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The EGFR Inhibitor Gefitinib Sensitizes Osteosarcoma Cells Against Anthracycline-Based Chemotherapy In Vitro

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Background:
Hyperactivation of the epidermal growth factor receptor (EGFR) by gene amplification, mutation as well as overexpression is a hallmark of multiple human carcinomas. However, in recent years data have accumulated that EGFR-mediated signals might also contribute to malignant progression and therapy resistance of human sarcomas.
Methods:
Consequently we have investigated if human osteosarcoma cell lines (n=9) express functional EGFR and its useability as therapeutic target. Cytotoxic activity was determined by MTT-assay and clonogenic assay. Changes of downstream pathway proteins were monitored by Western-blotting.
Results:
Osteosarcoma cells expressed distinctly differing level of EGFR reaching in some cases high amounts. However, even low expression levels were sufficient to mediate activation of both MAPK and PI3K pathways (determined by phosphorylation of ERK1/2 and S6, respectively) by EGF exposure in serum-starved cells. The EGFR-specific inhibitor gefitinib completely blocked EGF-mediated and attenuated serum-induced downstream signal activation. While gefitinib applied as single agent demonstrated only limited growth inhibiting activity in short term experiments (72h drug exposure), it led to reduced colony formation in long term experiments in the majority of cell lines. Importantly, gefitinb sensitized EGFR-expressing osteosarcoma cell lines against chemotherapy with doxorubicin and methotrexate, while it antagonised cisplatin-induced cell death.
Conclusion:
Summarizing, our data suggest that EGFR-mediated survival signals protect human osteosarcoma cells against the cytotoxic activity of several antineoplastic drugs. Consequently, combination approaches including EGFR inhibitors in addition to chemotherapy should be evaluated for treatment of high grade osteosarcoma patients.

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