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Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia with imatinib combined with a paediatric-based protocol

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Summary

Although the combination of tyrosine kinase inhibitors with chemotherapy is widely used for young adults with Philadelphia chromosome positive-acute lymphoblastic leukaemia (Ph+ ALL), the outcome and safety of this combination using intensive paediatric-based protocols has not been well described. The clinical course of 32 adults age 18–60 years with Ph+ ALL treated with a paediatric-based protocol plus imatinib was evaluated. The complete response rate was 94%. Grade 3–4 infections, neuropathy, myopathy and liver function abnormalities were common, resulting in major treatment delays and dose reductions, and declines in performance status (physical deconditioning), particularly in patients aged 41–60 years. Median and 3-year overall survival (OS) was 40·7 months and 53%, respectively, and median and 3-year even-free survival (EFS) was 30·1 months and 50%, respectively. OS and EFS were inferior in deconditioned patients. Of 16 patients who underwent haematopoietic stem cell transplantation (HSCT) in first complete remission, six died of non-relapse complications. There was no significant difference in OS and EFS between transplanted and non-transplanted patients, based on an intention-to-treat and time-to-donor identification analysis. The combination of imatinib with a paediatric-based regimen in adults produced high response rates, but was associated with considerable toxicity and high non-relapse mortality post-HSCT.

Keywords: leukaemia, chemotherapy, haematopoietic stem cell transplantation, acute lymphoblastic leukaemia, tyrosine kinase inhibitors.

Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) has long been recognized as a high-risk subset of ALL. Published data show a disappointing long-term survival of 20% or less with chemotherapy alone (Dombret *et al*, 2002; Faderl *et al*, 2010). The combination of BCR-ABL1 targeted tyrosine kinase inhibitors (TKIs), most commonly imatinib, with multi-agent chemotherapy regimens has improved outcomes, with complete response rates of 80–90%, and 5-year survivals in the 35–50% range (Thomas *et al*, 2004; Yanada *et al*, 2006; de Labarthe *et al*, 2007; Bassan *et al*, 2010; Fielding, 2010). Nevertheless, Ph+ disease remains a poor prognosis subgroup with unacceptably high relapse rates.

Allogeneic haematopoietic stem cell transplantation (HSCT) in first complete remission (CR1) remains the standard of care in most centres, and is the only treatment demonstrated to cure a significant proportion of patients. Consequently, the goal of most approaches is to optimize complete response rates and prolong remission duration, thereby permitting a larger proportion of patients to proceed to HSCT in CR1. The outcome of HSCT is largely influenced by transplant-related mortality (TRM) and post-transplant relapse. Early TRM is influenced by various factors, including pretransplant patient-related issues, toxicity of the conditioning regimen, and graft-versus-host disease (GVHD) (Sorror *et al*, 2005; Artz *et al*, 2006).

For Ph-negative ALL, a number of studies in adolescents and younger adults have shown encouraging results using paediatric-based protocols, which intensify asparaginase, corticosteorids and vinca alkaloids; these results appear superior

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to previous reports using adult-based regimens (Stock *et al*, 2008; Huguet *et al*, 2009; Storring *et al*, 2009). However, most studies reported to date for Ph+ ALL that combine chemotherapy with a TKI have used adult-based regimens, and it is unclear whether outcomes could be improved with the use of paediatric-based regimens in combination with a TKI. At the Princess Margaret Hospital we have been using a paediatric-based protocol, in combination with imatinib, for adults with Ph+ ALL, and now report our results.

Patients and methods

Patients

We evaluated the clinical course and outcome of all patients age 18–60 years with a new diagnosis of BCR-ABL1 positive precursor B ALL, treated at our institution between June 2001 and December 2008. Approval was obtained from the Institutional Review Board prior to initiation of this retrospective analysis. Patients were identified from the leukaemia database, and detailed toxicity and medication administration data were obtained from review of individual patient charts, pharmacy records and clinic notes. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8·5x11.pdf). Data were updated as of 31 December 2010.

