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Dual HER-2/EGFR tyrosine kinase inhibitors

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Keywords

Breast cancer, dual tyrosine kinase inhibitor, EGFR, HER-2

Context

Cancer therapy has been changing from conventional nonspecific treatments to selective targeted therapies. EGFR and HER-2 are co-expressed in a variety of tumour types. The available tyrosine kinase inhibitors are moving to phase II and phase III clinical trials, with a favourable toxicity profile. There is a biological rational for attempting to block the growth factors signalling pathways at several sites simultaneously. The use of a dual inhibitor of both EGFR and HER-2 could provide a therapeutic benefit to a broad patient population.

Significant findings

The authors developed seven potent quinazoline and pyrido-pyrimidine small molecules that are dual inhibitors of HER-2 and EGFR tyrosine kinases. These molecules exhibited potent antigrowth activity both in cancer cell lines and in mouse xenograft models. They are nearly equipotent on HER-2 and EGFR, >50-fold selective for these two receptors versus other proliferative kinases, and ninefold to >75-fold more potent on tumour cells than on normal cells. The most potent and selective compounds were GW2974 and, to a lesser extent, GW0277. Their mechanism of action seems to be related to a 90% reduction in autophosphorylation of both HER-2 and EGFR: short term exposure of HN5 and BT474 xenografts to GW2974 resulted in dramatic inhibition of autophosphorylation - of EGFR and HER-2, respectively - even though levels of overexpression of both receptors remained unchanged. Oral daily treatment of animal models with these compounds resulted in significant inhibition of tumour growth at doses of 10 mg/kg and 30 mg/kg, and tumour regression at higher doses. These compounds, particularly GW2974, were well tolerated.

Comments

GW2974 showed potent antiproliferative activity and high levels of selectivity in cancer cell lines and in mouse xenograft models. *In vivo* it also had oral bioavailability and low toxicity. Its mechanism of action deserves deeper evaluation, namely concerning a possible relationship between the reduced phosphorylation of EGFR and either the degree of cell proliferation and/or tumour shrinkage. Nevertheless, these promising results should encourage further development of this compound, targeting a patient population with tumours overexpressing EGFR and/or HER-2.

Methods

Tumour cell lines (The cell lines used were: normal HFF, breast BT474 [overexpresses HER-2], head and neck HN5 [overexpresses EGFR] and gastric N87 [overexpresses both]); BT474 and HN5 were grown as models for HER-2- and EGFR-driven tumour growth in subcutaneous mouse xenograft models, kinase assays, growth inhibition assays, immunoblot analysis, receptor phosphorylation assays, western blot

Additional information

References

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