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Myeloid mixed chimerism is associated with relapse in bcr-abl positive patients after unmanipulated allogeneic bone marrow transplantation for chronic myelogenous leukemia

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ABSTRACT

Background and Objectives. **Although bcr-abl polymerase chain reaction (PCR) positivity after bone marrow transplantation (BMT) for chronic myelogenous leukemia (CML) is significantly related to relapse, the predictive value of the assay is not very high and therefore most investigators consider that qualitative RT-PCR data alone are too imprecise to enable clinical decisions to be taken in individual cases. To define the clinical outcome of bcr-abl positive patients after unmanipulated BMT better, we sought the origin of hematopoiesis and traced its evolution over time.**

Design and Methods**. Forty-nine patients received allogeneic BMT for CML (39 in chronic phase and 10 in accelerated phase / blast crisis). Median follow-up was 61 months (range 4-92). mRNA and DNA were used to assess bcr-abl and chimerism status respectively. Quantitative VNTR-PCR on total cells and lymphoid or myeloid population allowed us to assign and measure the origin of hematopoiesis.**

Results**. Both bcr-abl positivity and the presence of mixed chimerism (MC) were significantly associated with relapse (*p*= 0.0009 and *p*< 0.0001 respectively). Relapse was observed in one of 39 patients with complete donor chimerism and in 6 of 9 patients with MC. These six cases showed increasing levels of host hemopoiesis and bcr-abl positivity in the CD15-positive population prior to relapse. The other three cases had decreasing or stable low-level MC which was restricted to the T-cells as well as bcr-abl negativity.**

Interpretation and Conclusions. **Whereas the simple detection of bcr-abl fails to identify patients who will relapse with certainty, the assessment of MC by VNTR-PCR does identify patients headed to relapse. Confirmation of myeloid involvement and increasing levels over time further elucidates the clinical outcome of bcr-abl positive patients after BMT.**

Key words: BMT, CML, chimerism, bcr-abl

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After bone marrow transplantation (BMT) incomplete engraftment and persistence of recipient hematopoietic cells can lead to a coexistence of donor and host-type hematopoiesis, a situation which is referred to as mixed chimerism (MC).[1,2] Characterization of this phenomenon might be of special importance in patients transplanted for leukemia, because the presence of recipient cells might disclose reappearance of the malignant clone. Although chimerism analysis cannot assess whether or not a re-emerging endogenous population contains leukemic cells, samples taken at intervals can provide evidence that the expansion rate of a re-emerging clone is consistent with malignant growth.[3] It is, however, still controversial whether patients with MC do have a higher risk of relapse or not.

Although chimerism and minimal residual disease (MRD) studies have indicated that MC is associated with relapse in patients with chronic myeloid leukemia (CML) receiving T-cell depleted BMT,[4-6] the incidence and significance of MC and MRD status in long-term survivors of unmanipulated BMT for this disease is not clearly defined.

In recent studies including long-survivors, we and others have shown that full donor chimerism (DC) as detected by polymerase chain reaction (PCR) assay is associated with prolonged disease-free survival and identifies patients with a low risk of leukemic relapse after unmanipulated BMT for CML.[7,8] However, several issues remain largely unclear, such as the true incidence of MC in this group of patients, the relationship between chimeric status, MRD and relapse risk, and the value of MC as a predictor of disease recurrence.

In this report we extend our earlier simultaneous analysis of chimerism by PCR, karyotyping, and detection of bcr-abl rearrangement in a group of 49 patients undergoing transplantation with non-depleted grafts for CML, with the following objectives: (i) to determine the frequency of transient and stable MC; (ii) to compare chimerism status assessed by VNTR-PCR with MRD as determined by RT-PCR of bcr-abl and (iii) to analyze the value of chimerism and MRD evaluations in predicting relapse.

