Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia

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ABSTRACT

We have previously reported on the efficacy and tolerability of hyper-CVAD regimen (cyclophosphamide, vincristine, Adriamycin, and dexamethasone) and imatinib followed by imatinib-based consolidation/maintenance therapy in 20 patients with newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Here, we present the 13-year follow up of our study. Fifty-four patients with newly diagnosed Philadelphia-positive acute lymphoblastic leukemia were enrolled: 39 (72%) with *de novo* disease, 6 (11%) whose disease was primary refractory after induction (without a tyrosine kinase inhibitor), and 9 (17%) in complete remission after one course of induction therapy (without tyrosine kinase inhibitor). Forty-two (93%) of the 45 patients treated for active disease achieved complete remission, one achieved complete remission with incomplete recovery of platelets, one achieved partial remission and one died during induction. Nineteen (35%) patients are alive and 18 are in complete remission. The 5-year overall survival rate for all patients was 43%. Significant negative predictors of overall survival were age over 60 years, p190 molecular transcript, and active disease at enrollment. Sixteen (30%) patients underwent allogeneic stem cell transplantation. Median overall survival was not significantly greater for patients who underwent transplant. Patients with residual molecular disease at three months had improved complete remission duration with transplant. The median time to hematologic recovery and severe toxicities with combination were not significantly different from those observed with conventional chemotherapy. Only one patient discontinued therapy due to toxicity. HyperCVAD chemotherapy and imatinib is an effective regimen for Philadelphia-positive acute lymphoblastic leukemia. Transplant may not be indicated in all patients with Philadelphia-positive acute lymphoblastic leukemia. (*clinicaltrials.gov identifier: NCT00038610*)

Introduction

Much progress has been made in understanding the biology of acute lymphoblastic leukemia (ALL). Accurate definition of prognostic subgroups based on cytogenetic-molecular markers has allowed successful institution of risk-oriented therapies.[1,2] Philadelphia chromosome-positive (Ph^+) ALL is more common in older patients (25%-35%), is frequently associated with leukocytosis, and confers a poor prognosis and a high relapse rate.[3,4] Prior to the advent of tyrosine kinase inhibitors (TKIs) the outcomes of adult patients with Ph+ ALL were dismal. Combination chemotherapy achieved complete response in a majority of adults with Ph^+ ALL. However, the responses were short-lived with long-term survival rates of less than 20%.[2,5-8] Slow and partial reduction of the leukemic clone by traditional cytotoxic chemotherapy may be responsible for the poor prognosis associated with Ph^+ ALL when compared with less aggressive variants of ALL.[9]

Heretofore, allogeneic stem cell transplant (ASCT) in first remission was the only effective curative option, and was offered to all patients in first remission who had a suitable donor.[10-12] ASCT can induce durable remissions. However, this approach can result in significant treatment-related mortality and morbidity and is only available to a limited number of patients.[13,14] Fielding *et al.* reported that only 28% of patients in their study actually underwent transplantation as intended per protocol. In their study, age over 55 years and occurrence of pre-transplant events were the main reasons patients were unable to proceed to ASCT.[10] Thus, alternative strategies were needed for adult patients with Ph^+ ALL.

The emergence of TKIs has created a paradigm shift in the management of adult patients with newly diagnosed Ph^+ ALL.[15-20] With improved response rates and the possibility of long-term survival in a proportion of adult patients with Ph^+ ALL who do not undergo transplant, the role of ASCT in first remission is being called into question.[17-19,21] Studies from the Childrens Oncology Group have shown significantly improved outcomes for children and adolescents with Ph^+ ALL treated with post-induction imatinib mesylate in combination with intensive chemotherapy.[21] The 5-year disease-free survival was similar for chemotherapy plus imatinib (70%±12%), sibling donor ASCT (65%±11%) and unrelated donor ASCT (59±15%; P=0.60). In those patients who do proceed to an ASCT, the durable and potent responses produced by TKI-based combination therapy increase the likelihood of identifying an ideal donor, significantly reduce the disease burden prior to transplant, and improve overall survival (OS).[22-25]

In the first clinical trial reporting the combination of a TKI with chemotherapy we noted that imatinib mesylate (imatinib)-based combined regimens were well-tolerated and effective in 20 patients with *de novo* Ph^+ ALL.[17] Patients enrolled on this trial received hyper-CVAD (cyclophosphamide, vincristine, adriamycin and dexamethasone, a

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dose-intensive chemotherapy regimen used at our institution to treat adult ALL since 1992) in combination with imatinib producing a complete response rate of 100% and a 2-year disease free survival of 85%.[26] Furthermore, molecular complete responses by quantitative reverse transcription-polymerase chain reaction (RT-PCR) were reported in 60% of the patients. This was followed by the recruitment of 34 additional patients. Herein, we present the 13-year follow up of our phase II study of imatinib with hyper-CVAD for the front-line treatment of adult patients with Ph+ ALL.

