aggressive clinical course.[4] In the present paper, we report our preliminary findings in six MDS patients with i(17q).

Between 1990 and 2000, we performed cytogenetic analysis at diagnosis in 383 cases of MDS diagnosed according to the FAB criteria. Six (1.57%) of these cases had i(17q)(Table 1), this incidence being similar to that in other series.[4] The 6 patients were aged from 31 to 68 years old; 4 were male, 2 female. All of them had moderate to severe anemia (hemoglobin 22-70g/L), a low to normal leukocyte count (0.7-9.8×10⁹/L), and platelet values ranging between 10 and 179×10⁹/L. Blood films showed dysgranulocytopoiesis, with pseudo Pelger-Hüet anomaly, confirming the previously reported association of Pelger-Hüet anomaly with 17p loss.[4] The predominant feature of the bone marrow smears was granulocytic hyperplasia with dysgranulocytopoiesis. Pelger-Hüet neutrophils were seen in all cases; other manifestations of neutrophil dysplasia included hypogranularity, ringed nuclei and cytoplasm containing varying numbers of small clear vacuoles. No eosinophilia, basophilia, or monocytosis was found in the bone marrow smears, which was not concordant with results reported by others.[2-4] Dysmegakaryocytopoiesis was observed in all the cases, and may be another morphologic feature of MDS patients with i(17q) (Table 1). Bone marrow biopsies from the patients did not show fibrosis in any case. Clinically, two patients had mild hepatomegaly (1.5 cm and 1.0 cm below the costal margin). Neither splenomegaly nor adenopathy was found in any of the 6 patients. An i(17q) was the only structural cytogenetic abnormality identified in all the cases. Two cases (# 2 and 3) had additional numerical abnormalities and another two (# 5 and 6) had a residual normal karyotype. As far as regards clinical outcomes, two patients (#1 and 4) were lost from follow-up, one (# 6) died from myocardial infarction 3 months later, two (# 2 and 3) developed AML 12 and 14 months later, respectively, with survivals of 15 and 18 months from diagnosis, respectively. Only one patient (# 5) is known to be alive after 6+ months of follow-up.

In conclusion, our findings support the concept that MDS patients with i(17q) should be considered as a unique subset, accounting for about 1% of MDS; this condition is characterized by a male predominance, severe anemia, hyposegmentation of neutrophils, increased micromegakaryocytes, and a poor prognosis.

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Evaluation of leukemic contamination in peripheral blood stem cell leukaphereses vs bone marrow after consolidation therapy in acute myeloid leukemia: not a critical factor in outcome?

Evaluation of leukemic contamination in peripheral blood stem cell leukaphereses and in bone marrow after consolidation therapy in 40 patients with acute myeloid leukemia presenting cytogenetic/molecular abnormalities at diagnosis shows a close relationship between persistence of the disease-related clone, adverse karyotype and poor prognosis.

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Autologous stem cell transplantation (ASCT) is increasingly used as treatment of acute myeloid leukemia (AML); however, one unresolved issue remains the optimal source of stem cells. While the use of peripheral blood stem cells (PBSC) has significantly lowered morbidity and mortality,[1] with the potential advantage of less leukemic contamination than present in bone marrow (BM) grafts,[2-3] the large amount of reinfused cells might increase the probability of contamination and relapse.[4] Investigation of residual disease (RD) in AML is limited to patients showing cytogenetic or molecular abnormalities at diagnosis, accounting for approximately 50 % of cases.[5] Furthermore, RD detection is of varied clinical relevance as AML1/ETO transcripts may persist in long-term survivors who have AML with t(8;21),[6] while detection of PML/RARα and CBFβ/MYH11 positive cells is highly predictive of relapse in acute promyelocytic leukemia (APL) and AML with inv16, respectively.[7-8]

Between January 1994 and June 2002 we used conven-

Table 1. Patients' characteristics.