Design and Methods

Patients

Between April 1982 and November 1997, forty-nine patients with Ph'-positive CML underwent unmanipulated allogeneic BMT and could be evaluated for detection of bcr-abl transcript and chimerism status by PCR analysis post-BMT. All patients had survived more than six months after BMT. All donors were siblings matched at HLA A, B and DR loci. The median age was 28.5 years (range 11-49) and the time from diagnosis to BMT was 4 to 107 months (median 13.2).

Thirty-six patients were conditioned with total body irradiation (TBI)(9 Gy), and cyclophosphamide (120 mg/kg). Thirteen patients were given busulphan (16 mg/kg) followed by cyclophosphamide (120 mg/kg). As graft-versus-host disease (GvHD) prophylaxis, patients received cyclosporine alone (n=20) or cyclosporine in combination with methotrexate (n=29). The characteristics of the patient group and the BMT procedure are outlined in Table 1.

Isolation of genomic DNA

High molecular weight DNA was extracted from donor and recipient peripheral blood mononuclear cells before transplantation using a salting out procedure.[9] After BMT, DNA was extracted from patients' peripheral blood at intervals in order to determine chimerism status. When a recipient sample was not available prior to BMT, constitutional DNA isolated from hair roots was used according to the procedure by Gill *et al.*[10]

PCR analysis of chimerism

For PCR amplification, we used specific primers designed to flank the repeat units of the following human minisatellite regions (VNTR-PCR): D1S80, 33.6, 33.1, 33.4, YNZ-22, APO-B, λg3, DXS52 and HVR-3'. The sequence of the primers and conditions for each reaction have been described elsewhere.[11-14] We defined a VNTR locus as being informative if analysis of recipient and donor samples prior to BMT showed a unique band for the recipient and another unique band for the donor, or when they showed a unique band for the recipient only.

Patients who exhibited complete donor hematopoiesis with all markers tested at all times were defined as full donor chimeras. Patients who exhibited mixed populations of donor and host cells on more than one occasion were considered as mixed chimeras (MC).

The VNTR-PCR assay allows the detection of a minor cell population at a level of 0.5-1.5%.[15]

Table 1. Characterisitcs of the patients.

No. of patients	49
Sex (males/females)	27/22
Age (yr), median (range)	28.5 (11-49)
Interval between diagnosis and BMT (mo) median (range)	13.2 (4-107)
Clinical phase at BMT:	
chronic phase	39
accelerated phase and blast cells	10
Leukocyte count at BMT, median (range)	9.82×10^9/L (3.3-70)
Platelet count at BMT, median (range)	280×10^9/L (72-1,000)
Preparative regimen:	
CY+TBI	36
CY+BU	13
GvHD prophylaxis:	
CsA	20
CsA+MTX	29

CY: cyclophosphamide; TBI: total body irradiation; BU: busulphan; GvHD: graft-versus-host disease; CsA: cyclosporine; MTX: methotrexate.

Quantitative VNTR-PCR

In order to evaluate the possible dynamics of chimerism after BMT we established a quantitative PCR approach. Briefly, standardized mixed chimeric samples were generated by mixing pre-transplant recipient and donor DNA in a range of percentages for each individual case. PCR analysis for the informative locus was carried out on sequential patient samples using the informative primer pair. PCR products were separated by agarose gel electrophoresis. After staining with ethidium bromide, signals were analyzed densitometrically and results were taken on the basis of individual standard curves. Post-BMT DNA samples were investigated in sequences and the signal intensities were compared to the standard curves.

RNA isolation

Total RNA was isolated from the patient's peripheral blood cells fractionated on Ficoll gradients by acid guanidinium thiocyanate-phenol-chloroform extraction as described by Chomczynski and Sacchi.[16] For each preparation of RNA obtained from CML cells, a positive (cell line K562) and negative control (cells from healthy BMT donors) were included. Each sample was divided into at least two aliquots and extracted separately on two different occasions.

In vitro amplification of bcr-abl transcript

Reverse transcription (RT) was performed on 1 µg of total RNA, after heating at 70ºC for 5 minutes, with random hexamers as reaction primers. The reaction was carried out at 42ºC for 45 minutes in the presence of 12 units of AMV reverse transcriptase. Five microliters of RT products were used for two rounds of PCR amplification of the bcr-abl transcripts using the protocol previously described by Saglio *et al.*[17] The second round PCR product was electrophoresed on a 1.5% agarose gel containing 1 µg/mL ethidium bromide and photographed.

