Table I. Treatment schedule.

Drug	Dose	Route	Days
Induction			
Cyclophosphamide	1200 mg/m^2 (800 mg/m^2)*	IV (3 h)	1
Daunorubicin	60 mg/m^2 (30 mg/m^2)*	IV (1 h)	1–3
Vincristine	1·3 mg/m^2†	IV (bolus)	1, 8, 15, 22
Prednisolone	60 mg/m^2	PO	1–21 (1–7)*
Imatinib	600 mg	PO	8–63
Methotrexate, cytarabine, dexamethasone	15 mg, 40 mg, 4 mg	IT	29
Consolidation #1			
Methotrexate	1 g/m^2	IV (24 h)	1
Cytarabine	2 g/m^2 (1 g/m^2)* twice a day	IV (3 h)	2, 3
Methylprednisolone	50 mg twice a day	IV (bolus)	1–3
Methotrexate, cytarabine, dexamethasone	15 mg, 40 mg, 4 mg	IT	1
Consolidation #2			
Imatinib	600 mg	PO	1–28
Methotrexate, cytarabine, dexamethasone	15 mg, 40 mg, 4 mg	IT	1
Consolidation #3	Repeat #1		
Consolidation #4	Repeat #2		
Consolidation #5	Repeat #1		
Consolidation #6	Repeat #2		
Consolidation #7	Repeat #1		
Consolidation #8	Repeat #2		
Maintenance‡			
Vincristine	1·3 mg/m^2†	IV (bolus)	1
Prednisolone	60 mg/m^2	PO	1–5
Imatinib	600 mg	PO	1–28

IV, intravenously; PO, orally; IT, intrathecally.
*For patients aged 60 and older.
†Maximum 2·0 mg.
‡Repeated every 4 weeks up to 2 years from the date of complete remission.

qualified with the log-rank test. The cumulative incidence of relapse was calculated with death during CR considered as a competing risk, and differences between the curves were qualified with Gray's test. STATA version 8 software (StataCorp, College Station, TX, USA) and R software version 2.4.0 (The R Foundation for Statistical Computing, http://www.r-project.org) were used for statistical analyses. P values ≤0·05 were considered to be statistically significant.

Results

Patients and treatment results

The median patient age was 45 years (range 15–64 years); 55 were male and 45 were female. Twenty-five patients were positive for major *BCR-ABL1*, and 75 for minor *BCR-ABL1*. Ninety-seven patients (97%) achieved CR. The median and maximum follow-up periods were 3·2 and 5·1 years respectively. The outcomes of 100 patients are detailed in Fig 1. Relapse occurred in 38 patients after a median CR duration of 7·3 months (range 2·1–37·4). Allogeneic HSCT was performed in 60 patients during first CR, and in 19 patients beyond first CR. For patients allografted in first CR, the median time to HSCT was 5·3 months (range 2·2–17·1). No patient underwent autologous HSCT. The probability of OS for the entire cohort was 55% at 3 years. The 1-year OS rate, the endpoint for the study extension, was 83% (95% CI 74–89%). Among the 97 patients who achieved CR, the probability of RFS was 46% at 3 years. Neither transcript types nor copy numbers at diagnosis were associated with RFS (P = 0·709 and P = 0·851 respectively).

MRD kinetics

The number of patients who underwent MRD monitoring decreased with time because of prior relapse, death, or transfer to allogeneic HSCT. Thus, the total number of follow-up samples was 367 (77% of all possible samples at all time points): 86 of 98 (88%) at day 28, 85 of 97 (88%) at day 63, 75 of 90 (83%) after the first consolidation (C#1), 55 of 73 (75%) after C#2, 31 of 38 (82%) after C#5, 22 of 32 (69%) after C#6, 11 of 15 (73%) at 1 year, and 2 of 9 (22%) at 2 years.

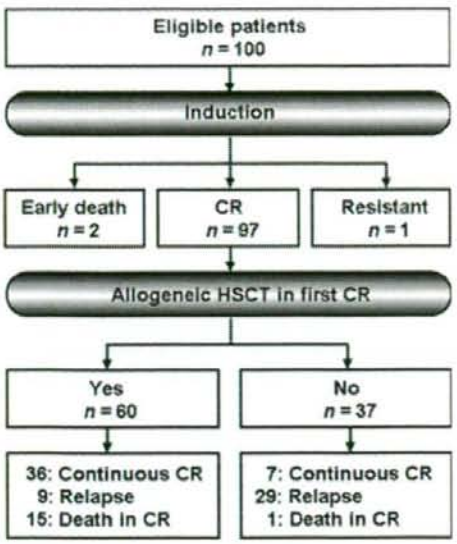

Fig 1. Flow diagram showing patient outcomes. CR, complete remission; HSCT, haematopoietic stem cell transplantation.