	Pts.	*Sex*	*Age (yrs.)*	*FAB*	*Karyotype*	*PCR analysis*
1	CM*	F	61	M3V	t(15;17)	PML/RARα
2	CG	M	58	M3	t(15;17)	PML/RARα
3	CL	F	40	M3	t(15;17)	PML/RARα
4	FV*	M	51	M3	t(15;17)	PML/RARα
5	DNN*	M	49	M3	t(15;17)	PML/RARα
6	CM	F	24	M3V	t(15;17)	PML/RARα
7	FM	F	38	M3V	t(15;17)	PML/RARα
8	DVA	M	29	M3	t(15;17)	PML/RARα
9	BG*	M	39	M3	t(15;17)	PML/RARα
10	CT*	F	54	M3	t(15;17)	PML/RARα
11	TF*	M	54	M3	t(15;17)	PML/RARα
12	CD*	F	37	M3	t(15;17)	PML/RARα
13	CS	M	44	M3	t(15;17)	PML/RARα
14	SB*	F	18	M3	t(15;17)	PML/RARα
15	RN*	M	20	M3	t(15;17)	PML/RARα
16	LD	M	36	M0	t(9;22)	P190
17	BR	M	57	M0	t(9;22)	P190,P210
18	AD	M	26	M1	t(9;22)	P190
19	EL	F	45	M1	t(6;11)	AF6/MLL
20	GA	F	65	M2	XX,6p-	–
21	MG	M	15	M2	46,XY	AML1/ETO
22	TG	M	39	M2	46,XY	AML1/ETO
23	UG	M	12	M2	t(8;21)	AML1/ETO
24	LR	F	41	M2	t(8;21)	AML1/ETO
25	TL	M	48	M2	t(8;21)	AML1/ETO
26	LP	M	44	M2	t(8;21)	AML1/ETO
27	GP	M	43	M2	t(8;21)	AML1/ETO
28	CP	M	44	M4	t(8;21)	AML1/ETO
29	ME	F	60	M4	46,XX,-18,+M	–
30	CN	M	26	M4	XY,t(6;17)	–
31	PC	M	51	M1	INV16	CBFβ/MYH11
32	CE	F	10	M4	INV16	CBFβ/MYH11
33	GG	M	45	M4	INV16	CBFβ/MYH11
34	DCG	M	34	M4EO	INV16	CBFβ/MYH11
35	MV	F	53	M4EO	INV16	CBFβ/MYH11
36	MG	M	45	M4EO	INV16	CBFβ/MYH11
37	GD	M	54	M4	INV16	CBFβ/MYH11
38	CG	F	50	M4	INV16	CBFβ/MYH11
39	DC	M	50	M4EO	INV16	CBFβ/MYH11
40	MS	M	31	M5	46,XY	CBFβ/MYH11

**Patients at first relapse.*

Table 2. Evaluation of leukemic contamination in PBSC harvests and post-consolidation BM and clinical outcome.

