Using cancer traps against glioblastoma

#teamBlue

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Glioblastoma background

2015 Brain Cancer Facts & Figures

22,850
Total estimated malignant brain cancer cases in the U.S.

12,900 9,950

Only one in 140 men and one in 180 women will develop a malignant tumor of the brain or spinal cord in his or her lifetime all cancer diagnoses.

Brain cancer is deadly

Five-year survival rates...

9/10 children with leukaemia now survive

9/10 people diagnosed with breast cancer will survive

2/10 people diagnosed with brain cancer will survive

<1/10 people with DIPG or glioblastoma will survive

Source: American Cancer Society

Source: AIHW National Cancer Statistic
GBM biology that drives failure

- Multifocal and diffusive disease – cells invade beyond surgery and radiation margin

- Residual cells develop resistance to continuous maximum tolerable dose treatment
Patient presentation
Clinician-choice treatment

Surgery ↓

HFSRT

Progression

... Pembrolizumab

... Bevacizumab
## Response rates

<table>
<thead>
<tr>
<th>Bev</th>
<th>Anti PD1 (e.g. Pembro)</th>
<th>Pembro+ Bev</th>
<th>HFSRT+ Bev</th>
<th>HFSRT+ Bev + Pembro</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.1%</td>
<td>7.8%</td>
<td>26.0%</td>
<td>52%</td>
<td>83.3%</td>
</tr>
<tr>
<td>95% CI: 16.7%-30-5%</td>
<td>95% CI: 4.1%-13.3%</td>
<td>95% CI: 16.3-41.5</td>
<td>95% CI: 28 %-89%</td>
<td>95% CI: 62 % - 95%</td>
</tr>
</tbody>
</table>

**Bev**: Bevacizumab, Anti-angiogenic agent  
**Pembro**: Pembrolizumab, Anti-PD1 (immunotherapy)  
**HFSRT**: Hypofractionated Stereotactic Radiotherapy
Survival analysis

*Progression Free Survival*

*Overall Survival*
Data to inform ETB, N=31

Histopathology
- Glioblastoma: 13
- Anaplastic astrocytoma: 1

Sex
- Male: 9
- Female: 5

Age
- < 50 years: 6
- ≥ 50 years: 8

Number of recurrence
- 1st: 9
- 2nd: 5

RANO progression criterion
- T1post: 2
- T2/FLAIR: 8
- T1post & T2/FLAIR: 2
- Clinical deterioration: 2

MGMT promoter methylation
- Methylated: 7
- Unmethylated: 6
- Unknown: 1

IDH mutation
- Positive: 3
- Negative: 10

EGFR vll mutation
- Positive: 5
- Negative: 5
- Equivocal: 1
- Unknown: 3

Tumor volumes

Lymphocyte counts

Neutrophils counts

White blood cell counts
Statistics-based prediction for clinician-choice therapy based on clinical trial data

Speed of evolution of resistance correlates with patient response to clinical trial protocol

\[ p = 0.007 \]

Machine learning classifiers

Predicting time-dependent probability of disease progression

Our patient is classified as Fast Evolution with 72% confidence
Evolutionary Tumor Board

radiation dose / dose fractionation

ecological trap

evolutionary dynamics guided protocols

Surgery

HFSRT

Progression

... Pembrolizumab

... Bevacizumab
Evolutionary Tumor Board

Ecological Trap to direct cells to the surgical cavity to be irradiated
Ecological trap

Habitat or other feature in an environment that appears to be fitness-enhancing, but actually reduces fitness

Wood thrush

New Zealand fantail
Ecological trap in GBM

- Therapeutic ecological trap: invasion of glioma cells throughout brain parenchyma.
- The cancer cell trap diverts the cancer cell migratory potential for therapy.
- A high radiation dose is delivered to cancer cells attracted to the trap.
Ecological trap in GBM

Perspective
Future Oncology

Translation of the ecological trap concept to glioma therapy: the cancer cell trap concept

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A new glioblastoma cell trap for implantation after surgical resection

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Reversing the Tumor Target: Establishment of a Tumor Trap

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Ecological trap in GBM

The cancer trap:  *Autier et al.* (2019)
- bacterial cellulose membrane
- close to FDA approval
- visible on MRI

The bait:  *Hira et al.* (2017)
- Stromal Cell-derived Factor-1 (SDF-1 or CXCL12)
- SDF-1 localized in GBM niches
- SDF-1 regulates migration of many cancer cell types (including in GBM)
- SDF-1 facilitates homing of glioma stem-like cells to tumor niches
Ecological trap in GBM

