Adaptive Therapy and Competition

Cancer Adaptive Therapy Models Virtual Meeting

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Treatment of prostate cancer: Recent Pilot Clinical Trial

Main advances of trial:

1. Treatment is **adaptive**: dosing depends on the actual tumor dynamics of each individual patient.

2. Treatment leverages **competition**: deliberately maintains a sensitive population to slow the growth of the resistant population.

Can we modify the adaptive therapy design and improve results?
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Assumptions

1. Adaptive therapy works because of competition
2. Larger populations generate more competition

Caveats

1. Interested in adaptive therapy in general
   a) Discussion is not restricted to prostate cancer
   b) Use PSA as a proxy for tumor burden
2. Adaptive therapy designed to competitively suppress resistance in order to contain the tumor for longer. Competitive Suppression and Containment
Role of initial tumor response?

Accept To Trial

Good candidate for containment?

Decline From Trial

Poor candidate for containment?
Strong Initial Response BUT Bad Candidate for Containment

- Standard therapy could clear tumor
- 50% reduction in PSA is too much
- Baseline PSA is too low
Poor Initial Response BUT Good Candidate for Containment?

These patients may have excellent potential to benefit from competitive suppression.
Modified Approach to Enhance Competition

Current Approach

A Possible Improved Approach

Modified Approach to Enhance Competition

Current Approach

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Important Reminder

1. Analysis assumes that competition is the main consideration
2. Larger populations generate more competition

But, in general we know ......

Populations interact in many different ways

1. Competition
   a) For space
   b) For nutrients
2. Cooperation
   a) Production of public goods
   b) Self-restraint behavior
3. Transfer between populations
   a) Mutation
   b) Epigenetic changes

Populations also interact with their environment
Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer

Pedro M. Enriquez-Navas, Yoonseok Kam, Tuhin Das, Sabrina Hassan, Ariosto Silva, Parastou Foroutan, Epifanio Ruiz, Gary Martinez, Susan Minton, Robert J. Gillies, Robert A. Gatenby

Conventional cancer treatment strategies assume that maximum patient benefit is achieved through maximum killing of tumor cells. However, by eliminating the therapy-sensitive population, this strategy accelerates emergence of resistant clones that proliferate unopposed by competitors—an evolutionary phenomenon termed “competitive release.” We present an evolution-guided treatment strategy designed to maintain a stable population of chemosensitive cells that limit proliferation of resistant clones by exploiting the fitness cost of the resistant phenotype. We treated MDA-MB-231/luc triple-negative and MCF7 estrogen receptor–positive (ER+) breast cancers growing orthotopically in a mouse mammary fat pad with paclitaxel, using algorithms linked to tumor response monitored by magnetic resonance imaging. We found that initial control required more intensive therapy with regular application of drug to deflect the exponential tumor growth curve onto a plateau. Dose-skipping algorithms during this phase were less successful than variable dosing algorithms. However, once initial tumor control was achieved, it was maintained with progressively smaller drug doses. In 60 to 80% of animals, continued decline in tumor size permitted intervals as long as several weeks in which no treatment was necessary. Magnetic resonance images and histological analysis of tumors controlled by adaptive therapy demonstrated increased vascular density and less necrosis, suggesting that vascular normalization resulting from enforced stabilization of tumor volume may contribute to ongoing tumor control with lower drug doses. Our study demonstrates that an evolution-based therapeutic strategy using an available chemotherapeutic drug and conventional clinical imaging can prolong the progression-free survival in different preclinical models of breast cancer.
Three Different Treatment Strategies

1. Standard Treatment (ST): Fixed dose twice a week for 2.5 weeks

2. Adaptive Therapy 1 (AT-1): Dose Modulating
   Treatment times fixed. Dose adapted to tumor response.

3. Adaptive Therapy 2 (AT-2): Treatment Skipping
   Treatment dose fixed. Treatment timing adapted to tumor response.

Immediate Questions

1) Is success of adaptive therapy due to competition?

2) Is treatment failure (progression) due to drug resistance?
Example using *E.coli* as model system

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Example using *E.coli* as model system

- **Resistant Only**
- **Mixed**
Example using *E. coli* as model system

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Adaptive Antibiotic Dosing
To Maintain Constant Bacterial Density

Example using *E. coli* as model system

Adaptive Antibiotic Dosing
To Maintain Constant Bacterial Density

Example using *E.coli* as model system

1) By matching drug in all vials, only difference between vials is presence/absence of sensitive cells
2) By comparing **Resistant Only** and **Mixed** we can measure the effect of sensitive cells.

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![Graph showing the growth and optical density over time for different conditions: Resistant Only, Mixed, and Sensitive Only. The graph illustrates the max allowed density.](image)

Example using *E.coli* as model system

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Hansen, Karslake, Woods, Read and Wood.
PLoS Biology, May 2020
Example using *E. coli* as model system

![Graph showing time on the x-axis and optical density on the y-axis, with a horizontal line indicating the max allowed density.](image-url)

Example using *E. coli* as model system

- Resistant Only
- Max Allowed Density
- Mixed
- Sensitive Only

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**Adaptive Approach**

- treatment
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**Adaptive Approach**

![Diagram of adaptive therapy process](Image)
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