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SUMMARY OF RESULTS

16 July 2018

A Phase II, single-centre exploratory study to assess the value of hypoxia imaging with [^{18}F]HX4 PET/CT in predicting outcome for patients with squamous cell carcinoma of head and neck and non-small cell lung cancer undergoing radical radiotherapy with curative intent

(OXYPET Study)

Protocol Number	PET_HX4_01
EudraCT Number	2013-003563-58
REC	Northampton Research Ethics Committee 13/EM/0377
Sponsor Reference Number	13MP003
Study Start Date	31st March 2015
Study End Date	25th July 2017
Funder(s)	Nottingham Hospitals Charity Materials/support from: Siemens PETNET Solutions Nottingham In Health PET/CT Centre Nottingham and Threshold Pharmaceuticals USA
Sponsor(s)	Nottingham University Hospitals NHS Trust
Name of Investigational Medicinal Product	3-[^{18}F]fluoro-2-{4-[(2-nitro-1H-imidazol-1-yl)methyl]-1H-1,2,3-triazol-1-yl}propan-1-ol, also known as **[^{18}F]HX4**
Indication Studied	Non small cell lung cancer Squamous cell carcinoma of head and neck
Study Centres	Single site: Nottingham University Hospitals NHS Trust
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Co-investigators	Dr Helen M. Betts Dr James Birchall Dr Judith A. Christian Dr Claire P. Esler Dr Karen Foweraker Dr Rakesh Ganatra Dr Sally Morgan Dr Abigail C. Pascoe Prof Poulam Patel Dr Vidhiya Vinayakamoorthy

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This study was carried out in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) and Nottingham University Hospitals NHS Trust (NUH) Research and Innovation (R&I) Procedures.

1. Introduction

Hypoxia (low oxygen concentration) is a common characteristic of neoplastic tissue which arises when oxygen demand exceeds supply.[1] Inefficient delivery of oxygen to the growing tumour is caused by poorly formed, hyper-permeable and irregular neovasculature, and under-developed supportive tissue stroma. In order to tolerate hypoxic conditions, cancer cells activate a series of intracellular survival responses. These mechanisms lead to local invasion and enhanced metastatic potential of the tumour cells. For patients, hypoxia correlates with disease progression and poor prognosis.[2,3]

Hypoxia has a detrimental effect on the efficacy of both cytotoxic chemotherapy and radiotherapy.[4] Evaluation of hypoxia during cancer staging has the potential to better inform the patient of their prognosis.

[^{18}F]Fluorinated radiotracers ($t_{1/2}$ = 109.7 min) based on 2-nitroimidazoles are selectively retained in regions of hypoxia.[5,6] [^{18}F]Fluoromisonidazole (FMISO) is the most extensively studied radiotracer of this class and has been examined in numerous clinical studies.[7] However, [^{18}F]FMISO hypoxia imaging is considered sub-optimal and has not been adopted into routine practice. The radiotracer investigated in this study is a fluorine-18 labelled compound of the 2-nitroimidazole class: 3-[^{18}F]fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol, known as [^{18}F]**HX4**.[8]

At the outset of this trial there had been few clinical studies of [^{18}F]HX4, with emerging (yet limited) evidence that [^{18}F]HX4 may have some favourable characteristics over [^{18}F]FMISO.[9,10,11,12] Our aim was to gather further clinical data on the use of [^{18}F]HX4 in hypoxia PET/CT imaging in cancer patients.

2. Study Summary

Recruitment opened	31 March 2015
First participant consented	July 2015
Last participant consented	April 2017
Study closed	25th July 2017 ([^{18}F]HX4 was no longer available to the Investigators)

Patients were recruited from the Oncology clinic at Nottingham University Hospitals NHS Trust, by members of the patients' direct care team. The trial was discussed at the treatment management appointment, and patients were provided with the patient information sheet. After being given time to consider taking part, written informed consent was taken by the consultant oncologist responsible for the patient, typically at the radiotherapy planning scan appointment. The consultant oncologist completed the pre-scan check list to document eligibility for the study. The study coordinator checked consent forms and eligibility, and made arrangements for [^{18}F]HX4 PET scan. The ARSAC certificate holder authorised the administration of [^{18}F]HX4 prior to appointment booking. [^{18}F]HX4 PET/CT scans were undertaken before patients began treatment.

