First in Human Use of ^{124}I-NM404, a.k.a. CLR1404, PET/CT in Primary and Metastatic Brain Tumors

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INTRODUCTION

NM404, a.k.a. CLR1404, is a refined, second–generation diapeutic phospholipid ether analogue that is characterized by preferential tumor uptake and prolonged tumor retention in 50/52 xenograft, spontaneous and transgenic preclinical tumor models, including gliomas. Isosteric iodine substitution in NM404 affords either a diagnostic/imaging agent (*e.g.*, using ^{124}I for cancer–selective PET imaging) or a molecular radiotherapeutic agent (*e.g.*, using ^{131}I for cancer–selective cytotoxicity), both of which are in clinical development. NM404 and related alkylphospholipids enter malignant cells via membrane lipid rafts which are overexpressed in cancer cells. Together with Novelos Therapeutics, Inc., our lab is developing radioiodinated NM404 as a diagnostic and therapeutic ("diapeutic") agent for the detection and treatment of multiple solid tumors, including primary and metastatic brain tumors. The purpose of this study is to demonstrate the first successful use of ^{124}I NM404 PET/CT in humans with gliomas and brain metastases.

METHODS

PET brain scans were acquired on a 64–slice PET/CT scanner (Discovery VCT, General Electric, Waukesha, WI) using a 90 minute dynamic acquisition sequence (2D, 9 frames @ 10 minutes each, VIP list mode on) and reconstructed (Advantage workstation version AW4.4, General Electric, Waukesha, WI, 30 cm DFOV, 128 x 128, OSEM Vue Point, 10 subsets with 2 iterations, standard Z–axis, attenuation correction and dead time, scatter, and decay correction).

One patient with multiple brain metastases from lung cancer was injected with 185 MBq of ^{124}I–NM404 and imaged with PET/CT at 5 time points over 6 days. One patient with WHO Grade IV astrocytoma (glioblastoma multiforme – GBM) and one patient with a WHO Grade II astrocytoma that transformed into a WHO Grade III astrocytoma was injected with 185 MBq of ^{124}I–NM404 and imaged with brain PET/CT at 3 time points over 3 days. Quantitative and qualitative analysis of the PET images were performed and compared to MRI. Tumor to background ratios (T:B) were calculated by placing regions of interest (ROI's) around tumors and comparing to ROI's placed in the contralateral normal brain.

RESULTS & ANALYSIS

In the brain metastases and glioblastoma multiforme patients, feint uptake of ^{124}I–NM404 was noted within 6 hours after injection, and significantly intensified at later time points. In the Grade III astrocytoma patient, there was significant uptake of ^{124}I–NM404 at 6 hours of injection which continued to intensify at later time points. There was no significant background uptake in normal brain, though blood pool uptake was present.

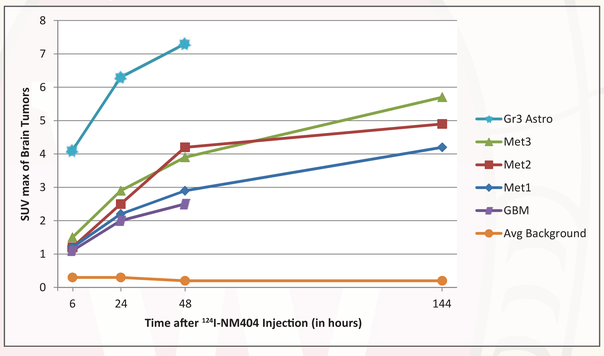
MRI images of multiple brain metastases in the same patient ranged in size from 0.8-2.7 cm in greatest dimension, showed peripheral contrast enhancement, and correlated very well with ^{124}I–NM404 PET/CT images (Figure 1). Normal brain background SUVavg was very consistent at 0.2-0.3 at all time points. SUVmax and (T:B ratios) for the 3 largest tumors ranged from 1.2-1.5 (T:B 4-5) at 6 hours, 2.2-2.9 (T:B 7.3-9.7) at 24 hours, 2.9-4.2 (T:B 14.5-21) at 48 hours, and 4.2-5.7 (T:B 21-28.5) at 144 hours (Graph 1).

MRI images of the glioblastoma multiforme tumor measured 3.7 – 4.1 cm in greatest axial dimensions and demonstrated heterogeneous T1 contrast enhancement and T2 signal. PET/CT images also demonstrated heterogeneous areas of ^{124}I–NM404 uptake, including areas of intense uptake and areas of mild uptake. There were areas of discordant contrast enhancement and mild or absent NM404 uptake (Figure 2). Normal brain background SUVavg was very consistent at 0.3 at all time points. SUVmax and T:B ratios were 1.1 and 3.7 at 6 hours, 2.0 and 6.7 at 24 hours, 2.5 and 8.3 at 48 hours (Graph 1).

