Optimal drug/radiation administration schedules to delay resistance

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How can we use predictive mathematical modeling of patient outcomes to identify optimum treatment strategies that prevent or delay resistance?
Optimization of Treatment Strategies

Currently FDA approved administration strategies for most therapies were not chosen by a systematic investigation of the entire possible search space.

Radiotherapy for brain cancer (glioblastoma) is given in 2 Gray fractions 5 days a week for 6 weeks.
Optimizing radiation response in glioblastoma

Charles et al, Cell Stem Cell 2010
Optimizing radiation response in glioblastoma

1. Understanding of intratumor heterogeneity based on mouse modeling of PN GBM

2. Mathematical modeling of treatment response

Leder et al, Cell 2014
Optimizing radiation response in glioblastoma

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1. Understanding of intratumor heterogeneity based on mouse modeling of PN GBM

2. Mathematical modeling of treatment response

- Optimum-1
- Scramble
- Standard double dose
- Single Dose
- Mock IR
- Standard
- Optimum-1
- Scramble
- Standard double dose

3. Identification of optimum schedule to maximize survival

- Monday: 8
- Tuesday: 2
- Wednesday: 5
- Thursday: 3
- Friday: 4, 5

One week of tx, total of 10 Gy, each dose is 1 Gy

4. Validation in mouse trials

Leder et al, Cell 2014
Enriching for stem cells in mice and men

Optimal schedule enriches for slower proliferating, radioresistant stem-like cells in the mouse model
  • Achieved by timing radiation fractions to maximize dedifferentiation process

Enrichment of stem-like cells is associated with prolonged survival in patients (n = 37): All patients received 60 Gy radiation + adjuvant temozolomide

Data from Pallini et al. Cancer 2011

HR = 0.84
p = 0.018

[Graph showing overall survival probability over time (months) with two lines representing stem-like cell enrichment above and below the median, indicating a significant survival benefit for the higher enrichment group.]
A pilot trial for refractory GBM at BWH/DFCI

- Comparison to control arm: 35 Gy in 10 fractions; 1 fraction/day; 5 days/week

- Identified schedule: 28 Gy in 7 fractions (1 fraction/day) then 9 Gy in 9 fractions (3 fractions/day)
  - Maximizes differentiated cell killing per fraction using hypofractionation at the start of treatment
  - Enriches for stem-like cells using ultrafractionation at the end of treatment
  - Hopefully easier to implement than Optimum-1 and infinitesimally worse

- IRB approved, starting to enroll now

Jamie Dean, Shyam Tanguturi, Brian Alexander
Upfront treatment: radiation plus temozolomide

Amanda Randles
Determining optimum administration schedules for radiation and temozolomide using a spatial model.
Workflow

1. Experimental Calibration: Finding proper dosage and initial parameter estimation
2. Construction of mathematical model, optimization, and survival analysis
3. Parameter sensitivity analysis
4. Parallel sensitivity analysis
5. Mouse model
This model was used to predict optimum administration schedules of 10 Gy over one week using over 4000 compute years on the world’s #2 supercomputer (Livermore National Labs)

<table>
<thead>
<tr>
<th></th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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</thead>
<tbody>
<tr>
<td>Optimized</td>
<td>--</td>
<td>1 Gy 9 a.m.</td>
<td>1 Gy 8 a.m.</td>
<td>1 Gy 9 a.m.</td>
<td>1 Gy 9 a.m.</td>
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<td>1 Gy 4 p.m.</td>
<td>2 Gy 9 p.m.</td>
<td>2 Gy 4 p.m.</td>
<td>1 Gy 5 p.m.</td>
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<tr>
<td>Suboptimal</td>
<td>2 Gy 2 p.m.</td>
<td>1 Gy 1 p.m.</td>
<td>1 Gy 2 p.m.</td>
<td>2 Gy 8 a.m.</td>
<td>1 Gy 5 p.m.</td>
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<td>1 Gy 5 p.m.</td>
<td>1 Gy 3 p.m.</td>
<td>1 Gy 11 a.m.</td>
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<tr>
<td>All</td>
<td>TMZ 50 mg/kg 3 p.m.</td>
<td>TMZ 50 mg/kg 3 p.m.</td>
<td>TMZ 50 mg/kg 3 p.m.</td>
<td>TMZ 50 mg/kg 3 p.m.</td>
<td>TMZ 50 mg/kg 3 p.m.</td>
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Validation in the mouse

- This prediction was validated in the RCAS/tv-a model (PDGFB+Cre in N/t-va;Ink4a/Arf-/-;PTENfl/fl;LucLSL/LSL)
Where do we go from here?

- Implementing this work as three clinical trials: pilot for feasibility, multi-institutional for efficacy or radiation alone, and trial for chemoradiation combination
- Modeling studies for combination treatment with radiation sensitizers, immunotherapy, and anti-angiogenic drugs
- Application of these methods to other cancer (lung, breast, AML, pancreatic, etc) and treatment (radiation, chemotherapy, targeted agents, immunotherapy, radiosensitizers etc) types
- Other physical sciences-based investigations into intra-tumor heterogeneity, metastasis, and treatment response
Acknowledgements

Michorlab

Shaon Chakrabarti
Simona Cristea
Émie Dean
Jeremy Ferlic
Jenn Ge
Michael Nicholson
Lin Liu
Thomas Madsen
Simon Maisel
Kamrine Poels
Jiantao Shi
Shayna Stein
Daniel Temko
Debra van Egeren
Hua-Jun Wu
Qiong Xu

The Dana-Farber Cancer Institute
Physical Sciences-Oncology Center (PSOC)

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Duke University: Amanda Randles

The Dana-Farber Cancer Institute
Center for Cancer Evolution (CCE)

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