Neuroprotective effects of melatonin and calpeptin in a rat model of focal cerebral ischemia

19

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Introduction: Melatonin is a potent-free radical scavenger and antioxidant. Previously, we have demonstrated beneficial effects of pretreatment with melatonin in mild and severe focal cerebral ischaemia in rodent models. Cerebral ischaemia increases intracellular Ca^{2+} concentrations, and activates several calcium-dependent proteases including calpain. Pretreatment with calpeptin, a novel calpain inhibitor, has been reported to reduce the cerebral infarct volume. In addition, it also decreases the neuronal apoptosis in hippocampal CA1 sector and improves the behavioural deficit in a rat stroke model. The aim of this study was to investigate the neuroprotective role of a post-ischaemia treatment with melatonin and / or calpeptin, and whether combining the two exerts synergistic or addictive effects in transient focal ischaemic stroke in rats.

Methods: Male Sprague-Dawley rats (6-8 weeks) were anaesthetised with sodium pentobarbital to undergo right-sided endovascular middle cerebral artery occlusion (MCAO) for 90 minutes followed by 24 hours of reperfusion before being sacrificed. A single or a combined dose of melatonin (50 μg/kg) and / or calpeptin (50 μg/kg) were given via an intracerebroventricular injection at 10-15 minutes after onset of the reperfusion. Sham group with injection of vehicle only was used as a control group. Neurological behaviour was assessed using Neurological Deficit Scoring System (NDSS) test and cerebral infarction volumes were evaluated by TTC-staining.

Results: Infarction volumes and NDSS scores were lower in the calpeptin group but not in melatonin group when compared with the control. The combining effects of melatonin and calpeptin will be studied further.

Conclusion: Our results suggest that post-ischaemia treatment with calpeptin but not melatonin at 50 μg/kg protects against focal MCAO model in rats.

Sorafenib combined with azacitidine is an effective post-remission therapy for FLT-ITD+ acute myeloid leukemia

20

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Introduction: Fms-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) occurs in 30% of patients with acute myeloid leukaemia (AML) and confers a poor prognosis.

Methods: A total of 23 patients with FLT-ITD+ AML were treated with sorafenib (200-400 mg twice daily). Of them, 22 patients achieved clearance of marrow blasts at a median of 25 days (range, 19-91 days); 13 patients received sorafenib single-agent as post-remission therapy, 6 patients received sorafenib combined with azacitidine, and 3 patients received sorafenib combined with high-dose cytarabine (HDAC) consolidation. To validate the clinical observation, synergism between sorafenib and azacitidine was evaluated in 2 FLT-ITD cell lines MOLM-13 and MV4-11. Leukaemic cells treated with sorafenib, azacitdine and in-combination were evaluated for cell viability and apoptosis, differentiation, and leukaemia-initiating activity by xenotransplantation.

Results: With a median follow-up of 182 (range, 61-694) days, the median progression-free survival (PFS) of the entire cohort was 71 days (95% confidence interval [CI], 59.7-82.3) and the median overall survival (OS) was 198 days (95% CI, 155-241). Nine patients who received combination post-remission therapy had a significantly better PFS (median 118 days vs 63 days, P = 0.008) and a trend towards better OS (median 227 days vs 182 days, P = 0.07). A favourable PFS was preserved when patients given HDAC were excluded (median 116 days with sorafenib plus azacitidine vs 63 days with sorafenib monotherapy, P = 0.05). In MOLM-13 and MV4-11 cell lines, treatment with combined sorafenib and azacitidine showed additive effect in terms of cell death and apoptosis. There was a trend towards enhanced myeloid differentiation with combination treatment. Sublethally irradiated anti-CD122 primed NOD/SCID mice transplanted with leukaemic cells treated with combined sorafenib and azacitidine showed remarkable suppression of leukaemic engraftment potential.

Conclusion: Information from this study suggests that sorafenib when combined with azacitidine is effective in prolonging remission in these patients and bridge these patients to definitive treatment like allogeneic haematopoietic stem cell transplantation.