Bcr-abl negative cells were included in all RNA extraction procedures as negative controls in order to assess cross-contamination between RNA samples. A blank control that included all reagents except RNA was added at the cDNA stage to control for contamination with the PCR product. Precautions were taken in order to ensure high PCR quality as recommended by Kwok and Higuchi.[18] Using this approach, we could detect a single bcr-abl positive cell in 10^5 normal cells.

Table 2. Clinical outcome of donor chimera versus mixed chimera patients.

	DC patients (n=39)	*MC patients (n=9)*	*p*
Sex (males/females)	20/19	6/3	NS
Age (yr), mean ± SE	27.7±1.5	36.0±2.5	NS
Interval between diagnosis and BMT (mo), mean ± SE	20.3±3.2	18.0±5.6	NS
Clinical phase at BMT (CP/AP+BC)	31/8	7/2	NS
Leukocyte count at BMT, mean ± SE	13.9±2.5×10⁹/L	17.8±8.4×10⁹/L	NS
Platelet count at BMT, mean ± SE	306.2±37.8×10⁹/L	486.6±107.9×10⁹/L	NS
Preparative regimen:			
CY+TBI	31	4	
CY+BU	8	5	
GvHD prophylaxis (CsA/CsA+MTX)	18/21	2/7	NS
Engraftment (days post-BMT)			
granulocytes >500, mean ± SE	18.3±0.7	22.1±4.5	NS
granulocytes >1,000, mean ± SE	21.6±1.0	27.0±5.1	NS
platelets >50,000, mean ± SE	34.6±4.4	37.5±11.3	NS
Acute GvHD			
grade 0-I	28	8	NS
grade II-IV	11	1	
Chronic GvHD			
no	18	6	NS
limited/extensive	9/12	1/2	
Relapses	1	6	<0.0001

DC: donor chimera; MC: mixed chimera; CP: chronic phase; AP: accelerated phase; BC: blast crisis; CY: cyclophosphamide; TBI: total body irradiation; BU: busulphan; GvHD: graft-versus-host disease; CsA: cyclosporine; MTX: methotrexate; NS: not significant.

Cytogenetic analysis

For cytogenetic analyses, cells from bone marrow and/or peripheral blood were cultured in McCoy's medium supplemented with 20% fetal calf serum and antibiotics for 48 hours. Chromosome preparations were stained with 5% Giemsa solution according to standard procedures. A minimum of 25 metaphases was analyzed per sample. This allowed the detection of a minor clone at the 5% level.

PCR analysis of minisatellites in highly purified cell subpopulations

In selected cases, cell separation of the myeloid and T-cell fractions was performed using immunomagnetic beads (Dynal®, Oslo, Norway) coupled with the specific antibody (CD3 and CD15). The purity of the popupations obtained by the Dynabead separation procedure was estimated to be more than 98%. This purity was assessed using the direct immunofluorescence technique with monoclonal antibodies conjugated with fluorescein-isothiocyanate or R-phycoerythrin from Becton-Dickinson (San José, CA, USA). Acquisition was performed in a FACScalibur cytometer with an argon laser tuned at 488 nm, and CellQuest software was used for the multiparametric analysis. DNA of distinct cell populations was isolated using a modified salting out procedure.[19] VNTR analysis was performed as described above.

Statistical analysis

Statistical analysis was performed using Fisher's exact test for categorical data and by one way analysis of variance for continuous data.

Results

Clinical outcome of the 49 patients is shown in Table 2. Thirty-six patients are alive after a median follow-up of 61 months (range 4-192). Hematologic relapse occurred in seven patients (UPNs 137, 154, 199, 286, 305, 2056 and 2072) at +19, +84, +26, +6, +11, +30 and +8 months respectively. Four of these patients died of progressive disease. Another nine patients died in complete hematologic and cytogenetic remission because of bacterial sepsis (n=4); interstitial pneumonitis (n=2); viral encephalitis (n=1) and hepatic chronic GvHD (n=2).

