Abstract 1913: Soluble TNFα blockade overcomes lapatinib resistance and induces an innate immune response in HER2-positive breast cancer

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Abstract

Lapatinib (LAP), a dual EGFR/HER2 tyrosine kinase inhibitor, is used as second-line therapy in women with HER2+ breast cancer (BC), but less than 25% of the patients achieve an objective response. An alternative therapeutic approach is needed to overcome LAP resistance in women with metastatic HER2+ BC, particularly in patients with central nervous system (CNS) metastasis where large biological molecules are not effective. Previously, we reported that women with HER2+ tumors that express transmembrane glycoprotein mucin 4 (MUC4) have worse survival, and that HER2+/MUC4+ cell lines resistant to trastuzumab (T) express higher levels of tumor necrosis factor α (TNF) than T-sensitive cell lines. In addition, we proved that inhibition of soluble TNF (sTNF) decreases the expression of MUC4 and reverses T resistance. The aim of this work is to evaluate the participation of sTNF and transmembrane TNF (tmTNF) in LAP resistance *in vivo* and in the anti-tumor innate immune response. We used the LAP-resistant human BC cell line JIMT-1 and compared etanercept (E), a fusion protein that non-selectively blocks both sTNF and tmTNF, with the dominant negative-TNF protein INB03 (DN), that neutralizes sTNF without affecting tmTNF. Nude mice bearing JIMT-1 tumors (~50 mm^3), received LAP (100 mg/kg) daily by oral gavage and IgG (5 mg/kg), E (5 mg/kg), DN (10 mg/kg), LAP+E or LAP+DN, twice a week i.p. Tumor volume was monitored routinely. At the

end of the experiment, tumor-infiltrating immune cells were evaluated by immunofluorescence and analyzed by flow cytometry. DN or E treatments did not exhibit any anti-tumor effect alone, but in combination with LAP (LAP+DN and LAP+E) tumor growth decreased in a 54% and 34% vs. IgG, respectively ($p<0.0001$). LAP+DN combination was significantly more effective in decreasing JIMT-1 tumor growth than LAP+E ($p<0.05$). Analysis of tumor-infiltrating immune cells showed that tumor growth inhibition was accompanied by an increase in NK cell activation and degranulation, and a decrease in monocytic-myeloid-derived suppressor cells in the tumor bed of LAP+E and LAP+DN treated groups ($p<0.01$, vs. IgG). This is the first report to show that TNF blockade is able to overcome LAP resistance. In addition, TNF neutralization together with LAP treatment unleashes an anti-tumor innate immune response. These data, combined with previous results, suggest that MUC4 expression in patients with HER2+ BC could act not only as a biomarker of T resistance but also of LAP resistance. Women with HER2+/MUC4+ tumors undergoing treatment with LAP would benefit from the combined administration of LAP with the selective sTNF inhibitor DN to help overcome resistance; a hypothesis to be tested in a clinical trial. This therapeutic strategy may be particularly useful in patients with CNS metastasis because LAP and DN cross the blood-brain-barrier.

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