CLINICAL SIGNIFICANCE OF OCCULT CENTRAL NERVOUS SYSTEM DISEASE IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA. A REPORT FROM THE CAMPUS ALL NETWORK MULTICENTER

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Aims

1) Evaluate the incidence of occult CNS positivity in a larger multi-centers series of acute lymphoblastic leukemia (ALL) patients treated from 2007 to 2017

2) Assess the impact of occult CNS status on outcome

CAMPUS ALL ACUTE LYMPHOBLASTIC LEUKEMIA

Clinical characteristics of patients according to the CNS status

	level	ALL	CNS	OCNSD	MCNSD	p
			75%	18%	7%	
n		**240**	**179**	**43**	**18**	
Sex (%)	F	103 (42.9)	76 (42.5)	20 (46.5)	7 (38.9)	0.835
	M	137 (57.1)	103 (57.5)	23 (53.5)	11 (61.1)	
Age (median [range])		45.00 [17.00, 80.00]	45.00 [17.00, 80.00]	46.00 [17.00, 72.00]	36.50 [18.00, 73.00]	0.302
Lineage (%)	B	184 (76.7)	140 (78.2)	34 (79.1)	10 (55.6)	0.088
	T	56 (23.3)	39 (21.8)	9 (20.9)	8 (44.4)	
WBC (median [range])		11000.00 [140.00, 573000.00]	11300.00 [140.00, 573000.00]	10600.00 [1440.00, 291500.00]	9400.00 [400.00, 133840.00]	0.799
Cytogenetic (%)	Abnormal	118 (64.5)	91 (63.6)	20 (69.0)	7 (63.6)	0.860
	Normal	65 (35.5)	52 (36.4)	9 (31.0)	4 (36.4)	
Treatment (%)	Conventional	91 (37.9)	70 (39.1)	15 (34.9)	6 (33.3)	0.400
	Intensified	120 (50.0)	85 (47.5)	23 (53.5)	12 (66.7)	
	Reduced	29 (12.1)	24 (13.4)	5 (11.6)	0 (0.0)	
LDH (median [range])		482.00 [21.00, 8332.00]	478.00 [21.00, 8332.00]	555.50 [55.00, 5532.00]	372.50 [180.00, 4086.00]	0.806
CSF WBC (median [range])		1.00 [0.00, 3000.00]	1.00 [0.00, 17.00]	1.00 [0.00, 7.00]	39.00 [7.00, 3000.00]	**<0.001**
CSF proteins (median [range])		36.50 [5.90, 326.00]	35.00 [5.90, 94.00]	38.50 [16.00, 161.00]	51.00 [23.00, 326.00]	**0.023**

