Imaging Hypoxia with Cu-ATSM PET.

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Clinical Study

• Patients with newly diagnosed non-small cell lung cancer (NSCLC) being evaluated for initial treatment with radiation therapy, chemotherapy or both

• Lesions $\geq 1.5$ cm in diameter

• 20 patients (mean age 68 years, range 55 - 84 years) with stages IA-IIIB

• CT follow-up (1 month, 3 months and 2 years)
\textbf{60Cu-ATSM}

- Human biodistribution and dosimetry
  - Human dosimetry based on human biodistribution data (liver is the dose-limiting organ with average radiation dose of 0.064 mGy/MBq)
    - Dynamic studies to allow generation of time-activity curves of the organ of interest and whole-body imaging at various times
    - Arterial blood samples (or imaging of the heart) to calculate blood residence time
Cu Dosimetry

Table 5. Internal organ radiation doses for $^{60}\text{Cu}$, $^{61}\text{Cu}$, $^{62}\text{Cu}$, and $^{64}\text{Cu}$. Radiation doses for $^{61}\text{Cu}$, $^{62}\text{Cu}$, and $^{64}\text{Cu}$ are derived from the measured biodistribution of $^{60}\text{Cu}$.

<table>
<thead>
<tr>
<th>Organ</th>
<th>$^{60}\text{Cu}$ (mGy/MBq)</th>
<th>$^{61}\text{Cu}$ (mGy/MBq)</th>
<th>$^{62}\text{Cu}$ (mGy/MBq)</th>
<th>$^{64}\text{Cu}$ (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.064</td>
<td>0.275</td>
<td>0.017</td>
<td>0.390</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.020</td>
<td>0.067</td>
<td>0.005</td>
<td>0.088</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.017</td>
<td>0.048</td>
<td>0.003</td>
<td>0.047</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>0.016</td>
<td>0.051</td>
<td>0.004</td>
<td>0.068</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.013</td>
<td>0.032</td>
<td>0.003</td>
<td>0.032</td>
</tr>
<tr>
<td>Heart wall</td>
<td>0.012</td>
<td>0.026</td>
<td>0.004</td>
<td>0.029</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.012</td>
<td>0.030</td>
<td>0.003</td>
<td>0.056</td>
</tr>
<tr>
<td>Upper large intestine</td>
<td>0.010</td>
<td>0.022</td>
<td>0.002</td>
<td>0.022</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.009</td>
<td>0.020</td>
<td>0.002</td>
<td>0.021</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.009</td>
<td>0.020</td>
<td>0.002</td>
<td>0.021</td>
</tr>
<tr>
<td>Total body</td>
<td>0.009</td>
<td>0.022</td>
<td>0.003</td>
<td>0.026</td>
</tr>
<tr>
<td>ED (mSv/MBq)</td>
<td>0.011</td>
<td>0.029</td>
<td>0.003</td>
<td>0.036</td>
</tr>
</tbody>
</table>

56-min after injection
Tumor Imaging

• Arterial blood sampling starting immediately after injection of $^{60}$Cu-ATSM up to 1 hr to assess the behavior of $^{60}$Cu-ATSM in the blood
  – Rapid movement of $^{60}$Cu-ATSM into tissues occurs in the first 5 min
  – $^{60}$Cu-ATSM blood levels are remarkably stable from 10 to 60 min
Graph A: The percentage of radioactivity extracted into the octanol phase over time. Extracted activity represents intact [Cu-60]ATSM.

