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Farnesyl-transferase inhibitor R115,777 enhances tamoxifen inhibition of MCF-7 cell growth through estrogen receptor dependent and independent pathways

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Abstract

Introduction We have previously shown that FTI-277, a farnesyl transferase inhibitor (FTI), enhances the efficacy of tamoxifen (Tam) in inhibiting the proliferation of the estrogen dependent MCF-7 cell line. As the cellular response to Tam is the result of an inhibition of both estrogen receptor-dependent and -independent pathways, we have used the estrogen receptor selective anti-estrogen ICI182,780 and N-pyrrolidine(-phenylmethyl-phenoxy)-ethanamine-HCl (PBPE), a selective ligand of anti-estrogen binding site (AEBS), to dissect out the mechanism(s) associated with the observed additivity resulting from combination treatment with FTI-277 and Tam. Moreover, for these studies, FTI-277 has been replaced by R115,777, a FTI currently in phase III clinical trials.

Methods The quantitative sulphorhodamine B (SRB) colorimetric assay was used to determine the growth inhibitory effect of agents on MCF-7 cells. Dose response interactions between R115,777-Tam, R115,777-ICI182,780 and R115,777-PBPE were evaluated, at the IC_{50} point, using the isobologram method. Apoptotic cell death (DNA fragmentation, nucleus condensation and cytokeratin 18 cleavage) and inhibition of the mevalonate pathway (western blot) were also determined.

Results Combinations of the specific FTI R115,777 with either ICI182,780 or PBPE exhibit a synergistic effect on MCF-7 cell growth inhibition, while its combination with Tam is additive, as previously reported for FTI-277. Apoptosis is detected after treatment with combinations of R115,777 with either Tam or PBPE but not with ICI182,780, suggesting that each combination inhibits cell proliferation by different mechanisms. Even though the ER pathway has not yet been deciphered, it is shown here that the AEBS pathway is able to interfere with the mevalonate pathway at the level of protein farnesylation.

Conclusion Overall, this work reveals that combinations of R115,777 with either selective ER ligands or a selective AEBS ligand are able to induce large increases in their anti-proliferative activities on MCF-7 cells. Moreover, these results suggest that it may be of definite interest to evaluate combinations of R115,777 with different anti-estrogens in the treatment of ER positive breast tumours. Based on these experimental data, such combinations may prove beneficial in different clinical scenarios or when used in specific sequences; studying the combination of R115,777 with ICI182,780 for early treatment and reserving combinations with either Tam or a selective AEBS ligand, such as BMS-217380-01, for more resistant disease.

Introduction

Tamoxifen (Tam) remains the most frequently prescribed agent for the treatment of hormone responsive breast cancer. Efficacy for Tam has been demonstrated in the treatment of all stages of breast cancer and it is also used as prevention therapy for women at high risk of developing breast cancer. Although Tam is effective initially in many patients, a major obstacle to its long-term use is tumour resistance. To resolve this problem, we decided to evaluate the effects of combining Tam with a farnesyl transferase inhibitor (FTI). Although the role of combination therapy versus sequential therapies with single agents remains controversial in the treatment of breast

AEBS = anti-estrogen binding site; ER = estrogen receptor; FTI = farnesyl transferase inhibitor; PBPE = N-pyrrolidine(-phenylmethyl-phenoxy)-ethanamine-HCl; PBS = phosphate-buffered saline; SRB = sulphorhodamine B; Tam = tamoxifen.