Correlation between CNS status and outcome

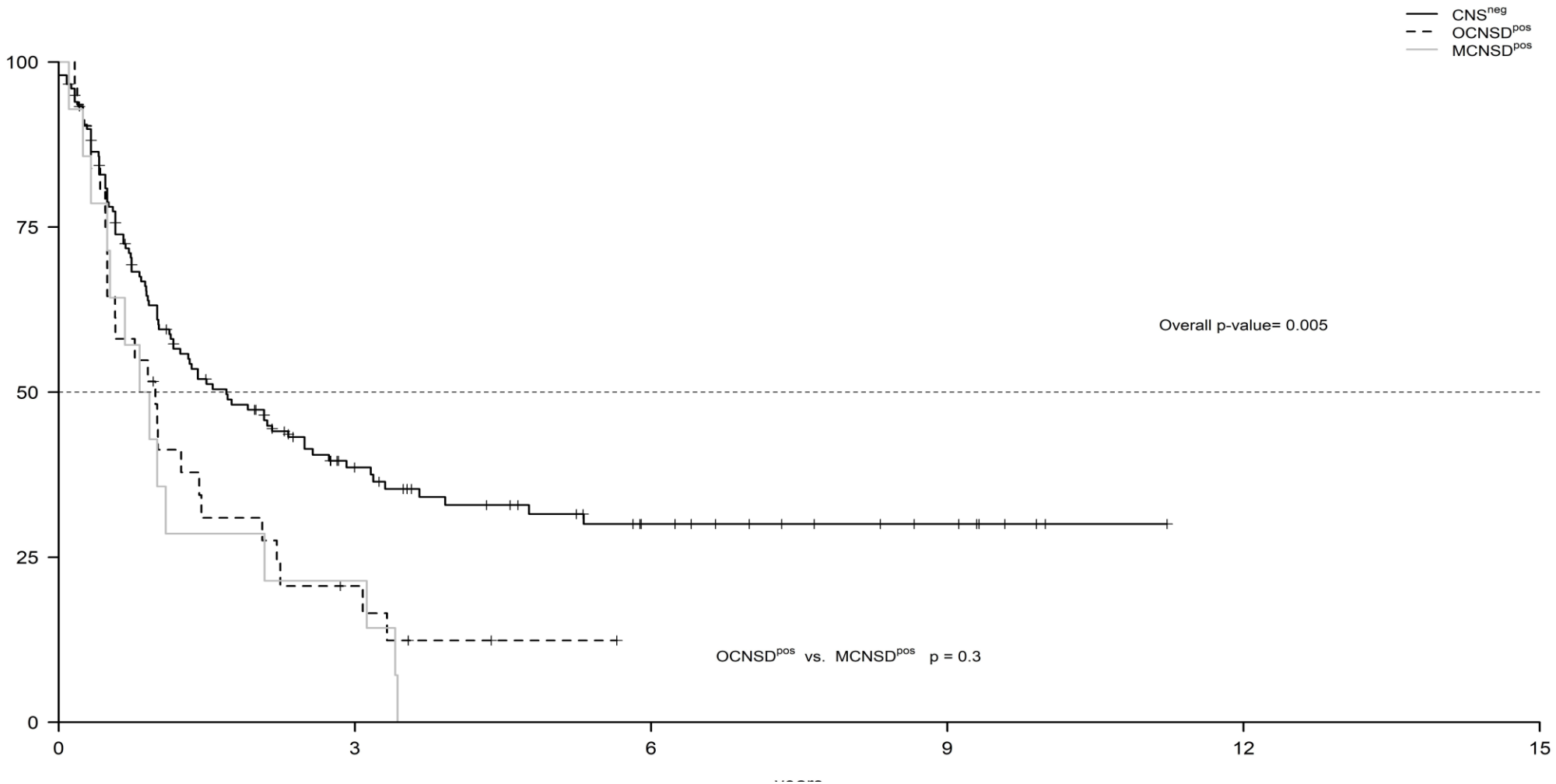
	level	ALL	CNS^{neg}	$OCNSD^{pos}$	$MCNSD^{pos}$	p
n		240	179	43	18	
Hematological response (%)	CR	198 (85.3)	152 (87.4)	32 (80.0)	14 (77.8)	0.317
	No CR	34 (14.7)	22 (12.6)	8 (20.0)	4 (22.2)	
ASCT (%)	No	88 (44.9)	65 (44.2)	17 (47.2)	6 (46.2)	0.944
	Yes	108 (55.1)	82 (55.8)	19 (52.8)	7 (53.8)	
Relapse (%)	No	78 (40.2)	70 (47.0)	7 (22.6)	1 (7.1)	**0.001**
	Yes	116 (59.8)	79 (53.0)	24 (77.4)	13 (92.9)	
Relapse site (%)	CNS	16 (16.8)	8 (12.7)	7 (31.8)	1 (10.0)	0.099
	BM	79 (83.2)	55 (87.3)	15 (68.2)	9 (90.0)	
OS 3 years	estimate (95% CI)	46.4(40.1-53.8)	52.9(45.5-61.5)	31.1(19.2-50.5)	22.2(9.4-52.7)	**<0.001**
DFS 3 years	estimate (95% CI)	34.3(27.9-42.2)	38.6(31-48)	20.6(10.2-41.9)	21.4(7.9-58.4)	**0.005**

