Hsp90 inhibitor 17-AAG reduces ErbB2 levels and inhibits proliferation of the trastuzumab resistant breast tumor cell line JIMT-1

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Abstract:

ErbB2, a member of the EGF receptor family of tyrosine kinases is overexpressed on many tumor cells of epithelial origin and is the molecular target of trastuzumab (Herceptin), the first humanized antibody used in the therapy of solid tumors. Trastuzumab, which is thought to act, at least in part, by downregulating ErbB2 expression is only effective in approximately 30-40% of ErbB2 positive breast tumors. Geldanamycin and its derivative 17-AAG are potential antitumor agents capable of downregulating client proteins of Hsp90, including ErbB2. To investigate the ability of 17-AAG to downregulate ErbB2 in trastuzumab resistant breast cancer cells and the possibility of 17-AAG and trastuzumab potentiating each other’s effect, the recently established trastuzumab resistant breast cancer cell line, JIMT-1 was compared to the known trastuzumab sensitive SKBR-3 line. Baseline and stimulus-evoked dimerization and activation levels of ErbB2, and the effects of trastuzumab and 17-AAG alone and in combination on cell proliferation and apoptosis, as well as on ErbB2 expression and phosphorylation have been measured. Baseline activation and amenability to activation and downregulation by trastuzumab was much lower in the resistant line. However, 17-AAG enhanced ErbB2 homodimerization after 5-10 min of treatment in both cell lines, and decreased proliferation with an IC50 of 70 nM for SKBR-3 and 10nM for JIMT-1. Thus, 17-AAG may be a useful drug in trastuzumab resistant ErbB2 overexpressing tumors. The antiproliferative effect of 17-AAG was positively correlated with phosphorylation and downregulation of ErbB2 and was dominated by apoptosis, although, especially at higher doses, necrosis was also present. Interestingly, IC50 values for ErbB2 downregulation and phosphorylation, in the 30-40 nM range, were not significantly different for the two cell lines. This observation and the negative correlation between resting ErbB2 levels and the antiproliferative effect of 17-AAG may indicate that activation of ErbB2 to some extent could counteract the overall cytostatic effect, especially at higher levels of ErbB2 expression. The usual therapeutic dose of trastuzumab did not change the IC50 of 17-AAG on the proliferation of either cell line, but nevertheless decreased overall ErbB2 phosphorylation and at low doses of 17-AAG further decreased cell growth in the sensitive SKBR-3, thus trastuzumab may be a good combination partner to counteract undesired activating effects of 17-AAG.

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