Relative Biodistribution and Tumor Uptake of ^{131}I-NM404, a.k.a. CLR1404, in Human Subjects with Advanced Colon Cancer

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INTRODUCTION

NM404, a.k.a. CLR1404, is a phospholipid ether analogue that interacts with distinct areas of the cell membrane that contain large accumulations of sphingolipids and cholesterol (lipid rafts) to gain entry into cells. As malignant cells contain more lipid rafts (6-10x) than normal cells and at the same time are relatively deficient in certain phospholipid metabolizing enzymes, NM404 demonstrates selective uptake and retention in cancer cells. Our lab is working with Novelos Therapeutics to develop radioiodinated NM404 as a diagnostic and therapeutic ("diapeutic") agent for the detection and treatment of multiple solid tumors. This study was performed to demonstrate the relative biodistribution and tumor uptake of the therapeutic agent, ^{131}I–NM404.

METHODS

Planar whole body images were acquired on a dual–head scanner (Infinia/Hawkeye, General Electric, Waukesha, WI) using scan speed of 10 cm/second, matrix 256 x 1024, peak set at 364 +/- 15% and scatter peaks of 312 +/- 15% and 424 +/- 15%, high energy all–purpose collimator, and display bone dual density. SPECT/CT images were acquired on a SPECT/CT scanner (Infinia/Hawkeye, General Electric, Waukesha, WI) using 128 x 128 matrix, 120 projections, 3 degrees/stop, 30 seconds/stop, with peak set at 364 +/- 15% and scatter peaks of 312 +/- 15% and 424 +/- 15%. The CT settings are helical using a pitch of 1.9, interval 4.42 mm, voltage 140 kV, current 2.5 mA, matrix 512 x 512, filter soft and pixel 1.10 mm. Processing was performed using Volumetrix MI.

Two patients with treatment–resistant metastatic colon cancer were injected with 185 MBq ^{131}I–NM404 (pre–therapy biodistribution scan). Whole body planar images were obtained at 6 time points over 6 days. Planar images were reviewed to confirm normal biodistribution prior to continuing to the treatment phase. Two weeks after the normal biodistribution scans, patient 1 was injected with 1 GBq and patient 2 was injected with 1.7 GBq of ^{131}I–NM404. Whole body planar and SPECT/CT images of areas of interest were obtained at 3, 6, 14, and 21 days after injection of ^{131}I–NM404.

RESULTS & ANALYSIS

Patient 1: Patient with a history of recurrent metastatic colon cancer status post hemicolectomy and remote TheraSphere therapy to the right hepatic lobe. There is known bilateral lung base and liver metastases seen on recent diagnostic CT scan.

Patient 2: Patient with a history of recurrent metastatic colon cancer status post multiple courses of chemotherapy. There is known peritoneal involvement including a left pelvic mass and malignant ascites.

Pretherapy study: Both patients had similar biodistribution. Blood pool activity slowly decreased over time. Uptake was identified within the liver and to lesser degree in the spleen. Faint uptake was seen early in the kidneys, decreasing throughout the study. No significant uptake was seen in the bladder. Mild bowel uptake was noted. No uptake was seen in the thyroid or bone marrow.

Treatment study: Biodistribution of the treatment dose in both patients was not significantly different than seen in the pre–therapy study.

In patient 1, with metastatic colon cancer to lung and liver, NM404 uptake was noted within multiple pulmonary and hepatic metastases. This starts as a mild–moderate uptake seen in SPECT images 72 hours after radiotracer injection (but not in planar imaging). Progressively, uptake increased, with most intensity seen by the end of day 21, significantly above normal background uptake. The most intense NM404 avid metastatic lesions were noted in the right lower lobe of the lung posteriorly. These metastases were not seen in the lower dose pre–therapy biodistribution planar scan. Smaller pulmonary metastases (1.3 to 1.8 cm in size) demonstrated mild to moderate uptake at the end of the study. Less than 1 cm pulmonary nodules did not demonstrate NM404 uptake. These were probably lesions smaller than the spatial resolution of the SPECT technique. NM404 avid hepatic lesions were seen in the right hepatic lobe, corresponding with known metastases seen in CT scan. Uptake in these lesions also increased with time, as well as a better contrast to background due to continued clearance of normal liver background (Figure 1a–c).

In patient 2 with metastatic colon cancer to an adnexal mass and malignant ascites, NM404 uptake was noted diffusely within areas of ascites fluid accumulation as well as within a 5.7 x 3.1 left pelvic mass. As with patient 1, uptake starts as mild accumulation that slowly intensifies over time. Uptake is seen by day 3 imaging and tumor uptake continues to increase while background activity continues to slowly decrease over time (Figure 2a–c).

