“APL in developing countries”

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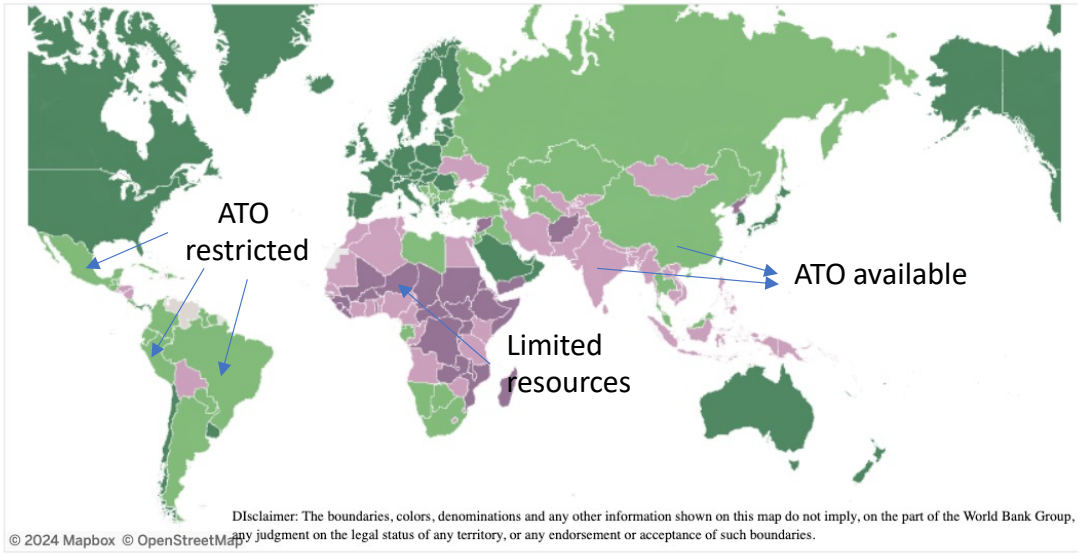
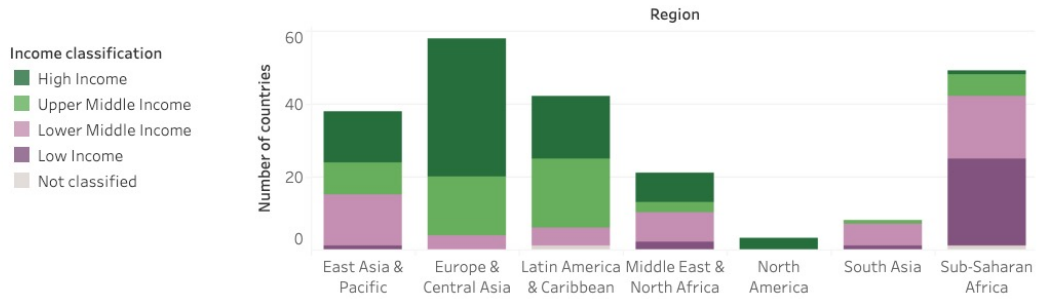
Disclosures of Eduardo M. Rego

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X				X	X	
Astellas	X				X	X	
TEVA	X				X	X	

Developing – low-, middle- or upper middle-income ?





Definitions

2024 fiscal year – based on GNI per capita, calculated using the World Bank Atlas method

low-income economies = of $1,135 or less in 2022;

lower middle-income economies between $1,136 and $4,465;

upper middle-income economies between $4,466 and $13,845;

high-income = $13,846 or more.

Outcomes ‘recently’ reported in retrospective, single - center, studies conducted in LMIC

Country (period)	Single x Multicenter	N	Age (~)	High-risk	Treatment	Follow -up	Death in induction	O.S
Pakistan (2005 – 2020)[1]	single	51	30y	46.1%	PETHEMA LPA99 or LPA2005 (72%)	32m	4%	76.5% (2y)
India (2003-2021)[2]	single	62	8y	50%	ATRA+Chemo		29%	70% (4 y)
India (2013-2019)[3]	single	90	<15y	53%	ATRA+ATO		5.5%	91% (3y)
South Africa (1998-2019)[4]	single	69	30y	39%	ATRA+chemo (LPA99)	35.4m	13%	76.5% (3y)
Brazil (2007-2017)[5]	single	61	36y	41%	ATRA+chemo (7+3) – 70%; LPA2205 30%	5y	20%	59% (5y)
Turkey (2003-2016)[6]	single	36	39y	31%	ATRA+Chemo (AIDA)	11.4m	33%	58% (2y)
UAE (	single	67	33y	52.2%	ATRA+chemo (64)		11.9%	n.r.