The diagnosis of B-ALL was established by bone marrow aspiration, with evaluation of morphology and immunophenotyping. Molecular testing for the *BCR-ABL1* fusion gene was performed by quantitative polymerase chain reaction (PCR) as previously described (Hughes *et al*, 2006). If PCR results were equivocal, fluorescent *in-situ* hybridization (FISH) for the Philadelphia chromosome was performed. All patients received a diagnostic lumbar puncture at initiation of induction chemotherapy.

Treatment

A modified version of the Dana Farber Cancer Institute (DFCI) protocol (Storring *et al*, 2009), in combination with imatinib, was used as the standard regimen for all patients. Details of the treatment protocol are given in Table I. No dose modifications for age were used. Induction chemotherapy was administered on an inpatient leukaemia unit, while all postremission therapy was intended to be administered on an outpatient basis. At diagnosis, once *BCR-ABL1* positivity was demonstrated, imatinib 400 mg daily × 16 d was started, with chemotherapy beginning on the third day. Patients with a positive initial cerebrospinal fluid (CSF) result received twice weekly intrathecal chemotherapy until clear on three successive evaluations. Patients who attained CR proceeded to central nervous system (CNS) prophylaxis, including 12 Gy cranial irradiation. Patients subsequently proceeded to a 30-week intensification phase, followed by a 72-week maintenance phase. Imatinib 400 mg daily × 14 d was added to each 3-week cycle postinduction, from the CNS phase until completion of maintenance. Upon completion of the maintenance phase, imatinib was continued at a dose of 600 mg/d until disease progression in non-transplanted patients. Imatinib was not given post-HSCT.

Table I. Treatment protocol

Induction (4 weeks)		
Imatinib	400 mg PO daily	Days −2–14
Prednisone	10 mg PO QID	Days 0–28
Doxorubicin	30 mg/m^2 IV	Days 0 and 1
Vincristine	2 mg IV	Days 0, 7, 14, 21
Methotrexate	4 g/m^2 IV over 1 h	Day 2 (with leucovorin rescue)
Asparaginase	25 000 iu/m^2 IM	Day 4
Cyt/Mtx/HC*	40/12/15 mg IT	Days 0, 14
Central nervous system therapy (3 weeks)		
Imatinib	400 mg PO daily	Days 1–14
Doxorubicin	30 mg/m^2 IV	Day 1
Vincristine†	2 mg IV	Day 1
6-Mercaptopurine	50 mg/m^2 PO QHS	Days 1–14
Cranial radiation	1200 cGy	Over 8 days
Cyt/Mtx/HC*	40/12/15 mg IT	Days 1, 4, 8, 11
Intensification therapy: 30 weeks (10 cycles – 21 days/cycle)		
Imatinib	400 mg PO daily	Days 1–14
Doxorubicin	30 mg/m^2 IV	Day 1 (cycles 1–7 only)
Vincristine†	2 mg IV	Day 1
6-Mercaptopurine	50 mg/m^2 PO QHS	Days 1–14
Dexamethasone	9 mg/m^2 PO BID	Days 1–5
Asparaginase	12 500 iu/m^2 IM	Days 1, 8, 15
Methotrexate	30 mg/m^2 IV	Days 2, 9, 16 (cycles 8–10 only)
Cyt/Mtx/HC*	40/12/15 mg IT	Every 18 weeks
Maintenance therapy: 72 weeks (24 cycles – 21 days/cycle)		
Imatinib	400 mg PO daily	Days 1–14
Vincristine†	2 mg IV	Day 1
6-Mercaptopurine	50 mg/m^2 PO QHS	Days 1–14
Dexamethasone	6 mg/m^2 PO BID	Days 1–5
Methotrexate	30 mg/m^2 IV/IM	Days 1, 8, 15
Cyt/Mtx/HC*	40/12/15 mg IT	Every 18 weeks

After completion of maintenance, imatinib 600 mg PO daily, indefinitely.

PO, orally; IV, intravenous; IM, intramuscular; IT, intrathecal; QID, four times daily; QHS, every night at bedtime; BID, twice daily.

*Cytarabine/methotrexate/hydrocortisone triple intrathecal therapy.

†Vinblastine 10 mg IV substituted for ileus or neuropathy.

