FLT3 ligand plasma levels in acute myeloid leukemia

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Supplemental file

AML treatments

LAMSA2002 : Pigneux et al, 2017;35(4):387–393.

Active Comparator: B • Induction therapy Idarubicin, 8mg/m2 d1-5; Cytarabine, 100mg/m2 d1-7 and Lomustine, 200mg/m d1) If CR ou PR • maintenance therapy every 3 months = 6 courses of reinduction with : -idarubicin (8mg/m2 d1),cytarabine (100mg/m2d1-5), subcutaneously • between the courses, a continuous regimen of methotrexate and 6-mercaptopurine.	Drug: chemotherapy treatment (see arms) Induction chemotherapy + maintenance chemotherapy Other Name: Induction chemotherapy + maintenance chemotherapy
Experimental: A • Induction therapy Idarubicin, 8mg/m2 d1-5; Cytarabine, 100mg/m2 d1-7 and Lomustine, 200mg/m d1) If CR ou PR • maintenance therapy every 3 months = 6 courses of reinduction with : ○ idarubicin (8mg/m2 d1),cytarabine (100mg/m2d1-5, subcutaneously) ○ 10 to 20 mg (according to body weigh) of norethandrolone daily • between the courses, a continuous regimen of methotrexate and 6-mercaptopurine.	

BIG STUDY (on-going study: www.ClinicalTrials.gov NCT02416388).

Experimental: R1-IDA Idarubicin	Drug: Idarubicin Induction chemotherapy : Idarubicin 9mg/m² /day, from D1 to D5 (IV, 30min) + cytarabine 200mg/m²/day from D1 to D7 (IV 24 h) Bone marrow aspirate on D15 : if medullary blasts rate < 5% → G-CSF (5 µg/kg/day) until hematopoietic recovery (PNN ≥ 1 G/L).
Active Comparator: R1-DAUNO Daunorubicin	Drug: Daunorubicin Induction chemotherapy : Daunorubicin 90mg/m²/day, from D1 to D3 (IV, 30min)

	+ cytarabine 200mg/m² /day from D1 to D7 (IV 24 h) Bone marrow aspirate on D15 : if medullary blasts rate < 5% → G-CSF (5 µg/kg/day) until hematopoietic recovery (PNN ≥ 1 G/L).
Active Comparator: R2-HDAC High dose cytarabine	Drug: HD Cytarabine Consolidation chemotherapy course (s) : -High dose cytarabine: 3g/m² /12h on D1, D3 and D5 For all patients, G-CSF (5 µg/kg/day) : SC or IV (30 min) from D8 until hematopoietic recovery (PNN ≥ 1 G/L) Up to 3 consolidation courses, depending on the patient AML risk group
Experimental: R2-IDAC Intermediate dose cytarabine	Drug: ID cytarabine Consolidation chemotherapy course (s) : -Intermediate dose cytarabine: 1.5g/m² /12h on D1, D3 and D5 For all patients, G-CSF (5 µg/kg/day) : SC or IV (30 min) from D8 until hematopoietic recovery (PNN ≥ 1 G/L) Up to 3 consolidation courses, depending on the patient AML risk group
Active Comparator: R3-MAC-MTX Methotrexate and mycophenolic acid	Drug: Methotrexate GvHD prophylaxis post allogeneic SCT : -15 mg/m² on D+1 then 10 mg/m² on D+3, D+6 and D+11 Drug: Mycophenolic acid (MPA) GvHD prophylaxis post allogeneic SCT : • 720 mg BID from D0 to D+28 for HLA-identical siblings • 720 mg BID from D0 to D+45 for 10/10 HLA allele-matched unrelated donors
Experimental: R3-MAC-MPA Cyclosporine and mycophenolic acid	Drug: Cyclosporine GvHD prophylaxis post allogeneic SCT : -Cyclosporine : 3 mg/kg /day from D-1 (IV) or 6 mg/kg/day from D-3 (PO). Not to be stopped before D100 Drug: Mycophenolic acid (MPA) GvHD prophylaxis post allogeneic SCT : • 720 mg BID from D0 to D+28 for HLA-identical siblings

	• 720 mg BID from D0 to D+45 for 10/10 HLA allele-matched unrelated donors
Active Comparator: R3-RIC-CICLO Cyclosporine	Drug: Cyclosporine GvHD prophylaxis post allogeneic SCT : -Cyclosporine : 3 mg/kg /day from D-1 (IV) or 6 mg/kg/day from D-3 (PO). Not to be stopped before D100
Experimental: R3-RIC-MPA Cyclosporine and mycophenolic acid	Drug: Cyclosporine GvHD prophylaxis post allogeneic SCT : -Cyclosporine : 3 mg/kg /day from D-1 (IV) or 6 mg/kg/day from D-3 (PO). Not to be stopped before D100 Drug: Mycophenolic acid (MPA) GvHD prophylaxis post allogeneic SCT : • 720 mg BID from D0 to D+28 for HLA-identical siblings • 720 mg BID from D0 to D+45 for 10/10 HLA allele-matched unrelated donors
Experimental: R4-VOS-IDAC Intermediate dose cytarabine and vosaroxin	Drug: vosaroxin Consolidation chemotherapy course (s) : -70 mg/m² on D1 and D4 Drug: ID cytarabine Consolidation chemotherapy course (s) : -Intermediate dose cytarabine: 1.5g/m² /12h on D1, D3 and D5 For all patients, G-CSF (5 µg/kg/day) : SC or IV (30 min) from D8 until hematopoietic recovery (PNN ≥ 1 G/L) Up to 3 consolidation courses, depending on the patient AML risk group
Active Comparator: R4-IDAC Intermediate dose cytarabine	Drug: ID cytarabine Consolidation chemotherapy course (s) : -Intermediate dose cytarabine: 1.5g/m² /12h on D1, D3 and D5 For all patients, G-CSF (5 µg/kg/day) : SC or IV (30 min) from D8 until hematopoietic recovery (PNN ≥ 1 G/L) Up to 3 consolidation courses, depending on the patient AML risk group

