MR-guided radiation therapy with gadolinium nanoparticles: from chalkboard to first clinical trials

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MR-GUIDED RADIATION THERAPY

High-Z elements act as radiosensitizers/dose enhancers
Gadolinium (Z=64): T1-MRI contrast agent
AGuIX: activation and guiding of irradiation by X-ray

Monitoring Companion tool

Gadolinium Silica

≈3nm

Therapy

Diagnosis
CHARACTERIZATION OF THE NANOPARTICLE

Complexation constant of DOTA on the NP for Gd
In β ~ 24.78

Relaxivity/MRI: 
\( r_2/r_1 = 1.14 \) (1.4T) 
\( r_2/r_1 = 2.2 \) (7T)

Freeze-Drying: long-term stability
~50 g lab-batches
700 g GMP

MAGNETIC RESONANCE IMAGING

High spatial resolution (<10 mm)
High soft tissue contrast
High versatility

Tumor characterization
MRI simulation delineation
MRI guidance
Following the treatment efficacy

Precocce use of companion tool
Enriched the patient population of « responders »
Adjusted treatment protocol
**MR IMAGING PROPERTIES**

- IV injection in non-human primate (0-5 min).
- 30 min.

Kotb et al. (Submitted).
Detappe et al., J Control Release 2016.

**MR IMAGING PROPERTIES**

- Fast and long-term tumor retention (24-72 hrs).

- NIR dye 111In 64Cu DOTA (radioactive species).

Verry & Dufort et al., Nanomedicine 2016.

**OTHER PRECLINICAL IMAGING MODALITIES**
**In vitro efficacy of AGuIX**

Different cell lines, different energies, different teams but similar nanoparticle, similar effects: +30/40%

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**In vivo efficacy of AGuIX**

Very nice efficacy at low dose (I.V.), even on very aggressive pathologies

Rats-bearing 9L tumors

Mice-bearing 816F10 tumors

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**Regulatory preclinical toxicity studies**

- Performed on rats and nonhuman primates
- 2 IV injections (D1 and D8)
- HED tested: from 60 to 145 mg/kg
- No difference of any ante-mortem or post-mortem parameter vs. control group for both species and sex at any dose, except minimal and reversible renal vacuolation in rodents
- Accumulation ratios: 0.92-1.08 / 0.85-1.04
- Blood half-life: 0.83-3.04 / 2.09-3.57

=> HED: 121 mg/kg
Clinical Trial Phase I

- First-in-Man
- CHU Grenoble (France) – C. Verry, MD (J. Balosso, MD-PhD / J.Y. Giraud, PhD)
- Multiple brain metastases including metastases from melanoma, lung or breast tumor (n=3 or large lesions)
- Life expectancy < 6 months
- Current treatment: 30 Gy in 10 sessions of 3 Gy, in toto IR
- Excluded: stereotactic IR, Cyberknife, Gammaknife

- Clinical trial phase I objectives
  - Safety and pharmacokinetics, with increasing doses
  - MRI properties: Distribution and tumor kinetics
  - Survival without IC progression, overall survival

Clinical Trial Phase I

Escalation doses: n=3/dose (Fibonacci) 15 to 100 mg/kg

Dose 1
Dose 2
Dose 3
Dose 4
Selected dose for phase II
Dose 5

Design of the study
- Dose escalation: 15 mg/kg → 30/50/75/100 mg/kg
- 3 patients / dose (15-20 patients)
CONCLUSION

- AGuIX might be used for MR guidance (T1 acquisitions)
- Boosted radiation therapy
- First clinical trial in progress for multiple brain metastases
- Other possible clinical trials:
  - Glioma, Pancreas, other (IV)
  - Uterus/prostate (IT)
  - Lungs (aerosolization)

In progress...

ACKNOWLEDGEMENTS

Olivier Tillément
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Shady Kotb
Alex Detappe

OMEIL

-founded in 2015...
Characterization of the platform

Radiotherapy:

Expected results:

- Significant benefit for the patient in terms of better local control, better tumor response, and increased patient survival.

Radiotherapy + radiosensitizer

Radiotherapy:

- Ionizing radiation
- Primary or secondary species
- Auger electrons
- Ejected-electron

Radiotherapy + radiosensitizer:

- Ionizing radiation
- Auger electrons
- Ejected-electron

Radio sensitization: Possible mechanism of action
**Radiosensitization: Possible Mechanism of Action**

*Auger shower effect*

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**Radiosensitization: Possible Mechanism of Action**

Nanodose effect: High doses are expected in the vicinity of the nanoparticles

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**In vitro Efficacy of AGuIX**

Highly metastatic melanoma cell line B16F10

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### Control

- 24Gy - 0.04
- 4.5Gy - 0.96
- SF2Gy - 52%
- SER2Gy - 2.08
- DEF - 1.3

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<tr>
<th>Dose (Gy)</th>
<th>Control</th>
<th>AGuIX</th>
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Kotb et al, Theranostics 2016
L'excédent de particules est évacué dans les urines.
Le patient est en voie de guérison.
Les cellules saines sont préservées.
Les cellules de la tumeur sont mieux détruites.
Le patient est soumis aux rayons X lors d'un traitement de radiothérapie localisé sur la zone et adapté à ce cancer radiorésistant.

**IN VIVO EFFICACY OF AGuIX**

Tumor accumulation:
- Long-term (24-72hrs)
- EPR effect
- Cell internalization

**REGULATORY PRECLINICAL TOXICITY STUDIES**

750 mg/kg/repeated, +1 week 750 mg/kg/repeated, +10 weeks

**AGuIX FOR PATIENTS**