour. Yoo et al⁵⁷ reported that tumour reduction was seen in 88.9% of tumours <4 cm, 65.5% of tumours between 4.1 cm and 6 cm and 25% of tumours >6.1 cm. The median survival ranges from 6 to 9 months.^{55,60} In a series involving 73 HCC patients treated with I-131 lipiodol, the overall survival rates at 6 months, 1, 2, 3 and 4 years were 69%, 38%, 22%, 14% and 10%, respectively.⁶³

The efficacy of hepatic intra-arterial I-131 lipiodol for the treatment of HCC is comparable to TACE. I-131 lipiodol appears to be better tolerated than TACE with fewer side effects experienced by the patients. Thus, radionuclide therapy is a reasonable alternative to TACE for the treatment of unresectable HCCs. There were 2 studies which compared the efficacy of hepatic intra-arterial I-131 lipiodol therapy with TACE. In the study by Bhattacharya et al,⁶² 69 patients with unresectable HCC received hepatic intra-arterial epirubicin-lipiodol emulsion and 26 patients received hepatic intra-arterial I-131 lipiodol. The survival benefit at 6 and 12 months for either modality was comparable. The actuarial survival at 6, 12 and 24 months was 40%, 25% and 6%, respectively, with epirubicin-lipiodol, and 58%, 25% and 0%, respectively, with I-131 lipiodol. Both groups show acceptable toxicity such as mild nausea, fever and abdominal pain. In a French prospective randomised trial,⁶³ 142 patients were randomised to receive either intra-arterial injection of I-131 lipiodol (73 patients) or chemoembolisation (69 patients). It was found that, in terms of patient survival and tumour response, both modalities showed similar efficacy in the treatment of HCC. The overall survival rates at 6 months, 1, 2, 3 and 4 years were 69%, 38%, 22%, 14% and 10%, respectively, in the I-131 lipiodol group and 66%, 42%, 22%, 3% and 0%, respectively, in the chemoembolisation group. Tolerance of I-131 lipiodol was significantly better with 3 severe side effects noted in the I-131 lipiodol group and 29 in the chemoembolisation group ($P < 0.001$).

There may also be a role for I-131 lipiodol therapy in some patients with portal vein thrombosis where TACE is generally contraindicated. I-131 lipiodol does not modify arterial flow and appears feasible in some patients with portal vein thrombosis. In a French randomised study,⁶¹ 14 HCC patients were randomised to I-131 lipiodol therapy and 11 HCC patients to medical support consisting of tamoxifen (5 patients), intravenous 5 fluorouracil (1 patient), non-steroidal anti-inflammatory drugs or corticosteroids (5 patients). The survival rates (95% confidence interval) at 3, 6 and 9 months were 71% (48% to 95%), 48% (12% to 55%) and 7% (1% to 31%), respectively, for the treatment group and 10% (1% to 33%), 0% and 0%, respectively, for the

control group. Overall, the tolerance was excellent in the treated group.

In general, intra-arterial I-131 lipiodol treatment of HCC is well tolerated.⁶¹⁻⁶³ Some reported side effects for this treatment include fever, mild abdominal pain, nausea, elevation of transaminases and radiation hepatitis.^{57,60} However, most of them are mild and tend to resolve with minimal or no intervention. Pre-treatment with Lugol's iodine will result in adequate thyroid blockage, thus reducing the effect of I-131 ions (dissociated from I-131 lipiodol) on the thyroid gland. There may be a possible role for the use of both radionuclide therapy and TACE together for palliative treatment of HCCs as there may be a synergistic effect. However, data on this form of combination therapy are lacking and we await further studies.

Y-90 microspheres

Y-90 is a stronger pure β emitter than I-131. It emits β rays with an average energy of 935 keV and has a half-life of 64 hours and a maximum penetration or β range of 11 mm. Y-90 does not emit γ rays and is not optimal for imaging purposes. Y-90 can be embedded in insoluble, non-biodegradable glass or resin microspheres (mean diameters of 25 μ m to 35 μ m). Administration of the Y-90 microspheres via the intra-hepatic, intra-arterial route will result in the deposition of the glass or resin microspheres in the tumour terminal vasculature. Since HCCs have a relatively greater arteriolar density compared with the normal liver, and are predominantly supplied by the hepatic artery rather than the portal venous system, this will result in a threefold or greater radiation dose in the tumour nodules relative to the normal liver.⁶⁴ Y-90 microspheres appear to be able to deliver a higher radiation dose to the liver tumour compared with I-131 lipiodol. Y-90 microspheres can be safely administered via intrahepatic, intra-arterial injection to patients with HCC and underlying cirrhosis at a dose of 100 Gy to the liver.^{65,66} With this technique, an initial scout dose with Technetium-99m macroaggregated albumin or other similar agent is required to document the presence of significant porto-systemic shunting in the presence of portal hypertension. Y-90 microspheres are generally not given when the lung uptake is >15%, which indicates significant porto-systemic shunting.⁶⁷ Extrahepatic shunting is the main limitation to this form of therapy.⁶⁵