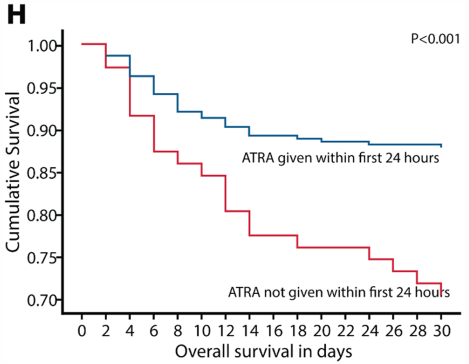
[1] Javed H et al. J Ayub Med Coll Abbottabad. **2022**;34(4):791-796. [2] Roy PS et al. Pediatr Hematol Oncol. **2023** ;40(2):117-130. [3] Srinivasan S et al. Indian J Pediatr. **2023**. [4] Shein R et al. Clin Lymphoma Myeloma Leuk. **2021** ;21(4):e348-e352. [5.] Silva WFD Jr, et al. Clin Lymphoma Myeloma Leuk. **2019**;19(2):e116-e122.[6] Akcay OF et al. Rom J Intern Med. **2020**;58(3):138-145.

Outcomes reported in prospective, multi center, studies conducted in HIC

	PETHEMA LPA99	PETHEMA/ HOVON LPA2005	GIMEMAAIDA2000
N	561	402	453
Age in years, median (range)	40 (2-83)	42 (3-83)	40.9 (18.0-61.0)
Main treatment outcomes			
CR rate, N(%)	511 (91)	372 (92)	420 (94.4)
Death in induction rate, N(%)	50 (8.9)	29 (7.4)	25 (5.6)
OS, %	83% at 4-y	88% at 4-y	87.4% at 6-y
DFS, %	84% at 4-y	90% at 4-y	85.6% at 6-y
CIR, %	11% at 4-y	9% at 4-y	10.7% at 6-y

Challenges in APL diagnosis, treatment and supportive care

- **Long delays between symptoms onset and therapy initiation**
- **Delay in actually giving ATRA after being prescribed**
- **A higher percentage of high-risk patients**
- **Poor management of DS and APL coagulopathy**
- **Irregular drug availability**
- **No MRD monitoring – higher mortality of relapsed pt**
- **Treatment abandonment**



Oluwatobi & Tallman Hematology Am Soc Hematol Educ Program, 2023, Figure 3.[1]

40- 50% HR vs 31% in PALG[2] or 29% in PETHEMA LPA2009 and 25% in LPA99[3]

Discontinuation of cheap drugs - daunorubicin

No MRD monitoring available in Brazil prior to ICAPL

Better documented in children. Roy et al [4]- 23.5% during 2003-2015 to nil during 2015-2021

[1] Odetola O, Tallman MS. Hematology Am Soc Hematol Educ Program. 2023 Dec 8;2023(1):248-253. [2] Sobas M et al.Clin Lymphoma Myeloma Leuk. 2020 Feb;20(2):105-113.[3] Sanz M et al. *Blood* (2010) 115 (25): 5137–5146. [4] Roy PS et al. Pediatr Hematol Oncol. 2023 ;40(2):117-130

International Consortium on Acute Leukemias (ICAL)

- Created in 2004 by ASH – networking to improve clinical care and national infrastructure
- First study – ICAPL2005 (APL - highly curable disease but with significant challenges)
- The establishment of a National network was a sine quo noncondition to participate. Then into larger multinational ntw
  - ✓ Brazil, Chile, Paraguay, Peru and Uruguay
- Protocol based on available drugs (ATRA and anthracyclines) – twin to PETHEMA2005 (M.A. Sanz)
- Incorporated anti-PML staining as a rapid Dx test (B. Falini / F. LoCoco)