Figure 2 shows the percentages of patients with negative and low (<50 copies/μg) MRD levels at each time point. There was a progressive increase in the percentage of patients with negative MRD during the early treatment courses, with 24% at day 28, 48% at day 63, 68% after C#1, and 67% after C#2. Nearly all samples measured at 1 year and at 2 years were negative for MRD, although only a small number of samples were analysed at these time points. The only patient whose MRD was positive (87 copies/μg) at 1 year experienced a relapse 8 months later. All of the three patients who experienced a relapse during maintenance therapy had showed MRD elevation prior to haematological relapse.

Rapid MRD clearance and outcome

RQ-PCR results at the end of induction therapy (day 63) were available for 85 patients. One patient with a *BCR-ABL1* level of 160 000 copies/μg failed to achieve CR. Figure 3 shows the RFS rates and cumulative incidences of relapse in 84 CR patients according to MRD detection at day 63. PCR negativity was not associated with a higher RFS rate (46% vs. 42% at 3 years, $P = 0{\cdot}800$; Fig 3A) or a lower relapse rate (40% vs. 41% at 3 years, $P = 0{\cdot}964$; Fig 3B). A relatively small number of patients ($n = 11$) whose MRD levels exceeded 1000 copies/μg at day 63 had trends toward lower RFS ($P = 0{\cdot}092$, Fig 4A) and higher relapse rate ($P = 0{\cdot}070$, Fig 4B). Neither PCR negativity at day 28 nor after C#1 was associated with higher RFS ($P = 0{\cdot}867$ and $P = 0{\cdot}549$) or lower relapse rates ($P = 0{\cdot}796$ and $P = 0{\cdot}667$).

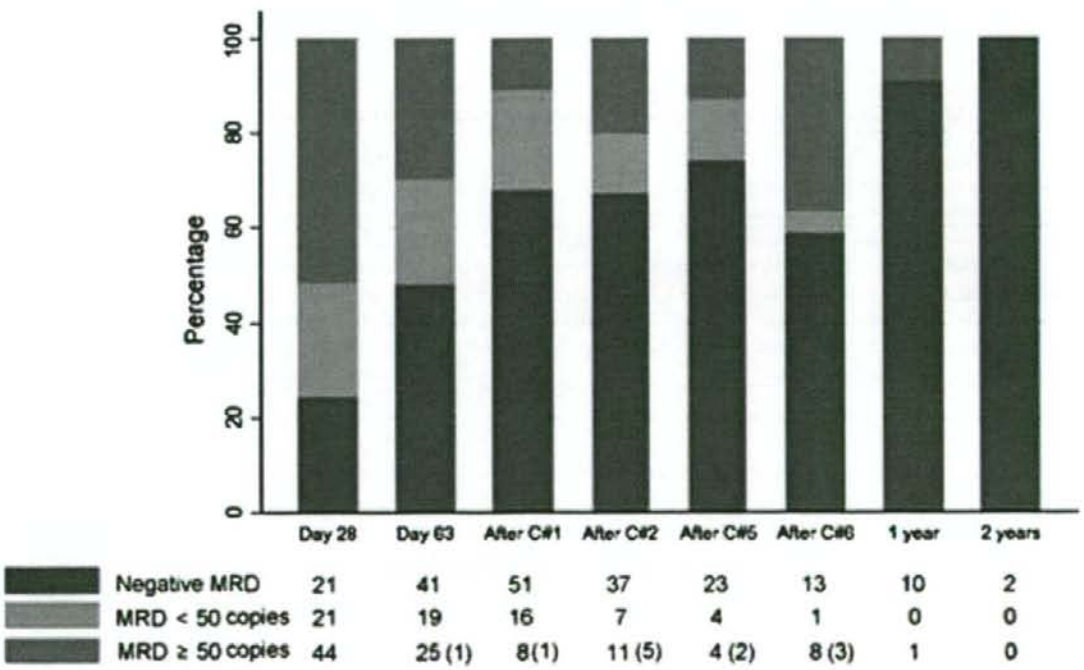

Fig 2. Frequencies of negative and low (<50 copies/μg RNA) *BCR-ABL1* transcript levels at each time point. Figures in parentheses represent the number of patients who developed haematological relapse at that time point.

