参考資料 7

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Phase I/II Study of gemtuzumab ozogamicin in combination chemotherapy for CD33+ refractory or relapsed AML: JALSG-AML206

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Background

- Current treatment results in young adults with non-APL-AML are improving (%CR >70%, 5Y-OS 40-50%), however, quite a few patients relapse or refractory to initial therapies.

STUDY	N	CR %	ED %	OS % (3-5 yr)
CALGB	474	72	9	34
GAMLCG	535	74	11	39
HOVON	253	77	7	38
ALFA	345	82	9	38
JALSG	1,064	78	4	51

Tallman M,2007

Study	N	%CR	OS	DFS
AML87	188	79.8	30.2	28.5
AML89	232	78.5	35.1	43.7
AML92	566	77.2	33.5	31.6
AML95	480	80.7	44.3	28
AML97	789	78.7	40.8	35.5
AML201*	1057	78	51	
IDR	532	78.6	53.1	41.8
DNR	525	77.5	49.1	42.2

* Obtake S, et al. Blood 108:566a #2000,2006

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Background

- Patients with relapsed or refractory AML have a poor outcome (%CR<50%, 5Y-OS<30%).
- Gemtuzumab ozogamaicin(GO)is a humanized anti-CD33 MoAb conjugated with cytotoxic antitumor antibiotic, calicheamicin, that target CD33 Ag. More than 80% of AML cells have CD33 on their surface.
- GO induces CR+CRp in about 30% of relapsed/refractory AML
- Several studies tested the use of GO in combination chemotherapy, either at diagnosis or at time of relapse and most of them are more promising than monotherapy.

ORR 76%

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AIMS and OBJECTIVES

- AIMS
  - In order to improve outcome of patients with AML, we investigate effective salvage therapies combining new agent (GO) with conventional chemotherapy (JALSG AML201 induction therapy regimen)
- OBJECTIVES
  - Determine: Maximum tolerated dose (MTD)
  - DLTs:
    - >Grade 4(CTCAE ver 3.0) of FN, Bleeding, Nausea & Vomiting, Infusion reaction, liver toxicity (hyperbilirubinemia, hypertransaminasis)
    - >Grade 3(CTCAE ver 3.0) or more of non hematologic toxicity not related to progression of AML
    - Prolongation of bone marrow suppression (ANC<500 μL, PLT<20,000/μL) over 6 weeks not related to AML
  - Toxicity profile (NCI-CTCAE ver3)
  - Response Rate (International Working Group Criteria)

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Eligibility

Inclusion Criteria

1. CD33+ de novo AML except APL ; refractory to the first remission induction therapy or first relapse (>6 months from CR1)
2. Age 20 – 64
3. ECOG performance status of PS 0 or 1
4. After 30 days or more from initial therapy and recovered to baseline from any toxicities of prior chemotherapy
5. Adequate hepatic, cardiac, renal, pulmonary function
6. Life expectancy ≥ 2 months

Exclusion Criteria

1. Previous MDS/MP
2. Secondary AML
3. CNS leukemia
4. Received Transplantation
5. Women who are pregnant or breastfeeding
6. Received therapy with anti-CD33 MoAb
7. Concurrent active malignant disease
8. Uncontrolled infection
9. HBV,HCV or HIV infection
10. Treated with investigational drugs
11. Previously received cumulative dose of >500 mg/m^2 of DNR(only for DAG arm)

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JALSG AML206-P1: Treatment Schedule

1. IDR arm (IAG)

IDR+Ara-C+GO Combination

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ara-C 100 mg/m²/day c.i.v.	↓	↓	↓	↓	↓	↓	↓
IDR 12or10mg/m²/day 4 i.v.	↓	↓	↓				
GO 1or 5mg/m²/day 2hr d.i.v.				↓			

2. DNR arm (DAG)

DNR+Ara-C+GO Combination

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ara-C 100mg/m²/day c.i.v.	↓	↓	↓	↓	↓	↓	↓
DNR 50mg/m²/day 4i.v.	↓	↓	↓	(↓)	(↓)		
GO 1or 5mg/m²/day 2hr d.i.v.				↓	(↓)	(↓)	

Level-1
IDR 10 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 3 mg/m² 2hr-DIV

Level-2
IDR 12 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 3 mg/m² 2hr-DIV

Level-3
IDR 12 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 5 mg/m² 2hr-DIV

Level-1
DNR 50 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 3 mg/m² 2hr-DIV

Level-2
DNR 50 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 3 mg/m² 2hr-DIV

Level-3
DNR 50 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 3 mg/m² 2hr-DIV

Level-4
DNR 50 mg/m² DIV
Ara-C 100 mg/m² CIV
GO 5 mg/m² 2hr-DIV

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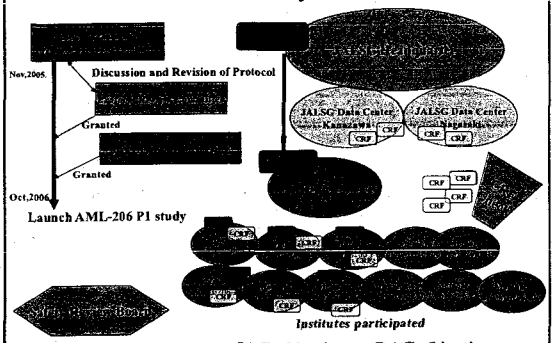
AML206 Study Schema