For prophylaxis against *Pneumocystis jiroveci*, patients received trimethoprim-sulphamethoxasole three times per week, or inhaled pentamidine monthly if sulpha sensitive, for the entire 2 years. During induction, fluconazole 400 mg daily was used as antifungal prophylaxis. Febrile neutropenia was treated with intravenous broad-spectrum antibiotics as per institution protocol. Haematopoietic growth factors were not routinely administered, but filgrastim 300 μg daily was permitted at the treating physician's discretion for severe

neutropenic infections. Calcium and vitamin D supplementation and bisphosphonates (alendronate or risedronate once weekly) were used to prevent corticosteroid-induced osteopenia.

Dose modifications during postremission therapy were as follows: For Day 1 of each cycle, if the absolute neutrophil count (ANC) was $<0{\cdot}5 \times 10^9$/l or platelet count was $<50 \times 10^9$/l, the cycle was delayed for 1 week and the 6-mercaptopurine (6-MP) and methotrexate (Mtx) doses were subsequently reduced by 20%. If ANC and platelet counts were normal at Day 1 of each cycle, the 6-MP and Mtx doses were increased by 20% (up to a maximum of 150% for 6-MP and 133% for Mtx). If the serum aspartate transaminase or alanine transaminase was >8×, or serum bilirubin >1·8×, the upper limit of normal, the asparaginase dose was held for that week, and the 6-MP and Mtx doses were reduced by 20%. Asparaginase was discontinued if pancreatitis was diagnosed. In the event of venous thromboembolism, asparaginase was temporarily stopped, then restarted after 1–2 weeks with continued full anticoagulation. Patients with grades 3 or 4 peripheral neuropathy or ileus were switched from vincristine to vinblastine. Dexamethasone was temporarily discontinued or dose-reduced for grades 3 or 4 myopathy.

Patients who achieved complete remission (CR) were referred for allogeneic HSCT once a matched related or unrelated donor was identified. Depending on age and comorbidities, patients were offered either myeloablative or reduced intensity conditioning (RIC) regimen according to the decision of the transplant team. Myeloablative HSCT preparative regimens consisted of cyclophosphamide (60 mg/kg × 2) plus total body irradiation (TBI, 12 Gy in 6 fractions) or fludarabine (50 mg/kg/d × 4), busulfan (3·2 mg/kg/d × 4) plus total body irradiation (4 Gy in two fractions). The RIC regimen consisted of fludarabine (30 mg/kg/d × 4), busulfan (3·2 mg/kg/d × 2) plus TBI (2 Gy in a single fraction). GVHD prophylaxis consisted primarily of ciclosporin and methotrexate; four patients received alemtuzumab.

Response and toxicity definitions

CR was defined as attainment of a normocellular marrow with <5% blasts, with an ANC $\geq 1{\cdot}0 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l. Induction death was defined as death occurring during the hypoplastic phase of the induction chemotherapy. Overall survival (OS) was defined as the time from initiation of induction chemotherapy until death or last follow-up. Event-free survival (EFS) was defined as the time from diagnosis until relapse, death or last follow-up.

Toxicities were determined by NCI-CTC Version 4, while Eastern Cooperative Oncology Group (ECOG) criteria were used to determine performance status. Physical deconditioning was defined as a decrease in performance status to ECOG 3 or 4. The cumulative dose of chemotherapy drug delivered during the intensification phase was calculated as a percentage of the intended dose from the start of intensification up to the time of HSCT, relapse or end of intensification.

Statistical analysis

Descriptive statistics were reported as median and range for continuous variables and frequencies and proportions for categorical variables. Fisher's exact test and Pearson's chi-square test were used to compare proportions. Wilcoxon rank-sum test was used to compare the continuous variables. OS and EFS were calculated using the Kaplan-Meier method. Differences between survival curves were analysed by Log-rank test. Cox-proportional hazard regression model was applied to estimate the hazard ratio (HR) and 95% confidence interval (CI). Two-sided tests were applied and results were considered significant when the *P*-value was <0·05. Statistical analyses were performed using Version 9.2 of the SAS system and user's Guide (SAS Institute, Cary, NC, USA).

Results

Presenting features

A total of 32 consecutive adult patients were treated with this protocol. The baseline patient characteristics are shown in Table II. The diagnosis was established by PCR testing for *BCR-ABL1* in 28 patients and by interphase FISH in the remaining four.