CAMPUS ALL ACUTE LYMPHOBLASTIC LEUKEMIA

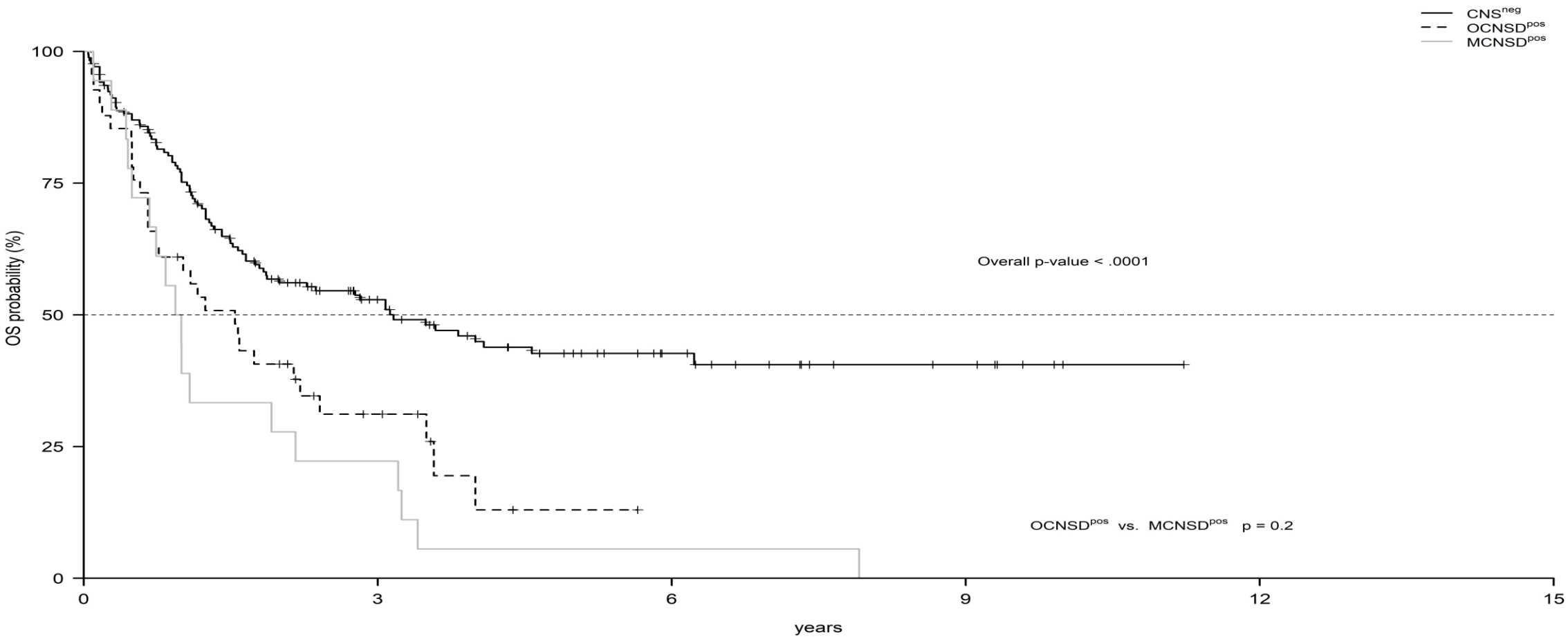
Univariate and multivariate analysis

	Univariate analysis				Multivariate analysis			
	HR	Lower 95%CI	Higher 95%CI	p	HR	Lower 95%CI	Higher 95%CI	P
Age	1.01	1	1.03	**0.0062**				
Sex: M vs F	1.044	0.739	1.474	0.8076				
Lineage T vs B	0.957	0.6367	14.375	0.8313				
WBC	1	1	1	0.3764				
Cytogenetic: Normal vs Abnormal	1.15	0.76	1.74	0.5101				
Treatment: Conventional vs intensified	0.61	0.42	0.88	0.0089	0.584	0.403	0.848	**0.0047**
Treatment: Conventional vs reduced	1.47	0.89	2.44	0.1295	1.708	1.027	2.842	**0.0393**
LDH	1	1	1	0.908				
CSF_WBC	1	1	1.001	0.5719				
CSF_proteins	1.008	1.002	1.013	**0.0071**				
ASCT yes vs no	0.564	0.387	0.823	**0.0029**				
$OCNSD^{pos}$ vs. CNS^{neg}	1.915	1.259	2.913	**0.0024**	2.03	1.333	3.093	**0.001**
$MCNSD^{pos}$ vs. CNS^{neg}	2.887	1.73	4.817	**<.0001**	3.392	2.015	5.71	**<.0001**

DFS based on CNS status



OS based on CNS status



CONCLUSION

FC allows to detect occult CNS disease, even in conditions of low spinal fluid leukemic count.