Pillars and Subcommittees

ICAL Clinical Network Activites		
Medical Education • Elaboration of protocols and manuals for the diagnosis, management, and supportive care • Establishment of regional guidelines endorsed by the National Hematology Societies • Discussion of special situations through virtual meetings • Training of young hematologists and lab personnel	Lab Activities • Establishment of National reference labs • Participation in an external quality control program • Minimal Residual Disease testing • samples have been exchanged among labs to assure reproducibility of results • Interaction with European and American investigators	Infrastructure • Support members in their plea to local authorities and pharmaceutical companies to ensure drug availability • Increase awareness about the disease among other medical specialties

ICAPL-2005 long-term follow-up: causes of ineligibility

1004 patients screened (2005 – 2020)

↓

806 eligible

Causes	N	% of enrolled patients	
Treatment with a different protocol	71	7.1	
PETHEMA LPA2005	11	1.1	
ATO+ATRA	60	6.0	
Death before receiving ATRA	3	0.3	←
Lack of genetic confirmation of the diagnosis	36	3.6	
PML/RARA not detected	24	2.4	←
Degraded samples	12	1.2	
Age < 15 or >75 years	21	2.1	←
Previous chemotherapy or radiotherapy	16	1.6	
ECOG = 4	19	1.9	
Refusal of informed consent	10	1.0	
Treatment at another hospital	10	1.0	
Pregnancy	4	0.4	←
HIV positive	2	0.2	
Hepatitis B	1	0.1	
Drug unavailability	4	0.4	
Liver enzymes > 5x ULN	1	0.1	
Total	198	19.7	

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ICAPL-2005 long-term follow-up: Some demographic characteristics

	All	Brazil	Chile	Paraguay	Peru	Uruguay	P
	(N=806)	(N=362)	(N=234)	(N=39)	(N=163)	(N=8)	
Age in years Median (range)	35 (15, 74)	36 (15, 73)	34 (15, 74)	38 (18, 72)	35 (15, 70)	25 (15, 34)	0.88
High-risk N (%)	294 (36.6%)	129 (35.9%)	84 (35.9)	12 (30.8%)	65 (39.9%)	4 (50%)	0.027
WBC median (Q1-Q3)	4.1 (1.5, 20.4)	4 (1.4, 19)	3.5 (1.3, 21.4)	1.9 (0.9, 10.7)	6 (1.9, 21.4)	9.5 (2, 17.5)	0.35
Fibrogen ≤ 170mg/dL N (%)	343 (56.3%)	205 (60.3%)	41 (67.2%)	11 (28.9%)	82 (50.3%)	4 (57.1%)	N/A
CNS bleeding N(%)	65 (8.1%)	21 (5.8%)	22 (9.4%)	2 (5.1%)	19 (11.7%)	1 (12.5%)	0.32

*: Due to a small size, Uruguay is omitted from group comparison for p-value calculation