This form of therapy appears to be safe. Andrews et al⁶⁸ conducted a phase I dose escalation study using intra-arterial Y-90 microspheres with estimated whole liver nominal absorbed doses ranging from 50 Gy to 150 Gy. They did not find any haematologic, hepatic and pulmonary toxicity during a mean follow-up period of up to 53 months. Reversible gastritis and duodenitis were encountered in 4

patients. Other reported side effects associated with this form of treatment included fever, elevation of liver enzymes and bilirubin and gastrointestinal toxicities such as ulcers, ileus and nausea.^{67,69} Most of the side effects did not require treatment and either resolved spontaneously or with treatment. There was a reported case of death resulting from radiation pneumonitis.⁶⁹ However, this patient had 39% pulmonary shunting and it is questionable whether he or she should have been eligible for treatment.

There have been several studies reporting the use of Y-90 microspheres for the treatment of HCC.⁶⁵⁻⁷⁴ The activity of Y-90 microspheres administered ranges from 1554 MBq to 5000 MBq for initial treatment with cumulative activity of up to 13,000 MBq from repeated treatments.^{66,67,69,73,74} Using the intra-arterial approach of administering the Y-90 microspheres, it is possible to deliver radiation doses of up to 748 Gy to the tumour at a single treatment session and cumulative tumour radiation doses of up to 1580 Gy.⁶⁷ An objective response rate of 80%, in terms of reduction of serum α -fetoprotein levels, has been reported.⁶⁷ Other authors have reported an objective response rate of 20% in terms of radiological regression of tumour.⁶⁹ Median survival of 9.4 months to 54 weeks has been achieved with the use of Y-90 microspheres.^{67,69} Interestingly, Lau et al⁶⁷ reported 4 patients whose tumours were converted into resectable ones and these underwent resection.

Use of Re-188 lipiodol

Re-188 has recently been used to treat HCCs. It has a physical half-life of 16.9 hours and emits β rays with an average energy of 795 KeV and γ rays of 155 KeV in 15% abundance. Gamma camera imaging for biodistribution studies is possible with this radionuclide. Re-188 is eluted from a tungsten-188/Re-188 generator, which has a long and useful shelf life of several months, thus providing a constant yield of carrier-free Re-188 on a routine basis. This could potentially be cost-saving when compared to the use of other radionuclides and would be particularly useful in the context of treating HCC in developing countries, where the incidence of HCC is among the highest in the world. The concentrated eluate from the tungsten-rhenium generator is heated with 4-hexadecyl 1-2, 9, 9-tetramethyl-4, 7-diaza-1, 10-decanethiol (HDD) in a water bath for 1 hour to produce a rhenium-HDD complex. In our institution, HDD lyophilised kits were obtained from Seoul National University Hospital in Korea. Lipiodol is added and centrifuged to extract the rhenium-HDD into the lipiodol. This method of preparation was previously described by Jeong et al⁷⁵ and Lee et al.⁷⁶ An International Atomic Energy Agency-sponsored multicentre pilot study using intra-arterial Re-188 lipiodol for the treatment of

inoperable HCC has recently been concluded.⁷⁷ Sixteen patients were treated with Re-188 lipiodol in this study. A “scout dose” was given, from which the maximal tolerated dose (MTD) was determined using a specially designed spreadsheet. The MTD is defined as the amount of radioactivity calculated to deliver no more than 12 Gy to the lungs, 30 Gy to the liver or 1.5 Gy to the bone marrow. These doses have been found to be safe. This method of treatment appears to be safe and well tolerated at doses up to 7400 MBq Re-188 lipiodol. The side effects were minimal and included slight elevation of liver enzymes (alanine transaminase and aspartate transaminase) at 24 hours, mild nausea, mild hypochondrial pain, fever and vomiting. The efficacy of this new radionuclide for the treatment of HCC has to be confirmed in a larger, multicentre phase 2 study.

