Name of Sponsor/Company : University Hospital of Bordeaux	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product : [18F]-FMISO	Volume :	
Name of Active Ingredient : Fluoromisonidazole	Page :	

Title of Study :
Methodological evaluation of Fluor 18 labelled Fluromisonidazole ([18F]-FMISO) Positon Emission Tomography-Computed Tomography (PET-CT) for non operated glioblastoma

Investigators :
Dr Aymeri HUCHET

Study centre(s) :
CHU de Bordeaux

Publication (reference) : not applicable

Studied period (years) : - date of first enrolment : 03/06/2009 - date of last completed : 16/01/2013	Phase of development : 2

Objectives :
Primary objective :
Determine the most effective [18F]-FMISO PET-CT data acquisition and processing methodologies for establishing tumor oxygenation status in glioblastomas.
Secondary objectives :
- Evaluate the prognostic value of [18F]-FMISO PET in glioblastoma.
- Exploratory evaluation of the potential role of a new hypoxia-sensitive biological target volume, defined on the basis of [18F]-FMISO PET data, for the delineation of radiotherapy fields when the patient's treatment includes this modality.
- Gain a better understanding of the pathophysiological processes underlying [18F]-FMISO uptake, by correlating tracer uptake with other parameters considered in the literature to be representative of tumor hypoxia, whether anatomopathological (micro-vessel density) or immunohistological (HIF1, CA-IX, LOX, p53).

Methodology :
It is a phase II exploratory methodological study and a cohort prognosis study enrolling all eligible consecutive patients. Patients followed clinically and paraclinically for one year after the end of treatment.

Number of patients (planned and analysed) :
- Number of patients planned : 35
- Number of patients analysed : 14

Diagnosis and main criteria for inclusion :
Medical condition : tumeurs cérébrales malignes primitives

Inclusion criteria :
- Patients over 18
- Patients with a malignant tumour glioblastomas (proposed for a radical treatment consisting in conformational radiotherapy and/or chemotherapy)
- Signed informed consent
- Subject affiliated to health insurance coverage.

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Exclusion criteria :

- Patients who can't undergo radiotherapy or chemotherapy
- Patients with distant metastases known before inclusion except renal cancer where patients with metastases can be included
- Patients suffering of a second cancer or treated before by radiotherapy in the tumour site.
- Pregnant or breastfeeding woman

Test product, dose and mode of administration, batch number
18F-FMISO
Dose : 3.7 MBq/Kg
Administration : IV
Batches numbers : FMISO 12-01 ; 11-08 ; 11-05 ; 11-03 ; 11-02 ; 11-01

Duration of treatment : 1 day

Reference therapy, dose and mode of administration, batch number : not applicable

Criteria for evaluation :

Efficacy : not applicable

Safety : not applicable

Other(s) : Feasibility of acquisition sequences, especially initial dynamics

Secondary criteria :

- Treatment resistance, locoregional recurrence, recurrence-free survival time, cancer (or cancer-related) mortality
- Evaluate the impact of hypoxic biological target volume in defining radiotherapy fields.
- The immunohistochemical expression of (HIF1-CA-IX, LOX) and p53 will be correlated with the hypoxic volume detected by PET-[18F]-FMISO in an exploratory manner, in an attempt to gain a better understanding of tracer binding mechanisms.

Statistical methods : For the 12 patients, GTV2 MRI volume range from 28 to 96 cc whereas GTV2 PET volumes range from 7 to 37.2 cc. GTV2 PET outside GTV MRI volume (RPET) ranges from 0.53% to 43.39% which represents small volumes from 0.16 to 10.15 cc. RMRI which in fact represents the hypoxic fraction of the GTV MRI, ranging from 19.57% to 67.2% (Mean = 45.36% +/- 14.49%).
As expected, the mean dose to PTV2 MRI (74.3 +/- 0.5) was higher than mean dose to PTV1 (60.7 +/- 40.2) volume which were larger than PTV2 PET volume themselves (50.6 +/- 26.5 cc). Treatments have been planned to ensure the same coverage between PTV2 PET and PTV2 MRI. Consequently, the results in term of mean dose to either PTV2 MRI or PTV2 PET do not reveal any difference.
The mean dose to brain is higher using PTV2 MRI (45.7 Gy +/- 7.4 Gy) for dose escalation than with PTV2 PET (44.9 +/- 7.6 Gy) or PTV2 PET + IMRT (44.7 +/- 7.5 Gy). The same order have systematically observed at individual level.
Planning standard radiotherapy (60 Gy) with PTV1 shows a lower probability of brain necrosis than dose escalation (with either PTV2 PET or PTV2 MRI).
Probability of brain necrosis after standard treatment is rather low (mean = 2% +/- 1%).
Planning a dose escalation protocol with PTV2 MRI leads to a risk of complication of 18% +/- 6%.

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Using PET for definition of a BTV for dose escalation result in a reduction of the risk to 15% (+/- 5%), using IMRT further reduce this risk to 14 +/- 6%.

Summary – Conclusions

Efficacy Results :

Abstract : Hypoxia plays a major role in poor local control by radiotherapy in glioblastoma treatment. [18F]-fluoromisonidazole-Positron Emission Tomography ([18F]-FMISO-PET) could be used for definition of target volumes for doses escalation protocols in glioblastomas.
Purpose : the aim of this study is to demonstrate the feasibility of using [18F]-FMISO-PET for the delineation of target volumes suitable for dose escalation.
Materials et Methods : Thirteen patients who had a biopsy for glioblastoma diagnosis underwent a [18F]-FMISO-PET and a T1-weighted gadolinium enhanced MRI before treatment. The different volumes were compared and a dosimetric analysis was performed. Normal tissue complication probability (NTCP) modeling was calculated to evaluate the potential impact of this exam on probabililty of brain necrosis.
Results : [18F]-FMISO uptake was observed in 12 out of 13 patients. [18F]-FMISO-PET volumes were included in TI weighted gadolinium enhanced MRI volumes. Mean hypoxic fraction was 41% +/- 15%. NTCP calculation revealed that using [18F]-FMISO for dose escalation results in lower complication rate than dose escalation based on aera of contrast on MRI. Data from IMRT technique dosimetry showed a decreased probability of complication.

Safety Results : no safety issue reported

Conclusion

Our study proves that [18F]-FMISO-PET could be a candidate for delineation of target volumes in dose escalation protocols in glioblastoma management.

Date of report : 13 janvier 2014