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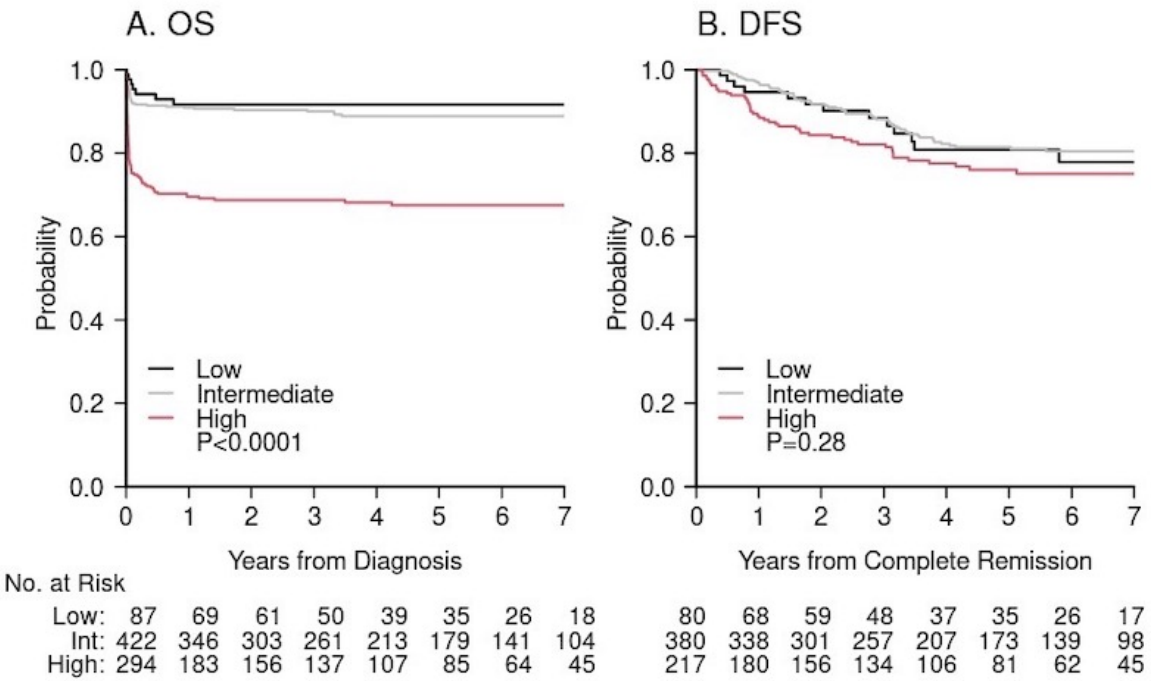
ICAPL-2005 long-term follow-up: Main Outcomes

Median follow-up: 53 months

Outcome	
CHR	85.4%
OS (4-year)	81%
Death in induction rate	14.5%
DFS (4-year)	80%
CIR (4-year)	80%



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ICAPL-2005 long-term follow-up: Differences among risk groups and among countries

	Overall Survival % (95% CI)	Non-relapse mortality % (95% CI)	Disease-free Survival % (95% CI)
Low-risk	92% (83, 96)	2.7% (0.5, 8.4)	81% (68, 89)
Intermediate-risk	89% (85, 92)	2.8% (1.4, 5)	81% (68, 89)
High-risk	68% (62, 73)	7.8% (4.6, 12)	78% (71%, 83%)
Value of P	< 0.001	0.014	0.28

No significant differences among risk groups regarding DFS and CIR

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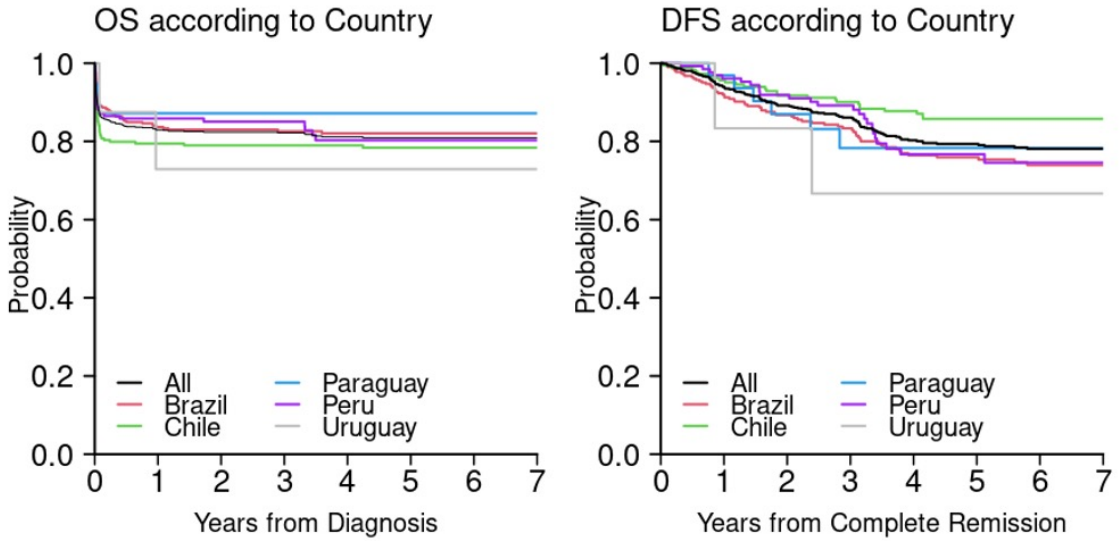
ICAPL-2005: Differences among countries