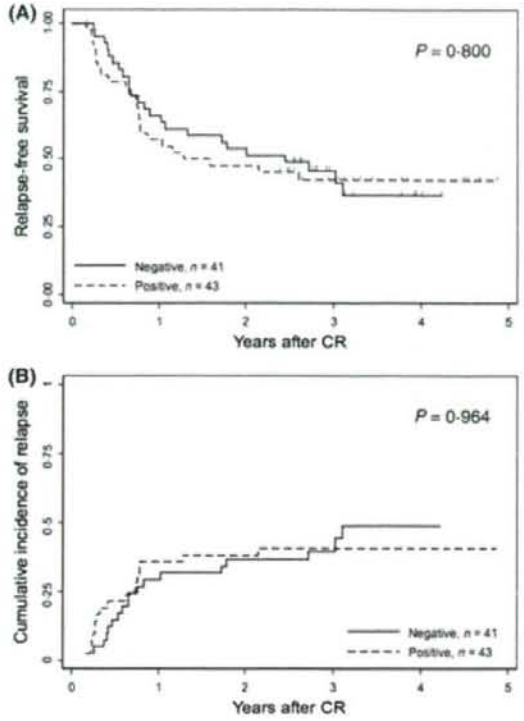

Fig 3. Relapse-free survival (A) and cumulative incidence of relapse (B) in patients with negative and positive *BCR-ABL1* transcript levels at the end of induction therapy.

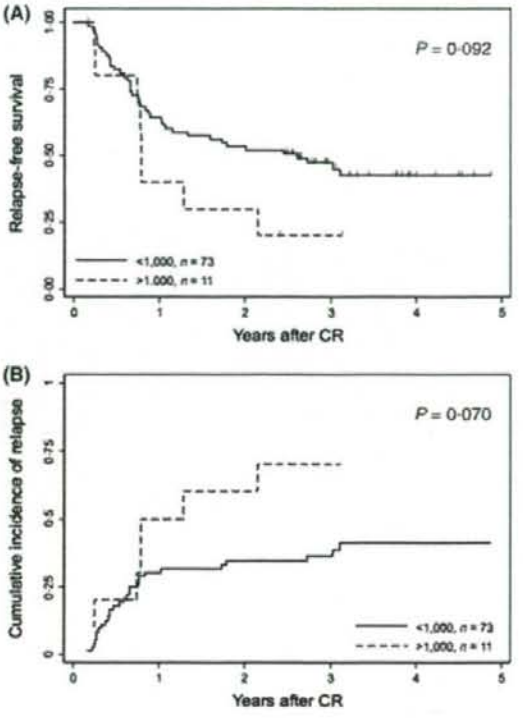

Fig 4. Relapse-free survival (A) and cumulative incidence of relapse (B) in patients with *BCR-ABL1* transcript levels below or above 1000 copies/μg RNA at the end of induction therapy.

MRD elevation during haematological remission

Elevated MRD levels during CR were documented in 29 patients. Of these, six patients experienced MRD elevation twice, and the second elevation was accompanied by simultaneous haematological relapse in five patients. The outcome and duration from the first observation of MRD elevation to relapse or allogeneic HSCT, whichever came first, in each patient are presented in Table II. Sixteen underwent allogeneic HSCT in first CR. The median duration from the first documentation of elevated MRD to allogeneic HSCT was 2·3 months (range 0·4–5·6). Death during first CR and relapse after transplantation occurred in three patients each, and 10 remained in first CR at a median of 2·9 years (range 2·0–4·6 months) after transplantation. In contrast, among the 13 non-transplantation patients, 12 had a relapse at a median of 2·0 months (range 0·5–35·0) after the first MRD elevation. Another patient once achieved PCR negativity after C#2, but showed detectable MRD below the threshold (<50 copies/μg) after C#5. However, MRD became negative after C#6, and the patient remained alive without relapse at 2·8 years after MRD elevation. The conversion from negative MRD to '<50 copies/μg' was observed in another six patients. Four remained in first CR after undergoing allogeneic HSCT, and the remaining two who had not undergone HSCT experienced a relapse.

Discussion

Minimal residual disease levels at various time points in CR, especially at the end of induction therapy, are considered an important prognostic factor in ALL (Pui *et al*, 2008). Although there were few studies that focused on Ph+ ALL with a relatively large number of patients (Dombret *et al*, 2002; Pane *et al*, 2005), Pane *et al* (2005) reported that significant reductions in *BCR-ABL1* levels after induction and consolidation therapy were associated with better outcomes. Most published studies on imatinib-combined chemotherapy include MRD findings (Thomas *et al*, 2004; Towatari *et al*, 2004; Lee *et al*, 2005; Rea *et al*, 2006; Wassmann *et al*, 2006; Yanada *et al*, 2006; de Labarthe *et al*, 2007; Ottmann *et al*, 2007a), but the prognostic significance of early treatment response remains to be determined. Our data remarkably demonstrated that the RFS rate for the patients with negative MRD at the end of induction therapy was similar to that for patients with positive MRD. We considered the possibility that this lack of difference was influenced by the confounding effect of allogeneic HSCT.

Table II. Outcome of patients who experienced an MRD elevation during haematological CR.

