

Data-driven mechanistic modeling of metastasis: cancer at the organism scale

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Metastasis (μετά = beyond, στάσιζ = place)

Metastases are the main cause of death (>90%) from solid cancers Lambert and Weinberg, Cell, 2017



Breast

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- 94% of cases are local or regional at diagnosis but 30% will relapse Pollard, N Eng J Med, 2016
- Estimate the amount of residual distant disease at diagnosis in order to personalize the adjuvant (chemo)-therapy
- Avoid unnecessary, heavy toxicities
- Lung
 - 57% of cases are metastatic
 - Decide whether to use whole brain radiation therapy or just (stereotactic) surgery
 - · Avoid cognitive impairment of the patient



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Mechanistic model of metastatic dissemination and growth



Metastatic burden (total number of metastatic cells)

$$M(t) = \int_{V_0}^{+\infty} v\rho(t, v) dv = \int_0^t d(V_p(t-s)) V(s) ds$$

Growth rates of primary and secondary tumors gp and g

$$\frac{dV_p}{dt} = (\alpha_p - \beta_p \ln(V_p)) V_p \qquad \text{(Gompertz)}$$
$$g(v) = (\alpha - \beta \ln(v)) v$$

Dissemination rate $d(V_p) = \mu V_p$

Size distribution of the metastases $\rho(t, v)$

$$\begin{cases} \partial_t \rho(t, v) + \partial_v (g(v)\rho(t, v)) = 0\\ g(V_0)\rho(t, V_0) = d(V_p(t))\\ \rho(0, v) = \rho^0 \end{cases}$$

Validation on animal data



 \Rightarrow same growth for PT and mets: $\alpha_p = \alpha$, $\beta_p = \beta$

Benzekry et al. (Ebos), Cancer Res, 2016



Data of a NSCLC patient with brain mets





The model with dormancy could describe best the data



Objective function

Model	Patient 1	Patient 2
Base	5.51	2.53
Secondary	5.43	2.3
Delay	5.23	1.53
Dormancy	4.93	1.71
Diff. growth	4.95	1.79

Dormancy estimated to 133 days $\pm 4.2\%$



Bilous et al. (Benzekry), biorXiv, 2018



2 Combination bevacizumab chemotherapy

Ínnía

Vascular normalization: a time window for improved pharmacokinetics?

- Bevacizumab = anti-VEGF monoclonal antibody ⇒ anti-angiogenic action (first approved in 2004)
- Only proved clinical efficacy when combined (concomitantly) with cytotoxics
- Possible explanation: transient normalization of the otherwise abnormal (leaky, tortuous) vascular architecture



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Vakoc et al., Jain, 2009, Nat Med
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Jain, Nat Med, 2001

Therapeutic question

What is the **optimal time gap** between administration of bevacizumab and cytotoxic chemotherapy? How to capture **inter-individual variability** for designing **personalized therapies**?

Hypothesis: sequential use of bevacizumab associated with chemotherapy would achieve better efficacy and modeling support could help to define the optimal timewindow



Imbs et al. (Benzekry), CPT: Pharmacometrics Syst Pharmacol, 2017

Semi-mechanistic mathematical model



Simeoni et al., Rocchetti, Cancer Res, 2004 Benzekry et al., CRAS, 2012 Mollard et al., Benzekry, Oncotarget, 2017 Imbs et al., Benzekry, CPT: Pharmacometrics Syst Pharmacol, 2018





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informatics mathematics



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Modeling



Beva + cytotoxics study



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*D. Barbolosi

Thanks for listening!

That's all Folks

We are looking for postdocs!

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