	OS		DFS		NRM	Relapse
Country	N	4-yr OS (95% CI)	N	4-yr DFS (95% CI)	4-yr NRM (95% CI)	4-yr Rel (95% CI)
All	806	81% (78,84)	679	80% (77, 83)	4.8% (3.3, 6.7)	15% (12, 18)
Brazil	362	82% (78,86)	310	76% (70, 81)	6.3% (3.8, 9.5)	17.3% (13, 22)
Chile	234	78% (72, 83)	187	88% (82, 92)	2.2% (0.7, 5.1)	10% (6.2, 15)
Paraguay	39	87% (72, 94)	34	78% (57, 90)	0%	22% (8.3, 39)
Peru	163	80% (72, 86)	141	77% (67, 84)	6.6% (2.6, 13)	17% (10, 25)
Uruguay	8	73% (28, 93)	7	67% (19, 90)	16.7% (0.5, 55)	17% (0.4, 56)
p-value*		0.53		0.03	0.16	0.12

*: group comparison without Uruguay



Differences among the 5 countries

Peru: Time from symptoms onset to diagnosis (in 74.4% of the patients this period was longer than 10 days), (13.5% with ECOG=3) and those in the high-risk subgroup.

The stratified regression analysis adjusted for the country effect, (data from Uruguay and Paraguay were combined - no significant differences in the outcomes

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Interval from the onset of symptoms to diagnosis

	All		Brazil		Chile		Paraguay		Peru		Uruguay		
Time from Sx to DX													<0.001
<24 hrs	59	8.1	29	8.8	30	14.5							
24-48 hrs	110	15	23	7	82	39.6			5	3.2			
48-72 hrs	76	10.4	10	3	62	30			4	2.6			
4-7 days	105	14.3	48	14.5	24	11.6	12	36.4	20	12.8	1	16.7	
8-10 days	55	7.5	35	10.6	3	1.4	4	12.1	11	7.1	2	33.3	
>10 days	327	44.7	185	56.1	6	2.9	17	51.5	116	74.4	3	50	
UNK	74		32		27		6		7		2		

ICAPL-2005: Deaths during induction

Induction Death Rate

	Death	No Death	total	%
Brazil	44	318	362	12.2
Chile	45	189	234	19.2
Paraguay	5	34	39	12.8
Peru	22	141	163	13.5
Uruguay	1	7	8	12.5
Total	117	689	806	14.5

Multivariable logistic analysis* for induction death

		Multivariable Logistic for achieving CR			
		OR	95% CI		p-value
Age (years)	>=40 vs <40	0.37	0.21	0.64	0.0004
ECOG	2 vs 0-1	0.81	0.41	1.59	0.53
	3 vs 0-1	0.14	0.07	0.29	<.0001
Morphology	M3v vs M3	0.76	0.34	1.70	0.51
Relapse risk	High vs Low/Int	0.35	0.20	0.62	0.0003
PML/RARA breakpoint	bcr3 vs bcr1/2	0.44	0.25	0.77	0.004
Time from symptom to DX	48-72 vs <48 hrs	0.20	0.08	0.53	0.0011
	>=4 days vs <48 hrs	0.30	0.12	0.78	0.01
CNS bleeding	Yes vs No	0.09	0.04	0.19	<.0001
Pulmonary hemorrhage	Yes vs No	0.14	0.05	0.42	0.0004

*: stratified by country. Due to small sample size, Uruguay and Paraguay were combined prior to stratification.