Methods

Patients

Adult patients (age ≥15 years) with Ph+ ALL, newly diagnosed or previously treated with induction therapy without TKI (either failing after one course or in complete remission after up to two courses of therapy without TKI), were eligible. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; adequate renal and liver function (with serum creatinine ≤2.0 mg/dL and serum bilirubin ≤3.0 mg/dL, unless considered due to tumor), and adequate cardiac status (no evidence of grade III or IV heart failure as defined by the New York Heart Association criteria). Patients were excluded if they had an uncontrolled active infection, active secondary malignancy, were pregnant or breastfeeding. This was a single center study. All patients signed an informed consent form approved by the Institutional Review Board of The University of Texas M.D. Anderson Cancer Center (*clinicaltrials.gov identifier: 00038610*).

Study design and treatments

The details of the imatinib with hyper-CVAD regimen have been described previously.[17,25] Odd courses (1, 3, 5, and 7) of hyperfractionated cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and dexamethasone were given alternately with even courses (2, 4, 6, and 8) of high-dose cytarabine and methotrexate. Central nervous system (CNS) prophylaxis included alternating intrathecal therapy with methotrexate and cytarabine on days 2 and 7 of each course for a total of 6 or 8 doses, depending on risk for CNS relapse.[27] Patients with active CNS leukemia at presentation received additional intrathecal chemotherapy with or without cranial irradiation. All patients received concurrent therapy with imatinib at a dose of 400 mg orally once daily days 1-14 of each cycle of intensive chemotherapy followed by imatinib at a dose of 600 mg daily during the maintenance phase, from April 2001 to December 2004. From April 2001 to December 2004, 35 patients were treated with the hyper-CVAD and imatinib mesylate regimen. Time to recovery from myelosuppression with each cycle of intensive chemotherapy appeared similar to that of hyper-CVAD alone. Toxicities encountered in this group were as expected related to the chemotherapy components of hyper-CVAD. By this time, the hyper-CVAD and imatinib mesylate regimen (with or without rituximab) using 600 mg daily days 1-14 of each intensive course of therapy had also been piloted in the setting of Philadelphia positive chronic myelogeneous leukemia in lymphoid blast phase and relapsed Philadelphia positive ALL and no significant increase in incidence of toxicities had been observed. Given the excellent tolerance of the 35 patients treated on our protocol to date and the known dose-response relationship of imatinib mesylate the protocol was amended to increase the imatinib mesylate to 600 mg orally daily days 1-14 of the intensive phase of chemotherapy, and to administer the imatinib continuously through the intensive phase, followed by imatinib at a dose of 800 mg daily during the maintenance phase. The treatment schema is provided in *Online Supplementary Figure S1*. Patients who were still on study and were tolerating imatinib at the initial 400 mg dose level were escalated to imatinib 600 mg daily during the intensive phase and 800 mg daily during the maintenance phase. Patients in first complete remission (CR) with an available matched donor had the option of ASCT.

Maintenance therapy was given for 24 months with 2 mg vincristine intravenously monthly and prednisone daily for five days per month; this was initiated after the completion of the eight courses of intensive chemotherapy (or earlier because of poor tolerability and toxicity). From April 2001 to December 2004, all patients received imatinib at a dose of 600 mg orally daily during the 24 months of maintenance; imatinib was continued indefinitely thereafter.[28] In December 2004, the protocol was amended and all patients received imatinib at a dose of 800 mg orally daily during the maintenance; imatinib was continued indefinitely thereafter. Maintenance could be interrupted in months 6 and 13 with intensification courses of hyperCVAD and imatinib. The dose of imatinib was reduced to 400 mg for grades 3 or 4 hepatotoxicity during the intensive phase (reduced to 600 mg if during the maintenance phase). Other dose reductions during the intensification and maintenance phase were permitted according to previously published parameters.[17,26] Imatinib mesylate was to be continued indefinitely after the 24 months of therapy.

