Tumor Growth rates to better capture therapeutic activity in cancer patients

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Statistical and biomedical models for imaging in cancer
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Background

Current decision making (go/no go decision) in early drug development relies mostly on:
RECIST for molecular targeted agents
irRC for Immune checkpoint blockers (IO : immuno oncology)

Contextual difficulties of phase 1 trials:
small number of pts
molecular profile poorly known
Difficulties related to RECIST:
arbitrary cut-offs (-20%, +30%)
most patients classified as Stable Disease (NOT informative group)
Inconstant correlation with outcome (OS/PFS)
No discrimination between treatment-effect and the course of the disease

Difficulties related to the irRC:
need two consecutive evaluations 4 wks apart (delay in evaluation)
2 dimensional (more complicated, more errors, require training)
arbitrary cut-off
validated in melanoma only
In the current situation (RECIST, iRRC), pre-treatment tumor kinetics are unknown.
Pre-treatment heterogeneity is substantial

Question: can we use the pre-treatment tumor kinetics to infer therapeutic activity?
Integrating pre-treatment kinetics allows to infer the therapeutic activity of a given experimental regimen. Before the trial, there is a wash-out period where the growth rate is measured. During the first cycle of the experimental regimen, the growth rate is evaluated. The opportunity to compute the variation in the tumor growth variations along the entire treatment sequence is shown.

Evidence of “Treatment activity”

Growth rate Before the trial
Growth rate During first cycle

Gomez-Roca et al, Eur J Cancer 2011
Ferté et al, Clin Cancer Res 2014
Ferté et al, Eur Urol 2014
Hypothetical case #1 of a fast-growing tumor treated by an active drug

- **Decrease in Tumor Growth Rate**
- **RECIST >20%**

Risk of discarding the patient of the trial for progressive disease, while there are signs of drug antitumor activity.

Risk of stopping the development of a potential active drug.
Hypothetical case #2 of a slow-growing tumor treated by an inactive drug

Before Baseline First eval.

Wash-out Drug

Growth rate

Before the trial During first cycle

0% 20%

Stability of the tumor kinetics and Stable Disease (as per RECIST)

→ Risk of assuming that the drug is benefiting to the patient, whereas there is a stability in the tumor growth kinetics without drug efficacy.

→ Risk of retaining the patient retained in the trial with evident Safety, ethical, cost issues

No evidence of Treatment effect
Tumor Growth Rate (TGR)

- Tumor size (D) was defined as the sum of the largest diameters (RECIST sums).
- Let t be the time between each tumor evaluation.
- Tumor volume (V) was approximated by $V = \frac{4}{3} \pi R^3$, where $R = D/2$.

\[
TGR = \frac{dV}{dt} = \frac{\ln(V_t/V_0)}{dt}
\]

(assuming the tumor growth follows an exponential growth)

- TGR is expressed as an increase in tumor volume during 1 month.
applications in oncology

- molecular targeted agents
- immune checkpoints blockers (i.e. IO agents)

- 209 ph 1 pts treated by MTA not IO agents
- 136 + 902 ph 3 pts treated by MTA not IO agents
- 112 pts treated by IO agents not MTA agents
205 pts enrolled in 19 phase I trials at Gustave Roussy

• To describe the variation of TGR along the introduction of experimental therapeutics in phase I patients.

• To compute the associations between TGR, the most commonly used prognostic score (RMH) and the outcome.

• To evaluate the effect of treatment, prognostic scores, histology, and the number of previous treatment lines on TGR.