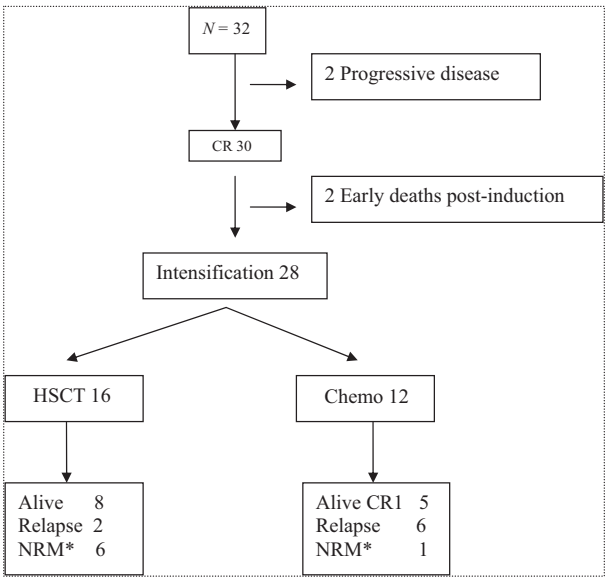
Outcome

The treatment outcomes are summarized in Fig 1. Of the 32 patients, 30 (94%) achieved CR with one induction. A postinduction molecular analysis by PCR was performed in 19 of these; two attained molecular CR, and seven others attained a >3 log reduction in *BCR-ABL1* transcript levels as compared to baseline; the remaining had a <3 log reduction. Two patients did not achieve CR with induction; one of these died during re-induction phase and the other is still alive after multiple relapses and multiple lines of treatment.

Table II. Baseline patient characteristics ($n = 32$)

Patient characteristic	Number
Age, years: median (range)	46 (18–60)
Age subgroups: 18–40 years/41–60 years	11/21
Sex: Male/Female	20/12
WBC count at diagnosis, $\times 10^9$/l: median (range)	22·4 (2·0–696·0)
High WBC disease ($>30 \times 10^9$/l)	13
Aberrant myeloid antigen expression	24
CD20 positivity	15
CD10 positivity	27
Central nervous system positivity at diagnosis	9

WBC, white blood cell.



* NRM = non-relapse mortality

Fig 1. Patient flow chart. CR, complete remission; CR1, first complete remission; HSCT, haematopoietic stem cell transplantation; NRM, non-relapse mortality.

There were two deaths in early CR before entering the intensification phase, due to multi-organ failure and traumatic subdural haematoma, respectively.

A total of 28 patients entered the intensification phase, of which 10 patients were $\leq$ 40 years old and 18 were 41–60 years of age. In 23 of these 28 patients, a suitable matched donor was identified – 11 sibling and 12 unrelated. A total of 16 patients (70%) underwent HSCT in CR1 – nine sibling and seven unrelated. Cyclophosphamide-TBI was the conditioning regimen in 10 and fludarabine-busulfan-TBI in 6. The reasons for not receiving HSCT included rapid relapse in three, poor performance status in two, patient decision in one case and donor issue in one. Six patients underwent HSCT before intensification cycle 5, six between intensification cycles 5 and 10, three during the maintenance phase and one patient after completing the entire 2-year protocol.

The survival curves for the entire cohort are shown in Fig 2. Eight patients relapsed, three during the intensification phase, one during maintenance, two after completion of chemotherapy (at 3 and 29 months, respectively), and two post-HSCT (at 10 and 12 months, respectively). Mutation analysis at relapse/progression was only performed in four patients; it was negative in two. One patient who did not attain CR demonstrated a kinase domain mutation with Phe 317 Leu substitution, and another patient who relapsed at 27 months postcompletion of maintenance had a Tyr 253 His mutation. The median OS was 40·7 months for the entire population with a 3-year OS of 53% (95% CI 34–68%). The median EFS was 30·1 months and 3-year EFS was 50% (95% CI 31–66%).

