Pubblicazioni di Ricerca sui tumori del sistema nervoso centrale sostenute da Amicodivalerio:

Expression of β-adrenergic receptors in pediatric malignant brain tumors.

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β-adrenergic receptors (β-ARs) are G protein-coupled receptors that activate signal transduction pathways involved in angiogenesis, resulting in enhanced tumor vascularization and more aggressive growth. In this study, we evaluated the expression of β-ARs in a population of 12 children affected by malignant primary brain tumors. We found a significant expression of β1- and β2-ARs in all 12 samples as well as the 3 cell lines tested (U87MG, T98G and DAOY). The mean absolute β1-AR mRNA level standardized to GAPDH was 5.81 (range, -7.91 to 11.29) for brain tumors and 8.59 (range, 6.046 to 12.59) for cell lines (U87MG, DAOY and T98G), respectively. The mean absolute β2-AR mRNA level was 4.74 (range, -9.30 to 8.45) for tumor specimens and 7.64 (range, 5.85 to 8.88) for cell lines. These real-time quantitative (qRT)-PCR expression data were confirmed by immunohistochemical analysis. Our study evaluated the presence of β1- and β2-ARs in malignant pediatric brain tumors and brain tumor cell lines.

Oncol Lett. 2013 Jan;5(1):221-225. Epub 2012 Oct 23
PMCID: PMC3525361
PMID: 23255924 [PubMed]

Pharmacological modulation of blood-brain barrier increases permeability of doxorubicin into the rat brain.

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Our group recently demonstrated in a rat model that pretreatment with morphine facilitates doxorubicin delivery to the brain in the absence of signs of increased acute systemic toxicity. Morphine and other drugs such as dexamethasone or ondansetron seem to inhibit MDR proteins localized on blood-brain barrier, neurons and glial cells increasing the access of doxorubicin to the brain by efflux transporters competition. We explored the feasibility of active modification of the blood-brain barrier protection, by using morphine dexamethasone or ondansetron pretreatment, to allow doxorubicin accumulation into the brain in a rodent model. Rats were pretreated with morphine (10 mg/kg, i.p.), dexamethasone (2 mg/kg, i.p.) or ondansetron (2 mg/kg, i.p.) before injection of doxorubicin (12 mg/kg, i.p.). Quantitative analysis of doxorubicin was performed by mass

spectrometry. Acute hearth and kidney damage was analyzed by measuring doxorubicin accumulation, LDH activity and malondialdehyde plasma levels. The concentration of doxorubicin was significantly higher in all brain areas of rats pretreated with morphine ($P < 0.001$) or ondansetron ($P < 0.05$) than in control tissues. The concentration of doxorubicin was significantly higher in cerebral hemispheres and brainstem ($P < 0.05$) but not in cerebellum of rats pretreated with dexamethasone than in control tissues. Pretreatment with any of these drugs did not increase LDH activity or lipid peroxidation compared to controls. Our data suggest that morphine, dexamethasone or ondansetron pretreatment is able to allow doxorubicin penetration inside the brain by modulating the BBB. This effect is not associated with acute cardiac or renal toxicity. This finding might provide the rationale for clinical applications in the treatment of refractory brain tumors and pave the way to novel applications of active but currently inapplicable chemotherapeutic drugs.

Am J Cancer Res. 2013 Aug 14;3(4):424-32.
PMID: 23977451 [PubMed]

Successful treatment with a low-dose cisplatin--etoposide regimen for patients with diencephalic syndrome

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Diencephalic syndrome (DS) is a rare but rapidly fatal condition, usually occurring during the first year of life, as a result of a hypothalamic/chiasmatic tumor. The purpose of this study was to induce an objective tumor response and to achieve rapid weight recovery by using ten three-day courses of reduced-dose cisplatin-etoposide. Between 2004 and 2009, eight pediatric patients with DS as a result of an hypothalamic tumor and with a median age at diagnosis of 6.5 months (range 4-60 months) received 10 monthly courses of cisplatin (25 mg/m(2)/day on days 1-3) and etoposide (100 mg/m(2)/day on days 1-3). Under chemotherapy, rapid weight recovery was observed for all patients; tumor response was observed for six (75 %; partial response in four and minimum response in two). The other two had stable disease at completion of treatment. Mean time to weight recovery was 6 months (range 5-7 months) for pilomyxoid astrocytoma patients, and 3.3 months (range 3-4 months) for those with pilocytic astrocytoma. For DS patients who received nutritional support (enteral or parenteral nutrition) the mean time for weight recovery was 5 months (range 3-7 months) whereas children who were able to orally ingest a high-energy diet had a mean time for weight recovery of 8.66 months (range 3-19 months). After follow-up ranging from 22 to 89 months (median 38 months) all patients are alive. A low-dose cisplatin-etoposide regimen is highly effective regarding tumor response and treatment of DS symptoms/cachexia without causing significant side-effects.

J Neurooncol. 2012 Sep;109(2):375-83. doi: 10.1007/s11060-012-0903-7. Epub 2012 Jun 21.

PMID: 22717669 [PubMed - indexed for MEDLINE]