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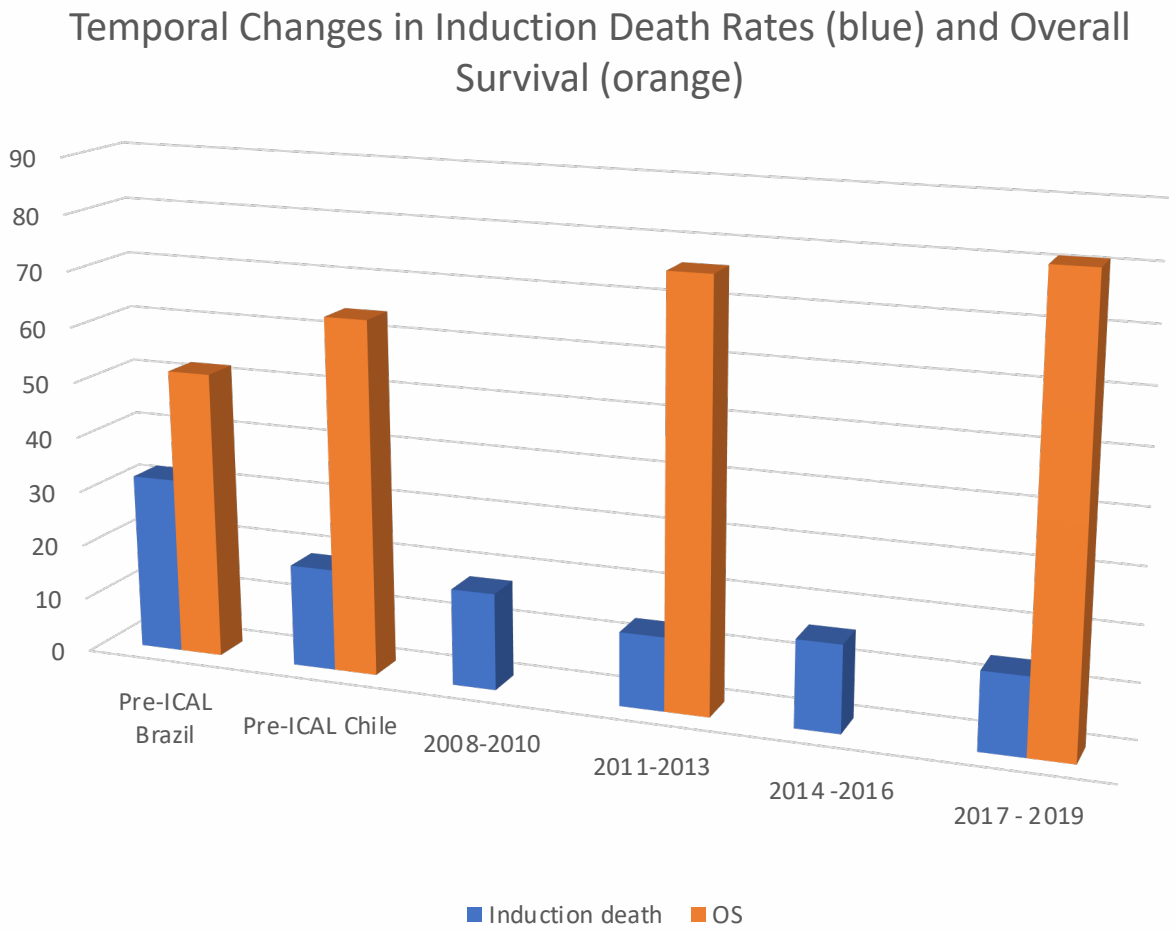

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ICAPL-2005 long-term follow-up: causes of death

	All	
	N	% of all deaths
Period in which death occurred		
Induction	117	78
Consolidation	13	8.7
Maintenance	11	7.3
FU	9	6.0
Total	150	100
COD during induction	% of deaths during induction	
Bleeding	69	59
Infection	33	28.2
Differentiation syndrome	6	5.1
Multiple causes	5	4.3
Congestive heart failure	1	0.8
Thrombosis	1	0.8
Missing	2	1.7
COD during consolidation	% of deaths during consolidation	
Infection	12	92.3
Congestive heart failure	1	7.7

