Long-term results of TAT versus TBT for low grade gliomas (WHO II)

Vector: Bi-213/Y-90 DOTA substance P

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Declaration of interest: founder of Novacurie Ltd

- 2018 EMEA approved clinical protocol for phase III study
- Phase I: Y-90 DOTA substance P (n±50) Basel 1999-2010
- Phase II: Bi-213/Ac-225 DOTA substance P (n±60) Basel & Warsaw 2000-2019
- Orphan drug status for Bi-213/Ac-225 DOTA substance P (10 years protection in EU28)
Toxicity \( = f(\text{range of energy source}) \)

**ideally:** highest energy at target site

**no sublethal damage:** tumor cell death
±0.08 mm alpha-particles / 5.84/8.5 MeV

1 mm Lutetium-177 / 0.13 MeV

5 mm Yttrium-90 / 2.1 MeV

10 mm GammaKnife

10-20 mm Photons
Malignant Gliomas WHO II-IV (orphan disease)

Major focus: GBM (grade IV)
About 10‘000 new cases in EU28 annually

Low grade gliomas (LGG) 15%
± 1500 new LGG cases annually in Europe

Classical orphan disease
• Biology: no qualitative difference between LGG and HGG

• Tumor cell proliferation slower

• **Tumor cell invasion** slower: no cure!!

• LGG: lower tumor burden!
So called „benign“ course of LGG (OG II): an example
$E_{\text{early}}/m_{\text{early}}$ & $E_{\text{late}}/m_{\text{late}}$

- Gray: equal
- $E_{\text{early}} \ll E_{\text{late}}$
Targeted Single Cell Radiotherapy

Yttrium-90/Bismuth-213/Lut-177 Radiopeptide Brachytherapy
DOTAGA-Substance P

[ X ] - DOTAGA - modified Substance P

Radionuclide                  Chelator

213Bi 1800 Daltons
NK 1-receptor mediated substance P-uptake

- NK1-R transfection in LN319 glioma cells

Graph showing median of fluorescence intensity (arbitrary units) over time (min).

- LN319 GBM cells
- pBRET-NK1R-GFP

Hoechst 33342
Bismuth

<table>
<thead>
<tr>
<th>mean tissue range</th>
<th>energy [MeV]</th>
</tr>
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<tbody>
<tr>
<td>81 µm</td>
<td>8.5</td>
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</table>

Advantages of $^{213}\text{Bismuth}$

=> high energy transfer to tissue
=> reduced collateral damage (esp. functionally critical areas!)
=> ± single cell targeting

Ratio astrocytes (tumor cells) : neurons = 10:1
Mode of application: intralesional
- Proposed vector
- 1800 Daltons
- Gallium-68 SP

- Intracavitary-intratumoral activity > 90% after 30 min (OAIII)
• Only bladder signal < 5% of injected activity
- hypodense area with enhancing rim (T1)
- transient perifocal edema reaction (T2)

- 2 weeks after $\alpha T$
- 18 months after $\alpha T$

- $t$ (months)
- 1.96GBq
3/2014 and 2018

- 12 years recurrence-free survival in a now 40-year old **diffusive infiltrative astrocytoma grade II** patient, no functional deficit, ± “clean“ MRI
dose finding empirical: dose escalation

- monitor side effects

- brain: confined space: radiogenic edema reaction leads to increased intracranial pressure (not controllable anymore by medication=limit)

- function of tumor mass (±50 GBq Bi-213)
Data presentation for regulatory EMEA

- GBM phase II study Warsaw 2012-2017
- summary (EMEA, London 2018)
- define subgroup with best efficiency

- $(213)$Bi-DOTA-SP analogue
- SURVIVAL SINCE RECURRENCE

• EMA defined as an endpoint for the Phase III study the Overall Survival (OS) calculated since diagnosis of recurrence (randomization in a controlled study) and not since first diagnosis

• The target population shows a median overall survival of 27.8 months since diagnosis of recurrence

• Best of care with TMZ, nitrosurea (carmustine, lomustine, bevacizumab) mono or combo, achieved median overall survival of 8 months as an average (median OS 6 to 11 months) since recurrence [1]

• Endpoint for Phase III study defined as OS of 15 months active versus 8 months control from randomization (diagnosis of recurrence)

(213)Bi-DOTA-SP analogue

SUBGROUP ANALYSIS

patients with NIH0 (N=6)
- median OS from primary diagnosis: 33.7 months
- median OS from recurrence: 27.8 months
- median OS from onset treatment: 17.1 months
- (median PFS from onset treatment: 5.4 months)

patients with NIH0 + NIH1 (only KPS ≥70 and tumor CSD <50mm) (N=10)
- median OS from primary diagnosis: 27.3 months
- median OS from recurrence: 20.35 months
- median OS from onset treatment: 12.15 months
- (median PFS from onset treatment: 4.05 months)
## Back-up: Alpha-therapy compared to standard of care:
### Overall survival (since first diagnoses)

