Sorafenib

Sorafenib (co-developed and co-marketed by Bayer and Onyx Pharmaceuticals as Nexavar), is a protein kinase inhibitor drug approved for the treatment of primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (hepatocellular carcinoma), and radioactive iodine resistant advanced thyroid carcinoma.

Sorafenib is a small inhibitor of several tyrosine protein kinases, such as VEGFR, PDGFR and Raf family kinases (more avidly C-Raf than B-Raf).

Sorafenib treatment induces autophagy,which may suppress tumor growth. However, autophagy can also cause drug resistance.

Neuroblastoma

Yang et al tested antitumor effects of sorafenib (≤ 10 μM) on four human neuroblastoma cell lines, CHLA255, CHLA171, CHLA90 and SK-N-AS. Sorafenib inhibited cell proliferation and induced apoptosis of neuroblastoma tumor cells in a dose-dependent manner. Sorafenib inhibited phosphorylation of Signal Transducer and Activator of Transcription 3 (STAT3) proteins at Tyr705 in these cells, associated with inhibition of phosphorylated JAK2, an upstream kinase that mediates STAT3 phosphorylation. Expression of a constitutively-activated STAT3 mutant (pSTAT3-C) partially blocked the antitumor effects of sorafenib on neuroblastoma cells. Sorafenib also inhibited the phosphorylation of STAT3 induced by IL-6 and sphingosine-1-phosphate (S1P), a recently identified regulator for STAT3, in these tumor cells. Moreover, sorafenib downregulated phosphorylation of MAPK (p44/42) in neuroblastoma cells, consistent with inhibition of their upstream regulators MEK1/2. Sorafenib inhibited expression of cyclin E, cyclin D1/D2/D3, key regulators for cell cycle, and the antiapoptotic proteins Mcl-1 and survivin. Finally, sorafenib suppressed the growth of human neuroblastoma cells in a mouse xenograft model. Taken together, these findings suggest the potential use of sorafenib for the treatment of pediatric neuroblastomas [1)].

Melanoma

Sorafenib is a multikinase inhibitor that induces apoptosis of melanoma cells in vitro. However, systemic administration has been ineffective because adequate tissue concentrations cannot be achieved.

A study investigated if convection-enhanced delivery (CED) of sorafenib would enhance tumor control and survival via inhibition of the signal transducer and activator of transcription 3 (Stat3) pathway in a murine model of metastatic brain melanoma.

Melanoma cells treated with sorafenib in vitro were examined for signaling and survival changes. The effect of sorafenib given by CED was assessed by bioluminescent imaging and animal survival.

The results showed that sorafenib induced cell death in the 4 established melanoma cell lines and in 1 primary cultured melanoma cell line. Sorafenib inhibited Stat3 phosphorylation in HTB65, WYC1, and B16 cells. Accordingly, sorafenib treatment also decreased expression of Mcl-1 mRNA in melanoma cell lines. Because sorafenib targets multiple pathways, the present study demonstrated the contribution of the Stat3 pathway by showing that mouse embryonic fibroblast (MEF) Stat3 +/+ cells

were significantly more sensitive to sorafenib than MEF Stat3 -/- cells. In the murine model of melanoma brain metastasis used in this study, CED of sorafenib increased survival by 150% in the treatment group compared with animals receiving the vehicle control ($p < 0.01$). CED of sorafenib also significantly abrogated tumor growth.

The data from this study indicate that local delivery of sorafenib effectively controls brain melanoma. These findings validate further investigation of the use of CED to distribute molecularly targeted agents [2].

1)
Yang F, Jove V, Buettner R, Xin H, Wu J, Wang Y, Nam S, Xu Y, Ara T, DeClerck YA, Seeger R, Yu H, Jove R. Sorafenib inhibits endogenous and IL-6/S1P induced JAK2-STAT3 signaling in human neuroblastoma, associated with growth suppression and apoptosis. Cancer Biol Ther. 2012 May;13(7):534-41. doi: 10.4161/cbt.19603. Epub 2012 May 1. PubMed PMID: 22406995.
2)
Zou Z, Yin Y, Lin J, Hsu LJ, Brandon VL, Yang F, Jove R, Jandial R, Li G, Chen MY. Convection-enhanced delivery of sorafenib and suppression of tumor progression in a murine model of brain melanoma through the inhibition of signal transducer and activator of transcription 3. J Neurosurg. 2015 Nov 6:1-9. [Epub ahead of print] PubMed PMID: 26544779.