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Comparing Arsenic Trioxide with Realgar-Indigo naturalis formula in children with Acute Promyelocytic Leukemia:

An Interim Report of Multicenter and Randomized clinical Trial (SCCLG-APL)

The Southern China Children APL Group.

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Background

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- **Realgar-Indigo naturalis formula (RIF)**
  - **a kind of oral arsenic**
  - **compound of traditional Chinese medicines, with tetraarsenic tetrasulfide, indirubin and tanshinone IIA as major active ingredients.**

tetraarsenic tetrasulfide

indirubin

tanshinone IIA

Background

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- **RIF was effective and safe in adult patients with APL**
  - **EFS is above 90% treated on protocol containing RIF+ all-trans retinoic acid (ATRA) +chemotherapy, which is comparable to that of patients on arsenic trioxide (ATO)+ATRA+chemotherapy**
- **In children APL, ATO +ATRA had been proven to be well tolerated, recently. However, the efficacy and safety of RIF in children is unknown.**

J Clin Oncol. 2013
NEJM. 2014
Br J Haematol.2016
Pediatr Blood Cancer. 2017
J Clin Oncol. 2017

Methods

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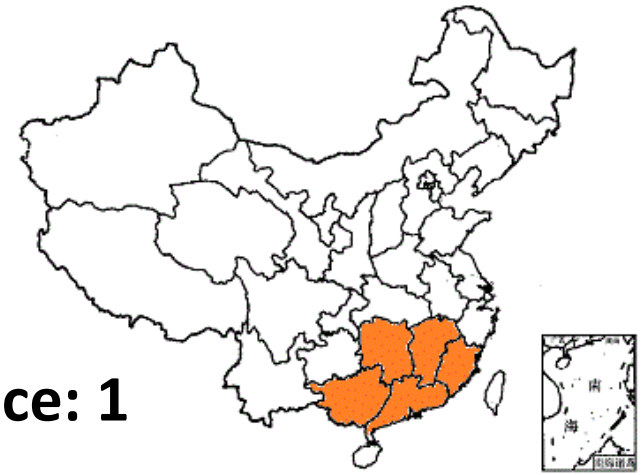
- South China Children Leukemia Group-APL （SCCLG-APL） protocol was started in August 2011.
- ClinicalTrials.gov ID: NCT02200978
- 16 hospitals participated in
  - Guangdong province: 10
  - Hunan province: 3
  - Guangxi, Jiangxi and Fujian province: 1



Methods

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- **Entry criteria**
  - **Patients＜16 years with newly diagnosed APL**
  - **PML/RARa positive by FISH and RT-PCR**
  - **Accept randomization**
- **Exclusion criteria**
  - **intracranial hemorrhage/central nervous system leukemia with coma, convulsion or nervous paralysis at diagnosis.**

Methods

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- **Risk criteria**
  - **High risk: initial WBC≥10×10^9/L**
  - **Non-high risk: initial WBC＜10×10^9/L**
- **Randomization:**
  - **stratified block randomization**
  - **done as soon as the result of PML/RARa was known.**

SCCLG-APL protocol

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Non-high risk patients		High risk patients
MA 10mg/m^2 d3	Induction ： ATRA+ATO/RIF*	MA 7mg/m^2 d2-4
MA 10mg/m^2 d1-2	Consolidation ①： ATRA×15 d	MA 10mg/m^2 d1-2
	Consolidation ②： ATRA+ATO/RIF×15d	AC 1g/m^2 q12h d1-2
MA 10mg/m^2 d1	Consolidation ③ ： ATRA+ATO/RIF×15d	MA 10mg/m^2 d1 AC 1g/m^2 q12h d1-2

- Maintenance therapy：96 weeks,12 weeks as a cycle
  - ✓ ATO/RIF+ATRA w1-2, and then MTX+6MP w3-12

* Arsenic was added on D5 to CR, base on the result of PML/APL gene.

Methods

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- MRD was monitored by qRT-PCR
  - At the end of induction and the 3rd consolidation, q3ms in the first year, and q6ms until treatment finished 1 year
- Analysis: intention to treatment
- Event: relapse, death of any reason
- Statistics: RFS and OS curve were computed according to the Kaplan-Meier.

