Ixabepilone and Lapatinib for HER2 positive advanced breast cancer; Preclinical rationale and Phase I trial

P. N. Mainwaring  T. Nguyen, C. Pike, O. Verter, Mater Health Services, Brisbane, Australia

Study Summary

Three different breast cancer cell lines BT-474, SK-BR3 (HER2 over-expressed) and MCF-7 (control; non-amplified), were seeded in 96-well plates. After 24 hrs, different combinations of irinotecan, paclitaxel and the dual anti-EGFR/HER2 tyrosine kinase, lapatinib, were added to each well. The effect of these drugs on the cells after 0, 3, 24, 48 and 120 hours of exposure were determined using MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium) viability assay. The drugs whose efficacy was proven in MCF-7 cells were studied in detail on the xCELLigence cell analysis system. These data recapitulated the MTT data and showed that combinations of ixabepilone, lapatinib, trastuzumab or paclitaxel were more effective single-agents against BT-474 and SK-BR3 cells than with trastuzumab combinations.

Results and Discussion

Figure 1: Single Drugs: The effect of single-drugs lapatinib, trastuzumab, paclitaxel, and ixabepilone on proliferation in BT-474 (HER2 over-expressed), SK-BR3 and MCF-7 cell lines.

- Ixabepilone + trastuzumab significantly reduced proliferation p < 0.001 at 120 hrs.
- Paclitaxel + lapatinib significantly reduced proliferation p < 0.001 at 120 hrs.
- Ixabepilone + trastuzumab significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.
- Paclitaxel + lapatinib significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.

Figure 2: Drug Combinations: The effect of drug combinations lapatinib + trastuzumab, lapatinib + paclitaxel, ixabepilone + trastuzumab, and ixabepilone + paclitaxel on proliferation in BT-474 (HER2 over-expressed), SK-BR3 and MCF-7 cell lines.

- Lapatinib + trastuzumab significantly reduced proliferation p < 0.001 at 120 hrs.
- Lapatinib + paclitaxel significantly reduced proliferation p < 0.001 at 120 hrs.
- Ixabepilone + trastuzumab significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.
- Ixabepilone + paclitaxel significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.

Background

Ixabepilone is a microtubule-inhibiting agent that is approved for the treatment of hormone-refractory, metastatic breast cancer. Ixabepilone works by stabilizing microtubules during mitosis leading to cell cycle arrest at the G2 – M phase and apoptosis (3).

Methods: Pre-Clinical - MTT Assay

Three different breast cancer cell lines BT-474, SK-BR3, and MCF-7 were seeded in 96-well plates. Cells were treated with various concentrations of irinotecan, paclitaxel and lapatinib and combinations thereof in a parallel dilution assay. After 24 hrs, cell viability was measured by the MTT assay. The results were plotted and compared to a standard curve and the IC50 was calculated. The results showed that lapatinib was more effective against HT-29 cells than with irinotecan and paclitaxel in vitro.

Aim

To evaluate the efficacy of the ixabepilone and the dual anti-EGFR/HER2 tyrosine kinase, lapatinib, in combination with irinotecan and paclitaxel, in various breast cancer cell lines.

Results and Discussion (cont'd)

- Lapatinib + paclitaxel significantly reduced proliferation p < 0.001 at 120 hrs.
- Lapatinib + trastuzumab significantly reduced proliferation p < 0.001 at 120 hrs.
- Ixabepilone + trastuzumab significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.
- Ixabepilone + paclitaxel significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.

Conclusions

Ixabepilone + trastuzumab significantly reduced proliferation p < 0.001 at 120 hrs.
- Paclitaxel + lapatinib significantly reduced proliferation p < 0.001 at 120 hrs.
- Ixabepilone + trastuzumab significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.
- Paclitaxel + lapatinib significantly reduced proliferation of all cell lines p < 0.001 at 120 hrs.

Future Directions

Ixabepilone + lapatinib are being evaluated in the phase I trial (ATHENA study) for visceral disease (T not limited) in combination with secondary liver surgery. The combination of ixabepilone + lapatinib has been shown to be well tolerated in a phase I trial and is expected to have activity in a variety of solid and hematologic malignancies.

References