Chimerism results

Forty-eight of the 49 patients were studied from one month to 16 years post-BMT. Chimeric assessment was not possible in one patient (UPN 134, syngeneic BMT) because there were not informative minisatellite loci between identical twins. A median of 6 analyses (range 1 to 9) was performed for each patient (Figures 1 and 2).

Donor chimerism

Thirty-nine of 48 patients studied (81.2%) were full donor chimeras at all samplings post-BMT (Figure 1).

Mixed chimerism

Nine patients exhibited MC post-BMT (18.8%) (see Figure 2). Two patients showed transient MC. UPNs 2084 and 2076 had low-levels of recipient cells at one month post-BMT, but converted at 4 and 5 months respectively to a full donor profile which persisted in subsequent analyses.

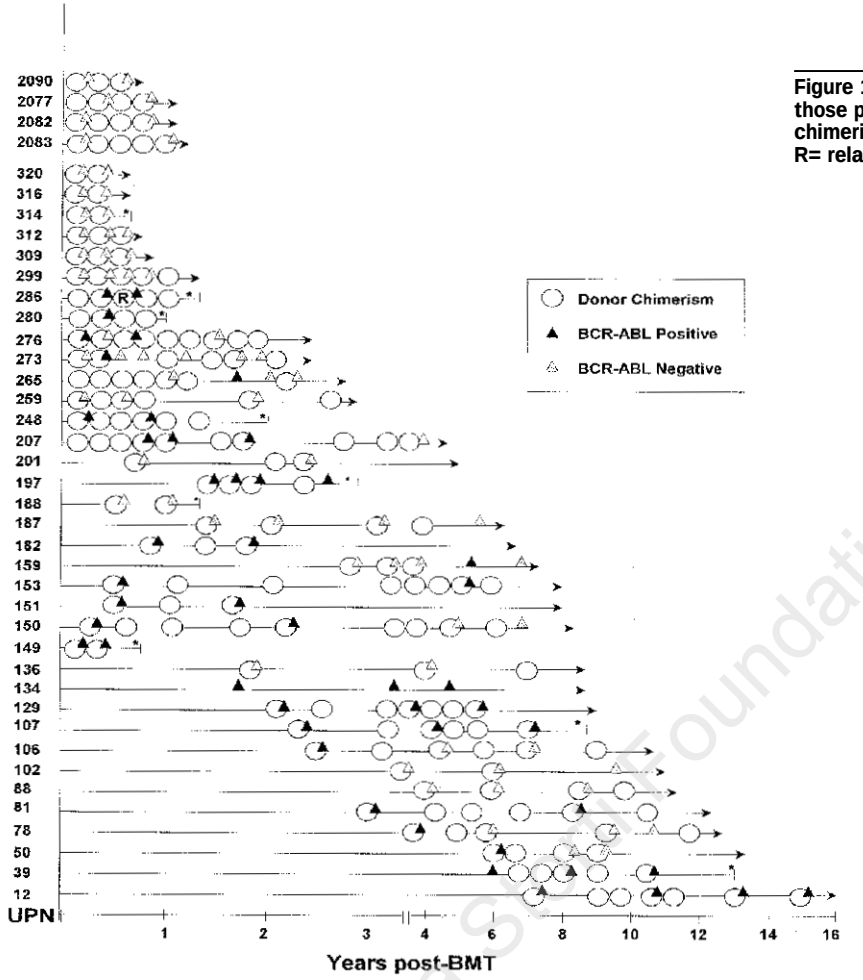

Figure 1. Analysis of MRD status in those patients with complete donor chimerism.
R= relapse; *= death.

In patient UPN 322 low levels, i.e. below 15% of host cells were still present in the last follow-up sample six months after-BMT.

