Imaging Lymphoma: $[^{18}\text{F}]\text{Fludarabine PET/CT from bench to bedside.}$

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Positron Emission Tomography (PET)

Cyclotron

Radiopharmaceutical

PET camera
Development of a novel PET radiopharmaceutical

*the steps*..........

Radiochemistry

\[ \downarrow \]

Animal models \[ \xrightarrow{\text{Proof of Concept}} \]

Clinical trial
Preparation of PET radiopharmaceutical
(for clinical trial)

1. Radiochemistry → Radiolabeling → Purification → Automation
2. Submission/approval dossier for IMPD to ANSM
3. Quality control procedure

Quality control procedure
- **Physicochemical tests**: Radionuclidic purity - Radiochemical purity and identity - Chemical purity - Residual solvents - Specific activity - pH - Stability.
- **Biological tests**: Bacterial endotoxin test - Membrane filter integrity - Sterility.

Toxicity
Radiation dose
Lymphoma: cancers of the lymphatic system

Classification

- non-Hodgkin lymphoma (NHL)
- Hodgkin lymphoma (HL)

B-cell lineage → Indolent lymphoma (low risk)
Aggressive lymphoma (intermediate risk)
Very Aggressive lymphoma (high risk)

T-cell lineage

Diagnosis: 74,340 people in US
12%HL
88%NHL

NHL: 5th most common cancer in the US
Conventional imaging techniques for lymphoma evaluation

CT scanning:
- High sensitivity and specificity in pretreatment staging
- Low specificity in response assessment following therapy

$^{67}$Gallium scanning:
- Spatial resolution, specificity, sensitivity were low
- Time involved in performing the scans (7-14 days after $^{67}$Gallium injection)

$^{18}$F-FDG-PET
- High sensitivity and specificity in Hodgkin’s Lymphoma (HL)
- and some indolent and aggressive Non-Hodgkin’s Lymphoma (NHL)
Application of PET(/CT) in lymphoma

- Pretreatment staging
- Restaging
- Therapy monitoring
- Post-therapy surveillance
- Assessment of transformation

Current limitations of \(^{18}\text{F}\)FDG PET scans

- Normal physiologic uptake in brain, heart, digestive tract
- Variability of \(^{18}\text{F}\)FDG avidity among histologies of lymphoma
- False positive: inflammation
- False negative: scanner resolution

Needs of more specific radiopharmaceutical
Fludara I.V (fludarabine phosphate)

An adenine nucleoside analogue

Significant antitumor efficacy in:

- Chronic Lymphocytic Leukemia (CLL)

Fludarabine is used in various combinations in

- Indolent non-Hodgkin’s Lymphoma (NHL)
Mechanism of action of Fludara I.V (2F-ara-AMP)

Plasma

- Fludarabine monophosphate
- 2F-ara-AMP

Dephosphorylation

Cell

- Deoxycytidine kinase
- 2F-ara-AMP

Nucleoside transporter

Apoptosis

- 2F-ara-A
- 2F-ara-ATP
- ARN
- ADN
Radiochemistry
Synthesis of labelling precursor 4

\[\text{2} \xrightarrow{i: \text{PhCOCl, Pyr, reflux}} \text{3} \xrightarrow{ii: \text{TBAN/TFAA/CH}_2\text{Cl}_2} \text{4}\]

93% 56%
Radiosynthesis of $[^{18}F]$Fludarabine ($[^{18}F]1$)

i: 4, CH$_3$CN, 55-60°C, 7min  
ii: MeOH/NH$_3$H$_2$O, 70°C, 20min

$[^{18}F]1$  $[^{18}F]5$

TLC

HPLC

$[^{18}F]$Fludarabine

$[^{18}F]$Fludarabine

$[^{18}F]5$

$[^{18}F]^{-}$
Animal model

*Proof of concept*
Materials and Methods

Animal models

a) SWISS mice CD1 (controls),
b) SCID mice CB17/ICR-Prkdc/Crl (displaying lymphoid depletion)
c) SCID mice 6 week old bearing RL7 human xenografted lymphomas.

