

Preliminary Experience in Radionuclide Therapy of Hepatocellular Carcinoma Using Hepatic Intra-arterial Radio-conjugates

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Abstract

Introduction: In a minority of the cases, resection of hepatocellular carcinoma (HCC) is potentially curative but local recurrence is common. Adjuvant intra-arterial radio-conjugate therapy could potentially reduce the rate of local recurrence and increase disease-free and overall survival. However, in the majority of cases, treatment of HCC is largely palliative. A wide range of palliative treatment options are available and these include external radiation, hepatic intra-arterial chemo-embolisation, systemic chemotherapy and percutaneous ethanol injection. The long-term survival rate is poor. Hepatic intra-arterial radio-conjugate therapy provides a new and promising means of palliation. **Materials and Methods:** We share our initial experience in the treatment of patients with HCC. A total of 32 patients were recruited between October 1999 and June 2001. Group 1 comprised 15 patients who had potentially curative resection of HCC who were treated with Iodine-131 (I^{131}) lipiodol as a form of adjuvant therapy. Group 2 comprised 17 patients with unresectable HCC, 12 of whom were treated with Yttrium-90 (Y^{90}) microspheres and 5 with Rhenium-188 (Re^{188}) lipiodol. The radio-conjugates were administered via the intra-arterial route. **Results:** Thirteen of the 15 patients in group 1 who were treated with I^{131} lipiodol following curative resection of HCC were free of disease, 1 patient died and 1 patient who developed recurrence was retreated with Re^{188} lipiodol and was subsequently free of disease. The 6-month disease-free survival rate was 100% and the 12-month disease-free and overall survival rates were 72% and 85%, respectively. Of the 12 patients in group 2 who were treated with Y^{90} microspheres for unresectable HCC, 6 had stable disease, 2 showed tumour regression and 4 died. The 6-month and 12-month survival rates were 75% and 66%, respectively. Of the 5 patients in group 2 who were treated with Re^{188} lipiodol for unresectable HCC, 4 had stable disease and 1 had regression of the right lobe tumour but progression of the left lobe tumour. **Conclusion:** Our results in the adjuvant treatment of patients with I^{131} lipiodol following curative resection of early HCC and in the palliative treatment of unresectable HCC using Y^{90} microspheres and Re^{188} lipiodol are preliminary and not fully conclusive. These preliminary results have to be confirmed in larger groups of patients and by prospective, randomised, controlled trials. This study highlights the preliminary experience in radionuclide therapy of HCC using hepatic intra-arterial radio-conjugates in a local context.

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Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. In Singapore, the age-standardised incidence rate is 18.9 per 100,000 per year. It is the fourth most common cancer in Singaporean males.¹

Following curative resection of HCC, early recurrence of HCC is common.²⁻⁴ This could be due to the microscopic disease present in the remnant liver. Hence, there may be

a role for adjuvant treatment with Iodine-131 (I^{131}) lipiodol following surgery for patients with resectable HCC with the hope of delivering a sufficient dose of radiation to the liver resulting in eradication of the microscopic disease.

The overall prognosis of HCC is poor. Okuda et al⁵ reported a median survival of less than 4 months for patients with unresectable HCC and those who suffered from relapse after resection.

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Treatment for unresectable HCC is mainly palliative and this includes external radiation, hepatic intra-arterial chemo-embolisation with or without lipiodol, systemic chemotherapy and percutaneous ethanol injection (PEI). Hepatic intra-arterial embolisation with radio-conjugates offers a new and promising means of palliation.

In cases of unresectable HCCs, hepatic intra-arterial radio-conjugates aim to deliver a sufficient tumoricidal dose to the hepatic tumour but at the same time limiting the radiation dose to the normal liver tissue and other organs to within tolerance limits. This is made possible by the fact that the liver has a dual blood supply. HCCs derive their blood supply primarily from the hepatic artery whereas the normal liver parenchyma obtains 80% of the blood supply from the portal vein and only 20% from the hepatic artery.⁶

In this paper, we present our initial experience with hepatic intra-arterial radio-conjugates in the treatment of 2 groups of patients with HCC. Group 1 consists of patients treated with I¹³¹ lipiodol following surgery for a resectable HCC. Group 2 consists of patients with unresectable HCC treated with Yttrium-90 (Y⁹⁰) microspheres or Rhenium-188 (Re¹⁸⁸) lipiodol.

