急性前骨髄球性白血病に対する寛解期での自家移植の意義：FBMTGの経験と文献的考察

Role of autotransplantation in the treatment of acute promyelocytic leukemia patients in remission: Fukuoka BMT Group Observations and a literature review

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Introduction

自家移植はAMLの寛解後療法として広く用いられているが，ATRA併用化学療法による治癒率が向上したAPL，特に地固め療法が終了した時点で分子学的寛解のAPLでは，自家移植は必ずしも必要とされない．APL治療は現在，ATRAとアントラサイクリンを中心に組み立てられ，シタラビン（CA）の意義が疑問視されるなど，治療強度が軽減されてきた．しかし最近ではハイリスク群の再発を抑えるため，CA大量療法の意義が見直され，EBMTのAPLに対する造血幹細胞移植のretrospective dataが報告されるなど，APL治療への考え方にも変化が見られる．FBMTGでは現在APLの第1寛解期（CR1）においてupfrontにauto-PBSCTを施行していないが，過去にCR1でauto-PBSCTを行なった20例と，第2寛解期（CR2）でauto-PBSCTを行った6例について，長期的な経過を検討し，リスク別層別化治療や亜ヒ酸（ATO）が導入された現在のAPL治療における自家移植の意義について，文献的考察を加えて報告する．

Patients characteristics

1992年4月～2008年11月に，FBMTGの6施設で寛解期に骨髄破壊的移植前治療の後にauto-PBSCTを行った，APLの26例を対象とした．全例がFAB分類でAPLと診断され，染色体検査で t(15; 17)(q22; q21)を認めるか，RT-PCR検査で PML/RARα キメラ遺伝子が検出された．

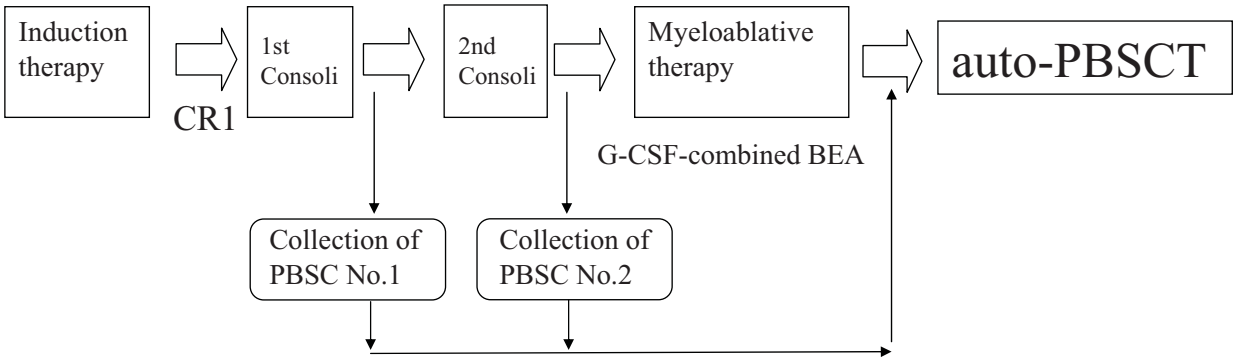
Patients characteristics

Patients received auto-PBSCT in CR1 between April 1992 to November 2002

Patient No.	Age/Sex	Initial WBC ($x10^9$/L)	Initial PLT ($x10^9$/L)	Additional chromosomal abnormality
1	34/F	2.5	7.0	6q-
2	37/M	21.9	10	complex
3	16/M	1.0	16	-7
4	45/F	0.6	59	no
5	51/F	17	12	no
6	41/M	10.2	10	no
7	53/M	0.85	11	+8
8	34/F	0.8	33	no
9	45/M	20.6	30	no
10	65/F	0.5	8	no
11	68/M	0.8	33	no
12	26/F	2.6	34	no
13	42/M	13.2	65	no
14	47/M	2.0	100	+8
15	47/F	1.8	17	no
16	31/M	5.5	1.0	+8
17	25/M	1.2	9.0	no
18	53/F	8.9	24	no
19	50/M	1.4	67	no
20	52/M	4.76	24	no