Anesthetized animals: Isoflurane (2%) in O₂:N₂0 (33:67%)

Injection: 5-11MBq of $[^{18}F]$-Fludarabine
7-11MBq of $[^{18}F]$-FDG

Micro-PET studies

Siemens INVEON
Acquisition 60min $[^{18}F]$-Fludarabine
Acquisition 90min $[^{18}F]$-FDG

Post imaging dissection
Biodistribution - Dosimetry

biodistribution
dosimetry
In murines
Specificity

Robustness during therapy

Evaluation of the specificity of $[^{18}F]$fludarabine PET/CT in a xenograft model of follicular lymphoma: comparison with $[^{18}F]$FDG and impact of rituximab therapy

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Promising approach for surveillance (detection of persistent viable lymphoid tissues) during or after treatment
Inflammation

Weaker $[^{18}F]$fludarabine uptake in inflammation

Comparative Analysis between $[^{18}F]$Fludarabine-PET and $[^{18}F]$FDG-PET in a Murine Model of Inflammation

Narine Hovhanessian,1,3 Martine Dhilly,3,4 Stéphane Guillonet,5,6,8 Michel Leporrier,5,6,8 and Louisa Barre5,6,8
Marked contrast between tumour / normal tissue

Considerable specificity
Pilot study • Caen 2014-2015
[¹⁸F]Fludarabine PET/CT
• 10 untreated patients (5 CLL; 5 NHL)
• **Injected Dose:** 4MBq/kg
• **PET/CT** (Discovery RV VCT 64, GEHealthcare)

**Protocol**

- **1st acquisition:** 0 - 10 min
- **2nd acquisition:** 15 - 25 min
- **3rd acquisition:** 30 - 50 min
- **4th acquisition:** 90 - 100 min
- **5th acquisition:** 180 - 190 min
- **6th acquisition:** 240 - 250 min
Tracer for lymphoma

$[^{18}F]Fludarabine : from bench to bedside$

Radiochemistry

Preclinical studies
Proof of concept

Clinical trial
First pilot study

Chronic Lymphocytic Leukemia

$[^{18}F]Fludarabine$

Cervical bilateral nodes

Axillary bilateral nodes

Spleen

Lumbar aortic bilateral nodes

Iliac bilateral nodes
Decay corrected anterior maximum-intensity projections (MIP) of PET with imaging intervals of 15-25, 30-50, 90-100, 180-190, 240-250 minutes after injection of $^{18}$F-Fludarabine in a CLL patient, displayed using the same color scale.
[18F]Fludarabine: from bench to bedside

- **Radiochemistry**
- **Preclinical studies**
  - Proof of concept
- **Clinical trial**
  - First pilot study

**Chronic Lymphocytic Leukemia**

- Cervical bilateral nodes
- Axillary bilateral nodes
- Spleen
- Lumbar aortic bilateral nodes
- Iliac bilateral nodes

**Non-Hodgkin Lymphoma**

- Cervical nodes

Before treatment
Tracers for lymphoma

$^{[18F]}$Fludarabine: from bench to bedside

Radiochemistry

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Chronic Lymphocytic Leukemia

Non-Hodgkin Lymphoma

Before treatment
After treatment

ASH, Orlando, USA, 2015
Conclusion and prospects

✓ Marked contrast between tumor / normal tissue

✓ Proof of concept of specific uptake of the $^{18}$F-fludarabine within lymph nodes • CLL and NHL

Multicentric clinical trials
Laboratoire de développement méthodologiques en Tomographie par émission de positons
Centre Cyceron – CAEN - France
Cyceron imaging platform

Fusion of public bodies established in 1985
CEA, CNRS, INSERM, Université de Caen, CHU de Caen, GANIL, CLC Baclesse, Région Basse-Normandie
Cyceron imaging platform

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Missions

Imaging platform operation
➢ At molecular, cellular and integrative levels.

Research team hosting
➢ Labeled by national research bodies

Provision of services for outside teams
➢ Clinical research / enterprises
Laboratoire de Développements Méthodologiques en TEP