

Optimizing Chemotherapeutic Dose-Schedule (CDS) by Norton-Simon Modeling: Capecitabine (Xeloda®)

Abstract
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ABSTRACT

INTRODUCTION: CDS is usually determined by time-consuming, costly laboratory and clinical experiments. Optimizing CDS more efficiently could maximize the benefit/toxicity ratio and speed drug development. Hence, we studied Xeloda® (X), an oral tumor-activated fluoropyrimidine carbamate active against metastatic breast and colorectal carcinoma, now used alone or in combination twice daily for 14 consecutive days every 3 weeks.

METHODS: Mice bearing MX-1 or MAXF401 human breast cancer xenografts received 6 weeks of X on one of 4 CDSs (days on/off): 14/7, 5/2, 2/5, 7/7. Each CDS evaluated 4 dose levels plus control, and all were effective at an appropriate dose (Yanagisawa, Proc. AACR #3086, 2004). We analyzed the data for the approved (14/7) CDS by measuring at each time point after the initiation of therapy the ratio of the (data-derived) expected Gompertzian growth rate in the unperturbed (control) state compared with that observed in the treated state. Curve-fitting was by non-linear mixed-effect population modeling using NONMEM software.

RESULTS and CONCLUSION: The time point of maximum impact of treatment is when the absolute value of the ratio of growth rates (perturbed/control) is greatest as determined by methods of calculus. For all dose levels analyzed this point averaged from 8.3-10.1 days into therapy, with the impact of treatment decreasing thereafter despite administration for 14 days. Schedules shorter than 14 days in length can deliver higher dose levels safely. Hence administering one week of treatment as often as clinically feasible (dose density) should provide optimal benefit vs. toxicity. This will be examined in a phase I-II clinical trial.

BACKGROUND

- Oral fluoropyrimidine
- Active in breast and colorectal cancer
- Usual dosing: BID x 14 consecutive days q 21 days

Chemotherapeutic dose schedule (CDS) usually determined by:

- Empiricism
- Laboratory experiments
- Clinical trials

Optimized CDS could expedite drug development by maximizing the benefit/safety ratio

- Yanagisawa et al* compared different schedules of capecitabine and used four dose levels (+ control) adjusted to the same total dosage over 6 weeks. This did not allow us to compare the different treatment schedules with each other in terms of dosage, toxicity, and efficacy. Our current report includes a new series of experiments designed to explore different schedules at four dose levels (+control) but also allowed for comparisons among different treatment schedules. The same daily dosages were given in each of the schedules for each dose level. This led to different total dosages over a 6-week treatment period.

*Yanagisawa, Proc. AACR #3086, 2004

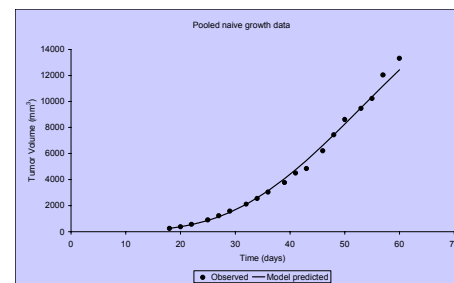
OBJECTIVE

- To demonstrate that mathematical modeling using the Norton/Simon model can predict maximal drug effect, thereby determining CDS for optimal efficacy to toxicity for capecitabine (Xeloda®).

METHODS

- Apply Gompertzian growth model to naive tumor growth data for the standard schedule of capecitabine (14 days on/7 day off) in animal model of breast cancer (14/7 CDS was chosen because it is FDA approved and 14 days of ongoing treatment allows sustained observation of drug effect measured as reduction of tumor volume.)
- Estimate drug effect for 1.5 and 2.25 mmol/kg/day groups during first cycle of treatment
- Determine when drug effect is maximal
- Data were analyzed using a non-linear mixed effects population modeling approach with the NONMEM software.
- Gompertzian growth model (Tumor volume (TV)): $dTV/dt = \alpha \cdot TV - ((\alpha/\log(TV_{inf})) \cdot TV \cdot \log(TV))$
- Drug effect (DE) model: $dTV/dt = (\alpha \cdot TV - ((\alpha/\log(TV_{inf})) \cdot TV \cdot \log(TV))) \cdot (1-DE)$

Figure 1: Pooled data of observed tumor volume of breast cancer in xenograft models (MX-1) compared with predicted tumor volume according to the Gompertzian model.