Six patients (UPNs 2056, 2072, 137, 199, 154 and 305) displayed progressive MC showing increasing percentage of recipient cells in serial post-BMT samples. In all these patients increasing MC heralded cytogenetic and clinical relapse.

UPN 154 exhibited a donor profile for five years after BMT. The last sample obtained one year prior to hematologic relapse disclosed a MC with 25% of recipient cells. Subsequent chimerism analysis at the time of relapse demonstrated >80% host cells.

UPN 305 showed more than 60% host cells in four sequential samples, however, cytogenetic relapse was firstly detected six months after BMT.

In UPN 2056 the first sample analyzed was obtained one year post-BMT. At that time a MC with 17% host-type hematopoiesis was detected. Increasing percentages were observed until relapse.

BCR-ABL mRNA assessment results

One hundred and forty-nine samples were collected from one month to 16 years post-BMT. The range was from 1 to 8 samples per patient. Fused bcr-abl transcript was confirmed in 72 of 149 samples from 49 patients (Figures 1 and 2). Twenty-one patients always had positive bcr-abl results or had both bcr-abl positive and negative results, the last sample being positive (bcr-abl positive patients). Another 28 patients had persistently bcr-abl negative assays or presented with initial positive assays followed by negative results on subsequent analyses (bcr-abl negative patients).

Of the 39 patients with persistently full donor chimerism, 26 were bcr-abl negative and 13 bcr-abl positive (Figure 1). Of the 9 patients who showed mixed chimerism by VNTR-PCR, 3 had no evidence of MRD as assessed by RT-PCR of bcr-abl (Figure 2).

Chimeric status, MRD and relapse

None of 28 patients who tested bcr-abl negative underwent clinical relapse, whereas 7 of 21 bcr-abl positive patients relapsed cytogenetically or hematologically. The difference in the incidence of disease relapse between the two groups of patients was highly significant (p= 0.0009, Table 3A).

Six out of the 9 patients with MC relapsed during

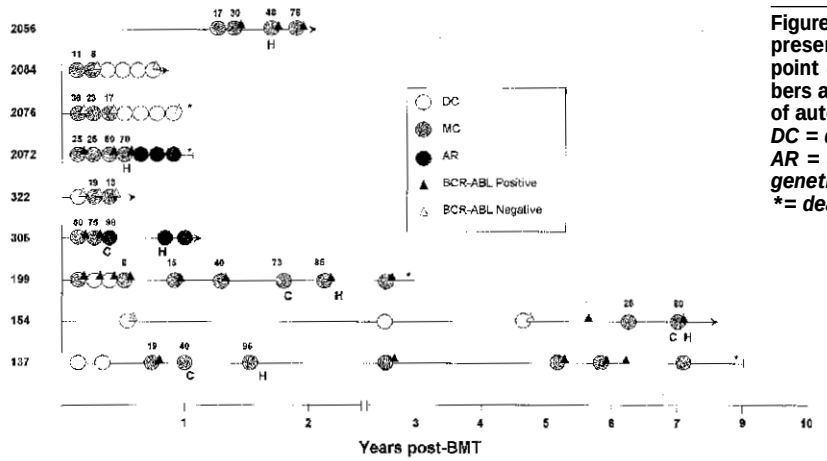

Figure 2. Analysis of MRD in patients who presented mixed chimerism in any time-point during the period of study. The numbers above the circles indicate the amount of autologous cell population in percent.
DC = donor chimera; MC = mixed chimera; AR = autologous reconstitution; C = cytogenetic relapse; H = hematologic relapse; *= death.

follow-up, whereas only one patient in the group of 39 cases with full donor chimerism did ($p < 0.0001$, Table 3B). As to patients with MC, two distinctive patterns could be observed in sequential analyses, i.e. progressively increasing MC levels in one group and decreasing or low-level stable MC in the other subset. All patients in the former category underwent subsequent relapse, while all patients in the latter group remained in complete remission ($p < 0.0001$).