The presence of occult CNS disease anticipates an adverse outcome.

Considering the heterogeneity of treatments, further prospective studies on larger series are needed to confirm these data.

PROPOSAL

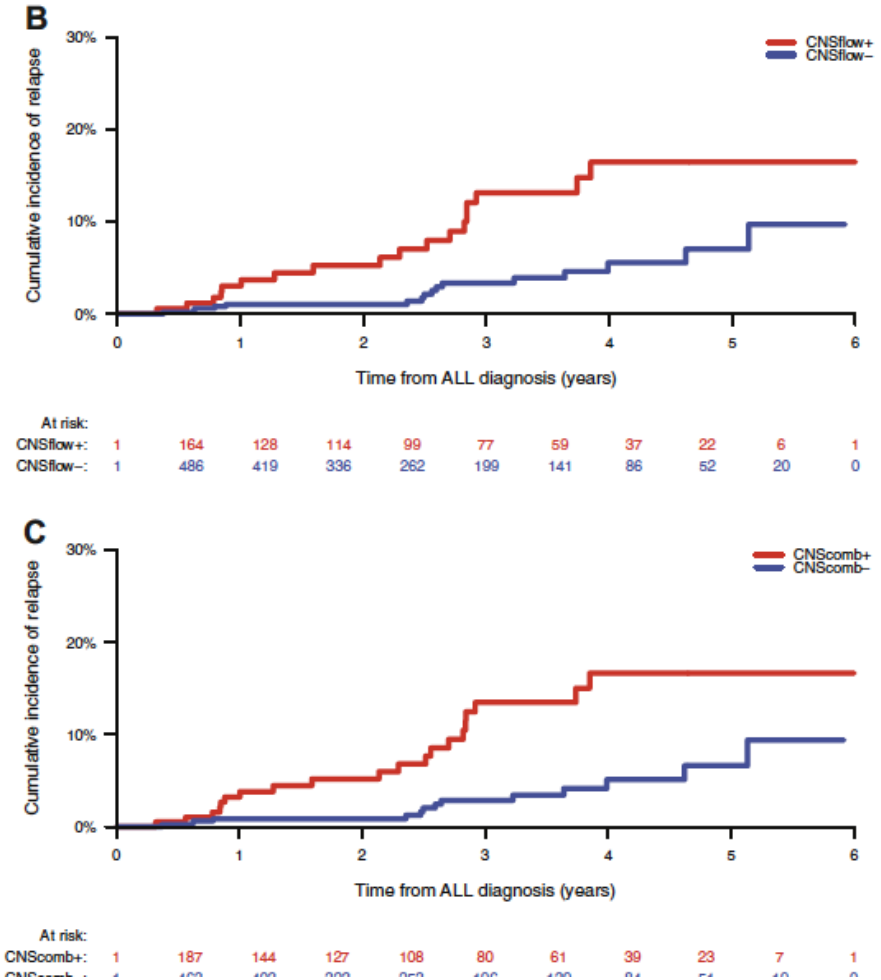


Table 3 Adjusted HR estimates from Cox proportional hazards models of event-free survival

	Adjusted EFS HR	95% CI	*P*-value
CNS status			
CNS_{comb+} vs. CNS_{comb-}	2.3	1.2–4.9	**0.011**
Sex			
Female vs. Male	0.9	0.5–1.6	0.65
Age			
Per 1 year	1.1	1.1–1.2	**<0.001**
WBC			
Per doubling	1.3	1.1–1.5	**0.0018**

Immunophenotype was included in the model as stratification factor. Significant *P*-values are highlighted in bold

HR hazard ratio, *CI* confidence interval, *CNS* central nervous system, *WBC* white blood cell count

Thastrup M, Marquart HV et al. Leukemia 2019; Sep 18. [Epub ahead of print

PROPOSAL

This study is the first to demonstrate that CNS_{flow+} at diagnosis is associated with higher risk of relapse in childhood ALL. This supports that flow cytometry should be incorporated into clinical practice together with cytospin for identification of CNS leukemia and stratification of CNS-directed therapy. However, whether CNS_{flow+} at any level should warrant increased CNS-directed therapy or this only should be indicated for patients with higher blasts level remains to be explored. Furthermore, the prognostic significance of persistent leukemic blasts in the CSF during induction therapy should be investigated in a larger patient cohort.