Materials and Methods

Radiopharmaceuticals

Three types of radiopharmaceuticals were utilised. These were I¹³¹ lipiodol, Y⁹⁰ microspheres and Re¹⁸⁸ lipiodol.

I¹³¹ radionuclide has a physical half-life of 8.05 days. It emits β rays with an average energy of 181 keV and γ radiation of 364 keV and this makes it suitable for both therapeutic and imaging purposes for biodistribution studies. Lipiodol is an iodised ethyl ester of the fatty acids of poppy seed oil containing 38% of iodine by weight. The dose of I¹³¹ lipiodol given to the group of patients with resectable HCC ranges between 50 and 60 mCi.

Y⁹⁰ has a physical half-life of 64.2 hours. It is a pure β emitter and the β rays emitted have an average energy of 935 keV. Y⁹⁰ is embedded in insoluble glass or resin microspheres with a mean diameter of 25 μ m. The dose of Y⁹⁰ microspheres administered to the patients with unresectable HCC ranges between 30 and 60 mCi.

Re¹⁸⁸ has a physical half-life of 16.9 hours. It emits β rays with an average energy of 795 keV and γ rays with energy of 155 keV in 15% abundance. Thus, imaging is also possible for biodistribution studies. Re¹⁸⁸ is eluted from the Tungsten-188/Re¹⁸⁸ generator system which has a very long useful shelf-life of several months, thus providing a high yield of carrier-free Re¹⁸⁸ on a routine on-demand basis. The dose of Re¹⁸⁸ administered to the patients with unresectable HCC ranges between 50 and 110 mCi.

The Singapore General Hospital Ethics Committee approved the use of the above radio-conjugates for the

treatment of unresectable HCC on compassionate grounds.

Patient Selection

A total of 32 patients were recruited between October 1999 and June 2001. They were divided into 2 groups. Group 1 comprised 15 patients treated with I¹³¹ lipiodol following curative resection of HCC. Group 2 comprised 17 patients who had unresectable HCC; 12 were treated with Y⁹⁰ microspheres and 5 patients with Re¹⁸⁸ lipiodol. In all patients, the tumour was histologically proven.

All patients had baseline chest X-rays, full blood counts, serum creatinine, bilirubin, α -fetoprotein and liver transaminases levels checked. A pre-treatment computed tomographic (CT) scan of the liver was also obtained.

The eligibility criteria for the patients in group 1 (i.e. those who had curative resection of the HCC) included recovery within 6 weeks of surgery, no fever, no sepsis, acceptable liver function tests (total bilirubin <50 mmol/L), satisfactory clotting profile (increase of prothrombin time <4 s) and a platelet count >100 $\times 10^9$ /L.

The exclusion criteria for the patients in group 1 included serious medical illness, intractable ascites, extrahepatic disease, portal vein thrombosis, women who were pregnant or breastfeeding and contraindication to hepatic angiography, e.g. vascular abnormalities, bleeding diathesis and allergy to contrast dye.

Patients in group 2 (i.e. those with unresectable HCCs) were staged using the Okuda's method.⁵ The stage of the disease was determined by the presence or absence of the following features: bilirubin >50 mmol/L, serum albumin <30 g/L, ascites and tumour replacement of the liver >50%. Patients without any of the above features were graded as stage 1. Those with 1 or 2 of the above features were graded as stage 2 and those with more than 2 of the above features were graded as stage 3. All group 2 patients who underwent the radio-conjugate therapy belonged to either stage 1 or 2. Patients with Okuda stage 3 were excluded from radio-conjugate therapy.

The eligibility criteria for the patients in group 2 were a total white count $\geq 2.0 \times 10^9$ /L, platelet count $\geq 100 \times 10^9$ /L, prothrombin time and activated partial thromboplastin time within normal limits, bilirubin <1.5 $\times$ upper limit; aspartate aminotransaminase (AST), alanine aminotransaminase (ALT) and alkaline phosphatase (ALP) <5 $\times$ upper normal limit.

The exclusion criteria for the patients in group 2 was similar to those in group 1.

Administration of Radio-conjugate

Prior to the administration of the radio-conjugate, hepatic angiography was performed by an interventional radiologist via a femoral puncture. The radio-conjugate was administered by the nuclear medicine physician via the

angiography catheter under fluoroscopic guidance over approximately 5 minutes taking care not to reflux the radio-conjugate into the gastroduodenal artery, thus minimising the risk of radiation gastritis.⁷

Post-procedure Care of the Patient

After the injection of the radio-conjugate, all patients who were treated with I¹³¹ lipiodol were admitted into a ward specially designed for patients receiving high-dose radiation.

