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^{131}I-Rose Bengal Therapy in Hepatoblastoma Patients

J. de Kraker, C.A. Hoefnagel and P.A. Voûte

If conventional treatment modalities have failed in hepatoblastoma patients and no distant metastases can be demonstrated therapy with radionuclide agents can be considered. In 6 patients diagnostic technetium-99m (^{99m}Tc)-disofenin and two iodine-131 (^{131}I)-rose bengal scans were made. 2 patients demonstrated specific uptake of disofenin. One of these had a positive scintigram with radiolabelled rose bengal. This patient was subsequently treated with 1.1 GBq ^{131}I-rose bengal. No toxicity was observed. A clear decrease in the level of alpha-fetoprotein indicated a response and demonstrated that this radiopharmaceutical can be used for tumour targeted radiation therapy in selected patients with therapy resistant tumours.
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INTRODUCTION

HEPATOBLASTOMA is a rare tumour in infancy and childhood. In the Netherlands they constitute less than 2% of all malignant tumours in this age group. Despite this low frequency it is necessary to look for new treatment modalities, because the cure rates are not good. The clinical course and prognosis largely depends upon the resectability of the tumour. Therefore it is of interest to see if unresectable tumours can be made resectable by retreatment with chemotherapy. In chemotherapy resistant cases, radiotherapy may be considered. Drawbacks of external beam irradiation, however, are damage to the normal liver cells and growth impairment of surrounding structures in young children.

Radiation can be delivered in a more specific way by targetting radionuclides to the tumour cells, either via immunological methods or via the metabolic route. Examples are the radiolabelled anti-ferritin antibodies in hepatoblastoma [1, 2] and ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) for the treatment of neuroblastoma [3]. In adults with hepatocellular carcinoma, radioiodinated lipidol [4] and ethiodol [5] have been applied for therapy.

A hepatoblastoma is usually soft to firm in consistency. It contains mesenchymal elements and vascular lakes are characteristic for this tumour type. Immature or abortive forms of bile ducts are often found. Alpha-fetoprotein (AFP) is present in approximately 90% of children with hepatoblastoma. There are conflicting data on the initial elevation of AFP due to carcinogens and the final elevation of AFP in association with the appearance of malignant cells and usually progression with tumour growth and metastases. In our hands it is a reliable index if elevated at diagnosis.

The hepatobiliary (radionuclide) agents disofenin and rose bengal are metabolically taken up by liver cells. Due to abnormal and non-communication bileducts in the tumour, a delayed excretion will be found in the tumour in comparison to normal liver. We performed diagnostic hepatobiliary scintigraphy in 6 hepatoblastoma patients, and report the case of a child who received a therapeutic dose of ^{131}I-rose bengal.

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PATIENTS AND METHODS

In 6 patients (5 boys and 1 girl) with a non-resectable primary tumour of the liver in combination with a raised (AFP) level, thrombocytosis and cystathionuria, hepatobiliary scintigraphy was performed.

Multiple digital scintigrams, aquiring counts over 5 minutes in a 256 × 256 matrix, were made at 5 minute intervals after intravenous administration of technetium-99m (^{99m}Tc)-disofenin (1.85 MBq per kg bodyweight) for 1 h. A large field of view gammacamera with a high resolution collimator, connected with an online computer system, was used.

In 2 patients the procedure was repeated using 18.5 MBq ^{131}I-rose bengal and making delayed images up to several days after administration. 1 patient, whose tumour concentrated and retained considerable amounts of ^{131}I-rose bengal, received a therapeutic dose of 1.1 GBq ^{131}I-rose bengal with a higher specific activity, which was administered intravenously via a Port-a-cath. For this treatment, the patient was admitted to the hospital's isolation facilities, with the parents actively participating in the care. In order to protect the thyroid from free ^{131}I an oral potassium iodide solution was given.

Prior to this treatment liver function tests, electrolytes, creatinine and AFP were measured and chest radiograms and ultrasonographic measurements of the tumour were done.

The response was measured by the AFP concentration in serum and the ultrasonographic assessment of the tumour size.

SCINTIGRAPHIC RESULTS

In 6 patients 7 diagnostic ^{99m}Tc-disofenin and 2 ^{131}I-rose bengal scintigrams were made. 2 patients demonstrated specific uptake of ^{99m}Tc-disofenin in the tumour (Fig. 1). In the other 4 patients the tumour presented as a cold spot (Fig. 2), and after hepatobiliary excretion no retention of ^{99m}Tc-disofenin was observed.

