Tariquidar

Tariquidar (INN/USAN) is a P-glycoprotein inhibitor undergoing research as an adjuvant against multidrug resistance in cancer.

Cyclin D1 (CCND1) is frequently overexpressed in malignant gliomas.

Zhang et al., have previously shown ectopic overexpression of CCND1 in human malignant gliomas cell lines.

Quantitative Reverse transcription polymerase chain reaction and Western Blot (WB) was performed to investigate the expression of CCND1 in glioma tissues and cell lines. The biological function of CCND1 was also investigated through knockdown and overexpression of BCYRN1 in vitro.

They reported that CCND1 expression was positively associated with the pathological grade and proliferative activity of astrocytomas, as the lowest expression was found in normal brain tissue (N = 3) whereas the highest expression was in high grade glioma tissue (N = 25). Additionally, they found that the expression level of CCND1 was associated with IC50 values in malignant glioma cell lines. Forced inhibition of CCND1 increased temozolomide efficacy in U251 and SHG-44 cells. After CCND1 overexpression, the temozolomide efficacy decreased in U251 and SHG-44 cells. Colony survival assay and apoptosis analysis confirmed that CCND1 inhibition renders cells more sensitive to temozolomide treatment and temozolomide-induced apoptosis in U251 and SHG-44 cells. Inhibition of P-gp (MDR1) by Tariquidar overcomes the effects of CCND1 overexpression on inhibiting temozolomide-induced apoptosis. Inhibition of CCND1 inhibited cell growth in vitro and in vivo significantly more effectively after temozolomide treatments than single temozolomide treatments. Finally, inhibition of CCND1 in glioma cells reduced tumor volume in a murine model.

Taken together, these data indicate that CCND1 overexpression upregulate P-gp and induces chemoresistance in human malignant gliomas cells and that inhibition of CCND1 may be an effective means of overcoming CCND1 associated chemoresistance in human malignant glioma cells [1)].

Studies in rodents suggest that flumazenil is a P-glycoprotein substrate at the blood-brain barrier. This study aimed to assess whether [11C]flumazenil is a P-glycoprotein substrate in humans and to what extent increased P-glycoprotein function in epilepsy may confound interpretation of clinical [11C]flumazenil studies used to assess gamma-aminobutyric acid A receptors. Nine drug-resistant patients with epilepsy and mesial temporal sclerosis were scanned twice using [11C]flumazenil before and after partial P-glycoprotein blockade with tariquidar. Volume of distribution, nondisplaceable binding potential, and the ratio of rate constants of [11C]flumazenil transport across the blood-brain barrier (K1/k2) were derived for whole brain and several regions. All parameters were compared between pre- and post-tariquidar scans. Regional results were compared between mesial temporal sclerosis and contralateral sides. Tariquidar significantly increased global K1/k2 (+23%) and volume of distribution (+10%), but not nondisplaceable binding potential. At the mesial temporal sclerosis side volume of distribution and nondisplaceable binding potential were lower in hippocampus (both ~-19%) and amygdala (both ~-16%), but K1/k2 did not differ, suggesting that only regional gamma-aminobutyric acid A receptor density is altered in epilepsy. In conclusion, although [11C]flumazenil appears to be a (weak) P-glycoprotein substrate in humans, this does not seem to affect its role as a

tracer for assessing gamma-aminobutyric acid A receptor density [2].

Brandt et al., selected a group of phenobarbital-resistant rats, which was subsequently treated by combinations of phenobarbital with the selective P-gp inhibitor tariquidar. Coadministration of tariquidar (15-20 mg/kg) fully restored the anticonvulsant activity of phenobarbital without altering plasma pharmacokinetics or neurotoxicity of the antiepileptic drug. These data demonstrate that inhibiting P-gp in epileptic rats with proven drug resistance counteracts resistance, providing the first proof-of-principle of the multidrug transporter hypothesis of medically refractory epilepsy [3].

References

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