Chemotherapy and collection of PBSC

Auto-PBSCT for CR1

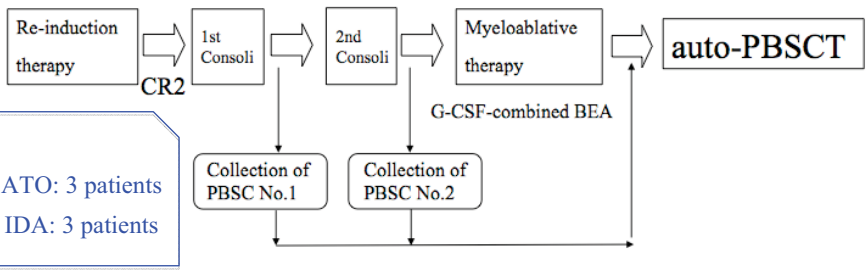


Patients characteristics

Patients received auto-PBSCT in CR2 between August 1993 to November 2008

Patient No.	Age/Sex	Initial WBC ($x10^9$/L)	Initial PLT ($x10^9$/L)	Additional chromosomal abnormality	Months from Diagnosis to Relapse	Types of Relapse
21	50/F	8.9	55	no	20	Hematological
22	39/M	3.3	2.0	no	8	Hematological
23	41/F	8.4	31	no	23	Molecular
24	37/F	1.5	7.0	no	54	Hematological
25	46/F	1.1	77	no	21	Molecular
26	45/M	1.5	101	-11q	12	Molecular

Chemotherapy and collection of PBSC



Re-induction therapy

Cytotoxic chemotherapy without ATO: 3 patients

ATO 0.15mg/m2 with or without IDA: 3 patients

Characteristics of 26 patients transplanted in CR1 and CR2

	CR1 (n = 20)	CR2 (n = 6)
Age	45(16-68)	46(37-50)
Sex (M / F)	12/8	2/4
WBC at Diagnosis		
>10x10^9/L	5	0
≦ 10x10^9/L	15	6
Additional chromosomal abnormality		
Yes	6	1
No	14	5
Months from diagnosis to auto-PBSCT	6 (5-13)	25.5 (12-61)
Months from auto-PBSCT to present	133(37-193)	41 (2-187)
Infused CD34+ cells (x10^{6}cells/kg)	7.1(1.03-20.2)	6.1(0.5-11.2)

G-CSF-combined BEA

			Day	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
G-CSF	**200 μ g/sqm,div.**			↓	↓	↓	↓	↓	↓	↓						
	400 μ g/sqm,div.										↓	↓				
CA	**100mg/sqm, div.**					↓	↓	↓	↓	↓	↓	↓				
BU	**4mg/kg,**	**po.**					↓	↓	↓	↓						
Etop	**20mg/kg,**	**div.**									↓	↓				
CA	**3g/sqm,**	**div. every 12hr**											↓ ↓	↓ ↓		

Auto-PBSCT

Results

	Auto-PBSCT in CR1 (n = 20)	Auto-PBSCT in CR2 (n = 6)
Days from auto-PBSCT		
Absolute granulocyte count > 0.5 x 10^9/L	**15 (13–24) days**	**11 (9–12) days**
Platelets > 20 x 10^9/L	**11 (8–210) days**	**14 (11–15) days**
Independence from platelet infusion	**11 (6–191) days**	**11 (8–15) days**
TRM	**0%**	**0%**
Median follow-up time	**133 (73–193) months**	**41 (2–187) months**
MRD (PML/RARα mRNA)		
Pretransplant BM	**–**	**Negative: 6 patients**
Graft (PBSC)	**Negative:14 patients**	**–**