MRI images of the left parietal WHO Grade III astrocytoma tumor measured 3.5 x 1 cm in greatest axial dimensions and demonstrated homogenous T1 contrast enhancement. PET/CT images demonstrated intense and homogenous ^{124}I–NM404 uptake corresponding to contrast enhancement on MRI (Figure 3). Less intense ^{124}I–NM404 uptake was present along the superomedial border of the tumor in a region without contrast enhancement on MRI, which was later confirmed to be malignant tumor on pathology. Normal brain background SUVavg was very consistent at 0.3 in early time points and 0.2 at the last time point. SUVmax and T:B ratios were 4.1 and 13.7 at 6 hours, 6.3 and 21 at 24 hours, and 7.3 and 36.5 at 48 hours (Graph 1).

Graph 1

Regions of Interest (ROIs) of ^{124}I–NM404 NM404 PET tumor uptake and normal cerebral background over time.



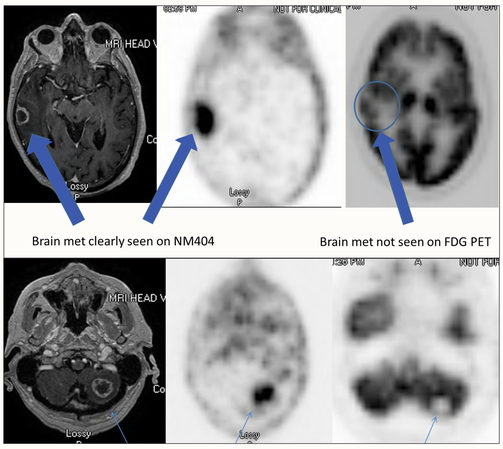


Figure 1
Brain Metastases

Patient with non–small cell lung cancer with newly diagnosed brain metastases.

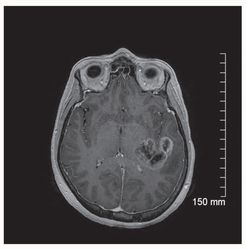
Top and Bottom Left
Contrast enhanced axial T1 MRI demonstrated ring–enhancing cerebral and cerebellar metastases.

Top and Bottom Center
^{124}I–NM404 PET/CT demonstrates intense uptake of NM404 in both the cerebral and cerebellar metastases.

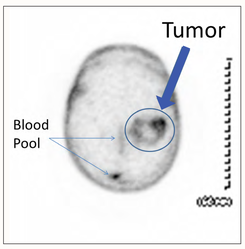
Top and Bottom Right
^{18}F–FDG PET/CT of same patient does not show obvious hypermetabolic activity in region of the right temporal brain metastasis, and shows hypometabolic activity in region of the left cerebellar metastasis.

Figure 2
Glioblastoma Multiforme

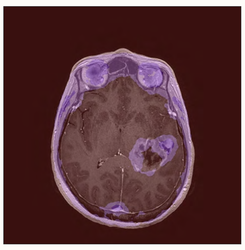
Patient with newly diagnosed WHO Grade IV astrocytoma (glioblastoma multiforme – GBM).



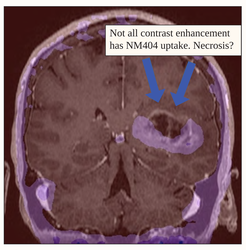
2a
Contrast enhanced axial T1 MRI.



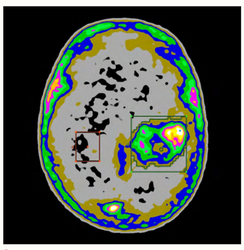
2b
^{124}I–NM404 PET/CT demonstrates heterogeneous NM404 uptake with most pronounced uptake peripherally and reduced uptake centrally, presumably in regions of tumor necrosis.



2c



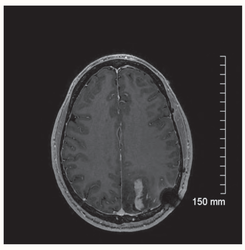
2d
Fused ^{124}I–NM404 PET/MRI images demonstrate a heterogeneous contrast enhancing mass on MRI with central areas of low–intensity.



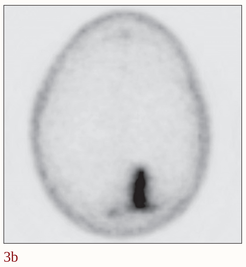
2e
^{124}I–NM404 PET regions of interest over tumor and normal brain background.

Figure 3
WHO Grade III Astrocytoma

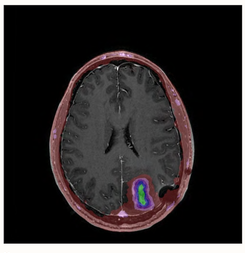
Patient with previously resected WHO Grade II astrocytoma that transformed into a WHO Grade III astrocytoma.



3a
Contrast enhanced axial T1 MRI demonstrated fairly homogenous contrast enhancement laterally and low signal intensity medially.



3b
^{124}I–NM404 PET/CT demonstrates intense tumor uptake of NM404 corresponding with enhancement on MRI.



3c
Fused ^{124}I–NM404 PET/MRI demonstrates concordant contrast enhancement and intense NM404 uptake.

CONCLUSIONS

^{124}I–NM404 PET/CT successfully images brain metastases and gliomas in humans and demonstrates significant tumor to background uptake and prolonged retention. These attributes make this novel agent a promising "diapeutic" candidate for brain tumors.

JW is a founder, CSO, and director of Novelos Therapeutics, Inc., which owns the licensing rights to NM404 and related technologies

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