Supportive care measures were according to standard guidelines.[17]

Assessments

Pre-treatment evaluations included complete history and physical examination, complete blood count with differential, comprehensive biochemistry panel, pregnancy test and counseling, and bone marrow aspiration for histology, multiplanar flow-cytometry, cytogenetics, fluorescent *in situ* hybridization (FISH), and quantitative RT-PCR for BCR-ABL transcripts. Patients with active

Table 1. Patients' characteristics.

Parameter		Number (%) / Median [range]
Disease status at study entry	Active disease	45 (83%)
	In CR	9 (17%)
Age (years)		51 [17-84]
White blood cell count (x10^9/L)		16.7 [2.0-594.5]
Hemoglobin (g/dL)		9 [5.1-12.5]
Platelets (x10^9/L)		50 [4.0-346.0]
Albumin (g/dL)		3.3 [1.8-4.6]
LDH (U/L)		1171 [285-5967]
ECOG performance status	0	7 (13%)
	1-2	47 (87%)
Molecular	p190$^{BCR-ABL}$	36 (67%)
	p210$^{BCR-ABL}$	18 (33%)
Cytogenetics	Ph+	10 (19%)
	Ph+ with others	35 (65%)
	‡Cyto neg. (FISH+)	7 (13%)
	*Cyto neg., FISH -, PCR +	2 (4%)
CNS disease at presentation		7 (13%)

**All of these patients had detectable BCR-ABL transcript by RT-PCR. ‡Undetectable on routine cytogenetics but identified on FISH for t(9:22). LDH: lactate dehydrogenase; CNS: central nervous system; CR: compete remission; Neg: negative; FISH: fluorescence-in-situ-hybridization; IM: insufficient metaphases.*