Discussion

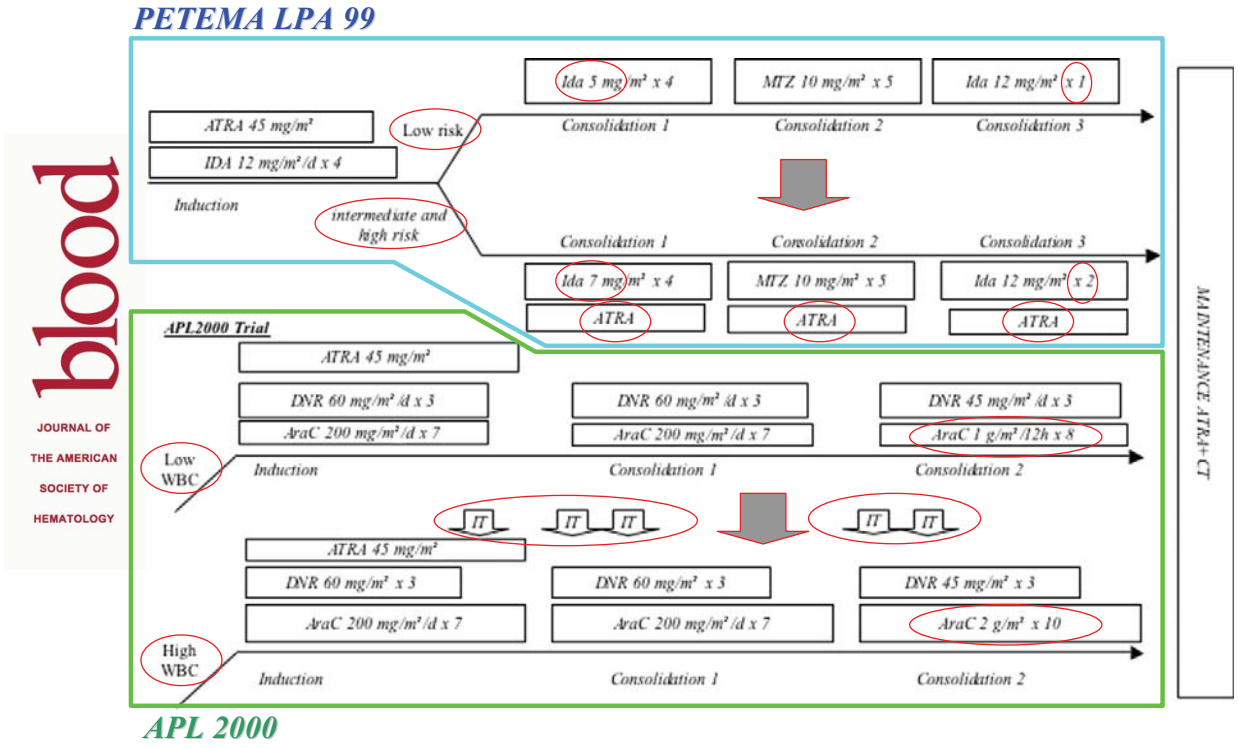
CR1

Autotransplantation results in APL

Author (Publication)	N	Age (Median)	Disease Status at Transplant	Source of autotransplantation	Pretransplant BM PCR	Graft PCR	TRM	Outocome
Mandelli et al	187	30	CR1: 129	BM	Not available	Not available	18%(CR1)	48% 7-years LFS(CR1)
(1994)			CR2: 58				23%(CR2)	31% 7-years LFS(CR2)
Meloni et al (1997)	15	38	CR2: 15	BM	Negative 8 Positive 7	Not available	0%	Median survival 28 months
Ferrant et al	36	Not available	CR1: 36	BM	Not available	Not available	Not available	70% 3-years LFS
(1997)								83% at 3-years OS
Roman et al (1997)	10	47	CR1: 8 CR2: 1 PR: 1	BM 4 PB 6	Negative 2	Not available	0%	90% median survival 41 monts
Lo Coco et al (1997)	8	40	CR2: 8	BM	Negative 8	Not available	0%	75% DFS at 9.5 months
Ottaviani et al (1998)	16	30	CR1: 13 PR: 1 CR2: 1 CR3: 1	BM	Negative 12 Posirtive 3	Not available	0%	Median duration of CR1: 55 months
Thomas et al (2000)	22	Not available	CR2: 22	BM 5 PB 17	Negative 9 Positive 1	Negative 2 positive 4	9%	79% at 3-years OS
Ferrara et al (2004)	6	38	CR2: 6	BM or PB	Negative 6	Negative 6	0%	83% at 36 months
de Botton et al (2005)	50	45	CR2: 50	BM 43 PB 7	Negative 28 Positive 2	Negative 20 Positive 2	6%	79.4% LFS at 7 years
Sanz et al	344	50(CR1)	CR1: 149	CR1: BM 92, PB 57	Not available	Not available	10%(CR1)	70% 5-years LFS(CR1)
(2007)		38(CR2)	CR2: 195	CR2: BM 91, PB 104			16%(CR2)	51% 5-years LFS(CR2)