<table>
<thead>
<tr>
<th></th>
<th>Bi-213</th>
<th>Ac-225</th>
<th>RX-TMZ-placebo*</th>
<th>RX-TMZ-avastin*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&gt; 24 m (2 years)</strong></td>
<td>9/20 (45%)</td>
<td>4/10 (40%)</td>
<td>118/463 (26%)</td>
<td>139/458 (30%)</td>
</tr>
<tr>
<td><strong>&gt; 30 m (2 1/2 years)</strong></td>
<td>6/20 (30%)</td>
<td>4/10 (40%)</td>
<td>53/463 (11%)</td>
<td>61/458 (13%)</td>
</tr>
<tr>
<td><strong>&gt; 36 m (3 years)</strong></td>
<td>4/20 (20%)</td>
<td>2/10 (20%)</td>
<td>15/463 (3%)</td>
<td>11/458 (2%)</td>
</tr>
<tr>
<td><strong>&gt; 42 m (3 1/2 years)</strong></td>
<td>3/20 (15%)</td>
<td>2/10 (20%)</td>
<td>None</td>
<td>1/458 (0.2%)</td>
</tr>
<tr>
<td><strong>&gt; 48 m (4 years)</strong></td>
<td>None</td>
<td>1/10 (10%)</td>
<td>None</td>
<td>None</td>
</tr>
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*: Overall survival (since first diagnoses), Chinot et al. NEJM 2014
• Conclusions from phase II study in Warsaw 2012-2017

• NIH 0 and NIH 1 qualified for phase III study

• TAT is suitable mainly for operated and/or smaller tumor residues (<5 cm diameter) in patients with good functional status (Karnofsky score 70-100)

• TAT is not suitable for rescue therapy in rapidly progressive pre-terminal glioma patients
The big challenge in LGG and in GBM is the control of tumor cell infiltration.

Clinical comparison between TBT and TAT.
• 2 index cases of long-term tumor control following local beta-irradiation, however, with a price:

• Late neurotoxicity after ± 10 years following beta-therapy (WHO grade IV and II cases)
14 year recurrence-free survival of GBM (molecular diagnosis) following targeted beta-radiotherapy, death due to myokardial infarction.

- 2005

- Dose: ± 400 mCi Y-90 substance P
- >1500 Gy
- Loss of contrast enhancement
- Cystic «e vacuo» transformation after 7 years (late toxicity)
2nd example: LGG case with high dose beta-therapy

- 16-year recurrence-free survival time following local **beta**-radiotherapy in oligodendroglioma WHO II (LGG)

- **however**, beta-related side effects (=neurological deficits) vascular postactinic lesion 10 years following beta-therapy moderate hemispastic lesion on the left from 12th year on following beta therapy

**Argument for switch to alphatherapy**
• 2003: 34 years old male
diagnosis oligodendroglioma WHO II
(diameter 4x5cm)

• neo-adjuvant beta-radiopeptide therapy
  locally targeted beta-therapy
  Y-90 DOTA substance P, 4x25 mCi

• Removal of necrotic liquefied tumor mass
  functions preserved 1 month following last beta-therapy cycle

• wait & see strategy

• 2008 (MRI) 4-years follow up: e vacuo effect following resection
- 10 years following targeted beta-therapy
- Headaches, new globular lesion right frontal at anterior rim of tumor area: suspicion of upgrade lesion
- Open resection: vascular nodular lesion compatible with post-actinic lesion, no malignant cells
- Further follow-up showed moderately progressive hemispastic lesion on the left (hand & foot)
- OS: +16 (y)
- no recurrence
- moderate hemispasticity L
- beta effective
  but risk of local neurological damage
  by long range radiation (5mm)
  - rapidly (Bi-213) diffusible > 7cm
Disadvantage of high MeV Beta (range ± 5mm)

Radiation necrosis in critical areas

But:
Proof of long-range diffusion (>7cm, also across midline)

TBT inferior to TAT in the brain
First alpha case in LGG

OGII, diagnosis 1999

19 years observation interval

- no late toxicity so far!

- no secondary dementia!
In 2000: Surgery followed by 0.9 GBq Y-90 SP

1.9 GBq Bi-213 SP (better tolerated than Y-90!)

- 2018: excellent condition, mild leg hemispasticty R
Can tumor cells infiltrating a functionally critical area of the brain be safely targeted?

Risk of damaging neurons?

Ratio astrocytes to neurons $\approx 10:1$

Range: $\beta$ 1-5mm  $\alpha$: 0.08mm
Progressive OG II (m 62y, focal seizures, 4 anticonvulsants): Location within motor cortex for tongue, face and left hand
Primary surgery destructive!
• intratumoral injection of 1.9 GBq Bi-213 SP (1x), volume 2ml

• 9 days after alpha-therapy:
• functionally disabling brachiofacial hemiparesis L BMA III
Transient neurological deficit, resolved after 6 weeks

Reduced seizure frequency (a few a months)

MRI: rim-enhancement of hypodense tumor area
partially cystic transformation of solid tumor
● 8 years stable course (2011-2019)
● no open surgery
• Alpha particles do not destroy adjacent neurons

• Minimal damage possible (subclinical)

• Alpha particles suitable to target functional areas

• Caveat: repetitive injections, pre-treatment
- age 24, male, astrocytoma II
- Jan 27 2016: 40 mCi Bi-213 substance P
- days 7 & 9 after injection
- high dose steroids
- antiepileptic drugs
**Conclusion LGG and alpha vs. beta**

Long term control for LGG (AII and OII) with alpha & beta

Recurrence-free survival: up to 19 years observed, no recurrence in primary cases so far

2 cases cross-over from beta to alpha: additional survival benefit of 6 years so far

Alpha-toxicity minimal and transient (cave pretreatment?)

1.875 GBq (=50 mCi) Bi-213 SP may be sufficient: size (E/m=Gy)

Good clinical condition, good tumor control
Source of Actinium-225

- Local therapy can rely on Bi-213
- usage of Ac-225/227 generators possible
- spallation of Thorium-232 valid Ac-225 source
- Ac-227 1% contamination of no concern!