	All	
	N	% of all deaths
COD during maintenance		% of deaths during maintenance
Infection	7	63.6
Thrombosis	1	9.1
Secondary AML	1	9.1
Hemorrhage	1	9.1
Missing	1	9.1
COD off-therapy	% of deaths after completion of the treatment	
Secondary AML	3	33.3
Car accident	1	11.1
Catastrophic antiphospholipid syndrome	1	11.1
Missing	4	44.4
Incidence of t-AML	% of cases after completion of consolidation	
t-AML	4	0.65

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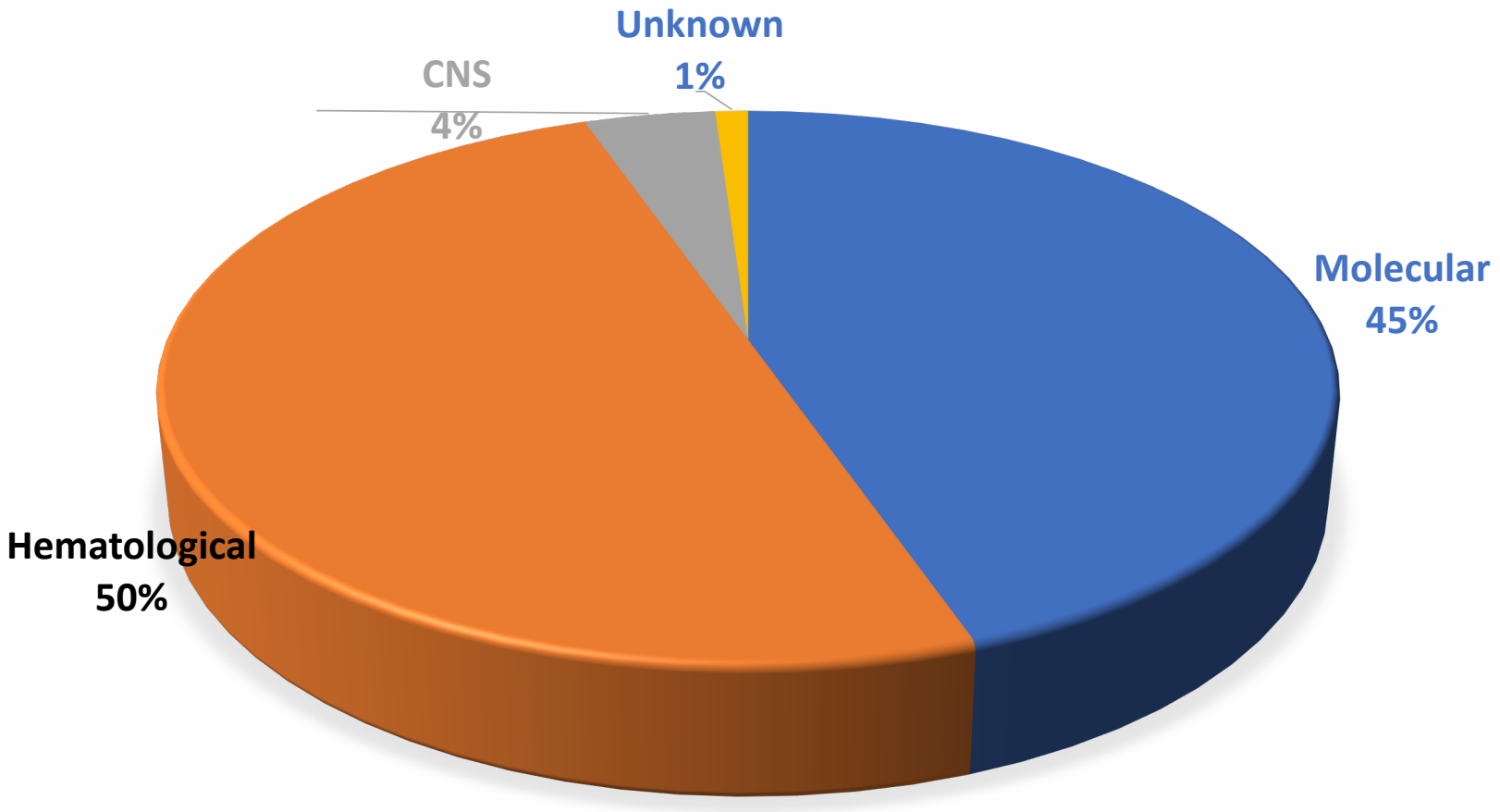
ICAPL-2005 long-term follow-up: 94 patients relapsed



