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Title: Detrimental effects of sequential compared to concurrent treatment of Pertuzumab plus T-DM1 in HER2+ breast cancer cell lines

Body: Background. Pertuzumab and T-DM1 are two recently approved monoclonal antibody based therapies targeting HER2+ breast cancer. Pertuzumab interferes with dimerization of HER family members, while T-DM1 binds to HER2 and interferes with its oncogenic function while also specifically delivering a cytotoxic agent (emtansine). One arm of the I-SPY 2 clinical trial is to investigate the efficacy of a combination Pertuzumab plus T-DM1 in HER2+ breast cancer patients. Methods. We performed pre-clinical screening of response to each agent alone and in combination in a set of 21 HER2+ breast cancer cell lines, with an end goal of identifying markers of response to the therapies. There were five treatment regimens employed in the initial screen: i) pertuzumab alone for 72 h; ii) T-DM1 alone for 72h; iii) pertuzumab plus T-DM1 concurrently for 72h; iv) pertuzumab for 24h followed by addition of T-DM1 for 48h more; and iv) T-DM1 for 24h followed by addition of pertuzumab for 48h more. Response was assessed using the Cell Titer Glo assay as a measure of cell viability. To assess the effects of drug combinations, we used a stringent measure of synergy and antagonism employing the median effect method of Chou and Talalay that included 95% confidence intervals to determine significance. Results. Initial screens showed that concurrent treatment of cells with pertuzumab plus T-DM1 gave significant synergistic interactions in 15/21 cell lines as measured by the median effect method, with combination indices (CI) less than 0.5 (and 95% upper confidence levels less than 1.0) for at least one drug concentration. However, 24h pretreatment with pertuzumab followed by T-DM1 significantly diminished the response of cells to T-DM1, resulting in significant antagonism in 17/21 cell lines test (CI>1.5, lower confidence level greater than 1). Since this could be due to a shorter exposure time to T-DM1, and since patients are scheduled to be treated with pertuzumab first followed by T-DM1 one hour later, we repeated the experiment with one hour between pertuzumab and T-DM1 rather than 24h. While the inhibitory effect was diminished, this treatment regimen still resulted in significant antagonism when T-DM1 was given 1 hour after pertuzumab in 5/5 cell lines tested, in contrast to concurrent pertuzumab plus T-DM1 treatment, which showed synergy. Conclusions. Pertuzumab plus T-DM1 appears to be beneficial when given concurrently, but pretreatment with pertuzumab appears to blunt the efficacy of T-DM1. This has important potential ramifications for patient treatment, and may further elucidate mechanisms of action for both compounds. Further testing will be necessary to determine whether these timing effects are operational in vivo and whether immune effects mitigate the antagonism.
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