Paclitaxel

Microtubule inhibitor

Paclitaxel (taxol) is a widely used chemotherapy drug for many solid tumors, while continual taxol treatment is revealed to stimulate tumor dissemination.

Tetrahedral framework nucleic acid (tFNA), entering U87MG cells and bEnd.3 cells, was chosen to deliver two aptamers, GMT8 and Gint4.T, and paclitaxel. GMT8 and Gint4.T, which specifically bind with U87MG cells and with PDGFRβ, were linked with tFNA, to form Gint4.T-tFNA-GMT8 (GTG). GTG was efficiently internalized by U87MG and bEnd.3 cells and penetrated an in-vitro blood-brain-barrier model. GTG loaded with paclitaxel (GPC) had potentiated anti-glioma efficacy. It inhibited the proliferation, migration, and invasion of U87MG cells, and enhanced apoptosis induction in these cells. The expression of apoptosis-related proteins was significantly changed after treatment with GPC, confirming apoptosis induction. The study demonstrated that the combination of GTG and paclitaxel has great potential for glioma treatment and tFNA shows great promise for use in drug delivery [1)].

Free taxol and liposome-encapsulated taxol were compared for their antitumoral activities on two human brain tumors serially grafted into female athymic mice in the scapular region. In the first experiment, a human glioblastoma (15th and 16th passages) was studied. In the second experiment, a fast growing human gliosarcoma (19th passage) was used. Free taxol and liposomal taxol were administered intraperitoneally, at the same dose; 12.5 mg/kg (i.e. 1/15 of the evaluated LD 50 value). In the first experiment, the treatment was performed for four consecutive days, with four courses separated by three rest periods of three days in between. Both free taxol and encapsulated taxol produced a statistically significant delay in tumor growth, and at the end of the experiment some total tumor regressions were obtained. However, liposomes were observed to be more effective in their action on the two consecutive passages of the glioblastoma, giving a marked increase of the number of total tumor regressions. In the second experiment another schedule of treatment was chosen because of the fast growth pattern of the xenografted human gliosarcoma: free taxol and liposome-encapsulated taxol were administered for five consecutive days and three courses of treatment were performed with two rest periods of two days. The two forms of taxol had a significant inhibitory effect on gliosarcoma tumor growth; as before encapsulation in liposomes was found to increase the anti-tumoral activity of taxol, although, in this case no tumor regression was observed [2)].

Paclitaxel (Taxol), an anti-cancer drug derived from Taxus species, was tested for its anti-migrational, anti-invasive and anti-proliferative effect on two human glioma cell lines (GaMg and D-54Mg) grown as multicellular tumour spheroids. In addition, the direct effect of paclitaxel on glioma cells was studied using flow cytometry and scanning confocal microscopy. Both cell lines showed a dose-dependent growth and migratory response to paclitaxel. The GaMg cells were found to be 5-10 times more sensitive to paclitaxel than D-54Mg cells. Paclitaxel also proved to be remarkably effective in preventing invasion in a co-culture system in which tumour spheroids were confronted with fetal rat brain cell aggregates. Control experiments with Cremophor EL (the solvent of paclitaxel for clinical use) in this study showed no effect on tumour cell migration, cell proliferation or cell invasion. Scanning confocal microscopy of both cell lines showed an extensive random organization of the microtubules in the cytoplasm. After paclitaxel exposure, the GaMg and the D-54Mg cells exhibited a

fragmentation of the nuclear material, indicating a possible induction of apoptosis. In line with this, flow cytometric DNA histograms showed an accumulation of cells in the G2/M phase of the cell cycle after 24 h of paclitaxel exposure. After 48 h, a deterioration of the DNA histograms was observed indicating nuclear fragmentation [3)]

Paclitaxel can be safely delivered concomitantly with radiation in patients with glioblastoma multiforme. Larger, randomized trials are required to establish the comparative efficacy of paclitaxel as a radiosensitizer in glioblastoma multiforme [4)].

Biodegradable crystalline cubic phases embedding cytotoxic drugs as paclitaxel and carboplatin might play an important role in local glioblastoma treatment [5)].