More importantly, when considering only 20 patients who were bcr-abl positive, six of six MC relapsed (100%) compared to one of 14 full DC (7.1%, p=0.0001). This latter patient showed a donor profile at the moment of relapse and was considered as having disease recurrence on donor cells.

In summary, patients who had a bcr-abl positive test and increasing MC during follow-up had a significantly increased risk of relapsing.

Lineage-specific chimerism analysis

Nine patients who had MC in their total white blood cell fraction during the study period were evaluated for lineage-specific chimerism in T-cell and myeloid subpopulations (Figure 3).

In three patients (UPNs 2084, 2076 and 322), CD15-positive cells were exclusively of donor origin and MC was restricted to the CD3-positive fraction (Figure 4A shows a representative example of this chimerism profile). In two patients (UPNs 2076 and 2084) this MC was transient and the patients converted to having DC in the last sample analyzed. These three MC patients were bcr-abl negative and remain disease free.

The other six patients exhibited host derived CD15-positive cells at different times during the study. All these patients were bcr-abl positive and relapsed. Myeloid cells of recipient origin were first detected between 2 and 12 months before disease recurrence.

CD3 chimerism in these six patients had a variable pattern. While four of the patients had MC, two patients had a full donor profile (Figure 4B).

In summary, regardless of the T-cell chimerism status, only patients with MC in the myeloid fraction underwent subsequent relapse.

Discussion

In recent years, two main molecular diagnostic procedures have been used to follow-up patients after allogeneic BMT for CML: analysis of hematologic chimerism and detection of residual malignant cells by amplification of bcr-abl hybrid transcripts.

Detection of bcr-abl fusion by conventional RT-PCR is of prognostic significance as shown by several investigators.[20-22] In fact, it has been demonstrated that two sequential positive assays after allogeneic BMT are predictive of relapse, whereas persistently bcr-abl negative patients have a very low risk of relapse. Accordingly, in the present study relapse occurred exclusively among patients with positive bcr-abl assays: seven of 21 patients with MRD developed cytogenetic and hematologic relapse. However, in our study 14 patients remain constantly or intermittently PCR-positive even after several years and in continuous cytogenetic remission. Identification of those bcr-abl positive patients who will eventually relapse is of particular interest because they could benefit from early therapeutic interventions such as donor lymphocyte infusion or α-interferon administration

Table 3. Correlation between chimerism, bcr-abl detection and relapse in the total group of patients (A) and in the bcr-abl positive group (B).

A

	bcr-abl (+)	*bcr-abl (-)*	*All*
Relapse	7	0	7
DFS	13	29	42
All	20	29	49

p=0.0009

B

	MC	*CDC*	*All*
Relapse	6	1	7
DFS	0	13	13
All	6	14	20

p=0.0001

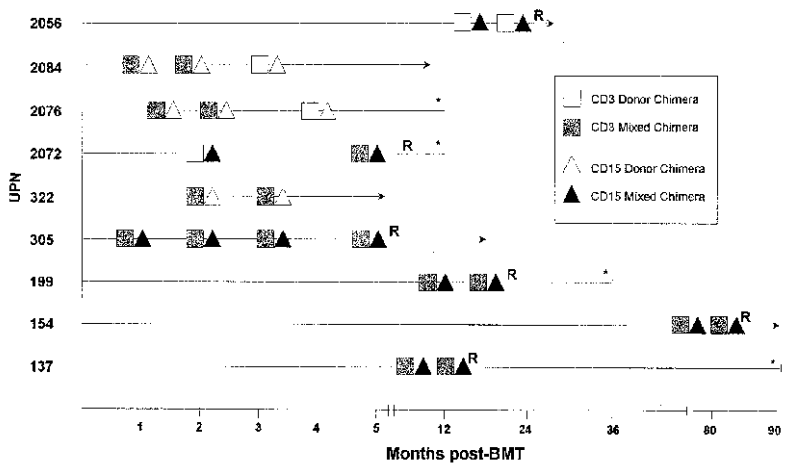

Figure 3. Monitoring of T-cell and myeloid lineage-specific chimerism in patients with mixed chimeras in the total white blood cell population. R= relapse; *= death.

