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Assessment of neratinib-resistance and cross-resistance in HER2-overexpressing breast cancer cells.

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Background: While current therapies approved for HER2-overexpressing breast cancer (BC) treatment has led to advances in treatment of this BC subtype, issues of innate/acquired drug resistance are evolving. Neratinib (N) is an irreversible EGFR, HER2 and HER4 tyrosine kinase inhibitor currently in phase III clinical trials for BC treatment. We aimed to investigate the ability of BC cells to acquire resistance to N and the implications of this in terms of potential cross-resistance to other drugs and phenotypic changes in cells. **Methods:** Neratinib-resistant (NR) cell line variants were developed by exposing HER2-overexpressing BC cell lines, HCC1954 and SKBR3, to increasing concentrations of N over several months. Proliferation assays were used to establish IC_{50} values for N in parent and NR variants; as well as to assess possible cross-resistance to lapatinib (L), afatinib (A) and docetaxel (D). Phenotypic changes in NR cell variants were examined using invasion, migration and *anoikis* assays. IGF1R expression was determined using immunoblots. **Results:** HCC1954-NR and SKBR3-NR cell variants were 6.5±0.4 and 194±47 fold more resistant to neratinib than parent cells, respectively. Furthermore, HCC1954-NR variants were cross-resistant to afatinib (37±7.23 fold) and lapatinib (10±0.8 fold). SKBR3-NR variants were cross-resistant to afatinib by >163.3±22.7 fold (IC_{50} not reached at 9μM afatinib where, on average, 65.5 % cell growth is maintained) and lapatinib (162.3±22 fold). No cross-resistance to

docetaxel was observed. Cells that have acquired N resistance are more invasive, migratory and resistant to *anoikis* than their parent controls. IGF1R expression is increased in NR cell variants compared to parent cells. **Conclusions:** Chronic exposure of BC cells to N results in acquired resistance to the drug. N resistance conferred cross-resistance to other HER2-targeting drugs and induced a more aggressive phenotype. Overexpression of IGF1R in NR variants suggested its role in the mechanism of N resistance.