Of the 16 patients who underwent HSCT, eight were alive at a median follow-up of 85 months (range 46–110 months). Non-relapse mortality accounted for six deaths and relapse for the remaining two. Causes of non-relapse mortality in the transplanted patients included GVHD in three, veno-occlusive disease in one (all deaths within 100 d of HSCT, influenza in one (4 months post-HSCT) and pneumococcal meningitis in one patient (1-year post-HSCT). Among the 12 patients who did not undergo HSCT and continued on chemotherapy plus imatinib, five are alive in CR1 with a median follow-up duration of 59 months (range 29–63 months); one patient is alive in second CR at 59 months.

Median time to donor identification was 153 d, and the median time to HSCT was 268 d. A donor *versus* no-donor comparison was performed, based on whether a related or unrelated donor was identified at 6 months from diagnosis. Of 17 patients who had a donor identified by 6 months, 13 underwent HSCT. The median OS for the donor group was 40·7 months and for the no donor group 41·2 months, with a 3-year OS probability of 56% for the donor group and 61% for the no donor group (P = 0·72, HR 1·23, 95% CI

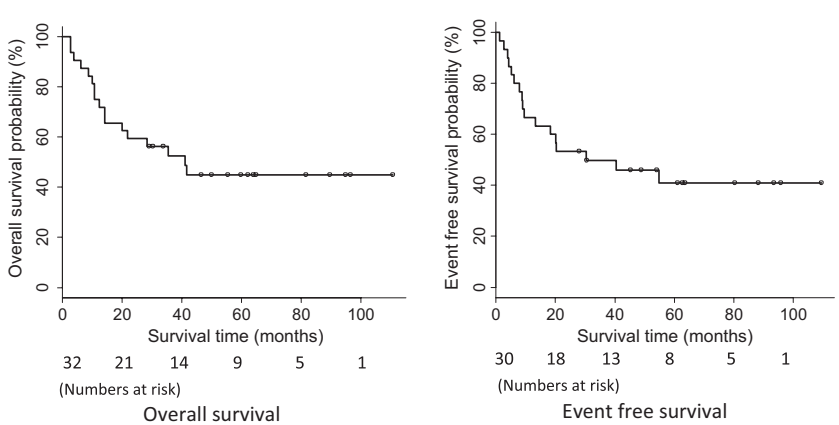


Fig 2. Overall survival and event-free survival of the entire group (n = 32).

0·41–3·66). The EFS was also not significantly different, with a median EFS of 20 months for the donor group and 40 months for the no donor group ($P = 0·88$). The 3-year EFS was 47% for the donor group and 73% for the no donor group ($P = 0·88$, HR 1·08, 95% CI 0·38–3·05).

The median time to undergo HSCT was approximately 9 months. Outcomes were compared for the 16 patients who were transplanted, *versus* the 10 patients who received only chemotherapy + imatinib, but were in continuous CR at 9 months. The median OS was not yet reached in the transplanted group, compared with 31·1 months in the chemotherapy group ($P = 0·34$). The 3-year OS was 56% vs. 50% in the non-transplanted group ($P = 0·34$, HR 0·58, 95% CI 0·19–1·79). The median EFS was not yet reached in the transplanted group vs. 54·3 months in the chemotherapy group. The 3-year EFS was 70% in the transplanted group *versus* 45% in the chemotherapy group ($P = 0·51$, HR 0·70, 95%CI 0·25–2·00).

Among the 15 surviving patients, eight had undergone HSCT. All eight patients who had undergone HSCT were PCR-negative for *BCR-ABL1* at last follow-up. Among the seven who did not undergo HSCT, three were PCR-negative at last follow-up, two had >3 log reduction and two had <1·5 log reduction in *BCR-ABL1* transcript levels.

Toxicities

Most of the pre-HSCT toxicities were observed either in the induction or the intensification phase. The grade 3 or higher induction toxicities, and new toxicities occurring during intensification, are summarized in Table III. There was a significantly higher incidence of infections, and a trend toward a higher frequency of grade 3–4 myopathy, ileus and elevated liver enzymes**,** during the induction phase in patients aged 41–60 years as compared to the group aged 18–40 years. Of the three patients with venous thrombosis, two presented with deep vein thrombosis and one with pulmonary embolism.