- Implant the cellulose membrane with attractant during surgery
- Glioma cells trapped for 4-6 weeks while patient recovers from surgery
- Trapped cells eradicated with high-dose radiotherapy
Diffusion PDE Trap Treatment

diffusion PDE for residual glioblastoma cell distribution

diffusion PDE for the trap
time

trap
spatial-temporal evolution

residual cell distribution shrinks
Evolutionary Tumor Board

radiation dose / dose fractionation

Surgery

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HFSRT

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Progression

... Pembrolizumab

... Bevacizumab
RT Today
RT + $50k in funding tomorrow
Modelling Radiation response

Challenges:

• Considers evolution of resistance to adapt RT dose
• Resampling antigens to immune system
• Target new sites of disease of progression

Personalized Adapted radiotherapy:

- Genome Based Patient Specific RT sensitivity and Growth Rate
- Single dose of HFSRT
- Assess response at 6 weeks or if symptomatic
- Growth or Symptomatic
- Adapt RT dose 1-8Gy based on volume change
- Hold RT
- Regression

Adapt RT dose 1-8Gy based on volume change
Hold RT
Regression

Growth or Symptomatic
In silico trial

- 5x6Gy – kills fast growing populations but non repeatable
- 6Gy every 6 weeks – No control of fast growth + Resistance builds up
- PART optimizes at a patient level and at every time step
Evolutionary Tumor Board

Evolutionary dynamics guided protocols
Evolutionary dynamics during Avastin / Pembrolizumab Tx

A Non-mechanistic Model of Tumor Volume over Time

\[
\frac{dV(t)}{dt} = (\lambda - \gamma(t))V(t)
\]

\[
\frac{d\gamma(t)}{dt} = -\epsilon\gamma(t)
\]

- With no treatment: Tumor grows exponentially
- With treatment: Tumor shrinks with rate \( \gamma(t) \) and the drug sensitivity decreases exponentially with rate \( \epsilon \)

- Continuous therapy: Keep using treatment
- Adaptive therapy: Treat if tumor volume exceeds initial volume, and stop treatment if volume decreases
Evolutionary dynamics during Avastin / Pembrolizumab Tx

R2=0.91
Evolutionary dynamics during Avastin / Pembrolizumab Tx

p=0.07
Treatment Recommendation

Surgery

Intermittent Radiation

PART

Evolutionary Trap

Progression

Pembrolizumab

Bevacizumab
Adaptive control
Adaptive control
Adaptive control
Adaptive control
Adaptive control

Evolutionary Tumor Board
Specific Aims

Specific Aim 1.
To analyze the response dynamics (tumor volume every 4-6 weeks, neutrophil & lymphocyte count every 2-4 weeks) of N=104 recurrent high-grade GBM patients treated with either avastin alone (N=20), pembrolizumab alone (N=20), HFSR+avastin (N=20), RT+avastin+pembro (N=32; MCC 17978) and RT+avastin+pembro+nivolumab (N=32; MCC 18661).

Specific Aim 2.
To simulate evolutionary therapies and evaluate model predictions vs. actual patient responses and outcomes.
Mechanistic Model of Avastin/Pembrolizumab Tx

\[
\frac{dC_T}{dt} = \alpha C_T - \beta C_T C_I \\
\frac{dC_I}{dt} = \delta_1 C_T C_I - \epsilon C_I
\]
Mechanistic Model of Avastin/Pembrolizumab Tx

\[
\frac{dC_T}{dt} = \alpha C_T f(\text{Bev}) - \beta C_T C_I f(P)
\]

\[
\frac{dC_I}{dt} = \delta_1 C_T C_I - \epsilon C_I + \delta_2 f(R) C_T C_I
\]

Low Evolution of Resistance Case
Mechanistic Model of Avastin/Pembrolizumab Tx
Mechanistic Model of Avastin/Pembrolizumab Tx

Low evolution of resistance case \(\rightarrow\) intermittent therapy is not beneficial
Outcomes & Deliverables

Phase I Trial of Hypofractionated Stereotactic Irradiation (HFSRT) Combined with Nivolumab, Ipilimumab and Bevacizumab in Patients with Recurrent High Grade Gliomas (NCT02829931)

- **I**: Ipilimumab, Q 3 weeks X4 with Nivolumab and Bevacizumab starting Day 1
- **N**: Nivolumab, Q 3 weeks (starting Day 1) X4 with Ipilimumab and Bevacizumab then Q 2 weeks for 4 months followed by Q 4-week doses
- **B**: Bevacizumab, Q 3 weeks (starting Day 1) X4 with Nivolumab and Ipilimumab then Q 2 weeks
- **HFSRT**: Daily for 5 days from Day 1+3 to Day 5+3
Budget

- $10K data abstraction
- $20K graduate student
- $10K postdoc mentor
- $7K statistical analysis
- $3K publication fee
Acknowledgement

- Patient J.D., evaluated by ETB
- Sandy Anderson
- Danae Paris
- Chef Anderson
- Ms. Francoeur & Mr. Butler
- Moffitt PSOC