IAG: 6 institutes DAG: 5 institutes

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Patients Demographics

	Overall	IAG	DAG
N	19	9	10
M:F	9:10	4:5	5:5
Age			
Median	59	61	58
Range	33 - 64	38 - 64	33 - 62
Relapsed	14	7	6
Refractory	5	2	4
AML Subtypes			
M0	1		1
M1	1	2	1
M2	7	3	5
M4	6	3	3
M5	1	1	
Karytype			
CBF	2	1	1
CN	10	6	4
11q23	1	1	
t(6;9)	1		1
Complex	3	1	2
Others	2		2

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Patients Demographics-2

	Overall	IAG	DAG
Pre-treatment Status			
WBC (x10³/μL)			
Median (Range)	3.0 (0.9-39.2)	3.7 (2.6-39.2)	2.1 (0.9-25.3)
Hb (g/dl)			
Median(Range)	10.9 (7.1-13.6)	12.5 (7.6-13.6)	10.6 (7.1-12.8)
PLT (x10⁴/μL)			
Median (Range)	8.8 (2.6-44.3)	5.9 (2.6-20.7)	13.5 (3.4-44.3)
%Blasts			
Median (Range)	42.8 (7.9-96.8)	56.4 (17.3-88)	29.9 (7.9-96.8)
%CD33 Blasts			
Median (Range)	89.4 (39-100)	92.9 (62.8-100)	80.6 (39-96.9)

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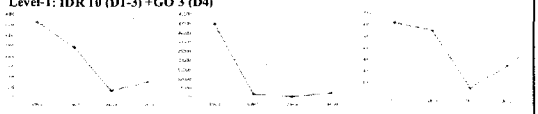
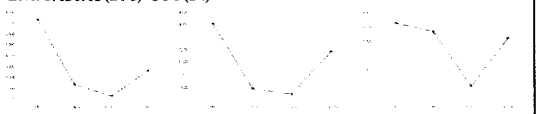
IAG: WBC & ANC

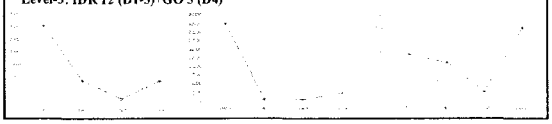
Level-1: IDR 10 (D1-3) +GO 3 (D4)



Level-2: IDR 12 (D1-3)+GO 3 (D4)



Level-3: IDR 12 (D1-3)+GO 5 (D4)



IAG: WBC & ANC

Level-1: IDR 10 (D1-3) +GO 3 (D4)

WBC	Level-1	Level-2	Level-3
Days of nadir	Days 11,9,16	Days 10,8,13	Days 9,8,10
Days of recovery	Days 33,58*,27	Days 27,37,38	Days 42,38,27**

*AML progression, ** Administration of G-CSF

Level-2: IDR 12 (D1-3)+GO 3 (D4)

Value of ANC	
Pre GO	517 (8-4374) /μL
Nadir	0 (0-78) / μL

Level-3: IDR 12 (D1-3)+GO 5 (D4)

ANC	Level-1	Level-2	Level-3
Days of nadir	Days 14,9,9	Days 10,10,10	Days 15,10
Days of recovery	Days 33,58,29	Days 27,37,38	Days 42,33,34*

*AML progression, ** Administration of G-CSF

IAG: Hematologic Toxicity

Hb	Level-1	Level-2	Level-3
Grade 0	0	0	1
Grade 1	1	1	1
Grade 2	2	1	1
Grade 3/4	0	0	0
Units of RBC-TF	4,4,12	4,6,2	8,16,4

Hb	Level-1	Level-2	Level-3
Days of nadir	Days 26,35,16	Days 18,27	Days 7,23
Days of recovery	Days none,39,35	Days 21,29	Days 30,27

Platelet	Level-1	Level-2	Level-3
Grade 3	3	2	3
Grade 4	0	1	0
Units of PLT-TF	90,130,100	130,130,50	70,220,70

PLT	Level-1	Level-2	Level-3
Days of nadir	Days 11,11,17	Days 13,13,17	Days 14,8,17
Days of recovery	Days 33,none,none	Days none,46,38	Days 28,90,34

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IAG: Non-Hematologic Toxicity

	Level-1 (N=3)	Level-2 (N=3)	Level-3 (N=3)
Febrile Neutropenia			
Grade 3	3	2	2
Grade 4			1
Infection (Grade 4)			
Sepsis			1
Cerebral Abscess			1
Hepatic			
Grade 2	1	1	1
Grade 3			2
Anorexia, Nause/ Vomiting			
Grade 2			2
Edema			
Grade 1			2
Skin rash			
Grade 2			1
Diarrhea			
Grade 1			1
VOD/SOS	0	0	0