Thirteen patients experienced a total of 18 episodes of >2 weeks of treatment delay during the intensification phase, primarily due to grade 3–4 toxicities. There were also extensive dose modifications or deletions due to toxicity: only 18 out of the 28 patients (64%) received at least 80% of the intended cumulative dose of vinca alkaloids during intensification phase, primarily due to progressive neuropathy. Dexamethasone was temporarily held or discontinued for grade 3–4 proximal myopathy; 12 out of the 28 patients (43%) received <80% of the intended cumulative dose of dexamethasone during intensification; 61% of patients aged 41–60 years received <80% of the intended dexamethasone dose, as compared with 10% of patients in the 18–40 year age group ($P = 0·02$). Asparaginase was held or discontinued mostly based on liver function abnormalities or significant deconditioning; one patient developed pancreatitis at intensification cycle 5. Only six out of the 28 patients (21%) received at least 80% of the intended cumulative dose of asparaginase during intensification phase; this did not differ between the younger and the older adults.

A total of 15 patients had a significant deterioration in their functional status (ECOG 3–4). This was termed 'physical deconditioning', and was mainly related to neuropathy, myopathy and/or liver function abnormalities. As shown in Table III, physical deconditioning began during the induction phase in 12 cases (most of these continuing through intensification), and was more commonly seen in patients aged 41–60 years, as compared with those aged 18–40 years (52% vs. 9%, $P = 0·02$); an additional three cases began during intensification.

Non-transplant prognostic factors

On univariate analysis, the following factors were found to have no significant association with either OS or EFS: presenting white cell count >30 × 10^9/l, sex, surface expression of CD20 or CD10, myeloid antigen co-expression, CSF positivity at presentation, and lactate dehydrogenase level. There was no significant difference in the cumulative incidence of relapse ($P = 0·32$) or EFS ($P = 0·32$) between patients who achieved a >3 log vs. <3 log reduction in *BCR-ABL1* transcripts at the completion of induction therapy (data not shown).

Of the 15 patients who developed physical deconditioning, only four (27%) are alive as compared with 11 of 17 (65%)

Table III. Grade 3–4 toxicities during induction and intensification phases.

	Induction				Intensification*			
Toxicity	$N = 32$	<40 years ($N = 11$)	41–60 years ($N = 21$)	P	$N = 28$	<40 years ($N = 10$)	41–60 years ($N = 18$)	P
Peripheral neuropathy	8 (25%)	3 (27%)	5 (24%)	NS	11 (39%)	4 (40%)	7 (39%)	NS
Ileus	7 (22%)	1 (9%)	6 (29%)	NS	1 (4%)	0	1 (6%)	NS
Myopathy	6 (19%)	1 (9%)	5 (24%)	NS	9 (32%)	3 (30%)	6 (33%)	NS
Deconditioning	12 (38%)	1 (9%)	11 (52%)	0·02	3 (11%)	1 (10%)	2 (11%)	NS
Infections	7 (22%)	0	7 (33%)	0·03	8 (29%)	4 (40%)	4 (22%)	NS
Abnormal LFTs	11 (34%)	3 (27%)	8 (38%)	NS	15 (54%)	8 (80%)	7 (39%)	NS

LFTs, liver function tests; *N*, number; NS, not significant.
*Excluding those continuing from induction phase.