Results

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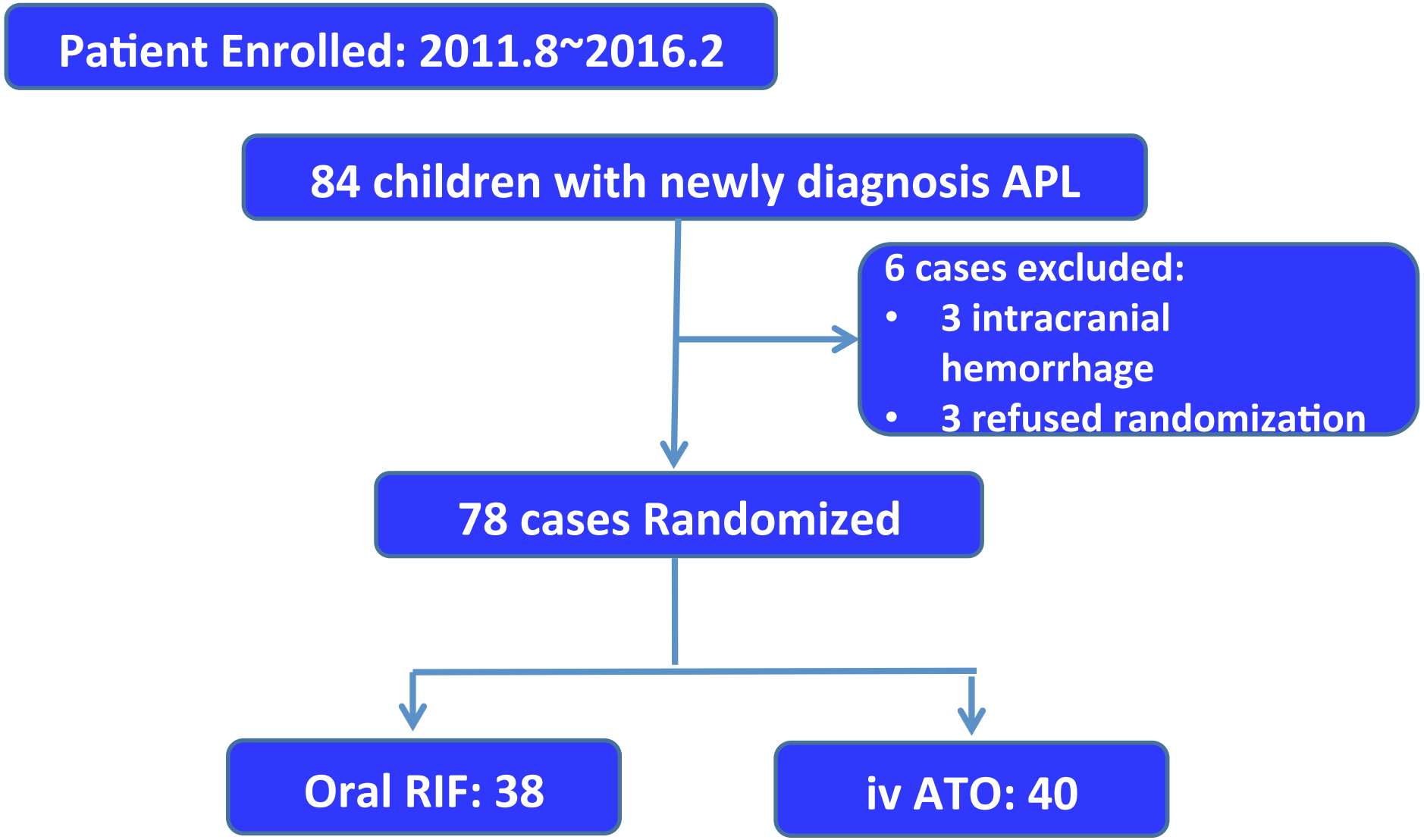

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Patient grouping by Randomization

	ATO group	RIF group	total
Non-high risk	27	29	56
High risk	13	9	22
total	40	38	78

Pearson X^2 test, P=0.387

Outcome

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- All reach CR after induction
- All reach MRD negative after consolidation
- There were two drop-out cases in ATO group during consolidation
  - one abandoned
  - the other deviated from the protocol because of adverse effect
- Median follow-up 2 years: no relapse, no death during treatment, including the drop-out cases.
- The 4y RFS and OS of both groups were 100%

Acute Toxicity

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	Induction		Consolidation	
	Oral RIF group	Iv ATO group	Oral RIF group	Iv ATO group
Headache and vomit/nausea	18%	18%	12%	12%
Significant infections*	8%	13%	8%	12%
WBC elevated**	73%	83%	No data	No data
P	＞0.05		＞0.05	

*including sepsis, pneumonia, cellulitis and etc.

**the WBC elevated more than $10\times10^9/L$ in 30% and 33% of non-high risk APL in ATO group and RIF group respectively

Conclusion

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- SCCG-APL protocol containing arsenic, ATRA and low-intensive chemotherapy obtained a good outcome in childhood APL, including high-risk patients.
- The short term side-effects were no difference between ATO and RIF in childhood APL.

Acknowledges

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Thanks for you attention

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