Ferté et al, Clin Cancer Res 2013
At the first evaluation, 78% of patients are classified as Stable Disease.
At the first evaluation, 77% of patients (158 out of 205 pts) exhibit a decrease of TGR

Pairwise comparison: p value < 1e-7 (Wilcoxon rank-signed test)

Each patient is used as his/her own control

RECIST
- PD
- SD
- PR

Ferté et al, Clin Cancer Res 2013
Distribution of the RECIST score according to the variation of TGR

<table>
<thead>
<tr>
<th></th>
<th>Decrease of TGR</th>
<th>Increase of TGR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response (PR)</td>
<td>19</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>106</td>
<td>24</td>
<td>130</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>34</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>42</td>
<td>201</td>
</tr>
</tbody>
</table>

→ Most patients are classified as SD, which is NOT informative

→ “mis-identification” 140 out of 159 pts (88%) that exhibit a decrease of TGR

→ “mis-identification” 24 out of 42 pts (57%) that exhibit an increase of TGR
Higher TGR during reference period is associated with progression in patients treated by MTA

Kruskal–Wallis test. P=0.004

For MTA agents:
- fast growing tumors before treatment are more prone to be progressive at the first evaluation
- integrating pre-treatment kinetics is relevant
What about the occurrence of ‘new lesions’?

- TGR is based on the sum of the RECIST diameters and thus has the same limitations than RECIST on ‘new lesions’. Similarly to RECIST, TGR does not capture new lesions.

- TGR provides information on the antitumor activity on the target lesions.

- New lesions observed at 1st evaluation are probably micro metastases already present before the treatment onset and may be driven by different biological state (i.e. epithelial mesenchymal transition).
TGR decrease (REFERENCE - EXPERIMENTAL) is associated with PFS (multivariate analysis)

<table>
<thead>
<tr>
<th></th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Decrease of Tumor Growth Rate*</td>
<td>0.91</td>
<td>0.85 - 0.96</td>
</tr>
<tr>
<td>RMH prognostic score</td>
<td>1.42</td>
<td>0.96 - 2.08</td>
</tr>
</tbody>
</table>

→ Every 10% decrease between TGR REFERENCE and TGR EXPERIMENTAL results in a 8% decrease in the progression hazard.

→ The fact that the decrease in TGR is associated with PFS but not with OS suggests the prominent influence of the experimental regimen of the TGR.

Ferté et al, Clin Cancer Res 2013
The experimental regimen is the only variable independently associated with the decrease of TGR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (estimate)</th>
<th>Significance (P Value)</th>
<th>proportion of variance explained ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial (Overall variable)</td>
<td>-</td>
<td>&lt;0.00001</td>
<td>31.1 %</td>
</tr>
<tr>
<td>Intercept (reference)</td>
<td>-0.46</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Trial #2: HSP inhib.</td>
<td>-2.36</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Trial #3: Cell-Cycle inhib.</td>
<td>1.42</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Trial #4: PI3K/Akt/mTOR inhib.</td>
<td>-2.49</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Trial #5: Antiangiogenic</td>
<td>2.89</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Trial #6: HDAC inhib.</td>
<td>2.13</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Trial #7: PI3K/Akt/mTOR inhib.</td>
<td>4.20</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Trial #8: MEK inhib.</td>
<td>5.36</td>
<td>0.0002</td>
<td></td>
</tr>
<tr>
<td>Trial #9: Antiangiogenic</td>
<td>4.65</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Trial #10: HER family inhibitor</td>
<td>3.30</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Trial #11: Antiangiogenic</td>
<td>4.35</td>
<td>0.00005</td>
<td></td>
</tr>
<tr>
<td>Trial #12: PI3K/Akt/mTOR inhib.</td>
<td>4.95</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>Number of previous lines of chemotherapy (N)</td>
<td>0.04</td>
<td>0.82</td>
<td>0.01 %</td>
</tr>
<tr>
<td>RMH prognostic score low score (0-1) vs.high score(2-3)</td>
<td>0.04</td>
<td>0.95</td>
<td>0.02 %</td>
</tr>
<tr>
<td>Age (N)</td>
<td>-0.009</td>
<td>0.67</td>
<td>0.08 %</td>
</tr>
</tbody>
</table>

NB: No interaction was observed between the variables trial type, previous lines of chemotherapy, age and RMH (ANOVA, data not shown)
TGR profiling reveals trial specific patterns of drug activity
(green circles = trials with evidence of antitumor activity)