2 repeat studies using ^{131}I-rose bengal had the following results: 1 patient had a positive scintigram, with tumour uptake of 21.6% and 17.6% of the administered dose after 24 and 48 hours respectively (Fig. 3). At 160 h after injection the tumour still retained the tracer; this patient was subsequently treated

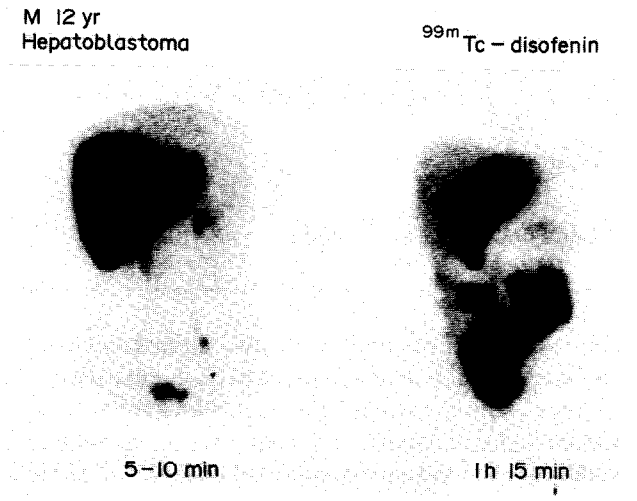

Fig. 1. Diagnostic ^{99m}Tc-disofenin scintigram. Specific uptake in the tumour with excretion to the gallbladder and intestines.

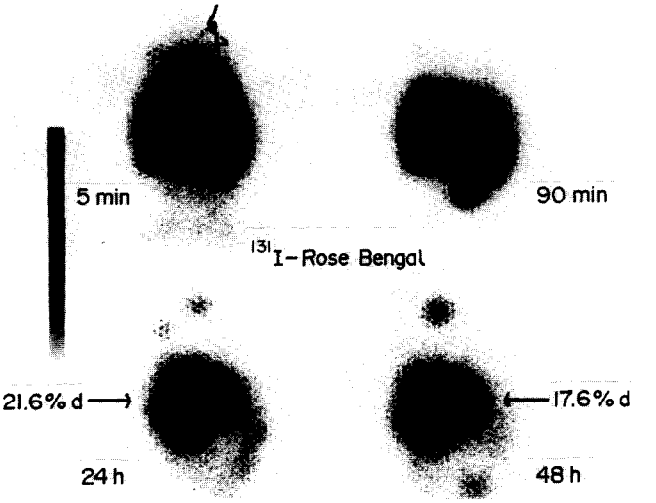

Fig. 3. ^{131}I-rose bengal scintigram showing a positive scintigram with tumour uptake.

with ^{131}I-rose bengal, as is described below; in the second patient, whose tumour did not accumulate ^{99m}Tc-disofenin, the ^{131}I-rose bengal scintigram was negative too.

CASE REPORT

A 3-month-old boy was presented at our outpatient clinic because of vomiting and abdominal pain. At physical examination he had a pale yellowish colour of the skin, a hepatomegaly and his left leg was conjested.

Laboratory data revealed anaemia, thrombocytosis, increased liver function and a raised serum concentration of AFP. The excretion of cystathionine in the 24 h urine sample was elevated. These findings together with an intrahepatic tumour on sonographic and computed tomography (CT) examination are concomittant with the diagnosis of hepatoblastoma.

The tumour was inoperable. He was treated with chemotherapy, vincristine, actinomycin D and cyclophosphamide (VAC) for 4 weeks. There was no response to this approach. Radiotherapy 10 Gy in 12 days resulted in a significant fall in AFP-concentration but the effect lasted for not more than 3 weeks. As a last resort, he was treated with 1.1 GBq ^{131}I-rose bengal. Sonographic studies revealed stable disease of the tumour. No toxicity was observed and his AFP level went down.

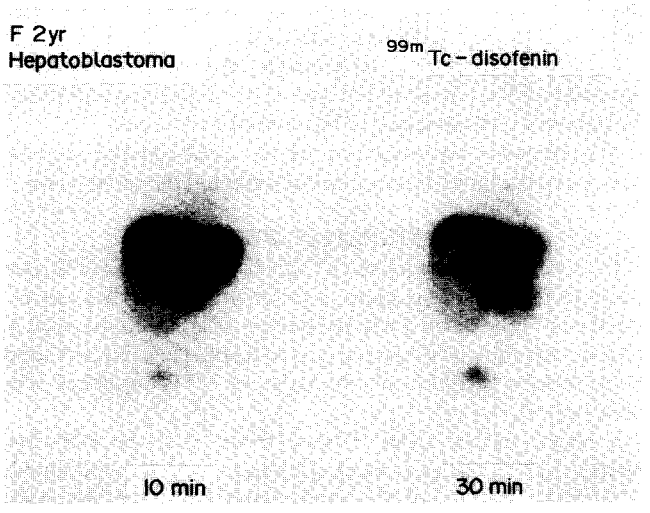

Fig. 2. Diagnostic ^{99m}Tc-disofenin scintigram demonstrating the tumour as a cold spot.

After 4 weeks AFP started increasing again and we abstained from further therapy (Fig. 4).

