Biomathematical modeling for description of metastatic processes and optimization of combined anti-angiogenic + cytotoxic therapies

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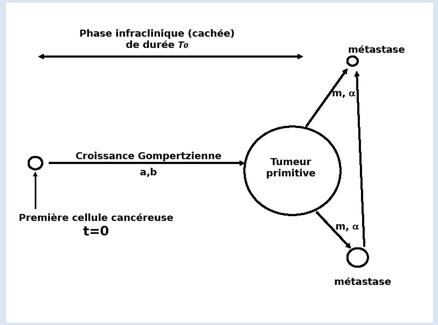
Introduction

The development of chemotherapeutic (CT) drugs and arrival of anti-angiogenic (AA) biotherapies allowed innovating possibilities in the clinic. However, validated combinations mainly rely on empirical approaches, or on availability considerations of the patient in the center.

Moreover, dual classification of the cancer pathology as localized or metastatic is a key-point in elaborating the therapeutic support. In the case of advanced infra-clinical metastatic state of the patient, this can lead to sub-optimal therapeutic strategy. There is probably a *continuum* between the two states. In order to **refine discrete classifications** like TNM, we develop an *in silico* tool, called **Metastatic Index**, based on a **mathematical model** describing the growth of the **metastatic population**. We show how this tool could be used in helping decision-making for oncologists or during clinical trials.

We also present a mathematical model for describing the complex pharmacodynamical **interactions** between an anti-angiogenic and a cytotoxic drug. This tool should allow identification of the associations demonstrating best antitumor efficacy. It could help for **optimization** of the temporal administration protocol for cytotoxic treatments in monotherapy or combined with anti-angiogenic biotherapy, both during clinical development and routine oncological practice.

Methods



Mathematical models for

- **Primary tumor** growth (Ordinary differential equations)
  - Gompertz : only cancer cells. Model used in the phase I trial **[You & al]** ⟹ CT
  - Folkman – Hahnfeldt **[Folk99] :** cancer cells + blood vessels ⟹ CT+AA
  - New model **[BCCEH11]** : cancer cells + stable/unstable vessels ⟹ CT+AA interactions
- **Metastatic population [IKS00], [BBHV08], [Ben11]** (Partial Differential Equation)
  - Evolution characterized by two parameters m and α
  - Metastatic module can be plugged on any tumoral model

Creation of a metastatic index : MI(t)

Results

Without therapy

Confrontation with a study of Koscielny [Ko84], [Barb11]

- 2648 patients treated for breast cancer at IGR

One patient = one set of parameters

Tumor size at diagnosis	% in silico of patients with at least one metastasis	% of patients with at least one meta from [TU 84]
1,5 cm – 2,5 cm	25,6 %	25%
4,5 cm – 5,5 cm	67,25 %	65 %
6,5 cm – 7,5 cm	76,5 %	78 %
9,5 cm – 10,5 cm	84%	85 %

Chemotherapy

Adapt number of cycles to each patient

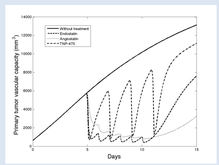
- Simulation of 4 virtual patients diagnosed T1N0M0
- Protocol : 6 cycles of 21 days (75mg DTX then 100mg EPI)
- Number of metastases after the treatment

m	6 cycles 126 days	9 cycles 189 days	12 cycles 252 days
1.3 x 10^-7	1	0	0
2.7 x 10^-7	2	1	0
4.0 x 10^ -7	3	2	1
6.1 x 10^-7	5	4	3

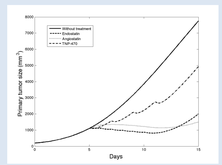
Anti-angiogenic monotherapy

Primary tumor (mice experiments) [Folk99]

- Endostatine 20 mg/kg/day
- Angiostatine 20 mg/kg/day
- TNP-470 30 mg/kg/qod

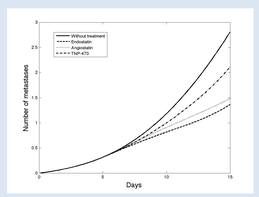


Vascular capacity



Tumoral growth

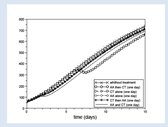
Metastases [Ben11]



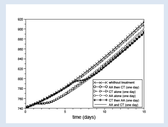
Number of metastases

Combined Anti-Angiogenic + Cytotoxic therapy [BCCEH11]

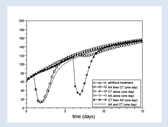
- Stable and unstable vessels ➞ quality of the vasculature
- Order of administration?



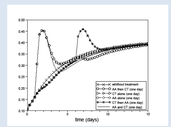
Tumoral growth



Stable vessels

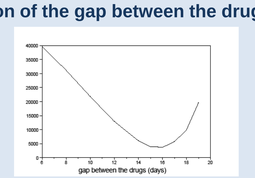


Unstable vessels



Quality of the vasculature

Optimization of the gap between the drugs



Final tumor size VS time gap between drugs (AA first)

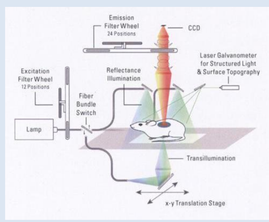
Conclusion

One of the main issue in cancer therapy is to evaluate the **metastatic risk** of the patient. Determining the best regimen and optimal dosing schedule is still an unsolved question in various clinical settings. Oncogenetics, pharmacogenomics and pharmacogenetics are new tools increasingly used that are dedicated to providing biomarkers for treatment efficacy and tolerance. Similarly, mathematical modeling could help to provide valuable information to the physician.

Another clinical open question is the optimization of combined therapies involving chemotherapy and anti-angiogenic drugs. Our results, based on simulations of a mathematical model, suggest the existence of an **optimal time gap** between administration of the two drugs, when the anti-angiogenic is administrated first. This time gap could be computed using our model, depending on each patient's parameters.

These theoretical, *in silico* results have to be **validated** by confrontation with data. We are currently performing mice experiments on xenograft mice for which we measure the number and size of metastatic colonies. The following steps are :

- Step 1 : Estimation of the model parameters and fit to the data
- Step 2 : Evaluation of the predictive performances. Statistical treatment of the results in terms of inter-animal variability, ….



Mice model : In vivo 3D imagery with bioluminescence (IVIS-Spectrum, Caliper Life Science) with support of ANR-09-BLAN-0217-01 « MEMOREX_PK » and ARC.

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