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ICAPL-2005 outcomes compared to other ATRA+Chemo trials conducted in HIC

	PETHEMA LPA99	PETHEMA/ HOVON LPA2005	GIMEMAAIDA2000	IC-APL2005
N	561	402	453	806
Age in years, median (range)	40 (2-83)	42 (3-83)	40.9 (18.0-61.0)	35 (15, 74)
ECOG ≥ 2, N (%)	138 (27)	67 (20)	n.a.	262 (32.5)
Relapse-risk group, N(%)				
Low	107 (19)	84 (21)	116 (25.6)	87 (10.8)
Int./High	453 (81)	318 (79)	337 (74.4)	716 (89.2)
WBC count, x 10^9/L, median (range)	2.2 (0.2-460)	3.0 (0.3-126)	2.3 (0.3-770.0)	4.1 (0.1-537.2)
Fibrinogen, mg/dL, N(%)				
170 or less	280 (54)	176 (48)	n.a.	343 (56.3)
More than 170	240 (46)	193 (52)	n.a.	266 (43.7)
Albumin, g/dL, N(%)				
≤ 3.5	107 (24)	66 (20)	n.a.	114 (22.7)
> 3.5	335 (76)	267 (80)	n.a.	388 (77.3)
Main treatment outcomes				
CR rate, N(%)	511 (91)	372 (92)	420 (94.4)	687 (85.4)
Death in induction rate, N(%)	50 (8.9)	29 (7.4)	25 (5.6)	117 (14.6)
OS, %	83% at 4-y	88% at 4-y	87.4% at 6-y	81% at 4-y
DFS, %	84% at 4-y	90% at 4-y	85.6% at 6-y	80% at 4-y
CIR, %	11% at 4-y	9% at 4-y	10.7% at 6-y	15% at 4-y

Open questions and ongoing endeavors

1. Can the inclusion of ATO improve the presently reported outcomes in the context of LMIC?
   - ✓ RIF+ATO ± minimal chemo – ICAPL current protocol
2. Can clinical network improve the outcomes of AML other than APL?
   - ✓ ICAML (National Lab performing NGS to better stratify risk and MRDs testing; – study (over 600 pts included)
3. How to increase awareness about APL among primary care and emergency practices ?

Conclusions

- Clinical networking resulted in the improvement of the outcomes of patients with APL treated in Latin America
- The infrastructure created is long-lasting
- The induction death rates decreased in about 50% in the first 5 years and remained in 11-14% over a period of 15 years
- Overall survival had a continuous improvement in the same period (OS-81% with 53m of FUP)
- Particularly for patients of low- and intermediate-reisk groups the treatment was efficent and with the expected toxicities

ACKNOWLEDGMENTS

American Society of Hematology
Nancy Berliner
Haesook T Kim
Martin Tallman,
Raul Ribeiro

Miguel Sanz
Francesco LoCoco (in memoriam)
Bob Lowenberg
David Grimwade (in memoriam)
Peter Valk
Richard Dillon
Arnold Ganser

Pablo Muxi
Carolina Oliver
Lem Martinez
Rosario Uriarte (in memoriam)

FAPESP
Luísa Koury,
Raul A. M. Melo,
Ana Beatriz F. Glória,
Katia Pagnano,
Elenaide C. Nunes,
Rosane I. Bittencourt,
Lorena L. Figueiredo-Pontes,
Fabiola Traina
Evandro M. Fagundes,
Bruno K.L. Duarte
Ricardo Pasquini
Ana Silvia G. Lima

Soledad Unduraga
Cristine Rojas

Juan R. Navarro
Ninoska Rojas,
Shirley Quintana,
Pamela Mora,
Percy Ortiz,
Jose Untama,

Victor Salinas
Ana Ayala-Lugo