Manufacture, quality control, and Qualified Person release of [^{18}F]HX4 was undertaken by PETNET Solutions, Nottingham City Hospital as described in our prior publication.[13] Patients received a single intravenous injection of [^{18}F]HX4 in the arm, and underwent a single PET/CT scan on a GE Discovery 710 PET/CT scanner at Nottingham InHealth PET/CT centre. The target dose of [^{18}F]HX4 was 370±10% MBq, based on previous investigations of [^{18}F]HX4 reported in the literature and the Investigator Brochure.[9] No fasting or other special preparation of the patient was required ahead of the [^{18}F]HX4 scan. Patients remained in the PET centre after injection of [^{18}F]HX4 prior to the scan, in the designated uptake rooms that are monitored by CCTV. Patients were asked not to eat or drink (other than water) during the 3 hour uptake period after injection of [^{18}F]HX4. Participants were able to go home immediately after the scan, and no further trial related visits were necessary. Patients' GPs were notified of their inclusion in the trial.

No placebos or controls were used.

The trial was open label, thus no blinding procedures were required.

No changes to the participants' drugs or other routine procedures were made for this study.

3. Amendments

Two substantial amendments were applied after first submission of documents:

1. Submission of the updated Investigator Brochure which was a condition stated on the notification of acceptance of trial from the MHRA.

2. Addition of a pregnancy test to the Protocol after query from the ethics committee.

4. Protocol Deviations

There were no deviations from the approved Protocol.

5. Recruitment

Recruitment to the study was slower and more difficult than anticipated. A practical difficulty encountered was integrating the [^{18}F]HX4 scan during the short period between completion of disease staging, and the patient commencing treatment. The participants had a busy schedule of appointments in this period, such as dental examination and gastrostomy placement. Since [^{18}F]HX4 was only available on Monday afternoons, some patients who consented were unable to be scanned.

Table 1: Recruitment summary

Planned recruitment	50
Total recruitment	8
Total participants undergoing HX4 scan	3/8

Two further patients expressed interest in to taking part, but were not consented. The first was excluded due to low kidney function, and the second was deemed too unwell by the oncologist. Recruitment ended earlier than anticipated as [^{18}F]HX4 was no longer available to the Investigators.

6. Objectives

Primary Objective:

1.1 To assess whether [^{18}F]HX4 PET/CT scanning is predictive of outcome at two years post-treatment in this patient group.

Secondary Objectives:

2.1 To assess the value of [^{18}F]HX4 PET/CT scanning in predicting long term survival (five years following treatment).

2.2 To compare the value of pre-treatment [^{18}F]HX4 and [^{18}F]FDG PET/CT scans in predicting patient outcome at two and five years, for the patients with non-small cell lung cancer.

2.3 To determine if there is correlation between tumour/nodal sizes (as measured by pre-treatment contrast enhanced CT or MRI) and SUV_{max} of the corresponding areas in the [^{18}F]HX4 PET/CT images.

The primary objective 1.1 was not met. The trial ceased recruitment after only three of 50 planned participants were scanned with [^{18}F]HX4. Recruitment was closed because [^{18}F]HX4 was no longer available for investigational use.

Due to the small number of participants recruited, neither the two year (primary objective 1.1), and five year follow up period (secondary objective 2.1) was justified, and thus collection of follow up data was ceased once [^{18}F]HX4 was no longer available. Secondary objective 2.2 was not fulfilled as all recruited patients were head and neck cancer patients. However, two out of three head and neck cancer participants had a pre-treatment [^{18}F]FDG scan available for comparison with the [^{18}F]HX4 scan. The comparative predictive values of the scans could not be evaluated because long term follow up was not collected and too few patients were recruited to perform relevant analysis.

Data for objective 2.3 to compare the relationship of tumour volume (from pre-treatment CT) to the SUV_{max} of [^{18}F]HX4 was collected but there is insufficient data to draw conclusions.

7. Safety Reporting

Patients were monitored for adverse effects. After [^{18}F]HX4 injection, during the uptake period, patients were monitored at the PET centre by CCTV from the control room. No adverse events or reactions were encountered. Contact details for any problems after the patient left the PET centre were provided to the participants, but none were reported. Hospital admissions records were checked, and there were no unplanned admissions for any of the participants.