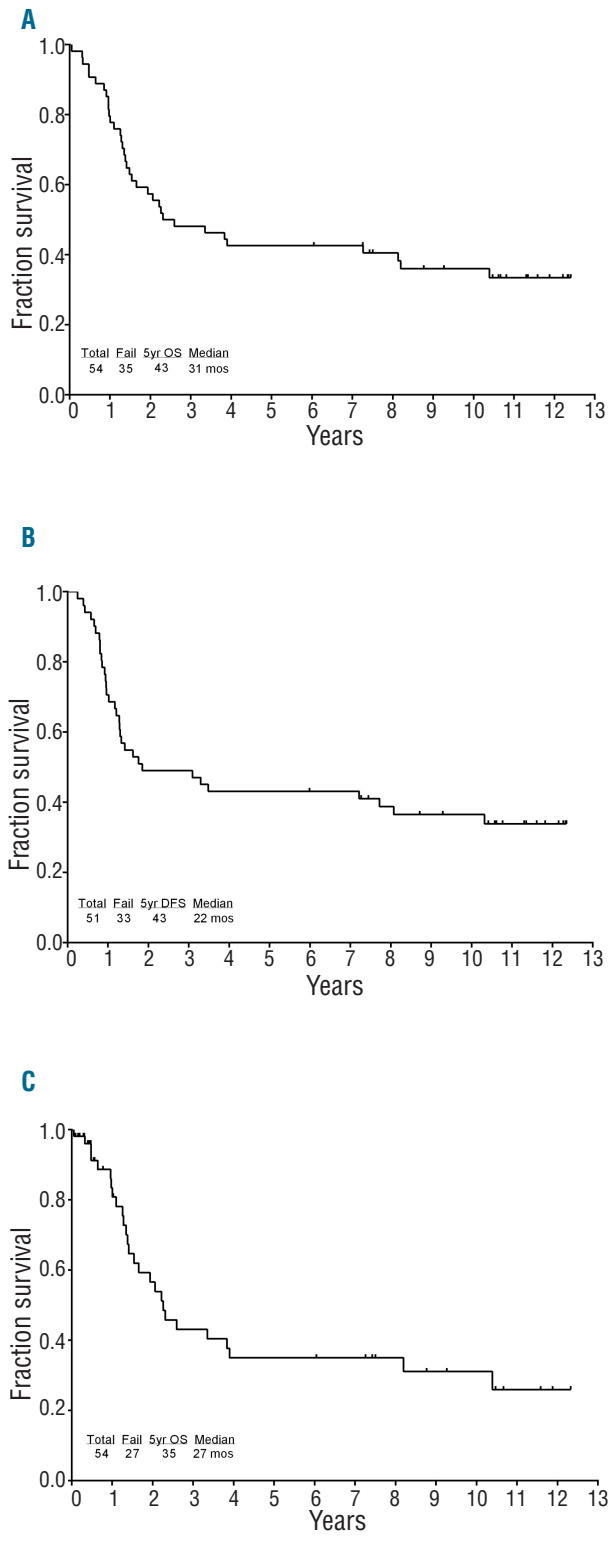

Figure 1. All 54 patients enrolled on the protocol and treated with imatinib in combination with hyper-CVAD chemotherapy are evaluated for overall survival (OS) (A) and disease-free survival (DFS) (B) from the time of initiation of protocol therapy. This includes newly diagnosed untreated patients (n=39) or patients previously treated with induction therapy without tyrosine kinase inhibitors (TKI): either failing after one course of chemotherapy without TKI (n=6) or in complete remission after up to two courses of chemotherapy without TKI (n=9). (C) Evaluation of OS censored for allogeneic stem cell transplant (ASCT).

Table 2. Patients' characteristics and analysis of factors associated with overall survival.

Parameter	N	Median OS (months)	UVA P
Age			
> 60 years	14	16.4	0.006
≤ 60 years	40	87.2	
Disease status			
At study entry			
De novo active disease	39	31.1	0.015
Refractory disease	6	16.0	
CR at start	9	111.0	
Sex			
Males	28	46.4	0.47
Females	26	26.9	
WBC			
≥ 30.0 (10^9/L)	20	36.8	0.18
< 30.0 (10^9/L)	34	18.5	
Hb			
≥ 10.0 (g/dL)	16	98.4	0.095
< 10.0 (g/dL)	38	25.7	
Platelets			
≥ 50 (10^9/L)	29	40.2	0.56
< 50 (10^9/L)	25	27.1	
ECOG PS			
0	7	87.0	0.26
1-2	47	27.1	
Albumin			
≥3.0 gm/dL	40	46.4	0.17
<3.0 gm/dL	14	15.0	
LDH			
>620 U/L	38	27.4	0.69
≤620 U/L	16	43.5	
CNS disease at presentation			
Yes	7	26.6	0.78
No	47	40.2	
Molecular transcript			
p190	36	24.0	0.04
p210	18	81.0	
Cytogenetics			
Ph^+	7	46.8	0.80
Ph^+ with others	35	27.1	
Neg Ph^+ ($FISH^+$)	4	19.4	
IM/Unknown	8	69.3	
MMR to induction			
Yes	15	40.3	0.22
No	14	16.1	
CMR to induction			
Yes	6	40.3	0.40
No	23	26.9	
CCyR to induction			
Yes	26	29.1	0.32
No	5	16.5	
Allogeneic SCT			
Yes	16	123.2	0.17
No	38	25.7	

WBC: white blood count; PS: performance status; LDH: lactate dehydrogenase; CNS: central nervous system; MMR: major molecular response; CMR: complete molecular remission; CCyR: complete cytogenetic remission; SCT: stem cell transplant; CR: complete remission; N: number; OS: overall survival; UVA: univariate analysis.

disease at entry had bone marrow aspirations for cytogenetics, FISH and quantitative RT-PCR on approximately days 14 and 21 of course 1. Subsequently, bone marrow aspirations with cytogenetics, FISH and quantitative RT-PCR were repeated every 2-4 courses while on therapy and every 4-6 months for five years from initiation of therapy. Cytogenetics, RT-PCR, and multiplanar flow-cytometry were performed at our institution by methods detailed previously.[18,29-32] The BCR-ABL quantification was a percent ratio of BCR-ABL1 to ABL1 transcript level.