No.	*FAB*	*BM*	*PBSC*	*CD34$^+$ cells 10^6/Kg*	*Graft*	*EFS (months)*	*OS (months)*	*Outcome*
1*	M3V	PCR-	PCR-	3.4	No	28	+49	Relapse,CR-3
2	M3	PCR-	PCR-	13.9	No	+28	+29	Alive,CR-1
3	M3	PCR-	PCR-	1.1	No	+41	+42	Alive,CR-1
4*	M3	PCR+	PCR-	3.2	ASCT	+71	+72	Alive,CR-2
5*	M3	PCRw	PCR-	1.3	ASCT	18	24	Relapse,death
6	M3V	PCR-	PCR-	26.3	No	+11	+12	Alive,CR-1
7	M3V	PCR-	PCR-	4.7	No	+2	3	Death in CR
8	M3	PCR-	PCR-	5.1	No	+4	+5	Alive,CR-1
9*	M3	PCR-	PCR-	5.4	BMT	11	12	Relapse,death
10*	M3	PCR-	PCR-	17.6	No	+10	+11	Alive,CR-2
11*	M3	PCR-	PCR-	9.6	ASCT	14	25	Relapse,death
12*	M3	PCR-	PCR-	7.3	No	19	+32	Alive,CR-2
13	M3	PCR-	PCR-	12.1	No	38	41	Relapse,death
14*	M3	PCR-	PCR-	7	No	+42	+44	Alive,CR-2
15*	M3	PCR-	PCR-	9	No	+3	+4	Alive,CR-2
16	M0	PCRw	PCRw	2.0	No	1	2	Relapse,death
17	M0	PCR+	PCR+	3.6	No	3	8	Relapse,death
18	M1	PCR-	PCR-	6	ASCT	7	20	Relapse,death
19	M1	PCR-	PCR-	19.4	ASCT	+4	+5	Alive,CR-1
20	M1	PCR-	PCR-	4.8	ASCT	+6	+7	Alive,CR-1
21	M2	CC-	CC-	4.5	ASCT	10	+20	Relapse,CR-2
22	M2	PCR+	PCR-	30.8	ASCT	+51	+52	Alive,CR-1
23	M2	PCR+	PCR-	21.7	ASCT	8	+60	Relapse,CR-2
24	M2	PCR-	PCR-	6.6	BMT	+10	+11	Alive,CR-1
25	M2	PCR-	PCR-	3.4	No	+3	+4	Alive,CR-1
26	M2	PCR+	PCR+	27.8	No	14	15	Relapse,death
27	M2	PCR-	PCR-	28	BMT	+22	+23	Alive,CR-1
28	M2	PCR-	PCR-	8	ASCT	+16	+17	Alive,CR-1
29	M4	PCR+	PCR-	7.5	No	12	+15	Relapse,alive
30	M4	CC+	CC+	57.7	ASCT	6	8	Relapse,death
31	M4	CC-	CC-	7	ASCT	7	8	Relapse,death
32	M4	PCRw	PCRw	28.5	ASCT	+16	+17	Alive,CR-1
33	M4	PCR+	PCR-	28	No	+4	+5	Alive,CR-1
34	M4EO	PCR-	PCR-	6.3	ASCT	10	+12	Relapse,CR-2
35	M4EO	PCR-	PCR-	5.2	ASCT	+5	+6	Alive,CR-1
36	M4EO	PCR+	PCR-	7.8	ASCT	23	35	Relapse,death
37	M4	PCR-	PCR-	28.6	ASCT	13	17	Relapse,death
38	M4	PCR+	PCR-	5.2	No	7	8	Relapse,death
39	M4EO	CC-	CC-	9.4	No	+45	+46	Alive,CR-1
40	M5	PCR-	PCR-	3.6	ASCT	+50	+51	Alive,CR-1

**Patients at first relapse: CC: conventional cytogenetics; PCRw: positivity after the 2nd step of PCR; ASCT: autologous stem cell transplantation; BMT: allogeneic bone marrow transplantation.*

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tional cytogenetics and/or reverse transcriptase polymerase chain reaction (RT-PCR) to evaluate the presence of residual leukemic cells after consolidation therapy in forty AML patients presenting with cytogenetic and/or molecular abnormalities at diagnosis who were planned to receive ASCT. The clinical characteristics of these 40 patients are shown in Table 1. Thirty-three cases (82%) expressing t(15;17), inv16 or t(8;21) were classified as having favorable cytogenetics, 7 patients (18%) as unfavorable. For remission induction, six patients with APL were treated with the GIMEMA/AIDA protocol, twenty-three patients entered the EORTC/GIMEMA AML10 trial; eleven patients (9 APL at first relapse and 2 older than 60 years) were given two courses of mitoxantrone plus intermediate dose cytarabine for 4 days.

All 40 patients in complete remission (CR) after the induction therapy received one consolidation course, followed by granulocyte colony-stimulating factor (G-CSF) 5 μg/kg/die from day +15 until the target dose of > 2.5×10^6/kg CD34$^+$ cells (median 7 days , range 5-12). A median of 13.11×10^6/kg CD34$^+$ cells (range 1.1–57.70) was collected. BM analysis confirmed morphologic complete remission (CR) in all patients.

Karyotypic analysis and RT-PCR procedures for amplification of BCR/ABL, PML/RARα, AML1/ETO, CBFβ/MYH11 and MLL/AF6 transcripts[9] were performed on PBSC harvests and BM at diagnosis, before and after consolidation therapy.

The persistence of leukemic contamination was detected in both PBSC and in BM (PBSC$^+$/BM$^+$) in 5 cases (12.9%), in BM only (PBSC$^-$/BM$^+$) in 8 patients (20.5%) while no residual contamination (PBSC-/BM-) was detected in 27 cases (66.6%) (Table 2). The three groups did not differ significantly in age, sex or number of harvested CD34$^+$ cells. Of note, more than 60% of PBSC$^+$/BM$^+$ patients had an unfavorable karyotype versus 0% and 15.4 % of PBSC$^-$/BM$^+$ and PBSC$^-$/BM$^-$ patients, respectively (p= 0.020).