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DAG: WBC & ANC

Level-1: DNR 50 (D1-3)+ GO 3(D4)

WBC	Level-1	Level-2	Level-3
Days of nadir	Days 10,13,10	Days 10,10,7,12	Days 8,10,12
Days of recovery	Days 27,27,36	Days 27,22,24,32	Days 38,29,26

Level-2: DNR 50 (D1-4)+ GO 3(D5)

Value of ANC	
Pre GO	429 (3-1250) /μL
Nadir	0 (0-1) / μL

Level-3: DNR

ANC	Level-1	Level-2	Level-3
Days of nadir	Days 10,11,11	Days 14,17,9,12	Days 12,12,17
Days of recovery	Days 29,32,36	Days 27,22,N/A,32	Days 39,29,31

DAG: Hematologic Toxicity

Hb	Level-1	Level-2	Level-3
Grade 0	0	2	0
Grade 1	3	1	1
Grade 2	0	1	2
Grade 3/4	0	0	0
Units of RBC-TF	18,0,6	0,6,10,10	6,6,8

Hb	Level-1	Level-2	Level-3
Days of nadir	Days 11,13,39	Days 13, 6	Days 22,14,21
Days of recovery	Days 20,15,36	Days 22,44	Days 28,25,26

Platelet	Level-1	Level-2	Level-3
Grade 3	2	4	3
Grade 4	1	0	0
Units of PLT-TF	150,60,90	50,70,110,170	170,60,40

PLT	Level-1	Level-2	Level-3
Days of nadir	Days 11,13,20	Days 13,10,11,12	Days 25,12,17
Days of recovery	Days 25,32,34	Days 36,24,N/A,46	Days 38,34,26

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DAG: Non-Hematologic Toxicity

	Level-1 (N=3)	Level-2 (N=4)	Level-3 (N=3)
Febrile Neutropenia			
Grade 3	1	3	2
Grade 4	2		
Hepatic			
Grade 2			2
Grade 3	1	1	
Anorexia, Nause/ Vomiting			
Grade 2	1		1
Colitis			
Grade 2	1		
Diarrhea			
Grade 2			1
Cardiac			
Grade 2		1	
Bleeding			
CNS		1*	
Laboratory			
Hypophosphatemia		1	
VOD/SOS	0	0	0

* Due to Disease Progression

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Assessment of DLT

	No of Pts	No of DLT	
IAG			
Level-1	3	0	
Level-2	3	0	
Level-3	3	3	Prolongation of neutropenia Prolongation of thrombocytopenia Grade 4 Infection (Brain Abscess)
DAG			
Level-1	3	0	
Level-2	4	0	
Level-3	3	0	
Level-4	SRB recommended not to proceed		

IAG-Level-3 is MTD
DAG-Level-4 will be MTD

Recommend Dose & Schedule: IAG-Level-2
DAG-Level-3

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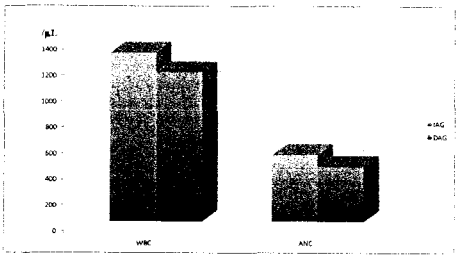
Median Counts of WBC & ANC at Administration of GO



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Response

	IAG			DAG			
	Level-1 (N=3)	Level-2 (N=3)	Level-3 (N=3)	Level-1 (N=3)	Level-2 (N=4)	Level-3 (N=3)	Total (N=19)
	(IDR 10/GO 3)	(IDR 12/GO3)	(IDR 12/GO 3)	(DNR 36/GO3 D4)	(DNR 46/GO 3 D5)	(DNR 50/GO 3 D6)	
CR	1	2				1	9
CRp							1
PR						1	2
NR (Blast Clearance)	1					1	4
Resistant Disease	1	1					3

ORR (CR+CRp)	10/19 (53%)
REL	8/14 (57%)
REF	2/5 (40%)
Karyo	
CN	4/10 (40%)
CBF	1/2 (50%)
Comp/Others	3/5 (60%)

Outcome:
Alive: 18 patients
Dead: 1 patient (DAG-level-2) died of CNS bleeding due to PD

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Conclusion

1. **Combination of GO with conventional(as JALSG) IDR+Ara-C or DNR-Ara-C is well tolerated and active in relapsed/ refractory AML**
2. **MTD of GO in the combination is considered 5 mg/m² (just after IDR or DNR administration)**
3. **Major toxicities are severe neutropenia, thrombocytopenia, febrile neutropenia**
4. **No VOD/SOS was observed**
5. **Both of IAG [IDR 12 mg/m² (D1-3)+Ara-C 100 mg/m² (D1-7)+GO 3 mg/m² (D4)] and DAG [DNR (50 mg/m² D1-5)+Ara-C 100 mg/m² (D1-7)+GO 3 mg/m² (D6)] therapies are recommend for phase II study to evaluate long term efficacy and safety**

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