Radio-labelled Monoclonal Antibodies to Treat HCC

There are a few monoclonal antibodies against antigens such as CEA, ferritin and α -fetoprotein, which have some degree of specificity for HCC. Both anti-CEA and antiferritin antibodies have been labelled with I-131 and Y-90, and are administered parenterally for the treatment of HCC.⁷⁸⁻⁸³ The results have been encouraging, although experience with this method of treatment is limited to only a few centres. Fan et al⁸² treated 37 patients with I-131 labelled anti-HCC ferritin antibody and 4 patients with I-125 labelled anti-HCC ferritin antibody. All 41 patients also underwent hepatic artery ligation and received doses between 370 MBq and 1480 MBq given between 1 and 3 times. The decline in AFP was seen in 67.5% for the treated group against 42.9% for controls; shrinkage of tumour was achieved in 68.3% for the treated group against 33.9% for controls. The 1-year and 3-year survival rates for the treated group were 61% and 25%, respectively, against 37.3% and 6.9%, respectively, for controls. Tang et al⁸³ treated 32 patients with unresectable HCC using I-131 anti-HCC monoclonal antibody and reported reduction of tumour in 72% of the patients. There were 17 patients who subsequently underwent resection of tumour. The efficacy of this form of treatment may be limited by the fact that the tumour cells are generally heterogeneous and not all the cells express the same antigen. There is also a possibility of developing human-antimouse antibodies with the use of antibodies of murine origin, thus preventing subsequent treatment.

Adjuvant Treatment with I-131 Lipiodol after Curative Resection of HCC

Resection of HCC is potentially curative, but the recurrence rate is 100% at 5 years.⁸⁴ It is hypothesised that the high recurrence rate is due to microscopic metastatic

disease or metachronous multicentric tumour present in the remnant liver not detected before and at the time of surgery by the usual imaging methods.

Various systemic and locoregional chemotherapy agents have been tried to reduce the rate of recurrence. The overall results show marginal or no significant improvement in disease-free survival.⁸⁵⁻⁸⁸ The efficacy of these forms of therapy is also limited by the toxicity of the chemotherapeutic agents. The presence of underlying cirrhosis further limits the ability of the liver remnant to tolerate these agents. In adjuvant therapy, there appears to be a role for radionuclide therapy in improving disease-free and overall survival following curative resection of HCC. Lau et al⁸⁹ randomised 21 patients to receive one 1850 MBq dose of intra-arterial I-131 lipiodol and 22 patients to no adjuvant treatment following curative resection of HCC. The median disease-free survival in the treatment and control groups was 57.2 months and 13.6 months, respectively. The 3-year overall survival for the treatment and control groups were 86.4% and 46.3%, respectively. In a more recent study, Partensky et al⁹⁰ reported a median time to detected recurrence of 28 months (range, 12 to 62 months) for 28 patients. Each patient was treated with one 1110 MBq dose of intra-arterial I-131 lipiodol following curative resection of HCC. The overall survival rates were 86% at 3 years and 65% at 5 years. In our preliminary study, the 6-month disease-free survival rate was 100% and the 12-month disease-free and overall survival rates were 72% and 85%, respectively, for 15 patients who had received I-131 lipiodol adjuvant therapy following curative resection of HCC.⁹¹ This form of adjuvant therapy appears to be safe with no clinically adverse side effects reported. Adjuvant radionuclide therapy may also have a possible role in reducing the rate of tumour recurrence after minimally invasive percutaneous treatment of small HCC, such as PEI and RFA.

Conclusion

Treatment of HCC involves multidisciplinary collaboration. In cases of multisegmental or large HCCs, palliative treatment using radionuclide therapy is a viable alternative to TACE. The survival rates are similar for both modalities, but radionuclide therapy appears to be better tolerated with less severe side effects. In rare instances, unresectable tumours may be converted to resectable tumours after radionuclide therapy. Radionuclide treatment in a curative intent may be possible for small HCCs in instances where surgery or percutaneous treatment is not possible due to tumour location or severe concurrent medical illnesses. Adjuvant radionuclide therapy appears to have a promising role in reducing the rate of tumour recurrence after surgery for resectable HCCs and after percutaneous treatment of small HCCs.

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