Radiation hazard to the public was minimised by temporarily isolating the patient. The radiation from the patient was measured daily by the radiopharmacist or the radiation physicist. The patients were discharged when the activity within the body fell below 33 mCi or the dose rate at 1 meter was below 7 mrem/h, a level recommended by the US Nuclear Regulatory Commission, Regulatory Guide 8.39.⁸ The period of hospitalisation varied between patients and this was dependent on the effective half-life of the radio-conjugate inside the patient. On average, this was between 2 and 4 days.

During the hospital stay, no children and pregnant women were allowed to visit the patient. The other visitors were restricted to a visiting time of 10 minutes only.

All liquid drainage, including from the sink and toilet, were drained into an underground storage tank where the radioactive liquid wastes were stored for a minimum period of 6 months before being disposed into the normal sewage. Solid wastes were sent to the Nuclear Medicine department for storage for 6 months. The level of activity was measured before disposal.

Patients treated with Y⁹⁰ need not be specially isolated from the general public and may be admitted to the general ward, since Y⁹⁰ is purely a β -emitter. Radiation exposure to members of the public resulting from activities normally administered for therapeutic purposes is minimal.

According to the US Nuclear Regulatory Commission, Regulatory Guide 8.39, patients treated with Re¹⁸⁸ lipiodol may be discharged if the radiation level within the body is below 790 mCi. Based on this recommendation, it was possible to admit these patients into a general ward.

Results

Group 1 comprised 15 patients treated with I¹³¹ lipiodol following curative resection of HCC. After treatment, 13 patients were free of disease, 1 patient died and 1 patient had a recurrence and was re-treated with Re¹⁸⁸ lipiodol approximately 1½ months after treatment with I¹³¹ lipiodol. She was subsequently disease free on follow-up. The period of follow-up for all the patients ranged from 0.6 to 15 months. The 6-month disease-free survival rate was 100% and the 12-month disease-free and overall survival

rates were 72% and 85%, respectively.

Group 2 comprised 17 patients who had unresectable HCC. Twelve patients were treated with Y⁹⁰ microspheres and 5 patients with Re¹⁸⁸ lipiodol.

Of the 12 patients treated with Y⁹⁰ microspheres for HCC, 6 patients had stable disease, 2 showed tumour regression and 4 died. One of the 4 patients who died had had 2 treatments of Y⁹⁰ microsphere approximately 3 months apart with a total cumulative dose of 90 mCi. The period of follow-up ranged from 0.5 to 15.5 months. The 6- and 12-month survival rates were 75% and 66%, respectively.

Of the 5 patients treated with Re¹⁸⁸ lipiodol for unresectable HCC, 1 showed regression of the right lobe tumour but progression of the left lobe tumour. The other 4 had stable disease. The period of follow-up was short ranging from 0.8 to 6.9 months. All the patients were alive at the time of follow-up.

Discussion

Early intrahepatic recurrence is common after resection of HCC due to microscopic disease present in the remnant liver or metachronous multicentric tumour within the liver remnant not detected before the surgery by conventional imaging modalities.

Various systemic and intra-arterial locoregional chemotherapy agents have been used as adjuvant therapy following curative resection of HCC. Results range from marginal to no significant improvement in disease-free survival. The efficacy of the treatment is also limited by the toxic side effects of the chemotherapy agents.⁹⁻¹²

Adjuvant treatment with I¹³¹ lipiodol for patients with curative resection of HCC has shown promising results. There was a reduction in the rate of local recurrence and an increase in the disease-free and overall survival rates.

In a Hong Kong study, Lau et al¹³ reported a 3-year survival of 86.4% in the treatment group as compared to 46.3% in the control group. The study went on to propose that I¹³¹ lipiodol be considered as a standard postoperative treatment for patients who had undergone curative resection for HCC.

In our 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 patients who had received I¹³¹ lipiodol adjuvant therapy following curative resection for HCC. Based on our preliminary results and evidence from the study by Lau et al,¹³ we are currently evaluating the efficacy of this form of adjuvant treatment in an ongoing prospective, randomised, controlled trial at the National Cancer Centre, Singapore.

It is worthwhile to note that 1 of our patients developed

local recurrence following I^{131} lipiodol adjuvant therapy and was treated again with Re^{188} lipiodol 1½ months later. She was subsequently noted to be disease free on follow-up. Thus, there is a possible role for repeated radio-conjugate treatment even following local recurrence.