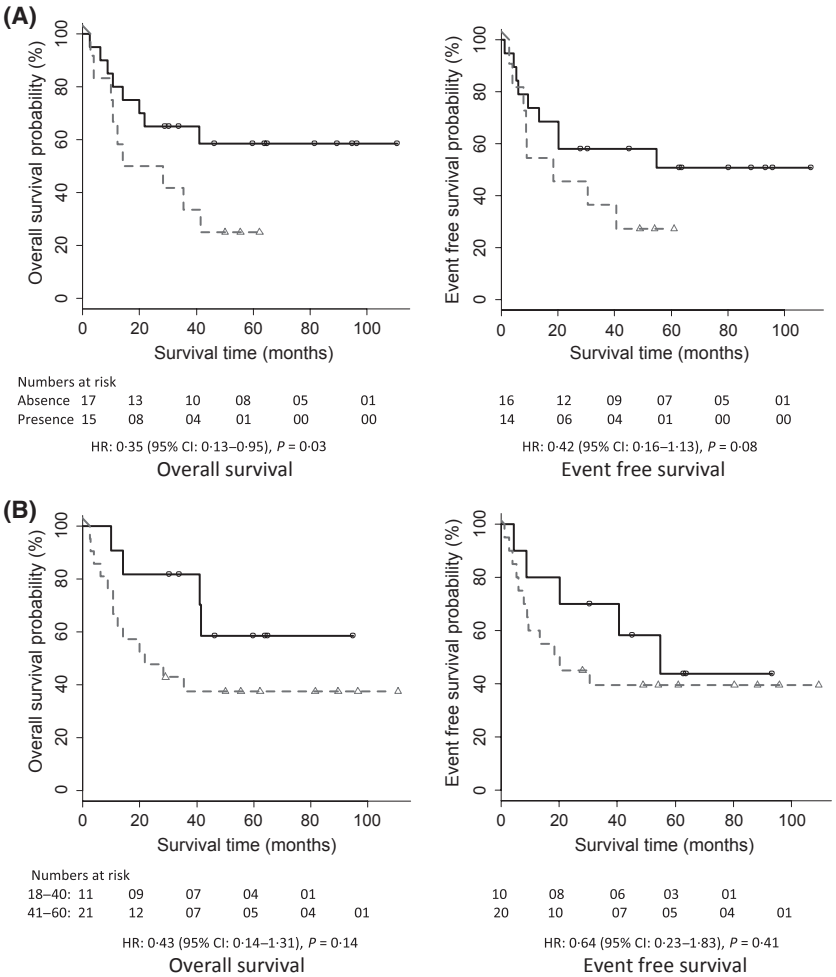


Fig 3. (A) Overall survival and event-free survival according to absence (solid line) or presence (dotted line) of physical deconditioning. (B) Overall survival and event-free survival according to age groups 18–40 years (solid line) or 41–60 years (dotted line).

who did not experience deconditioning. Fig 3A shows the survival according to whether deconditioning was observed. The 3-year OS in the deconditioned group was 32%, as compared with 71% in the group that did not experience deconditioning ($P = 0{\cdot}03$). The 3-year EFS was 43% in the deconditioned group, as compared with 63% in the non-deconditioned group ($P = 0{\cdot}08$). Fig 3B shows the survival according to age group. Although there was a trend for better OS and EFS in patients aged 18–40 years compared to those aged 41–60 years, these differences was not statistically significant ($P = 0{\cdot}14$ for OS, $P = 0{\cdot}41$ for EFS).

Discussion

A number of recent studies suggested that paediatric-inspired chemotherapy regimens produce superior results in younger adults with Ph-negative ALL (Stock *et al*, 2008; Huguet *et al*, 2009; Storring *et al*, 2009), but most reports using chemotherapy in combination with BCR-ABL1-directed TKIs for Ph+ ALL have used adult-based regimens. The current study has evaluated the feasibility of combining imatinib with a paediatric-based regimen for adults with Ph+ ALL. Our complete response rate of 94%, with a 10·5% molecular complete response rate and >3 log reduction in *BCR-ABL1* transcript level of 36·8% with one cycle of induction chemotherapy demonstrates the high activity of the induction phase. These response rates are similar to other reports combining TKIs with induction chemotherapy (Thomas *et al*, 2004; Yanada *et al*, 2006; de Labarthe *et al*, 2007; Bassan *et al*, 2010**;** Fielding, 2010). The median OS of 40·7 months with 3-year OS rate of 53% and median EFS of 30·1 months with 3-year EFS of 50% are a significant improvement from the preimatinib era, and are similar to other reports using imatinib combined with chemotherapy (Thomas *et al*, 2004; Lee *et al*, 2005; Wassmann *et al*, 2006; Yanada *et al*, 2006; de Labarthe *et al*, 2007; Fielding, 2010; Ribera *et al*, 2010).

