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# Study protocol for the Cytarabine (Ara-C) in Children With Acute Promyelocytic Leukemia (APL) (NCT01191541)

**Principal Investigator**

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## Eligibility criteria

Eligible patients were those who were less than 14 years old, were newly diagnosed with APL, and had not previously received chemotherapy. A molecular diagnosis was not required for enrollment, but a subsequent molecular confirmation, including the demonstration of PML-RARA transcripts, was required for inclusion in the analysis. Written informed consent was obtained from all patients before study entry.

## Study design and treatment groups

The study was a prospective, randomized, single-centre trial. It was designed to determine whether the combination of ATRA and ATO is safe and effective in

paediatric APL and whether Ara-C can be omitted when ATO is added for 2 courses. Patients were assigned to receive ATRA plus ATO for induction followed by 1 consolidation course of idarubicin (IDA) and 1 consolidation course of a 28-day cycle of ATO. The patients were then randomly assigned using a computer-generated random allocation schedule to receive 2 courses of either daunorubicin (DNR) or DNR+Ara-C. Patients who were treated with DNR alone were included as the no-Ara-C group. Patients who were treated with DNR+Ara-C were included as the Ara-C group. The patients were subsequently treated with maintenance therapy consisting of oral ATRA, 6-mercaptopurine, and methotrexate for 1.5 years. When CR was achieved, all patients received a prophylactic intrathecal injection (cytarabine, methotrexate, and dexamethasone) for the first time. The patients with an initial white blood cell count $>10\times10^{9}$/L then received intrathecal injection once every course. Patients with an indication of CNS leukaemia received intrathecal injection once every other day until normal results were achieved.

All children were monitored using reverse transcription polymerase chain reaction (RT-PCR) of bone marrow samples. After consolidation, the patients were assessed every 3 months for 1 year and then every 6 months for 1 year.

**Criteria for response and end points**

Haematological complete remission (HCR) and haematologic relapse were defined as described in previous publications. Molecular remission was defined as undetectable PML/RARa fusion transcripts. Molecular relapse was defined as the detection of the fusion oncogene PML/RARa in multiple samples within 2 weeks in the same patient.

Early death (ED) was considered a death that occurred within two weeks of the beginning of treatment.

**Supportive measures and management of complications**

Coagulopathy was treated using fresh frozen plasma or fibrinogen. Platelet transfusions were administered to maintain a platelet count above $50\times10^{9}$/L until any significant sign of coagulopathy was resolved. The patients were administered hydroxyurea (1-1.5 g per day), or homoharringtonine (HHT, 1-2 mg per day for 5-10 days) when their peripheral white blood cell (WBC) counts were greater than $25\times10^{9}$/L. At the earliest manifestation of suspected differentiation syndrome, ATRA, arsenic trioxide, or both were temporarily discontinued, and intravenous dexamethasone was administered at a dose of 5-10 mg/m$^2$ until these signs and symptoms disappeared. Antibiotics and antifungal drugs were administered for fever when required.