- Trial #1: HSP inhib. (n=8, P=0.45)
- Trial #2: Cell-Cycle inhib. (n=21, P=0.4)
- Trial #3: Cell-Cycle inhib. (n=12, P=0.3)
- Trial #4: PI3K/Akt/mTOR inhib. (n=9, P=0.3)
- Trial #5: PI3K/Akt/mTOR inhib. (n=8, P=0.11)
- Trial #6: HDAC inhib. (n=20, P=0.097)
- Trial #7: PI3K/Akt/mTOR inhib. (n=12, P=0.00049)
- Trial #8: MEK inhib. (n=13, P=0.00024)
- Trial #9: Antiangiogenic (n=13, P=0.00024)
- Trial #10: HER family inhibitor (n=17, P=0.00011)
- Trial #11: Antiangiogenic (n=20, P=1.3e-05)
- Trial #12: PI3K/Akt/mTOR inhib. (n=19, P=7.6e-06)

P values computed from pairwise wilcoxon signed-rank tests. Only trials with n>8 pts were analyzed.

Ferté et al, Clin Cancer Res 2013
what about patients not treated in phase 1 trials?

136 + 902 ph 3 pts treated by MTA not IO agents
Expand to specific treatment periods (pairwise comparisons)

Ferté et al, Eur Urol 2013
Tumor Growth Rate Provides Useful Information to Evaluate Sorafenib and Everolimus Treatment in Metastatic Renal Cell Carcinoma Patients: An Integrated Analysis of the TARGET and RECORD Phase 3 Trial Data.

**TARGET phase III trial: Sorafenib vs. placebo**
- IGR pts n=84 pts
- entire TARGET cohort n=902 pts

**RECORD-1 phase III trial: Everolimus vs placebo**
- IGR pts n=52 pts

_Ferté et al, Eur Urol 2013_
Pairwise comparisons of TGR in pts enrolled in the TARGET trial (sorafenib vs. placebo)

Ferté et al, Eur Urol 2013
Pairwise comparisons of TGR in pts enrolled in the RECORD-1 trial (everolimus vs. placebo)

136 + 902 ph 3 pts treated by MTA not IO agents

Ferté et al, Eur Urol 2013
what about immune checkpoint blockers?
pseudoprogression under immune checkpoint blockers

stable disease or partial response after two consecutive observations per irRC

AND

who exhibited tumor progression at the first evaluation (RECIST)

112 pts treated by IO agents not MTA
Most of PSPD patients exhibit a decrease of TGR between REFERENCE and EXPERIMENTAL periods.

TGR during the EXPERIMENTAL period

TGR during the REFERENCE period

INCREASE in TGR
"No antitumor activity"

DECREASE in TGR
"Antitumor activity"

Variation of Tumor Growth Rate (TGR) across the Reference and Experimental periods

Most of PSPD patients exhibit a decrease of TGR between REFERENCE and EXPERIMENTAL periods.

112 pts treated by IO agents not MTA
Variation of TGR between REFERENCE and EXPERIMENTAL periods

Variation of TGR (%)

wilcoxon test
P = 0.0013
wilcoxon test
P = 0.0051
wilcoxon test
P = 5.2e–08

modified irRC classes

CR or PR
PSPD
SD
PD

112 pts treated by IO agents not MTA
Different results from those observed with molecular targeted agents (Ferté et al, CCR 2014):
- is it related to the mechanism of action of immune checkpoint blockers?
- is the TGR during the EXPERIMENTAL period responsible for the variation of TGR?
TGR on treatment: informative!

112 pts treated by IO agents not MTA

modified irRC classes

NB: target lesions only
Conclusions

• For MTA agents only:
  - The variation of TGR (REFERENCE to EXPERIMENTAL periods) allows to early infer the therapeutic activity of drugs.
  - Higher TGR during the REFERENCE period is associated with higher risk of tumor progression.

• For Immune checkpoint inhibitors only, it seems that:
  - The TGR during the EXPERIMENTAL period only allows to early identify therapeutic activity of these drugs.
  - The occurrence new lesions of new lesions at fist eval do not automatically mean absence of therapeutic activity of the drug.

Confirmatory studies are warranted
• Monitoring tumor kinetics along the treatment sequence is critical whatever the treatment type

• Tumor kinetics to provide insights of expected benefit of phase II-II (rather than predict survival)