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PROPOSAL

A PROSPECTIVE, OBSERVATIONAL , MULTICENTER STUDY OF CLINICAL SIGNIFICANCE OF OCCULT CENTRAL NERVOUS SYSTEM INVOLVEMENT IN ADULT PATIENTS AFFECTED BY ACUTE LYMPHOBLASTIC LEUKEMIA. CAMPUS ALL

PROPOSAL

Experimental Design

At diagnosis, all patients affected by ALL routinely underwent at diagnostic lumbar puncture. Usually, all samples of CSF are evaluated by CC exam.

In our study, all samples of CSF will be evaluated by CC and FCM exam.

STUDY ENDPOINTS

Primary endpoint

To evaluate the correlation between occult CNS disease and disease free survival (DFS)

Secondary endpoints

To evaluate the incidence of occult CNS disease in adult patients with ALL

- To correlate the occult CNS disease with:
- Overall survival (OS)
- Relapse rate
- Hematologic or extra hematologic relapse
- Cumulative incidence of relapse (CIR)
- Minimal residual disease levels
- Molecular markers detected on CSF

PATIENT SELECTION

Inclusion Criteria

Patients aged ≥18 years with newly ALL underwent to diagnostic-therapeutic lumbar puncture

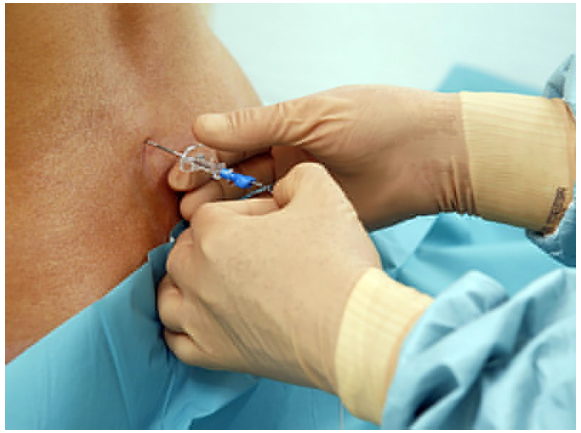
Signed written informed consent according to ICH/EU/GCP and national/local laws

Exclusion Criteria

Patients aged <18 years

ALL not at diagnosis

METHODS



- ✓ Morphologic examination will performed on cytospin preparation stained with May-Grunwald-Giemsa. CNS leukemia is defined as unequivocal morphologic evidence of leukemic blast in the CSF and/or mononuclear cell count ≥5/ml.
- ✓ For FCM exam, CSF samples of sufficient volume must be obtained via lumbar puncture.
- ✓ After sampling, CSF will be processed within 1 hour to avoid cell deterioration or specific fixative (TransFix/ethylenediaminetetraacetic acid EDTA; Immunostep SL Salamanca, Spain) will be used.
- ✓ A cocktail of 8 monoclonal antibodies will be used.
- ✓ All samples will be acquired until the exhaustion.
- ✓ The CSF acquisition will be local but 3 independent, expert operators will review each case.

METHODS

FLUOROCHROMES	FITC	PE	PERCPCy5.5	PE CY7	APC	APC CY7	V450	V500
B LINEAGE	CD10	CD22 or CD58	CD38	CD19	CD34	CD20	-	CD45
T LINEAGE	CD7 or CD2	CD99	CD3	CD4	CD1	CD8	CD5	CD45

METHODS

Sample Size

We calculated that sample side should be 361 patients. This sample size achieves 80% power to detect a difference of 5% .

CONCLUSION

This prospective, observational study could help us better understand the role of occult localization in the CNS and how to manage it to avoid extramedullary relapses on the one hand and excessive neurological toxicity on the other

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