Lapatinib

Asari et al., investigated the effect of a potent dual tyrosine kinase inhibitor, lapatinib, on ACTH production and cell proliferation in AtT-20 mouse corticotroph tumor cells. Lapatinib decreased proopiomelanocortin (Pomc) mRNA levels and ACTH levels in AtT-20 cells and also inhibited cell proliferation, induced apoptosis, and decreased pituitary tumor-transforming gene 1 (Pttg1), a hallmark of pituitary tumors, mRNA levels. KSN/Slc nude mice were subcutaneously inoculated with AtT-20 cells. After 1 week, the mice were randomized either to control or lapatinib groups. The inhibitor decreased the tumor weight of AtT-20 allografts in vivo versus control mice. Lapatinib also significantly decreased Pomc and Pttg1 mRNA levels in the tumor and plasma ACTH and corticosterone levels in vivo. Thus, lapatinib decreases the ACTH production and proliferation of corticotroph tumor cells. An EGFR-targeting therapy could be an important treatment for Cushing's disease [1)].

The efficacy of lapatinib and nilotinib in combination with radiation therapy in a model of NF2 associated peripheral schwannoma.

Neurofibromatosis type 2 (NF2), a neurogenetic condition manifest by peripheral nerve sheath tumors (PNST) throughout the neuroaxis for which there are no approved therapies.

In vitro and in vivo studies presented examine agents targeting signaling pathways, angiogenesis, and DNA repair mechanisms. In vitro dose response assays demonstrated potent activity of lapatinib and nilotinib against the mouse schwannoma SC4 (Nf2 -/-) cell line.

Paldor et al. examined the efficacy of everolimus, nilotinib, lapatinib, bevacizumab and radiotherapy (RT) as mono- and combination therapies in flank and sciatic nerve in vivo NF2-PNST models. Data were analyzed using generalized linear models, two sample T-tests and paired T-tests, and linear regression models. SC4(Nf2 -/-) cells implanted in the flank or sciatic nerve showed similar rates of growth ($p = 0.9748$). Lapatinib, nilotinib and RT significantly reduced tumor growth rate versus controls in the in vivo flank model ($p = 0.0025$, 0.0062, and 0.009, respectively) whereas bevacizumab and everolimus did not. The best performers were tested in the in vivo sciatic nerve model of NF2 associated PNST, where chemoradiation outperformed nilotinib or lapatinib as single agents (nilotinib vs. nilotinib + RT, $p = 0.0001$; lapatinib versus lapatinib + RT, $p < 0.0001$) with no observed toxicity. There was no re-growth of tumors even 14 days after treatment was stopped. The combination of either lapatinib or nilotinib with RT resulted in greater delays in tumor growth rate than any modality alone. This data suggest that concurrent low dose RT and targeted therapy may have a role in addressing progressive PNST in patients with NF2 [2)].

Lapatinib is presumed to cross the blood brain barrier, and exhibits clinical activities for treatment of HER2 positive breast cancer. A 43-year-old woman was treated for early breast carcinoma with total mastectomy, axillary lymph-node dissection, and adjuvant chemotherapy with cyclophosphamide plus doxorubicin. After the end of adjuvant trastuzumab therapy, she was diagnosed with panhypopituitarism due to pituitary metastasis. Surgical removal and whole brain radiation therapy were performed, but a portion of viable tumor remained. Only taking lapatinib, the size of the metastatic lesion began to shrink. Trastuzumab may have controlled the micro-metastasis of breast cancer, but it was unable to control its progression to the central nervous system. Lapatinib is a possible option for HER2 positive breast cancer brain metastases [3)].

1)
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2)
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