The overall survival (OS) and the disease-free survival (DFS) were estimated by the Kaplan Meier method and compared by the log-rank test. The effect of different variables on DFS and OS was evaluated in univariate and multivariate analyses by the Cox proportional hazard model.

At a median follow-up of 17 months (range 3-72), OS was 34.2±4.2, 52.0±10.6 and 10.0±2.2 months in the PBSC$^-$/BM$^-$, PBSC$^-$/BM$^+$ and PBSC$^+$/ BM$^+$ patients, respectively. At univariate analysis the difference was not statistically significant (p= 0.18). The DFS in the PBSC$^-$/BM$^-$ and PBSC$^-$/BM$^+$ groups was better than in PBSC$^+$/ BM$^+$ patients, but this difference did not reach the level of statistical significance (27.3±4.2 vs 32.0±10.6 vs 7.3±2.2 months, respectively)(p= 0.12). In multivariate analysis, unfavorable karyotype was the only variable with prognostic significance for DFS (RR= 32.46, 95% CI= 5.01-210.1) and OS (RR= 7.04, 95% CI 1.26-39.25).

In conclusion, we found that PBSC were less frequently contaminated than BM. No correlation with the number of harvested CD34$^+$ cells was observed. Leukemic contamination after consolidation therapy was not significantly predictive of OS, while PBSC$^+$/BM$^+$ status was associated with unfavorable cytogenetics and a higher relapse rate. Our data are in agreement with Grimwade's analysis, showing a close relationship between persistence of the disease-related clone in harvested marrow, adverse karyotype and poor prognosis.[10] This suggests that post-consolidation leukemic contamination does not in itself matter, its clinical significance depending on the underlying genetic abnormalities. In other words, the presence of residual disease has a critical role in the high-risk cytogenetic group, while autologous transplantation seems able to eradicate residual leukemia in the favorable cytogenetic group.

The identification of residual disease in AML at the end of consolidation therapy is important in order to address therapy using a patient-oriented approach. Although in this study patients with adverse cytogenetics were under-represented, consistent with their poor remission rate and tendency to relapse rapidly, such a poor outcome suggests alternative strategies would be useful.

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Once weekly recombinant human erythropoietin therapy is very efficient after allogeneic peripheral blood stem cell transplantation when started soon after engraftment

We enrolled 13 recipients of an allogeneic peripheral blood stem cell transplant (PBSCT) in a trial of recombinant human erythropoietin (rHuEpo) therapy (500 U/kg/wk once weekly) started on day 30 after PBSCT. Ten patients who did not receive rHuEpo served as controls. The overall probability of achieving a hemoglobin level >13g/dL was 91% in rHuEpo-treated patients versus 14% in controls (*p*=0.0001).

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We recently showed that recombinant human erythropoietin (rHuEpo) therapy was very efficient when the therapy was started 35-1444 days after an allogeneic hematopoietic stem cell transplant.[1] In this study, we first studied endogenous erythropoietin production in a cohort of 10 allogeneic peripheral blood stem cell transplant (alloPBSCT) recipients (control group) with the aim of defining the best time to start rHuEpo therapy after alloPBSCT. We then enrolled 13 alloPBSCT recipients in a trial of recombinant human erythropoietin (rHuEpo group) therapy at a dose of 500 U/kg/wk, given once a week (qw) starting on day 30 after PBSCT (Table 1) with the aim of achieving hemoglobin levels of 13 g/dL (complete response). Results were compared with those in a group of 13 similar patients[1] receiving rHuEpo at the same dose given thrice weekly starting on day 35 after PBSCT (historical group).

The trigger for packed red blood cell transfusions was a hemoglobin (Hb) 8 g/dL for all patients receiving rHuEpo and 8 g/dL (N=6) or 9 g/dL (N=4) for patients included in the control group. One of 13 patients in the rHuEpo group, 2/13 in the historical group (*p*=NS) and 4/10 in the control group (*p*=NS) had a major ABO incompatibility with their donor. Once the target Hb had been achieved, the dose of rHuEpo was reduced so as to use the lowest dose capable of maintaining the Hb between 12 and 14 g/dL. Laboratory as well as statistical analyses were carried out as previously reported.[2-5]

After PBSCT, serum erythropoietin levels peaked on day 0 with a mean observed-to-predicted (O/P) erythropoietin[6] of 1.15±0.09 (*p*=0.03 compared with O/P Epo in 31 healthy donors) (Figure 1A) but became inappropriately low for at least 6 months thereafter.