Response definitions

Complete response was defined as the presence of 5% or less blasts in the bone marrow, with a granulocyte count of $1.0x10^9$/L or over, a platelet count of $100x10^9$/L or over, and no extramedullary disease. Molecular CR was defined by the attainment of RT-PCR negativity in patients with hematologic CR. Major molecular response was defined by RT-PCR for *BCR-ABL* transcript of less than 0.1%. Complete recovery except platelets (CRp) was defined as for CR, except for recovery of platelet count to less than $100x10^9$/L. Partial remission (PR) was defined as a bone marrow with more than 5% and less than 25% blasts with a granulocyte count of $1.0x10^9$/L or over and a platelet count of $100x10^9$/L or over. Relapse was defined by recurrence of more than 5% lymphoblasts in the bone marrow aspirate or by the presence of extramedullary disease after achieving CR. Induction death was defined as death occurring after start of therapy without meeting the definition of CR or resistant disease. Resistant disease included patients who survived the induction treatment peri-

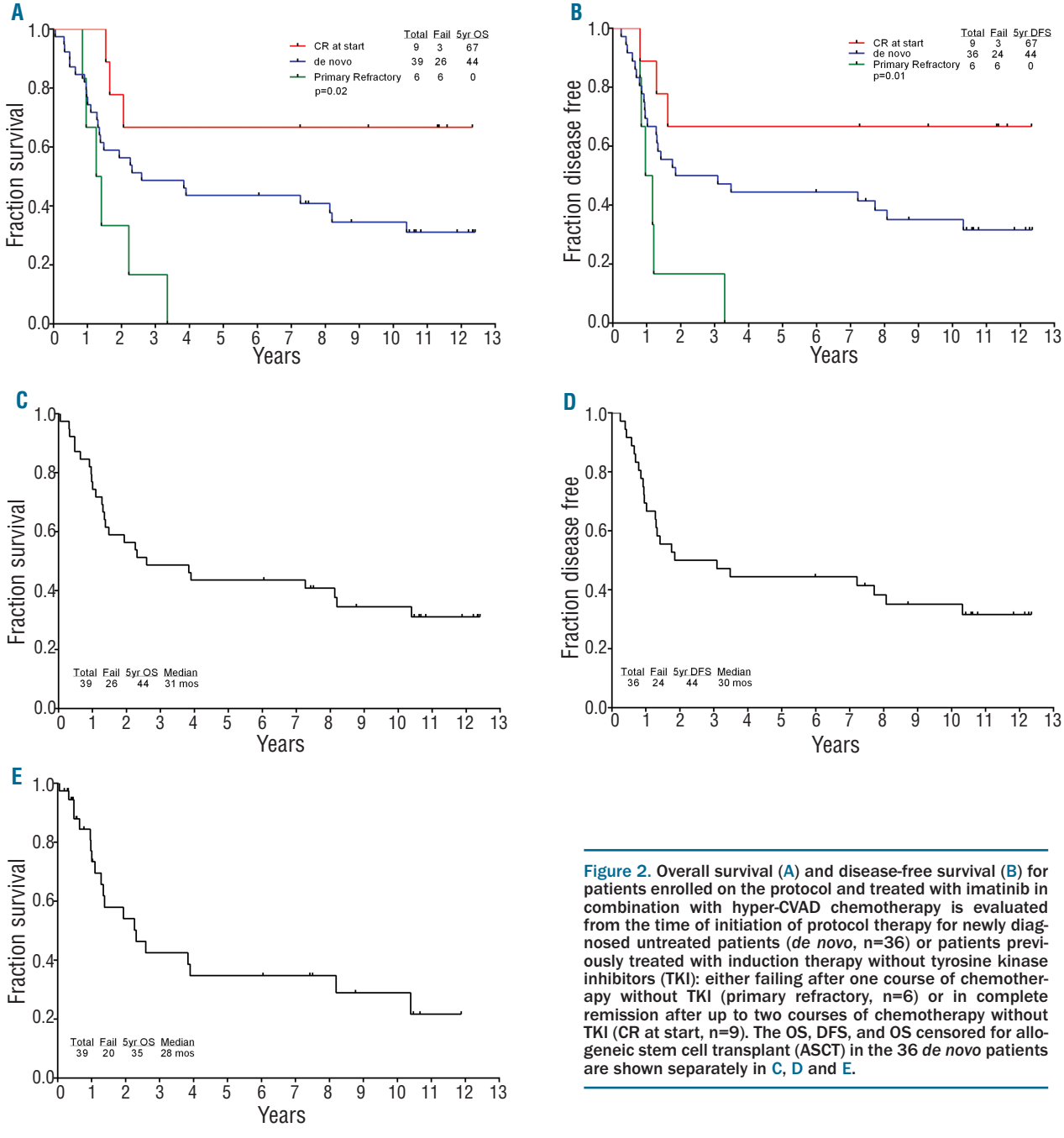

Figure 2. Overall survival (A) and disease-free survival (B) for patients enrolled on the protocol and treated with imatinib in combination with hyper-CVAD chemotherapy is evaluated from the time of initiation of protocol therapy for newly diagnosed untreated patients (*de novo*, n=36) or patients previously treated with induction therapy without tyrosine kinase inhibitors (TKI): either failing after one course of chemotherapy without TKI (primary refractory, n=6) or in complete remission after up to two courses of chemotherapy without TKI (CR at start, n=9). The OS, DFS, and OS censored for allogeneic stem cell transplant (ASCT) in the 36 *de novo* patients are shown separately in C, D and E.

od but had persistent leukemia. CR duration was calculated from the time of CR until relapse. Disease-free survival (DFS) was calculated from the time of CR until relapse or death due to any cause. Overall survival was calculated from the date of initiation of therapy until death. Toxicity evaluation was based on the National Cancer Institute Common Toxicity Criteria version 2.0.

Statistical analysis

Differences among variables were evaluated by the χ^2 test and Mann-Whitney U tests for categorical and continuous variables, respectively. All P values were two-sided and $P<0.05$ was considered significant. Survival distributions were estimated using the Kaplan-Meier method and compared using the log rank test.33 Statistical analyses were carried out using IBM SPSS Statistics 21 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Study group

