Activity of Capecitabine and Docetaxel Doublets With and Without Trastuzumab in a Breast Cancer Xenograft Model

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Background

Capecitabine and docetaxel have both demonstrated considerable single-agent activity in breast cancer1,2. In preclinical models, docetaxel upregulates thymidine phosphorylase (TP), resulting in synergistic anti-tumor activity with capecitabine3. In a randomized phase II trial, overall survival time to disease progression, and response rate were significantly improved with the addition of capecitabine to docetaxel4. The humanized anti-HER2 monoclonal antibody trastuzumab (H), is considered a standard of care in patients with HER2+ breast cancer5. Capecitabine plus H shows at least additive activity in vivo6 and the combination has consistently demonstrated high activity in clinical studies7,8.

We evaluated doublet and triplet combinations of capecitabine plus docetaxel ± H in a KPL-4 human breast cancer xenograft model.

Materials and Methods

Part I: Capecitabine and Docetaxel Combination vs Monotherapy

— Primary objective to evaluate capecitabine (days 1-14 every 21 days) in combination with weekly docetaxel in estrogen receptor-negative, HER2+ KPL-4 breast cancer xenograft models
— The optimal doses (OD) in nude mice were established as 400 mg/kg/day for 4 days (for capecitabine)9 and 20 mg/kg/week for docetaxel (data not shown)
— Treatment: combinations of
  — Vehicle orally once-daily, days 1-14, q2d ip tertiarly: days 1, 8, 15, q2d
  — Capecitabine 200 mg/kg (X) or 400 mg/kg (X) orally once-daily: days 1-14, q2d10
  — Docetaxel 10 mg/kg (T) or 20 mg/kg (T) ip tertiarly: days 1, 8, and 15, q2d11
— Increase in lifespan (ILS) was calculated using the formula below, with a survival cut-off of 500 mm

\[ ILS = \frac{\text{Tumor Growth Inhibition (TGI)} \times 100}{\text{median days of death}} \times \text{median days of death} \]

— Median survival was calculated using the Kaplan-Meier method
— Morbidity was determined as 20% body weight loss
— On day 7 after treatment, tumors from 5 mice from the control arm and the X and T monotherapy arms were harvested for assessment of the effects on TP using immunohistochemistry

Part II: Addition of Trastuzumab to Capecitabine/Docetaxel Combination

— In the second part of the study, the optimal doublet from the first part was tested with or without H.
— Trastuzumab 20 mg/kg intraperitoneally 2x/week x 6

Results

Part I: Capecitabine and Docetaxel Combination vs Monotherapy

— None of the treatments resulted in morbidity (Figure 1)
— However: 1/2X + T led to drug-related mortality in 3 of 10 mice. Therefore X + T (both doses) was not evaluated as it was assumed to be toxic

Table 2 shows interim statistical comparison of capecitabine/docetaxel doublets ± H to increased toxicity
— The combination of 1/2X and 1/2T was significantly superior to other monotherapy for both
  — TGI (t-test ANOVA, post-hoc Bonferroni, P < 0.05 for 1/2X or 0.001 for optimal dose; Mann-Whitney Rank Sum)
  — ILS (P = 0.0001 for all comparisons, Breslow-Gehan-Wilcoxon)
— TP was induced by T monotherapy as previously reported; this TP induction was significant with 1/2X and T (data not shown)

Part II: Addition of Trastuzumab to Capecitabine/Docetaxel Combination

— 1/2X and 1/2T was well tolerated (Figure 3), resulting in neither morbidity nor mortality
— In all treatment groups, there were significant differences from the control group in % TGI (P < 0.001) and % ILS (P < 0.0001)
— Figure 4 shows anti-tumor activity of doublet and triplet combinations
— At day 370, complete responses were maintained in 4/10 of the X + 1/2T + H group (ILS > 1270%, analysis ongoing)
— Cumulative survival with capecitabine/docetaxel doublets ± H is shown in Figure 5
— Analysis is ongoing with the triple combination of X + 1/2T + H

Conclusions

— The addition of H to capecitabine/docetaxel doublets inhibits tumor growth and increases survival
— Our findings support the use of the highest capecitabine dose density in triplet combinations to sustain tumor responses. Increased docetaxel dose generally led to increased toxicity
— Based on these results, clinical evaluation of capecitabine/docetaxel doublets (+ H in HER2+ disease) in the neoadjuvant setting is ongoing
— First efficacy and safety results are presented at this meeting (Poster #2.129)

References