**H0-05  Effect of arsenic trioxide on the cell proliferation of human neuroblastoma cell line IMR-32 cells**

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**Introduction:** Neuroblastoma is one of the commonest pediatric tumors and is derived from neural crest precursors cells. Spontaneous regression and maturation of neuroblastoma to ganglioneuroma suggest that differentiation therapy might be potentially useful. Arsenic trioxide (As$_2$O$_3$) is an effective therapeutic agent for acute promyelocytic leukemia (APL), and induces both differentiation and apoptosis of leukemic cells *in vivo*. However, the underlying molecular mechanisms are not fully understood. In this study, we used a human neuroblastoma cell line, IMR-32, as our *in vitro* model to study the potential application of As$_2$O$_3$ as a differentiation agent for neuroblastoma.

**Method:** IMR-32 cells were treated with increasing concentrations of As$_2$O$_3$ (0.1 to 5.0 µM). MTT assays were performed to examine the effect of As$_2$O$_3$ on cellular proliferation. Western blot analysis was performed to identify the potential signaling molecules involved.

**Results:** At high concentrations of As$_2$O$_3$, cellular proliferation of IMR-32 was significantly inhibited (~35% at 1.5 µM and ~78% at 5.0 µM). Western blot analysis of differentiation markers suggested that As$_2$O$_3$ induced differentiation of IMR-32 cells at low concentrations (≤2.5 µM), but led to apoptosis at high concentrations (5.0 µM). As$_2$O$_3$ induced the phosphorylation of p42/44 MAP kinases (Erk1/2) and protein kinase C (PKC) in a dose and time-dependent manner. Pre-treatment of IMR-32 cells with Ro-31-8220 (1 µM), a specific PKC inhibitor, partially blocked the effect of As$_2$O$_3$.

**Conclusion:** We conclude that As$_2$O$_3$ is capable of inhibiting the cell proliferation of a human neuroblastoma cell line IMR-32 via cell differentiation and apoptosis. Signaling molecules such as Erk1/2 and PKC might play crucial roles during the anti-proliferation action of As$_2$O$_3$. The study was supported by the Kadoorie Charitable Fund.

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**H0-06  Oral arsenic trioxide in the treatment of relapsed acute promyelocytic leukaemia**

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**Introduction.** Arsenic trioxide (As$_2$O$_3$) induces a remission in over 90% of patients with relapsed acute promyelocytic leukemia (APL). To date, only the intravenous (i.v.) preparation of As$_2$O$_3$ has been used. We have recently developed an oral preparation of As$_2$O$_3$ that achieves blood levels of elemental arsenic comparable with those of i.v. As$_2$O$_3$ (Eur J Clin Pharmacol Oct 11, 2002 online). In this study, we used a human neuroblastoma cell line, IMR-32, as our *in vitro* model to study the potential application of As$_2$O$_3$ as a differentiation agent for neuroblastoma.

**Materials and methods.** Twelve consecutive unselected patients with relapsed APL were treated with oral-As$_2$O$_3$ (10 mg/day) until remission.

**Results.** Eight patients in first relapse achieved a second complete remission (CR2) after a median of 37 days of oral-As$_2$O$_3$. Subsequent consolidation with idarubicin or oral-As$_2$O$_3$ plus all-trans retinoic acid (ATRA, 45 mg/m$^2$/day) resulted in continuous CR2 in seven patients (median follow-up: 12 months). Four patients in second relapse (from CR2 induced by intravenous-As$_2$O$_3$) achieved CR3 after a median of 31 days of treatment with oral-As$_2$O$_3$/ATRA. After subsequent consolidation with oral-As$_2$O$_3$/ATRA, all had remained in CR3 at a median follow-up of 14 months. Patients in CR were negative for PML/RARA 3-6 months post oral-As$_2$O$_3$ treatment. Toxicity of oral-As$_2$O$_3$ was mild, including leucocytosis without the ATRA syndrome, skin rashes, headache and transient liver function derangement. Cardiac arrhythmias were not observed.

**Conclusion.** These results show that oral-As$_2$O$_3$ is a safe and efficacious treatment for relapsed APL.