Between April 2001 and November 2006, 54 patients with newly diagnosed Ph$^+$ ALL were enrolled on the study and treated with imatinib in combination with hyperCVAD chemotherapy (Table 1). Thirty-nine patients (72%) presented with *de novo* disease, 6 (11%) were refractory to standard induction therapy, and 9 (17%) entered the study in CR after one course of standard induction therapy. No patients had prior exposure to TKI therapy. Fourteen patients (26%) were older than 60 years. The type of *BCR-ABL* transcript could be determined in all patients. The minor breakpoint transcripts e1a2 and e1a3 encoding for the p190$^{BCR-ABL}$ were identified in 36 patients (67%). The major breakpoint transcripts e13a2 and e14a2 encoding the p210$^{BCR-ABL}$ protein were identified in 18 patients (33%). None of the patients demonstrated concurrent expression of major and minor *BCR-ABL* transcripts.

Nineteen patients (35%) remain alive at this time. Median follow up is 130 months (range 73-149 months) for surviving patients, and 29 months (range 0.6-149 months) for all patients. The median number of intensive courses was seven (range 1-8). Thirty-five patients received imatinib at the dose of 400 mg daily during the eight courses of induction/consolidation. Subsequently, the protocol was amended and 19 patients received the amended dose of 600 mg daily during induction/consolidation.

Nineteen patients came off study during induction/consolidation (cycles 1-8) with hyperCVAD and imatinib: stem cell transplant (n=13), died in CR/PR (n=3), died in induction (n=1), switched to alternate therapy due to persistent cytogenetic aberrations (n=1), and imatinib discontinued due to toxicity (n=1). Thirty-five patients (65%) went on to receive imatinib during maintenance. The starting daily dose of maintenance imatinib in these 35 patients was 800 mg in 11 patients, 600 in 19 patients, and 400 mg in 5 patients. Twenty-two patients came off study during maintenance therapy: relapsed (n=10), died in CR (n=6), stem cell transplant (n=3), switched to alternate TKI due to positive MRD (n=1), secondary MDS (n=1), and taken off due to toxicities (n=1). Only 14 (26%) patients completed the induction/consolidation and 24 months of maintenance. Of these 14 patients, 10 are still alive and in CR. The 4 patients who are not alive at the time of this analysis were on imatinib for a median of 51 months (range 42-98). Six of the living patients remain on imatinib (3 at 400 mg/day, 2 at 600 mg/day, and 1 at 800 mg/day)