A total of 12 patients with a recurrence of a glioblastoma multiforme underwent re-resection and received an intracavitary application of paclitaxel and carboplatin cubic phases in different dosages. Six of the patients received more than 15 mg paclitaxel and suffered from moderate to severe brain edema, while the remaining patients received only a total of 15 mg paclitaxel. In the latter group, brain edema was markedly reduced and dealt medically. Intracavitary chemotherapy in Glioblastoma recurrence using cubic phases is feasible and safe, yet the clinical benefit remains to be examined in a clinical phase II study [6)].

Results suggest that optimal biological dosage and scheduling of PEG-IFN-alpha and paclitaxel combination is a potent strategy for glioblastoma patients as a new synergistic anti-endothelial treatment [7)].

The use of weekly Paclitaxel and Fractionated Stereotactic Radiation Therapy (FSRT) in Gliomas is well tolerated with a survival of 14 months [8)].

If the doses and dose ratio can be successfully adjusted, the oral co-administration of HM30181A and paclitaxel can be used to treat tumors in the brain [9)].

In previous studies, Bonomi et al. demonstrated that human mesenchymal stromal cells without genetic manipulation but primed with Paclitaxel (PTX) acquire a potent antitumor activity, providing an interesting new biological approach for drug delivery [10)].

A work demonstrated that AC1MMYR2 appeared to be a promising strategy in combating taxol induced cancer metastases by targeting miR-21/CDK5 axis, which highlighted the potential for development of therapeutic modalities for better clinic taxol application [11)].

Complications

Paclitaxel, often induces painful peripheral neuropathy and at present no effective drug is available for treatment of the serious side effect.

Intra-arterial catheters were placed in the right common carotid artery of rats. Mannitol was injected to transiently open the brain-blood barrier (BBB), followed by high-dose drug (paclitaxel and rapamycin) injection. The optimal time interval of transient BBB opening for maximal drug penetration was determined to be 10 minutes. Paclitaxel and rapamycin were intraarterially administered in various doses. All the rats were neurologically evaluated, and their brain tissues were histologically

examined.

Results: Neither neurological deficits nor histological abnormalities were observed in all the rats [12].

Zhu et al. tested if intragastrical application of bulleyaconitine A (BLA), which has been approved for clinical treatment of chronic pain in China since 1985, could relieve the paclitaxel-induced neuropathic pain. A single dose of BLA attenuated the mechanical allodynia, thermal hyperalgesia induced by paclitaxel dose-dependently. Repetitive administration of the drug (0.4 and 0.8mg/kg, t.i.d. for 7 d) during or after paclitaxel treatment produced a long-lasting inhibitory effect on thermal hyperalgesia, but not on mechanical allodynia. In consistence with the behavioral results, in vivo electrophysiological experiments revealed that spinal synaptic transmission mediated by C-fiber but not A fiber was potentiated, and the magnitude of long-term potentiation (LTP) at C-fiber synapses induced by the same high frequency stimulation was ~50% higher in paclitaxel-treated rats, compared to the naïve rats. Spinal or intravenous application of BLA depressed the spinal LTP, dose-dependently. Furthermore, patch clamp recordings in spinal cord slices revealed that the frequency but not amplitude of both spontaneous excitatory postsynaptic current (sEPSCs) and miniature excitatory postsynaptic currents (mEPSCs) in lamina II neurons was increased in paclitaxel-treated rats, and the superfusion of BLA reduced the frequency of sEPSCs and mEPSCs in paclitaxel-treated rats but not in naïve ones. Taken together, we provide novel evidence that BLA attenuates paclitaxel-induced neuropathic pain and that depression of spinal LTP at C-fiber synapses via inhibiting presynaptic transmitter release may contribute to the effect [13].

Convection-enhanced delivery (CED) of paclitaxel in patients with recurrent malignant gliomas is associated with a high antitumor response rate, although it is associated with a significant incidence of treatment-associated complications. Diffusion-weighted MR images may be used to predict a response by demonstrating the extent of convection during treatment. Optimization of this therapeutic approach to enhance its efficacy and reduce its toxicity should be explored further [14].

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