Treatment of unresectable HCC is mainly palliative. The main treatment options for palliation includes external radiation therapy, chemo-embolisation, systemic chemotherapy, hormonal therapy e.g. tamoxifen and PEI.

External radiation therapy for HCC is ineffective for palliation.¹⁴ The dose that can be delivered to the tumour in the liver is limited by the tolerance of the normal liver parenchymal tissue. The maximum dose that can be delivered to the liver by external radiation therapy, without excessive risk of radiation hepatitis, is 30 to 35Gy.¹⁵ This is far below 120 Gy which is generally regarded as a tumoricidal dose.¹⁶

Chemo-embolisation has been widely used as a palliative measure. Some side effects are associated with chemo-embolisation and these include abdominal pain, fever, nausea, jaundice, abscess and encephalopathy. This procedure cannot be carried out in patients with portal vein thrombosis. Randomised trials have failed to show survival benefits of chemo-embolisation over conservative therapy.¹⁷⁻²⁰

Systemic chemotherapy, with single agents or combination regimes, also does not prolong the survival rate of patients with unresectable HCC.²¹

A randomised controlled trial has shown that hormonal therapy using tamoxifen is not effective in prolonging survival of patients with HCC.²²

Percutaneous ethanol injection has been used for treatment of small (<5 cm) but unresectable HCC. Large series have been reported with results for ethanol injection similar to those who have surgical resection of HCC.²³ This technique may be associated with abdominal pain, abscess formation, haemorrhage and possible risk of dissemination of malignant cells.

Promising results have been reported with hepatic intra-arterial radio-conjugate treatment which is an attractive alternative to the above palliative procedures. Dancey et al²⁴ reported a response rate of 20% and a median survival rate of 54 weeks in 22 patients using Y^{90} microspheres. Lau et al⁷ reported a median survival of 9.4 months (range, 1.8 to 46.4 months) in 71 patients. The overall response rate in terms of changes in α -fetoprotein levels was 89% (partial response of 67% and complete response of 22%) among 46 patients with raised α -fetoprotein levels. They also reported that there were 4 patients whose HCC became resectable following treatment with Y^{90} microspheres of which 2 cases achieved complete remission. Ho et al²⁵ reported a 17% to 92% response rate as well as a case of complete

remission of unresectable HCC using I^{131} lipiodol.

Elevations in liver enzymes and bilirubin, gastrointestinal toxicities (e.g. ulcers, haemorrhage, ileus and nausea) and radiation pneumonitis are some of the known reported side effects associated with the technique of hepatic intra-arterial radio-conjugate treatment. However, most of these side effects do not require treatment or usually resolve either spontaneously or with treatment.²⁴ We have 1 patient who developed pleural effusion following treatment and this was possibly due to radiation pneumonitis.

In our study, the 6- and 12-month survival rates for those patients with inoperable HCC treated with Y^{90} microspheres were 75% and 66%, respectively. This compares favourably with the study conducted by Lau et al⁷ who reported a median survival of 9.4 months (range, 1.8 to 46.4 months) in 71 patients with unresectable HCC treated with Y^{90} microspheres. A prospective, randomised, controlled trial of radio-conjugate therapy of patients with unresectable HCC using Y^{90} microspheres versus intra-arterial chemotherapy would be useful to confirm the impact of Y^{90} on the survival of patients with unresectable HCC.

In our study, all patients treated with Re^{188} lipiodol were alive at the time of follow-up. However, this result is not conclusive and it is not possible, at this point in time, to apply a meaningful statistical analysis of this group of patients using the Kaplan-Meier method of survival analysis due to the small number of patients and the limited period of follow-up. The efficacy of this treatment will be validated by an international multicentre trial for the treatment of unresectable HCC with Re^{188} lipiodol radio-conjugate therapy, under the auspices of the International Atomic Energy Association (IAEA). We have previously reported 1 case of response to Re^{188} lipiodol for a right lobe HCC.²⁶

Conclusion

Our results in the adjuvant treatment of patients with I^{131} lipiodol following curative resection of early HCC and in the palliative treatment of unresectable HCC using Y^{90} microspheres and Re^{188} lipiodol are preliminary and not fully conclusive. These preliminary results have to be confirmed in larger groups of patients and by prospective, randomised, controlled trials. This study highlights the preliminary experience in radionuclide therapy of HCC using hepatic intra-arterial radio-conjugates in a local context.

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