Graph B: The overall amount of radioactivity (mCi) contained within each ml of blood over time.
Tumor Imaging

• **Analysis of $^{60}$Cu-ATSM**
  – Kinetic modeling - a classic 3-compartment model identical to that used for FDG kinetic analysis (Patlak, $K = (K1\cdot k3)/(k2+k3)$)

The $K1$ and $k2$ represent transport in and out of the tissue, respectively. The $k3$ parameter represents the rate of trapping of Cu-ATSM in the cell
• 3 Compartment: no difference in k3 ("trapping") value between the tumor (k3 = 0.052/min) and muscle (k3 = 0.062/min)

• The slopes: clear different between tumor and muscle (when blood activity is constant, the estimate of net trapping of a radiotracer in a tumor (K), is merely the slope of tumor activity divided by blood activity)

• The final estimate (slope index) of ⁶⁰Cu-ATSM tumor trapping requires dividing the tumor slope by the muscle average activity
Tumor Imaging

• Analysis of $^{60}$Cu-ATSM
  – The ratios of maximum tumor-to-mean muscle uptake (T/M)
  – Maximum standardized uptake value (SUV$_{max}$), the ratio of decay-corrected activity per unit volume tissue to the administered activity

• Estimates of $^{60}$Cu-ATSM uptake in NSCLC
  – T/M - 2.3 ± 1.0
  – SUV - 3.1 ± 1.0
  – Peak slope index (% change/min) - 2.3 ± 1.3%/min
Does the tumor uptake of $^{60}\text{Cu-ATSM}$ predict response to therapy?

Does the tumor uptake of $^{60}\text{Cu-ATSM}$ predict survival?
Measurement of Hypoxia with $^{60}$Cu-ATSM-PET: NSCLC

- $^{60}$Cu-ATSM (T/M, not SUV) predictive of response to therapy by RECIST (n = 14)
- T/M differed significantly in responders ($1.5 \pm 0.4$) and nonresponders ($3.4 \pm 0.8$) ($p = 0.002$)
- Peak slope index was significantly lower in responders compared with nonresponders ($1.7 \pm 1.2\%/\text{min}$ vs. $3.6 \pm 0.95\%/\text{min}$) ($p = 0.02$)
  - All responders (n=8) had T/M < 3.0
  - All nonresponders (n=6) had T/M $\geq 3.0$

Responder

Pre-therapy FDG-PET

Pre-therapy Cu-ATSM-PET

Pre-therapy CT

Post-therapy CT

SUV = 4.9

T/M = 1.3

Non-Responder

Pre-therapy FDG-PET

SUVmax = 17

Pre-therapy Cu- ATSM-PET

T/M = 3.6

Pre-therapy CT

Post-therapy CT

60Cu-ATSM-PET in Cervical Cancer

- Cervical cancer (n = 38, 1b1-IIIB)
- 60Cu-ATSM uptake (T/M & peak slope index) was predictive of disease-free and overall survival
  - T/M of 3.5 or (5 %/min peak slope index) distinguished patients with better prognosis from those with poorer prognosis

Survival Based on $^{60}$Cu-ATSM Uptake in Cervical Cancer (n=27)

Dehdashti et al., Int J Radiol Oncol Biol Ohys 2003; 55:1233
Responder

FDG-PET

SUV = 13.3

Pre-therapy

$^{60}$Cu-ATSM-PET

T/M = 2.3
Peak slope index = 2.2%/min
Non-Responder

FDG-PET
Pre-therapy
SUV = 11.7
Post-therapy

$^{60}$Cu-ATSM-PET
Pre-therapy
T/M = 5.1
Peak slope index = 7.1%/min
Measurement of Hypoxia with $^{60}$Cu-ATSM-PET

- Rectal cancer: $^{60}$Cu-ATSM prior to neoadjuvant chemoradiotherapy (n = 17)
  - $^{60}$Cu-ATSM (T/M) was predictive of survival
    » Patients with T/M < 2.6 have better overall survival than patients with T/M > 2.6
  - T/M correlated with downstaging after chemoradiotherapy
    » The pretherapy $^{60}$Cu-ATSM uptake was lower in tumors that downstaged after therapy (2.2 ± 0.8 vs. 3.3 ± 0.5, p = 0.03)

Unpublished data
Survival Based on $^{60}$Cu-ATSM Uptake in Rectal Cancer (n=17)

