PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA (APL) IN LATIN AMERICAN CHILDREN. IS IT POSSIBLE TO WORK TOGETHER? THE CLEHOP INITIATIVE.

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Cancer – Latin America

- Latin America and Caribbean region has approximately 8 % of the world's population. (604 millons)
- Approximately 26% of the region's population is younger than age 15 years. (159 millons)
- The region has 18000 cases of childhood cancer annually (12% of all childhood cancers worldwide: 800 cases in Caribbean; 4700 in Central America and 12000 in South America)
- (Fuente Globocan 2012)

Cancer en Latinoamérica y Caribe (Globocan 2012)	Total	0-14	15-39
All cancers excl. non-melanoma skin cancer	1096056	**17819**	104118
Bladder	24844	37	589
Brain, nervous system	27392	**3111**	**5296**
Colorectum	87474	36	3696
Gallbladder	15278	4	320
Hodgkin lymphoma	6184	**522**	**3039**
Kaposi sarcoma	1860	8	749
Kidney	21183	874	1228
Larynx	16481	5	348
Leukaemia	29123	**6449**	**6234**
Lip, oral cavity	20633	129	1340
Liver	30442	373	1147
Lung	84520	55	1464
Melanoma of skin	13731	95	1777
Multiple myeloma	9484	18	304
Nasopharynx	1639	60	265
Non-Hodgkin lymphoma	29124	**1383**	**4960**
Oesophagus	21180	6	434
Other pharynx	8859	137	446
Pancreas	27723	21	665
Stomach	60852	21	2701
Thyroid	27628	141	9037

CLEHOP

- 2015: Consorcio Latinoamericano de Enfermedades Hematooncológicas Pediátricas (CLEHOP).
- Comprise:
- Regional Group: AHOPCA (Central America)
- National Groups: PINDA (Chile); GATLA (Argentina)
- Local Centers: Brazil, Colombia, Peru, Mexico and Venezuela

APL- Latin America

- Population from Latin America have a higher incidence of APL.
- Compared to North America, the assessed APL risk among AML cases was more than two times higher in Central / South America.
- Higher incidence of APL (> 20% of AML) : Irak, Paquistán, Cuba, Nicaragua and Venezuela.
- Incidence APL: 15-20% of AML were diagnosed in Central or South America(Costa Rica, Chile, Bolivia, Guatemala, Honduras ,El Salvador)
- Brazil, Argentina: 10 - 15 %

LPA- CLEHOP – 01 Protocol

Non randomized study to compare Arsenic Trioxide (ATO) combined to ATRA versus standard ATRA and anthracycline – based chemotherapy for newly diagnosed Acute Promyelocitic Leukemia (APL) in children