No samples or laboratory evaluations were undertaken for this study. One participant was female, but a pregnancy test was not required due to her age (71).

8. Results

The [^{18}F]HX4 injection and scan were well tolerated by the patients with no adverse events encountered. Participant and scan parameters are summarised in Table 2.

Table 2: Summary of PET scan results

Number of participants scanned	3
Participant age range	53-71
Gender	2 Male, 1 Female
Primary tumour sites	tongue base; tonsil; oropharynx
Gross tumour volume of evaluated site (range)	60-134 cm^3
HX4 SUV_{max} primary tumour (range)	0.9-2.5
HX4 SUV_{mean} nodal disease (range)	1.0-5.2
Tumour to mediastinal ratio (range)	1.0-3.5
FDG SUV_{max} nodal disease (range)	10-15 (n=2)

9. Statistical Analysis

As an exploratory study, no statistical analysis was anticipated. With only three participants at completion of the study, no statistical analysis was warranted.

10. Conclusions

There were no safety concerns arising from administration of [^{18}F]HX4 to patients. [^{18}F]HX4 PET/CT imaging identified a spectrum of normoxia to hypoxia within a small group of three patients with squamous cell head and neck cancer. Due to the small number of participants it was not possible to make conclusions as to the prognostic value of [^{18}F]HX4 scans to the treatment outcome.

11. Dissemination of Findings

The study results have been submitted for publication in a peer reviewed journal and are under review.

12. References

[1] Brown JM. The Hypoxic Cell: A Target for Selective Cancer Therapy. Cancer Res 1999;59:5863-5870.

[2] Gray LH, Conger AD, Ebert M, et al. The Concentration of Oxygen Dissolved in Tissues at the Time of Irradiation as a Factor in Radiotherapy. Brit J Radiol. 1953;26:638-648.

[3] Bredell MG, Ernst J, El-Kochairi I, Dahlem Y, Ikenberg K and Schumann DM. Current Relevance of Hypoxia in Head and Neck Cancer. Oncotarget. 2016;7(31):50781-50804.

[4] Moeller BJ, Richardson RA, Dewhirst MW. Hypoxia and Radiotherapy: Opportunities for Improved Outcomes in Cancer Treatment. Cancer Met Rev. 2007;26:241-248.

[5] Mees G, Dierckx R, Vangestel C et al. Molecular Imaging of Hypoxia with Radiolabelled Agents. Eur J Nucl Med Mol Imag. 2009;36:1674-1686.

[6] Kizaka-Kondoh S, Konse-Nagasawa H. Significance of Nitroimidazole Compounds and Hypoxia-Inducible Factor-1 for Imaging Tumor Hypoxia. Cancer Sci. 2009;100(8):1366-1373.

[7] Ting Lee S, Scott AM. Hypoxia Positron Emission Tomography Imaging with ^{18}F-Fluoromisonidazole. Sem Nucl Med. 2007;37(6):451-461.

[8] Siemens Medical Solutions, Nitroimidazole Hypoxia Imaging Agents, US20070921932P.

[9] Doss M, Zhang JJ, Bélanger M-J, et al. Biodistribution and Radiation Dosimetry of the Hypoxia Marker 18F-HX4 in Monkeys and Humans Determined from Whole-body PET/CT. Nucl Med Commun. 2010; 31:1016-1024.

[10] Chen L, Zhang Z, Kolb HC, et al. ^{18}F-HX4 Hypoxia Imaging with PET/CT in Head and Neck Cancer: a Comparison with 18F-FMISO. Nucl Med Commun. 2012;33:1096-1102.

[11] van Loon J, Janssen MHM, Öllers M et al. PET Imaging of Hypoxia using [^{18}F]HX4: a Phase I Trial. Eur J Nucl Med Mol Imag. 2010;37(9):1663-1668.

[12] Zegers CML, van Elmpt W, Wierts R, et al. Hypoxia Imaging with [^{18}F]HX4 PET in NSCLC: Defining Optimal Imaging Parameters. Radiother Oncol. 2013;109:58-64.

[13] Turton DR, Betts HM, Dutton D, et al. Automated Radiosynthesis of GMP Quality [^{18}F]HX4 for PET Imaging of Hypoxia. Nucl Med Biol. 2015;42:494-498.