LAM 2006CBF: Jourdan et al, Blood 2013;121(12):2213–2223.

TREATMENT DESIGN Induction course Systematic timed-sequential induction (arm A) DAUNORUBICINE (DNR): 60 mg/m2/day IV (30 min), Day 1, 2, and 3 CYTARABINE (AraC): 500 mg/m2/day Continuous infusion, Day 1 to 3 DAUNORUBICINE (DNR): 35 mg/m2/day IV (30 min), Day 8 and 9 CYTARABINE (AraC): 1 gr/m2/12 h IV (2h), Day 8, 9, and 10 Response-adapted timed-sequential induction (arm G) DAUNORUBICINE (DNR): 60 mg/m2/dayIV (30 min), Day 1, 2, and 3 CYTARABINE (AraC): 200 mg/m2/dayContinuous infusion, Day 1 to 7

Peripheral blood and bone marrow evaluation at Day 15. The following second induction course will be administered in patients with persistent marrow disease at Day 15 :

DAUNORUBICINE (DNR): 35 mg/m2/day IV (30 min), Day 16 and 17 CYTARABINE (AraC)1 gr/m2/12 h IV (2h), Day 16, 17, and 18 Persistent marrow disease at Day 15 is defined by more than 10% leukemic blasts in a non aplastic or non very hypoplastic bone marrow aspiration sample.

Salvage course In patients not reaching CR after the first induction course (either SI or TSI), a salvage course will be administered. Salvage therapy should not be initiated before Day 35 of arm A and Day 42 of arm G.

CYTARABINE (AraC) :3 gr/m2/12h IV (2h), Day 1, 3, 5, and 7 AMSACRINE : 100 mg/m2/day IV (30 min), Day 5 to 7 G-CSF lenograstim : from Day 8 until myeloid recovery (> 500 PMN/µL)

Consolidation cycles Three monthly cycles of consolidation will be administered in all patients reaching hematological CR after induction or induction + salvage.

CYTARABINE (AraC): 3 g/m2/12h IV (2h), Day 1, 3, and 5 G-CSF lenograstim : from Day 8 until myeloid recovery (> 500 PMN/µL)

Univariate analysis.

	2-year PFS	**2-year OS**
Age		
<60 years old	60% (44-80)	61.8% (43-87)
>=60 years	50·6% (34-75) p=0·36	55·5% (38-80) p=0·20
sFLc groups		
FLI	79·1% (64-87)	80·3% (66-97)
FLD	54·9% (36-82)	58·6% (39-86)
FLL	11·4% (12-66) p<0·001	18·7% (34-1) p=0·09
Median sFLc at day+15 induction		
<median(2952 pg/mL)	38·2% (23-62)	44·6% (26-76)
>=median	71·8% (56-90) p=0·02	73·3% (58-91) p=0·24
Median sFLc at day+22 induction		
<median (1390 pg/mL)	38·9% (24-63)	47·6% (29-75)
>=median	72·1% (57-90) p=0·02	73·6% (59-91) p=0·34
Higher sFLc during induction		
<median (4138 pg/mL)	40% (25-63)	48.5% (30-76)
>=median	72.9% (58-91) p=0.02	71.4% (56-90) p=0.38
ELN 2010		
Favorable	67·1% (44-1)	70·9% (52-96)
Int1 + Int2	57·1% (40-80)	61·1% (44-84)
Adverse	33% (14-74) p=0·06	42·.8% (20-88) p=0·18
% of blasts <median	50·9% (35-72)	53·2% (34-81)
>=median	60% (42-84) p=0·25	64·5% (46-88) p=0·26
WBC <20 Giga/L	53·8% (40-71)	55·7% (40-77)
>=20 Giga/L	58·3% (36-94) p=0·56	67·7% (47-97) p=0·75

Multivariate analysis

Progression-free survival	HR	95%CI	P value
sFLc groups	3·62	1·65-7·94	0·001
ELN 2010	1·74	0·98-3·10	0·05
Median sFLc at day+15	0·99	0·99-1·00	0·37
Median sFLc at day+22	1·00	0·99-1·00	0·24

Age not retained in the model.

Overall survival	HR	95%CI	P value
sFLc groups	2·0	1·12-6·07	0·02
ELN 2010	1·44	0·76-2·71	0·25
Age	1·02	0·97-1·07	0·374
Median sFLc at day+22	1·00	0·99-1·00	0·43

Median sFLc at day+15 not retained in the model.

Abbreviation: sFLc: soluble FLT3 ligand concentration.