METHODS

Figure 2: Pooled data of tumor volume over time for xenograft models (MX-1) treated with capecitabine at two doses (1.5 mmol/kg/day and 2.25 mmol/kg/day) on a 14/7 CDS

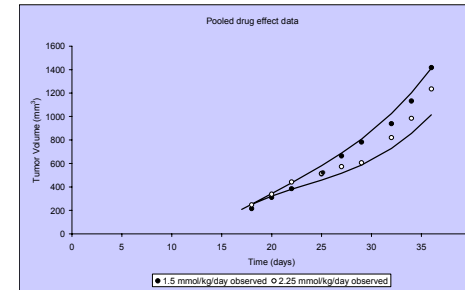


Figure 3: Impact of treatment for xenograft models (MX-1) treated with capecitabine at a dose of 1.5 mmol/kg/day on a 14/7 CDS.

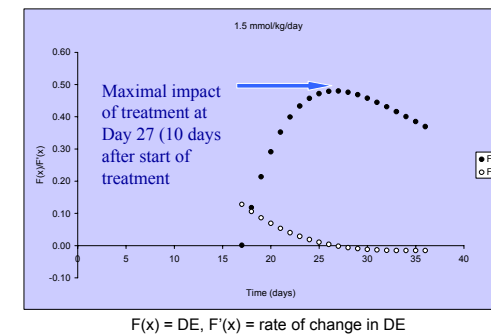
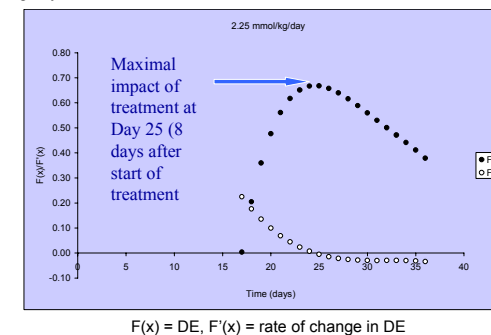


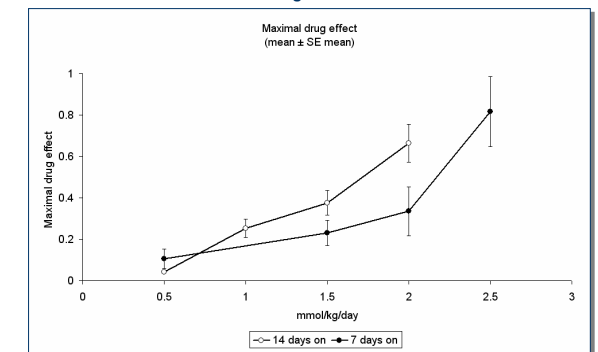
Figure 4: Impact of treatment for xenograft models (MX-1) treated with capecitabine at a dose of 2.25 mmol/kg/day on a 14/7 CDS.



RESULTS

- Time point of maximum impact (TPMI) of treatment: when the absolute value of the ratio of growth rates (perturbed/control) is greatest.
- For the two dose levels analyzed, this point averaged from 8.3-10.1 days into therapy.
- The impact of drug effect (DE) decreases after TPMI despite continued therapy.
- A follow-up experiment compared 7 days on and 7 days off therapy with "standard" dosing (see figure below).
- 7on/7off CDS allowed delivery of a higher daily dose yielding increased maximal DE compared with 14on/7off CDS (Figure 5).

Figure 5



CONCLUSIONS

- Administration of capecitabine in 7on/7off CDS vs 14on/7off CDS allows for:
 - Higher daily dosage (dose dense)
 - Increased efficacy
 - Optimized clinical benefit.
- A phase I/II trial of capecitabine 7on/7off CDS in patients with metastatic breast cancer is ongoing to confirm these findings.

ACKNOWLEDGMENT

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