Several authors have shown that the monitoring of bcr-abl mRNA expression during the course of the disease by a quantitative PCR protocol provides clinically useful information on the proliferative activity of the residual leukemic clone in this particular group of patients, allowing for early detection of progressive disease and, consequently, reliable prediction of relapse.[23,24] However, this technique has problems of standardization and reproducibility between laboratories and, moreover, requires customized assays, which can prove tedious and time consuming. Thus, it is still regarded as an investigational approach available in a limited number of laboratories.

On the other hand, the detection of host-type hematopoiesis after BMT usually reflects persistence of malignant cells and in consequence could be associated with a higher risk of post-BMT recurrence.[1,2] In this context, we have previously reported that MC may predict hematologic or cytogenetic relapses by several months in those patients who are persistently bcr-abl positive after unmanipulated BMT for CML.[7] In the present study we have updated our results including 49 patients.

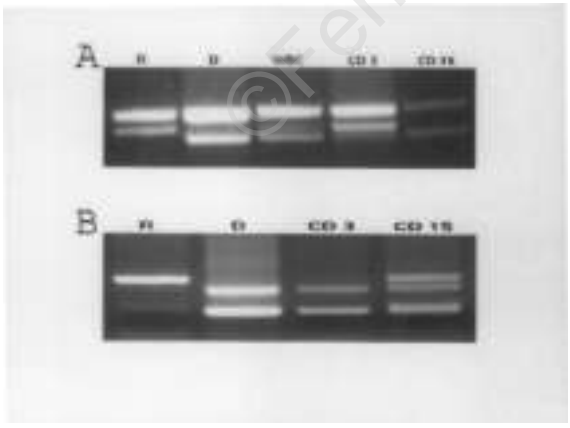

Figure 4. A) Amplification of the APO-B locus in patient UPN 322 at +3 months post-BMT. *D= donor; R= recipient before transplant.* A mixed chimerism profile can be observed in the total white cell fraction and in the T-cell fraction. CD15 cells were of donor origin. B) Amplification of the D1S80 locus in patient UPN 2072 at +2 months post-BMT. A donor profile is observed in CD3 positive cells, whereas myeloid cells presented a mixed chimera pattern.

Our data show that MC is a rare event in long-term survivors following unmanipulated BMT for CML. Thirty-nine of 48 patients (81.2%) evaluated at serial time-points post-BMT were full donor chimeras. Nine of 48 patients (18.8%) showed persistence/reappearance of host cells. Two of these patients converted to donor chimerism, thus 41/48 recipients (85.5%) of non-T-cell depleted BMT exhibited donor profile at the end of the study period. Considering that our series includes ten patients transplanted in accelerated phase or blast crisis, this low incidence of MC contrasts with that observed by others authors. Elmaagacli *et al.*[25] reported a high incidence of MC (64% within 24 months of BMT) in 28 male recipients (most of them grafted in accelerated phase/blast crisis) of unmanipulated female marrow for CML, and Gardiner *et al.*[8] found a 21% incidence of MC among 14 patients transplanted in chronic phase. The sensitivity of our method (0.5-1.5%), which is lower than that employed by Elmaagacli *et al.* (amplification of Y-chromosome-specific sequences) and Gardiner *et al.* (short tandem repeat-PCR) (0.1-0.001%) may contribute to explain such discrepancies. However, the incidence of MC observed after grafting is dependent not only on the sensitivity of the method applied but also on the population of cells under investigation, the frequency of sampling and perhaps, most importantly, on the time interval between BMT and sampling.[26] For instance, the number of patients with MC reported by both authors decreased if only those patients studied two years post-BMT were considered. In this respect, eleven of our DC cases were first studied 24 months post-BMT.