UPN	Outcome	Months from MRD elevation to relapse	UPN	Outcome	Months from MRD elevation to HSCT	Outcome after HSCT
63	CCR without HSCT	–	36	HSCT	1·0	CCR
17	Relapse	0·5	72	HSCT	1·0	CCR
43	Relapse	0·9	12	HSCT	2·1	CCR
50	Relapse	1·5	77	HSCT	2·2	CCR
58	Relapse	1·5	10	HSCT	2·6	CCR
82	Relapse	1·6	1	HSCT	2·9	CCR
62	Relapse	1·9	81	HSCT	3·3	CCR
14	Relapse	2·0	94	HSCT	3·6	CCR
85	Relapse	3·6	55	HSCT	4·8	CCR
56	Relapse	4·3	8	HSCT	5·1	CCR
51	Relapse	7·9	34	HSCT	0·4	Relapse
60	Relapse	8·4	87	HSCT	2·0	Relapse
18	Relapse	35·0	47	HSCT	2·4	Relapse
			48	HSCT	1·9	NRM
			16	HSCT	2·0	NRM
			49	HSCT	5·6	NRM

UPN, unique patient number; MRD, minimal residual disease; HSCT, haematopoietic stem cell transplantation; CCR, continuous complete remission; NRM, non-relapse mortality.

However, MRD negativity was not beneficial in terms of relapse rate ($P = 0·964$) or even in terms of RFS after we censored patients who underwent allogeneic HSCT at the time of transplantation ($P = 0·470$). A trend toward a higher relapse rate in the 11 patients (13%) with MRD levels of ≥1000 copies/μg suggests that MRD levels at the end of induction therapy may be helpful in identifying a small subgroup of patients at high risk for relapse. However, the finding that negative MRD was not associated with a favourable outcome precludes prognostication of the remaining majority of patients, and indicates that relapse risk in these patients depends on factors unrelated to initial treatment response. Acquisition of resistance during treatment may explain why rapid molecular response is not prognostically relevant.

Another important finding of this study was the significant relationship between MRD elevation and relapse. This finding is in accordance with those of several studies published in the 1990s in which the conversion from negative to positive RT-PCR results was associated with subsequent relapse in Ph+ ALL patients (Miyamura *et al*, 1992; Preudhomme *et al*, 1997; Radich *et al*, 1997; Mitterbauer *et al*, 1999). Our results suggest that an increase in the MRD level at a single time point is predictive of subsequent relapse, but such patients can be successfully treated with allogeneic HSCT. Given a median duration of only 2 months from MRD elevation to haematological relapse, an alternative therapeutic intervention should be considered immediately after MRD elevation. Because of its rapid availability, cord blood transplantation may be a practical treatment option for patients without a related donor, if they are fit for the procedure. Switching from imatinib to other novel tyrosine kinase inhibitors, such as dasatinib (Talpaz *et al*, 2006; Ottmann *et al*, 2007b) and nilotinib (Kantarjian *et al*, 2006), may also be a reasonable option for patients without a mutation resistant to these agents. Additionally, frequent MRD monitoring increases the chances of detecting MRD elevation during CR, prolonging the duration prior to haematological relapse, and enabling the use of alternative therapies in patients who would otherwise experience an overt relapse.

When MRD data are analysed in relation to outcome, differences in conditions such as treatment and sampling time points can affect results. In this regard, strength of this study is that all samples were collected at scheduled time points during a uniform treatment protocol. On the other hand, one limitation of our study is that samples were not obtained from all patients at all time points. Nevertheless, the percentage of available samples collected at the end of induction therapy was 86% (84 of the 97 CR patients). Furthermore, sample availability did not seem to be a significant source of selection bias: we found no difference in RFS between patients whose samples were available or not at the end of induction therapy ($P = 0·345$). Also the utility of MRD elevation in predicting subsequent relapse would have been strengthened if the proportion of missing samples had been smaller. Finally, it may be disputed that our detection method was partly different from those used in other countries, specifically in that results were reported as a copy number normalized by the control gene and in that PCR negativity was not confirmed by nested PCR. Nevertheless, we believe this point would not impair our main results.

In summary, our prospective MRD monitoring of Ph+ ALL patients treated with imatinib-combined chemotherapy revealed that rapid molecular response is not associated with a superior prognosis and that a single observation of elevated

MRD is strongly predictive of subsequent relapse but allogeneic HSCT can override its adverse effect. Such patients may also benefit from novel tyrosine kinase inhibitors. We conclude that frequent MRD monitoring is beneficial in clinical decision making for Ph+ ALL patients treated with imatinib-combined chemotherapy. Incorporating MRD data into a treatment protocol will be necessary in future clinical trials of Ph+ ALL.

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