After two weeks of treatment, transfusion independence was achieved in 12/13 (92%) patients in the rHuEpo group, 11/13 (85%) in the historical group (*p*=NS) and 5/10 (50%) patients in the control group (*p*=0.05). Eleven of 13 patients in the rHuEpo group, 7/13 in the historical group (*p*=NS) versus 3/10 patients in the control group (*p*=0.0131) did not require red blood cell transfusions between days 50 and 150 after the transplant. Hb values of 12 and 13 g/dL as well as a 2 g/dL Hb increment were achieved after a median of 3, 7 and 3 weeks in the rHuEpo group, 6 (*p*=NS), 8 (*p*=NS) and 3 (*p*=NS) weeks in the historical group, and >>15 (*p*<0.001), >>15 (*p*<0.001), >> 15 (*p*=0.002) weeks in the control group. The overall actuarial 150-day probability of achieving a complete response was 91% in the rHuEpo group, 90% in the historical group versus 14% (*p*<0.001) in the control group (Figure 1B).

Table 1. Characteristics of the patients.

Patient number	Diagnosis	Age (years)	Sex	Source of stem cells	Type of donor	ABO Rhesus (Recipient/donor)	Acute GVHD (stage)
Control group							
1	MDS	56	M	PBSC	Sibling, HLA_{id}	A+/A+	II
2	AML	46	M	PBSC	Sibling, HLA_{id}	A+/A+	II
3	CML	36	M	PBSC	Sibling, HLA_{id}	0+/A+	II
4	AA	16	F	PBSC	Sibling, HLA_{id}	0^-/B+	0
5	MDS	45	F	PBSC	Sibling, HLA_{id}	0+/A+	0
6	NHL	13	M	PBSC	Sibling, 1 mismatch	0^-/A^-	0
7	CML	43	M	PBSC	Sibling, 1 mismatch	A+/0+	II
8	AML	47	F	PBSC	Daughter, 1 mismatch	A+/0+	I
9	AML	4	F	PBSC	Sibling, HLA_{id}	0+/0+	0
10	MDS	8	M	PBSC	Sibling, HLA_{id}	A+/A+	0
rHuEpo group (once weekly)							
11	AML	42	F	PBSC	Sibling, HLA_{id}	0+/0+	0
12	ALL	26	M	PBSC	Sibling, HLA_{id}	A+/A+	0
13	AML	37	F	PBSC	Sibling, HLA_{id}	A+/0+	0
14	MDS	43	M	PBSC	Unrelated, HLA_{id}	0+/A^-	0
15	ALL	31	M	PBSC	Sibling, HLA_{id}	AB+/B+	0
16	AML	24	M	PBSC	Sibling, HLA_{id}	0+/0+	II
17	CML	39	F	PBSC	Sibling, HLA_{id}	A+/A+	0
18	AA	16	M	PBSC	Sibling, HLA_{id}	0+/0+	0
19	ALL	9	M	PBSC	Unrelated, HLA_{id}	A+/0^-	0
20	NHL	27	M	PBSC	Father, 1 mismatch	B+/0+	I
21	AML	52	M	PBSC	Sibling, HLA_{id}	0^-/0+	0
22	AML	26	M	PBSC	Sibling, HLA_{id}	A+/A+	0
23	AML	52	F	PBSC	Sibling, HLA_{id}	0+/0+	0

AML: acute myeloid leukemia; NHL: non-Hodgkin's lymphoma; CML: chronic myeloid leukemia; AA: aplastic anemia; MDS: myelodysplastic syndrome; ALL: acute lymphoblastic leukemia; ET: essential thrombocythemia; M: male; F: female; PBSC: peripheral blood stem cells; BM: bone marrow; HLA_{id}: HLA identical.

Mean Hb levels were significantly higher in the rHuEpo and historical groups than in the control group from day 60 after the transplant (Figure 1C). Average soluble transferrin receptor TfR levels remained at the lower end of normal values in patients not receiving rHuEpo (Figure 1D). However, they rapidly increased above the upper normal limit with rHuEpo therapy but progressively decreased when the dose of rHuEpo was reduced.

In this study, we first show that endogenous erythropoietin levels were adequate or inappropriately high for the degree of