This regimen was associated with certain major toxicities (Table III). Grades 3–4 peripheral neuropathy, paralytic ileus, proximal myopathy and elevated liver enzymes were particularly common. We also observed a prominent decline in

performance status to ECOG 3 or 4, an entity we called 'physical deconditioning', in nearly 40% of patients, which appeared to result largely from a combination of these major toxicities. The onset was mostly during the induction phase (12/32), although three additional patients developed this during intensification, and these effects continued throughout the intensification phase. This deconditioning was predominantly observed in patients aged 41–60 years, as were the associated toxicities. The resulting decline in performance status resulted in major disruptions in treatment, with withdrawal of, or major dose reductions in, many of the active chemotherapy agents. This may have contributed to the inferior outcome on these deconditioned patients. It may also have contributed to the high treatment-related mortality post-HSCT, as other studies have found inferior outcomes post-HSCT in patients with poor performance status and high co-morbidity indices (Sorror *et al*, 2005; Artz *et al*, 2006; Xhaard *et al*, 2008; Guilfoyle *et al*, 2009; Deeg & Sandmaier, 2010).

Although the toxicities seen in this study were greater than those we had previously reported with this chemotherapy regimen in BCR-ABL1 negative patients (Storring *et al*, 2009), the median age in the current study was higher, which probably contributed to the higher toxicity rates. However, we cannot exclude an additional influence of imatinib. As a potent CYP3A4 inhibitor, imatinib could theoretically increase the exposure to vincristine and dexamethasone, both of which are metabolized by the enzyme (Duckett & Cameron, 2010; Green *et al*, 2010; Nebot *et al*, 2010).

Despite the improved anti-leukaemic activity of TKI + chemotherapy combinations, HSCT remains the only potentially curative modality in a substantial proportion of Ph-positive ALL patients. Accordingly, it does not seem advisable to administer regimens that may potentially have an adverse impact on outcomes post-HSCT. Furthermore, in patients not undergoing HSCT, physical deconditioning resulting from such intensive therapy was associated with inferior outcomes in our cohort, probably due to major reductions in dose intensity. The excessive toxicity of the regimen in patients aged 41–60 years suggest that modifications would be required in this age group in order to prevent major declines in performance status and permit patients to proceed to HSCT with adequate organ function and favourable co-morbidity scores. These may include reducing the cumulative corticosteroid dose, switching from vincristine to vinblastine, and eliminating or reducing the dose of asparaginase.

Recent data (Vignetti *et al*, 2007; Foa, 2011; Foa *et al*, 2011) have shown that remission induction therapy with TKIs and steroids, but without any chemotherapy, was able to achieve a 100% complete response rate in older adults without major toxicity. Such an approach may permit more patients to proceed to HSCT with improved overall performance status and organ function, compared to the more intensive approach used in our population. However, it is unclear whether this 'minimalist' approach would result in improved OS, because these patients are likely to go to transplant with a higher leukaemic burden. Furthermore, it is possible that a less intensive approach may result in higher relapse rates prior to transplant, for those who require more prolonged unrelated searches, or for those in whom a donor cannot be found.

A comparison of outcome with HSCT *versus* chemotherapy/TKI alone is fraught with problems. A major issue with retrospective studies is 'survivor treatment selection bias' (Fielding, 2011), owing to the time required to identify a donor, particularly in the unrelated setting (Rowe, 2011). Simple donor *versus* no donor comparisons would potentially include patients who have relapsed prior to the identification of a donor. In order to address this, we compared outcomes with HSCT *versus* chemotherapy alone, using the median time to identify a donor, in a donor *versus* no donor comparison. We also compared outcomes for those undergoing HSCT with those receiving chemotherapy alone, but were in continued remission at the median time to transplant. We did not find any significant difference in either OS or EFS between HSCT and chemotherapy/TKI alone, using this manoeuvre. However, interpretation of this is limited by the small patient numbers.

The relatively longer time to donor identification in our series was driven mostly by patients from varied ethnicities, for whom the identification of unrelated donors took longer, and by siblings living abroad. It is possible that outcomes post-HSCT could potentially be improved by earlier identification of donors, as well as by the use of less toxic pretransplant chemotherapy. Further follow-up is also required to evaluate the long-term outcomes, particularly in non-transplanted patients, as the majority of these patients have molecular evidence of residual disease and thus are potentially at risk of late relapse. Studies with larger cohorts, followed for a longer time period, are required in order to further address the question of whether some patients may be managed without early HSCT (Fielding, 2011).

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