Objectives - CLEHOP LPA 01

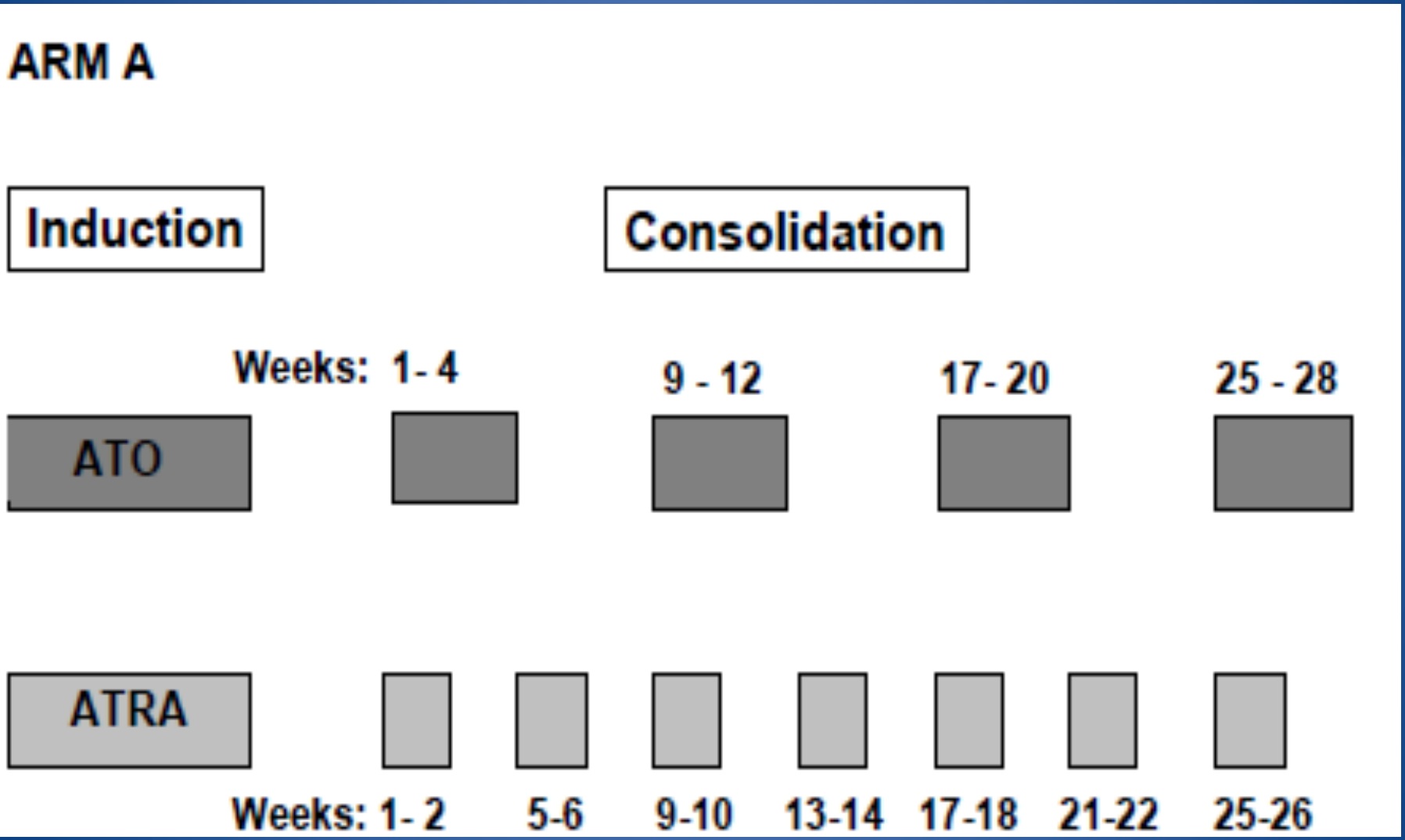
- **Primary**: To compare EFS in the two arms.
- **Secondary**: To compare CR and OS rates in the two arms.

  To compare the toxicity.
- **Investigation :**
- **Epidemiologic study**

- **Open study, multicenter, multinational**

APL – CLEHOP – 01 Protocol

- Age: 0 – 18 years
- Newly diagnosed APL confirmed by the presence of t(15;17) or PML/RAR α fusion by PCR


ARM A
Induction
Consolidation
Weeks: 1- 4
9 - 12
17- 20
25 - 28
ATO
ATRA
Weeks: 1- 2
5-6
9-10
13-14
17-18
21-22
25-26

Overview of Treatment Plan (arm A): ATRA + ATO

- Treatment on this study will consist of an Induction course to achieve an CRh/CRhi, followed by 28 weeks of Consolidation.
- There is no randomization in this study.
- Patients will be stratified into risk groups based on WBC at diagnosis. The **standard risk group** includes patients with WBC

  < 10,000/µL, and the **high risk group** includes patients with WBC **≥** 10,000/µL.

Overview of Treatment Plan

- Induction therapy consists of daily ATO and twice daily ATRA for all patients.
- Patients with high risk APL will also receive 2 doses of anthracyclines .

- Prophylaxis dosing of prednisone to help prevent differentiation syndrome.

Overview of Treatment Plan

- Induction will last a minimum of 30 days.
- Beginning on Day 30 of Induction, patients will have bone marrow testing every 2 weeks as needed to confirm morphologic remission.
- Induction may last up to a maximum of 60 days.
- Once in morphologic remission, Consolidation therapy will start a minimum of 14 days after Induction and upon count recovery, whichever occurs later.