Thirugnanam R et al (2009)	14	33	CR2: 12 CR3: 2	PB	Negative 14	Not available	0%	83.3% 5-years EFS
FBMTG	26	45	CR1: 20	PB		CR1: Negative 15	0%	100% 11-years LFS(CR1)
(2010)			CR2: 6		CR2: Nevative 6			100% 3-years LFS(CR2)

Discussion

Design of the LPA99 and the APL2000 trials



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JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Ades, L. et al. Blood 2008;111:1078-1084

Discussion

CR1

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Discussion

CR2

Autotransplantation results in APL

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Discussion

Mmimal residual disease (MRD)

Induction: ATRA-based chemotherapy

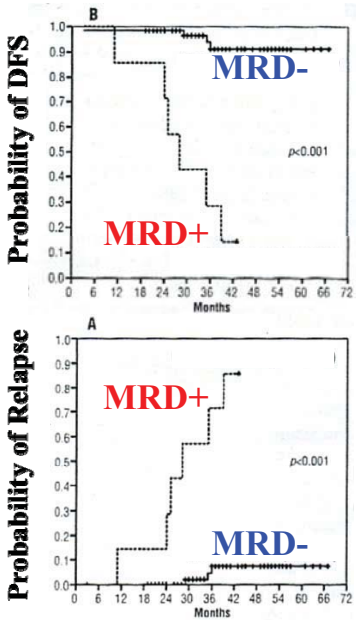
Three consolidation course: 1st consoli : IDA 5mg d1-4

2nd consoli : Mit 10mg d1-5

3rd consoli : IDA 12mg d1

Maintenance : ATRA(15d/3months) + 6MP+ MTX

	MRD-	MRD+
Induction	34/69(49.3%)	35/69(50.7%)
	GIMEMA 60.3%	
	PETHEMA 51.3%	
1st consoli	23/35	12/35
2nd consoli	10/12	2/12
3rd consoli	1/2	1/2



Lee. et al. Hematologica 2007;91:671-674

Conclusion

1. auto-PBSCTをCR1で行った20例，CR2で行った6例ともに，重篤なRRTやTRMを認めず，安全に施行できた.

2. 初診時WBC 10000/μl以上の症例を5例を含む，CR1でのauto-PBSCT施行した20例は，観察期間中央133ヶ月で全例が無再発生存していた.

3. CR2でauto-PBSCTを行った6例は，分子学的寛解に達した後の再発であり，auto-PBSCT後，観察期間41ヶ月で全例が無再発生存していた.

4. CR1でauto-PBSCTした20例中，検査した14例全例がgraft（PBSC）中のMRD陰性で，CR2でauto-PBSCTした6例全例が移植前の骨髄MRDが陰性だった.