Dietz et al. Dis Colon Rectum, in press
Responder

$^{60}$Cu-ATSM-PET

$T/M = 2.3$

FDG-PET/CT
Non-Responder

$^{60}\text{Cu-ATSM-PET}$

T/M = 3.1

FDG-PET/CT
Can Cu-ATSM be used to Direct Therapy?
Cu-ATSM-Directed Radiation Therapy

Gross Tumor Volume

CT

60Cu-ATSM-PET

Tumor Hypoxic Map

Chen et al., IJROBP 2001; 49:1171-1182
How to Make Cu-ATSM Method Available Worldwide?
Comparison of $^{60}$Cu- and $^{64}$Cu-ATSM

- $T_{1/2}$ of $^{60}$Cu (23.7 min) limits widespread clinical use – requires on-site cyclotron
- $T_{1/2}$ of $^{64}$Cu (12.7 hrs) allows for regional distribution and possible delayed imaging
- Image blurring increases with positron energy
  - Better spatial resolution with $^{64}$Cu than $^{60}$Cu (4.7 vs. 6.3 mm)
- $^{64}$Cu-ATSM has potential as a therapeutic agent

Comparison of $^{60}$Cu-ATSM and $^{64}$Cu-ATSM (IND 62,675)

- Assessed quality of $^{60}$Cu-ATSM-PET and $^{64}$Cu-ATSM-PET images
- Crossover study of 10 patients with cervical CA (IB1 in 1, 1B2 in 1, IIB in 3, IIIA in 1 and IIIB in 4)
- Patients studied with $^{60}$Cu-ATSM-PET and $^{64}$Cu-ATSM-PET in 2 separate days (range 1 - 9 days, averaged 5.8 days)
Comparison of $^{60}\text{Cu}$-ATSM and $^{64}\text{Cu}$-ATSM (IND 62,675)

- **Analysis:**
  - Subjective – comparable; but, $^{64}\text{Cu}$-ATSM images less noisy
    » $^{64}\text{Cu}$-ATSM-PET were less noisy than $^{60}\text{Cu}$-ATSM-PET
  - T/M evaluation
    » T/M of $5.9 \pm 1.6$ for $^{60}\text{Cu}$-ATSM and $7.3 \pm 1.9$ for $^{64}\text{Cu}$-ATSM ($r = 0.95$, $P < 0.0001$)
    » Generally better target-to-background ratio
      (tumors seen more clearly on $^{64}\text{Cu}$-ATSM-PET in most cases)

Comparison of $^{60}$Cu-ATSM and $^{64}$Cu-ATSM (IND 62,675)

- Correlation of T/M for $^{60}$Cu-ATSM and $^{64}$Cu-ATSM

![Graph showing correlation between T/M ratio for $^{60}$Cu-ATSM and $^{64}$Cu-ATSM. The graph includes a linear trend line with an $R = 0.9$ and $P < 0.0001$.](image-url)
Fused FDG-PET/CT

FDG-PET

$^{60}$Cu-ATSM-PET

$^{64}$Cu-ATSM-PET
Summary

• Tumor hypoxia can successfully be measured by imaging $^{60}\text{Cu-ATSM-PET}$
  – Feasible to study hypoxia of human tumors in vivo
  – Favorable radiation dosimetry
  – Clinical evidence that $^{60}\text{Cu-ATSM-PET}$ is:
    » Predictive of response to therapy
    » Predictive of survival
Summary

• Tumor hypoxia can successfully be measured by imaging $^{60}\text{Cu-ATSM-PET}$
  – $^{60}\text{Cu-ATSM-PET}$ with CT co-registration has the potential to direct therapy
  – $^{60}\text{Cu-ATSM-PET}$ has the potential to monitor the effect of therapeutic strategies known to overcome hypoxia

• $^{64}\text{Cu-ATSM}$ is an optimal substitute for $^{60}\text{Cu-ATSM}$
Collaborators

- Barry A. Siegel
- Perry W. Grigsby
- Jason S. Lewis
- Ramaswamy Govindan

Thank You