Mathematical Modelling of Chemotherapy Scheduling

Metronomics @ Mumbai
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Where does the MTD paradigm come from?

- **Skipper-Schabel-Wilcox** seminal papers in the 1960’s
- Basic principle = proliferation
- **Exponential** growth of the tumor cell population $N(t)$

\[ \frac{dN}{dt} = aN \quad a \sim T^{-1} \quad T = \text{doubling time} \]
Where does the MTD paradigm come from?

Log-kill hypothesis

a given dose kills a **given fraction** of the tumor cell population

\[
\frac{dN}{dt} = aN - e^{C(t)}N
\]

- Established on leukemic cell lines
- Focus: **curability**

“(… ) it appears that high-level, short-term schedules offer considerably greater potential for obtaining “cures”. This preference does not necessarily hold with regard to achieving **maximum increase in life span** of animals which die in spite of therapy”

*Skipper, Schabel and Wilcox, Cancer Chemother Rep, 1964*
The Norton-Simon hypothesis: tumor growth model

- Relative growth rate is not constant in time, it *decelerates*
- Challenges the exponential model ⇒ Gompertz growth

\[
\frac{dN}{dt} = a e^{-bt} N
\]
The Norton-Simon hypothesis

Second hypothesis: effect of the therapy is proportional to the proliferative fraction only

\[
\frac{dN}{dt} = a e^{-bt} N - eC(t)e^{-bt} N
\]

• Suggested densification of adjuvant chemotherapy protocols in breast cancer
• Subsequently validated in phase III study

\[\text{Citron et al., J Clin Oncol, 2003}\]

still focuses on tumor eradication

\[\text{Norton, Simon, Cancer Treat Rep, 1976}\]
Tumor heterogeneity and re-sensitization

Minimizing Long-Term Tumor Burden: The Logic for Metronomic Chemotherapeutic Dosing and its Antiangiogenic Basis

*Philip Hahnfeldt*, †Judah Folkman§¶ and Lynn Hlatky†‡

J Theor Biol, 2003
Tumor heterogeneity and re-sensitization

- In the context of tumor heterogeneity, **long-term minimization** may often be the more practical objective
- **Metronomic scheduling** is the best way to achieve it
- Lends theoretical support to the **anti-angiogenic basis** of metronomic therapy as endothelial cells because of higher ability to desensitize
A dedicated model for metronomic chemotherapy

Hypotheses:

1. Chemo has an **anti-angiogenic** effect by killing proliferative endothelial cells.
2. Cancerous cells develop **resistances** to the CT whereas endothelial cells don’t.
3. At low dose, the killing action of the drug is stronger on the endothelial compartment than on the tumor one

\[
\begin{align*}
\frac{dN}{dt} &= aN \ln \left( \frac{K}{N} \right) - \alpha_1 e^{-R \int_0^t C(s) ds} C(t)N \\
\frac{dK}{dt} &= bN - dN^{2/3} K - \alpha_2 C(t)K
\end{align*}
\]

- AA effect
- Resistance
- CT effect

\[ N = \text{tumor cells} \]
\[ K = \text{carrying capacity} \]
\[ = \text{vascular support} \]

+ PK/PD model for exposure of the drug given the concentrations
A dedicated model for metronomic chemotherapy

MTD schedule: 100 mg at day 0 of 21-days cycle

Metronomic schedule: 10 mg/day every day without resting period

Docetaxel PK/PD parameters

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**Tumor cells**

- Untreated
- MTD
- Metronomic

**Carrying capacity (vasculature)**

- Untreated
- MTD
- Metronomic

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Benzekry, Barbolosi, Andre et al., MMNP, 2012
Modeling of toxicity and scheduling of vinorelbine in NSCLC

Barbolosi, André et al., Cancer Chemother Pharmacol (2014)
Elharrar, Barbolosi, André et al. (2016)

⇒ ongoing phase I trial
Adaptive therapy

- **Evolutionary** viewpoint of resistance to therapy. Darwinian selection
- **Complex** dynamics are hard to control. Why, then, use fixed, rigid protocols of drugs, dose and timing?
- Gatenby suggests to rather adapt the protocol as the tumor evolves in response to therapy

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A change of strategy in the war on cancer

Patients and politicians anxiously await and increasingly demand a ‘cure’ for cancer. But trying to control the disease may prove a better plan than striving to cure it, says Robert A. Gatenby.

Gatenby, Nature, 2009

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Gatenby et al., Cancer Res, 2009
Primary tumor VS metastases

Injection → Primary tumor (PT) → Time

PT growth law: $g_p(V_p)$

Dissemination law: $d(V_p)$

Metastases

Mets growth law: $g(v)$

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Benzekry, M2AN, 2012
Benzekry, Ebos et al., Cancer Res, 2015

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Primary tumor

- No treatment
- Endostatin
- Angiostatin
- TNP-470

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Metastases

- No treatment
- Endostatin
- Angiostatin
- TNP-470
CT/AA combination. What sequence?

Bevacizumab D0 Etoposide D8 \textit{versus} Etoposide D0 Bevacizumab D8

⇒ The best sequence is different for the PT and the mets
Conclusions

- Although mathematics are a discipline far from medicine, theoretical models have often driven the paradigms underlying chemotherapy schedules.

- Rational design of chemotherapy protocols…

- ...and sequences in combination therapies (CT/AA, radio-immuno therapy)

\[\text{Benzekry, Pasquier, Andre et al., Semin Cancer Biol, 2015}\]
Thank you for your attention!