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

Sébastien Benzekry
Work in collaboration with the group of mathematical modeling in oncology of Marseille

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Clinical problematics

- “Metastasis is the main cause of death in cancer disease”
  *Weinberg, 2006*

- Metastatic cancers are **systemic diseases** which have to be thought at the **organism scale**.

- Micrometastases (size $< 10^7$ cells) invisible with imaging techniques. How to predict their evolution and administer adjuvant therapy (after surgery) without seeing anything?

- What is the best **scheduling** for: chemotherapy (CT), anti-angiogenics (AA), CT + AA?

**The tools**

- A ”simple” modelling (with **few parameters**)
  - of the disease (tumoral and/or metastatic evolution)
    - tumoral growth model (ODE)
    - renewal model for the metastases (PDE)
Cancer as a diffuse disease: **continuum** between localized pathology and metastatic cancer.
Mathematical models

- **Primary tumor growth (ODEs)**
  - Gompertz. Model used in the phase I trial only cancer cells ⇒ CT 
    
    You et al., ASCO 2007
  - Hahnfeldt - Folkman cancer cells + blood vessels ⇒ CT + AA 
    
    Hahnfeldt et al., Cancer Research 1999
  - New model cancer cells + stable/unstable vessels ⇒ CT+AA interactions 
    
    Benzekry et al., 2011

- **Metastatic population (PDEs)**
  - Evolution characterized by two parameters: metastatic aggressiveness $m$ fractal dimension of the vasculature $\alpha$ 
  - Metastatic module can be plugged on any tumoral model 
  - Creation of a **Metastatic Index**
Confrontation with a study of Koscielny, Tubiana & al.

Verga PhD thesis

- 2648 patients treated for breast cancer at the IGR between 1954 and 1972.

- Proportion of patients which develop at least one visible metastasis in terms of the initial tumor size.

**One patient = One set of parameters**

<table>
<thead>
<tr>
<th>Primary tumor size</th>
<th>% computed by our model</th>
<th>% observed by Koscielny</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 2.5 cm</td>
<td>25.5%</td>
<td>27%</td>
</tr>
<tr>
<td>2.5 - 3.5 cm</td>
<td>44.25%</td>
<td>42%</td>
</tr>
<tr>
<td>3.5 - 4.5 cm</td>
<td>60.5%</td>
<td>56.7%</td>
</tr>
<tr>
<td>4.5 - 5.5 cm</td>
<td>68.6%</td>
<td>66.5%</td>
</tr>
<tr>
<td>5.5 - 6.5 cm</td>
<td>75.5%</td>
<td>72.8%</td>
</tr>
<tr>
<td>6.5 - 7.5 cm</td>
<td>78.25%</td>
<td>83.8%</td>
</tr>
<tr>
<td>7.5 - 8.5 cm</td>
<td>83.25%</td>
<td>81.3%</td>
</tr>
<tr>
<td>&gt;8.5 cm</td>
<td>89.25%</td>
<td>92%</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy

Barbolosi, Benabdallah, Hubert, Verga (2010)

Take into account inter-individual variability

- We simulate 10 **virtual patients** with breast cancer classified T1N0M0.
- Protocol from **Viens & al., Am. J. Clin. Onc. 2001**: 6 cycles of 21 days (75mg of DTX then 100mg d’EPI) VS optimized protocol
- Number of visible metastases ($> 10^8$ cel.) 5 years after the end of the treatment.
- Adapt the number of cycles to each patient

<table>
<thead>
<tr>
<th>$m$</th>
<th>Viens Protocol</th>
<th>Optimized protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 cycles</td>
<td>9 cycles</td>
</tr>
<tr>
<td></td>
<td>126 jours</td>
<td>189 jours</td>
</tr>
<tr>
<td>$1.3 \times 10^{-7}$</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$2.7 \times 10^{-7}$</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>$4.0 \times 10^{-7}$</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>$6.1 \times 10^{-7}$</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Anti-angiogenic monotherapy

Testing the drugs from **Hahnfeldt et al., Cancer Res. 99** (mice data):

- Endostatine 20 mg/kg/day
- Angiostatine 20 mg/kg/day
- TNP-470 30 mg/kg/q.o.d

**Graphs:**
- Vascular capacity
- Tumoral growth
- Metastatic evolution
CT/AA combination. Order of administration?

Tumor size
CT/AA combination. Optimization of the time gap between the drugs.

Final tumor size VS time gap between AA and CT
Example of metronomic administration for breast cancer, adapted from Baruchel & al., Eur. J. Cancer 2005

- Maximal Tolerate Dose (MTD) : DTX 100 mg at day 0.
- Metronomic for DTX : 10 mg per day, every day.

- Long term advantage of metronomic therapy.
- If the dose of the drug is too low (< 8 mg), the treatment is ineffective.

Tumoral growth | Vascular capacity | Visible metastases
Conclusion

- The **metastatic index** derived from our model could be used to refine existing classifications.
- The best drug/schedule can be different for primary tumor and metastases.
- Our mathematical model for CT/AA combination suggests the existence of an **optimal time gap** between AA and CT.

Perspectives

- The theoretical, *in silico* results have to be **validated** by confrontation with data.
- We are currently performing mice experiments (ANR MEMOREX-PK project)
Thematic school - Present challenges of mathematics in oncology and biology of cancer: Modeling and mathematical analysis

CIRM, Marseille France
March 19-23, 2012

Organizing committee:
A. Benabdallah
S. Benzekry
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- Contacts: mcc@latp.univ-mrs.fr
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benzekry@phare.normalesup.org