Overview of Treatment Plan

- Consolidation therapy will be the same for patients with standard risk and high risk APL.
- Consolidation consists of 28 weeks of therapy including 2 weeks of ATRA every 4 weeks
- (7 cycles of ATRA) and 4 weeks of ATO every 8 weeks (4 cycles of ATO).

Protocol Study Groups

1. **STANDARD RISK : ATO + ATRA**
2. **HIGH RISK : ATO + ATRA + Anthracycline**

3. **STANDARD RISK : ATRA + Chemotherapy**
4. **HIGH RISK : ATRA + Chemotherapy**

Arm B – ATRA + Chemotherapy

Induction	*Consolidation*			*Maintenance*
ATRA + Anthracycline	ATRA + Anthracycline (SR) + HD Ara C (HR)	ATRA + Anthracycline	ATRA + Anthracycline (SR) + HD Ara C (HR)	6 MP + MTX + ATRA

Overview of Treatment Plan – ARM B

- Induction with ATRA + anthracycline
- Three Blocks of Consolidation (with or without HD Ara C according risk)
- Maintenance : 6MP – MTX – ATRA (2 years)

Assessment of Response:

- BMA should be done after induction , after to 3er consolidation (ATRA) o 3er cycle (ATO)
- BMA should be done between 7-14 days after stopping ATRA, but not less than 7 days .

- Estimated Accrual: 55 – 60 pts/year.

Conclusions

- To launch this protocol in next few months
- To accrue a large number of patients
- To share experience
- Cooperative international study
- To improve of the treatment of APL in the whole continent

You may say I'm a dreamer,
but I'm not the only one
- John Lennon

Latinoamérica

- Resultados no uniformes e inferiores a los de los países desarrollados.
- Características específicas de la región (económicas, sociales, poblacionales,etc)
- Educación y distribución
- Detección precoz
- Registros poblacionales

- **« Collaborative works by North American and European pediatric oncology consortia have been a centerpiece »**
- **« Cancer care in LMICs must not be limited to copying unrealistic strategies used in HICs—it demands innovation. »**
- **« We believe that regional consortia are an ideal platform and potential catalyst for development and coordination »**

(C Rodriguez Galindo y col. J Clin Oncol 33, 2015)

Standard Risk – Inducción - ATO

Días	1	2	3	4	5	6	7	8	9	10	11	→		60
ATO	X	X	X	X	X	X	X	X	X	X	X	X		X
ATRA	X	X	X	X	X	X	X	X	X	X	X	X		X

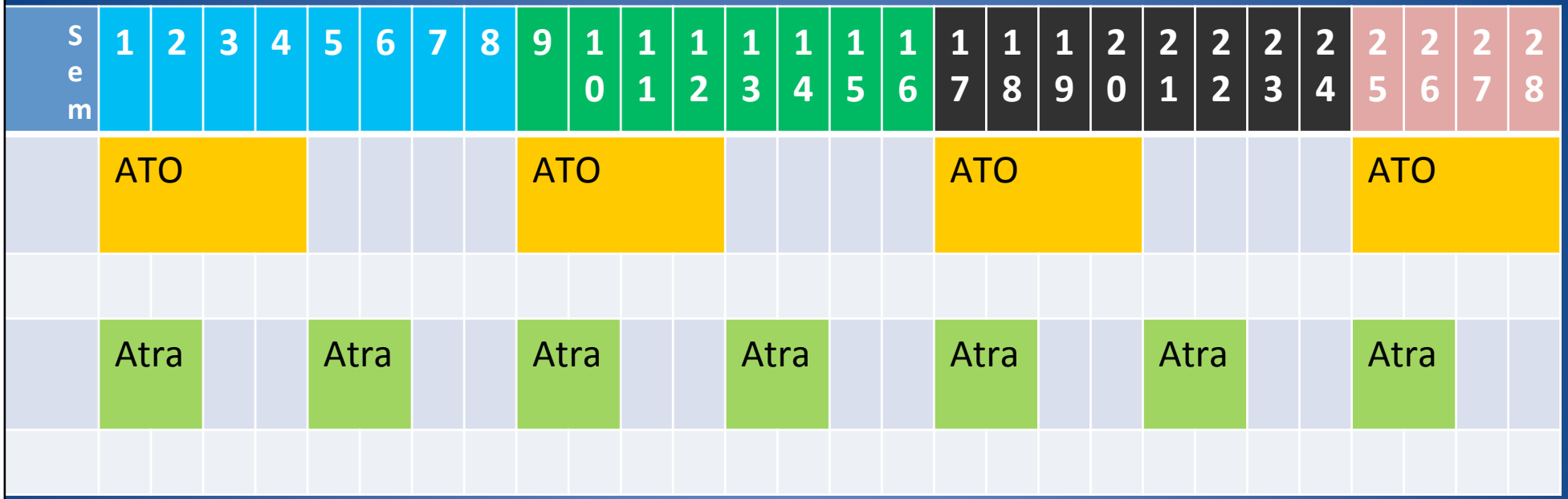
ATO: 0.15 mg/Kg/día EV en infusión de 2 hs (Máximo 60 días)