More important than simple documentation of the incidence of MC is the assessement of its relevance in relation to clinical outcome. Our data show that DC patients can still have MRD. This finding is not surprising because the sensitivity of PCR in detecting bcr-abl (10^{-5}) is greater than its sensitivity in detecting chimerism (0.5-1.5%). It is remarkable that patients

with DC, regardless of the bcr-abl status, have a very low risk of relapse (only one of 48 patients in our series relapsed and this relapse occurred on donor cells). Our findings confirm those of three other series published in the literature: Lawler *et al.*[1] studied 32 patients after BMT for their chimerism status and found no relapse in patients without MC post-BMT. Elmaagacli *et al.*[25] recorded 10 out of 28 patients with DC during the observation period and none of them relapsed. Finally, Gardiner *et al.*[8] reported 14 recipients of unmanipulated BMT who exhibited donor chimerism at the end of the study period, and found that all of them remained in complete remission.

On the other hand, we show here that MC is not always associated with bcr-abl positivity. Patients with these characteristics form an important group because none of our three MC/bcr-abl negative recipients relapsed. Although a speculative interpretation of this finding may be that healthy hematopoietic cells have an advantage over malignant cells in surviving pre-transplant conditioning therapy, our cell-lineage specific analysis of chimerism rather indicates that this MC reflects the transient persistence of recipient T-cells that escape control by allogeneic immune effector cells, probably conditioned by the use of immunosuppressive therapy against acute GvHD during the first months post-BMT. As the T-cell compartment is not part of the leukemic clone in CML, the persistence of host T-cells after transplant is a variable that is independent of residual leukemia detection.[6]

All 6 patients in our study who had MC and the bcr-abl fusion gene relapsed. Regardless of the origin of T-cells, all these patients showed MC in the myeloid population as demonstrated by cell-lineage specific analysis. Moreover, all these patients showed increasing amounts of autologous cells in contrast to patients who developed MC in the recovery phase who showed decreasing or stable autologous signals which persisted in complete remission. These results suggest that tumor-cell burden gradually and progressively increases in the CML patients destined to relapse. Conversely, chimerism analysis seems poorly informative in predicting relapse after BMT in patients with acute leukemia.[27-28] This may be explained by the hypothesis that in these latter cases the expansion of the clone is so rapid an event that it is unlikely to be predicted in antecedent analyses.[29-30]

Interestingly, in these 6 patients, host cells were detected between 3-6 months before cytogenetic relapse and between 5-21 months before hematologic relapse. This time interval between detection of MC and relapse is of crucial importance for therapeutic decisions. Knowing that many bcr-abl positive patients will relapse without intervention, regular follow-up with VNTR-PCR should be performed to detect host hematopoiesis. Adoptive immunotherapy with donor leukocytes could then be given to patients who present increasing myeloid mixed chimerism in order to achieve molecular remission. Moreover, this state of MC is prognostically important since persistence of PCR detectable donor cells prior to leukocyte infusion is associated with molecular remission without risk of severe aplasia, whereas absence of chimerism correlates with the ocurrence of severe myelosuppression.[31]

In conclusion, our results suggest that serial and quantitative analysis of hematopoietic chimerism in patients with CML transplanted with unmanipulated marrow can potentially identify patients at the highest risk of relapse. Increasing numbers of recipient cells in bcr-abl positive patients form a rational basis for the use of immunomodulation strategies aimed at reducing the rate of relapse from CML following allo-BMT.

Contributions and Acknowledgments

JR and JSe were the main investigators and designed the study, reviewed clinical and molecular data and performed the literature revision; both of them wrote the article and were responsible for the data interpretation. MCR, MLR and MGG carried out the chimerism and bcr-abl analyses. AJ, JAC, IG, JSa and JM were responsible for the inclusion of patients, clinical management and direct clinical data acquisition. AT was the main co-ordinator of the group and reviewed the article to obtain the final form. Name appearance has been decided according to previous criteria.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- PCR positivity for BCR-ABL is predictive of an imminent relapse after unmanipulated BMT for CML only if associated with a mixed chimerism in the myeloid lineage.
- Increasing amounts of recipient cells in BCR-ABL positive patients provide a rational basis for the use of immunomodulation strategies after BMT for CML.

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