DISCUSSION

By nuclear targeting it is attempted to increase the therapeutic index of radiotherapy by selectively localising radionuclides in the tumour. In case of hepatic cancers this has been done using antibodies raised in heterologous species against tumour-associated antigens such as ferritin [1] and carcinoembryonic antigen. These mostly polyclonal antibodies were radiolabelled with either yttrium-90 or iodine-131. The principal toxicity was haematological. Immediate fever, bronchospasm and transient liver function test abnormalities were also observed. In nearly all patients a second course of treatment had to be postponed because of this toxicity. If the excretion of bile is blocked because of blind ending bileducts, as can be seen in hepatoblastoma in children, another way to target radionuclides of the tumour is to use radiolabelled hepatobiliary agents which are excreted by the hepatocytes. In the past ^{131}I-rose bengal was used for the detection of biliary atresia in newborns. It has since been replaced by technetium-99m labelled iminodiacetic acid (IDA) derivates, which enable a better image quality at a lower radiation burden to the patient. After retention of ^{99m}Tc-disofenin in the tumour had been demonstrated by a tracer study, we have chosen to use ^{131}I-rose bengal for therapy. This radiopharmaceutical does not have the limiting side-effect of radiolabelled antibodies and may yield considerably higher tumour concentration, as was shown in the patients described here.

However, until now the tumour has shown the capability of uptake and storage of disofenin and consequently of rose bengal in only 2 out of 6 patients. It is concluded that, if conventional

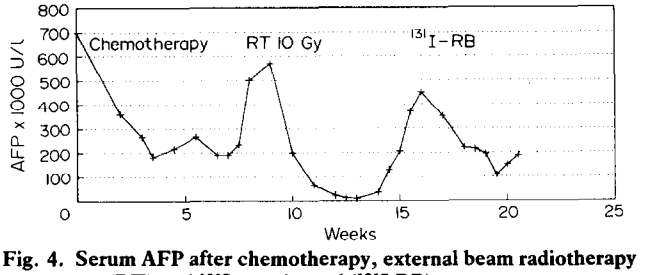

Fig. 4. Serum AFP after chemotherapy, external beam radiotherapy (RT) and ^{131}I-rose bengal (^{131}I-RB) treatment.

therapy of hepatoblastoma has failed and liver transplantation is not feasible, it seems worthwhile to consider ^{131}I-rose bengal as a potential radiopharmaceutical for tumour targeted radiation therapy, in the hope of making the tumour resectable.

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The Need for Immediate Monitoring of Treatment Parameters and Uniform Assessment of Patient Data in Clinical Trials

A quality control study of the EORTC Radiotherapy and Lung Cancer Cooperative Groups

Caro Schaake-Koning, Anne Kirkpatrick, Robert Kröger, Nico van Zandwijk and Harry Bartelink

A quality control study was performed during the EORTC phase III study 08844: radiotherapy combined with low dose cisplatin (cDDP) in inoperable non-metastatic non-small cell lung cancer. Radiation alone (55 Gy, split course) was compared to radiotherapy with 30 mg/m^2 cisplatin once a week and to radiotherapy with 6 mg/m^2 cisplatin daily. The purpose of the control study was to check to which degree protocol guidelines were followed and to measure the extent of differences in assessment of tumour response, recurrence and toxicities between the individual institutes. A review team, consisting of a data manager, a diagnostic radiologist, a chest physician and two radiotherapists reviewed entry criteria, treatment data, tumour responses, recurrences and late toxicity of 177 patients (a total of 300 patients was required for the trial). Only departments which had entered more than 5% of this number of patients were visited. There was a 15% difference in T staging of the patients and a 17% discrepancy in N stage scoring between the review team and the local investigators. Radiotherapy field sizes were insufficient in 15% of the eligible patients during a period of the radiotherapy; in another 17% patients the tumour free margin was less than 1 cm. Radiation doses were incorrectly given to 7% of the patients. The given doses of cisplatin deviated in 10% of the patients treated with combined modalities. The interpretation of chest X-rays and computed tomography (CT) showed important differences in tumour response, tumour recurrence and late toxicity. From these data it is concluded that immediate checks can detect errors in treatments as planned at the local level and will make corrections possible at an early stage in multicentre studies. The quality of trial results will thus be improved. Uniform assessment of treatment outcome, tumour progression and forms of toxicity will lead to more sound trial conclusions.
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INTRODUCTION

CLINICAL TRIALS are an instrument for investigating scientific questions and thereby improving medical care. Protocol violations, however, present a problem in interpreting the results of these single and multicentre trials. These variations, although present in daily clinical practice, can easily dilute the trial results and lead to wrong conclusions. A possible improvement of a specific therapy can therefore easily be missed in spite of its presence, or overestimated. Some retrospective studies have shown that survival was worse for patients in whom the treatment was accompanied by major protocol violations than for patients who had been treated according to the protocol [1–3].

The EORTC Cooperative Group of Radiotherapy already has an established tradition in quality control studies in centres participating in clinical trials. Objects of the studies were testing equipment, beam quality, phantom measurements and evaluation of treatment techniques used in the centres [4–7].

The results of these studies have already lead to improvements such as corrections of calibration procedures, radiation techniques and equipment. The evaluation of treatment techniques