ATRA: 25 mg/m2/día VO dividido en dos dosis (Máximo 60 días)

APL- Riesgo Standard - ATO

- **Consolidation**
- **ATRA** 25 mg/m^2/day x 15 days (day 1 → day 15). Treatment will be administered for 2 weeks on 2 weeks off for a total of 7 cycles (last cycle administered on weeks 25-26).
- **ATO** 0.15 mg/kg/day *EV* x 2 hrs for 5 days every week. Treatment will be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles (last cycle administered on weeks 25-28).

Standard Risk - Consolidation



ATO: 0.15 mg/Kg/día EV infusión de 2 hs, por 5 días cada semana, durante 4 semanas x 4 ciclos

Atra: 25 mg/m2/día VO por 2 semanas cada 2 semanas por 7 ciclos

Duración: Ciclos 1,2 y 3: 56 días

Duración Ciclo 4 : 28 días

APL- High Risk - ATO

- **HIGH-RISK**
- **Induction**
- **ATRA** 25 mg/m^2/day x 60 days (day 1 → continued until hematological CR or for a maximum 60 days)
- **ATO** 0.15 mg/m^2/day EV x 2 hrs starting on day 1 and continued until hematological CR or for a maximum of 60 days
- IDA , 12 mg/m2/d x 2 or **DNR** 45 mg/m^2/day x 2 consecutive days (day 1, 2), short infusion

APL – R. Standard SIN ATO

- **STANDARD-RISK**
- **Induction**
- **ATRA** 25 mg/m^2/day x 30 days (day 1 → day 30)
- IDA 12 mg/m2/d x 3 dosis en 1 hora or **DNR** 45 mg/m^2/day x 3 consecutive days (day 3, 4, 5), short infusion. If WBC ≥ 10 x 10^9/L during first days of ATRA, IDA/DNR has to be start immediately

APL- R.Standard SIN ATO

- **Maintenance**
- **6-MP** 50 mg/m^2/day orally. The dose will be adjusted according to toxicity during the follow-up period. The treatment must be continued for 2 years
- **MTX 15** mg/m^2/week orally, starting one month after recovery from third consolidation course. The dose will be adjusted according to toxicity during the follow-up period. The treatment must be continued for 2 years
- **ATRA** 25 mg/m2/day x 15 days every 3 months until a 2 year period is completed. The first course will begin four months after recovery from the last consolidation course. During the days of ATRA administration , the treatment with MTX and 6-MP will be discontinued

APL-High Risk- SIN ATO

- **HIGH-RISK**
- **Induction**
- **ATRA** 25 mg/m^2/day x 30 days (day 1 → day 30)
- **IDA**, 12 mg/m2/d x 4 days or **DNR** 45 mg/m^2/day x 4 consecutive days (day 2, 3, 4, 5), short infusion. If WBC ≥ 30 x 10^9/L, IDA or DNR has to be started immediately

- Líneas de Investigación (opcional)
  - Evaluación Económica
  - Presencia FLT3
  - Anti PML (inmunofluorescencia ?, citometría?. Hablar con Raúl Ribeiro)
  - Presencia Ag CD56/CD2/CD22

  - Reporte Eventos Adversos
  - Procesos de Revisión Central en MO dudosas