FIGURE 1

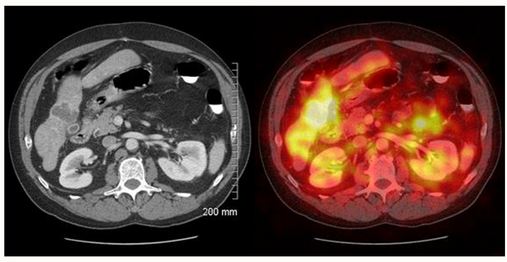


Figure 1a

Patient 1 with metastatic colorectal cancer. Diagnostic contrast enhanced CT (left) and SPECT/CT (right) obtained 21 days after injection of 1 GBq of ^{131}I–NM404. Liver metastasis demonstrates intense uptake of ^{131}I–NM404.

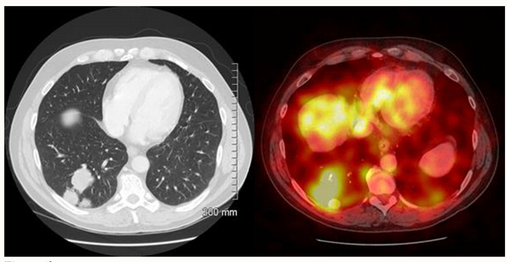


Figure 1b

Patient 1 with diagnostic CT (left) and SPECT/CT (right) obtained 21 days after injection of 1 GBq of ^{131}I–NM404. Pulmonary metastases demonstrate intense uptake of ^{131}I–NM404.

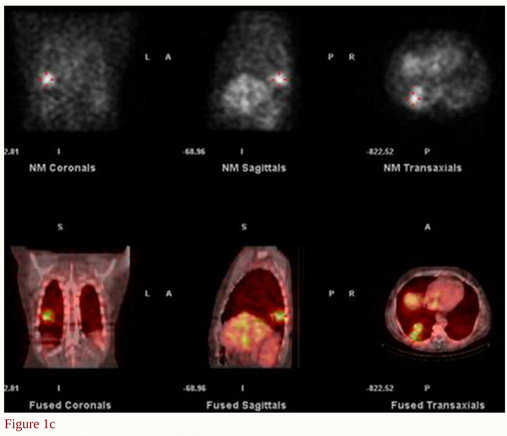


Figure 1c

Patient 1 with SPECT images (top) and SPECT/CT images (bottom) obtained 21 days after injection of 1 GBq of ^{131}I–NM404. Pulmonary metastases demonstrate intense uptake of ^{131}I–NM404.

FIGURE 2

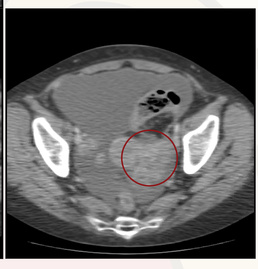


Figure 2a

Patient 2 with metastatic colorectal cancer. Diagnostic CT images demonstrate a 5.7 x 3.1 cm left adnexal mass and a large amount of ascites fluid.

Figure 2b

Patient 2 with fused SPECT/CT (left) and coronal SPECT image (right) obtained 3 days after injection of 1.7 GBq of ^{131}I–NM404. Normal biodistribution is present in the liver and bowel. Tumor uptake is evident in the pelvic mass and ascites fluid.

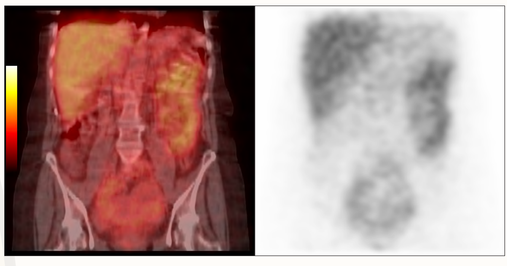
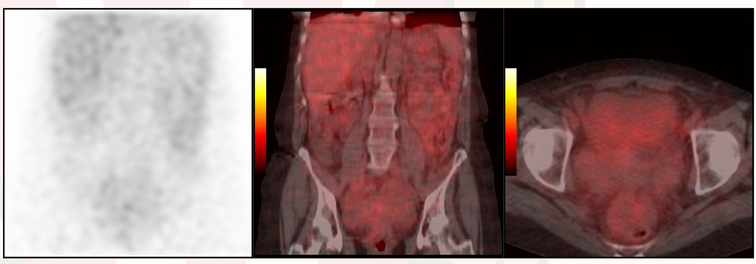


Figure 2c

Patient 2 with coronal SPECT (left), fused coronal SPECT/CT (middle), and fused axial SPECT/CT (right) images obtained 21 days after injection of 1.7 GBq of ^{131}I–NM404. Uptake of ^{131}I–NM404 is localized to the left pelvic mass and ascites fluid throughout the abdomen and pelvis.



CONCLUSIONS

^{131}I–NM404 pre–therapy planar imaging can demonstrate normal biodistribution prior to a therapeutic treatment dose of ^{131}I–NM404. Additionally, post–therapy ^{131}I–NM404 SPECT/CT successfully demonstrates selective tumor accumulation and prolonged retention in 2 patients with treatment resistant metastatic colon cancer. This novel "diapeutic" (diagnostic and therapeutic) compound has potential for use as a diagnostic and therapeutic agent for metastatic colon cancer.

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