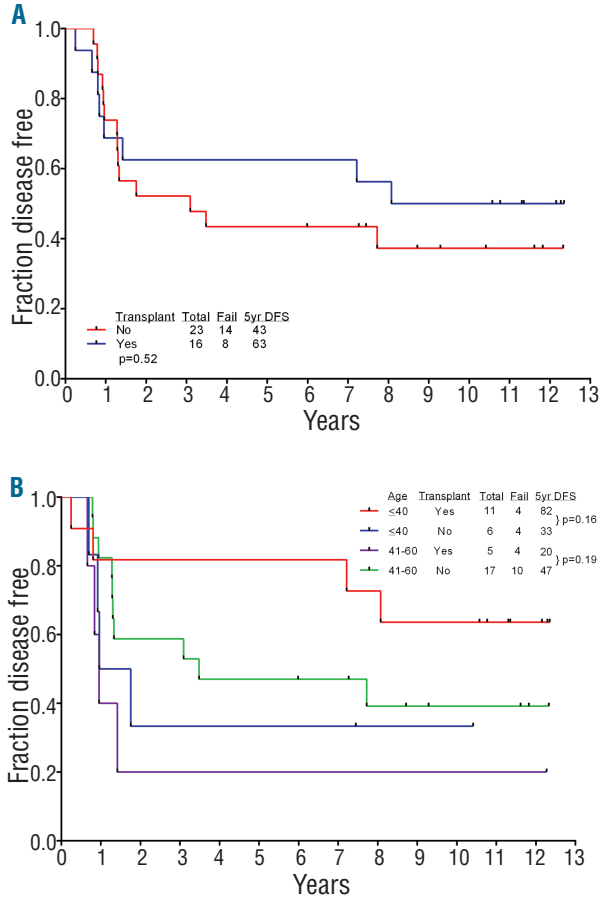

Figure 3. Disease-free survival in patients treated with hyper-CVAD and imatinib followed by imatinib-based consolidation/maintenance therapy by transplant *versus* no transplant for all patients under 60 years of age (A) and by transplant versus no transplant for patients aged 40 years or under and patients aged 41-60 years (B).

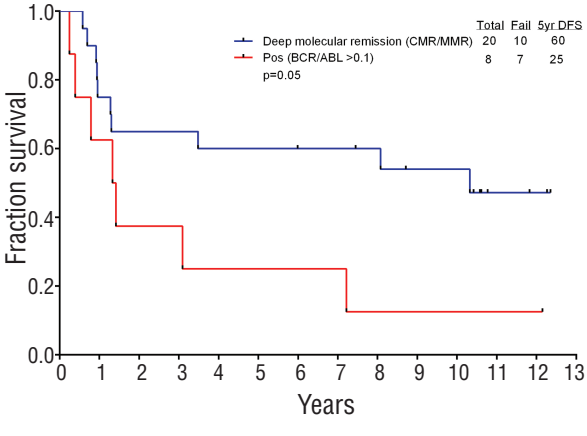

Figure 4. Disease-free survival in patients treated with hyper-CVAD and imatinib followed by imatinib-based consolidation/maintenance therapy by molecular response status [deep molecular remission (CMR/MMR) *versus* no deep molecular remission] at three months.

for a median of 118.5 months (range 87-148). Among the other 4 living patients, one patient was on imatinib for 34 months, was switched to dasatinib due to severe gastrointestinal problems, and has been on dasatinib for 54 months. One was on imatinib for 52 months, was switched to nilotinib due to pleural and pericardial effusions, and was on nilotinib for 20 months before being lost to follow up. The remaining 2 patients were on imatinib for a median of 118.5 months (range 112-125): one has discontinued due to severe muscle cramps and the other because of pleural effusions.

Response to therapy

We had 9 patients with Ph^+ ALL who had received prior induction with a non-TKI containing regimen and achieved morphological CR (with persistent disease on cytogenetics or molecular evaluation) prior to enrolling on the protocol. The remaining 45 patients were evaluable for response to induction therapy with hyperCVAD in combination with imatinib. Forty-two (93%) of the 45 patients with active disease at the time of enrollment achieved CR, one patient achieved CRp, one patient achieved PR and one patient died during induction. Of the patients who achieved CR, 40 (95%) achieved CR after one course of therapy and 2 (5%) achieved CR after two courses of therapy. The median time to CR, ANC recovery of $1x10^9$/L, and platelet recovery of $100x10^9$/L was 20 days (range 17-56), 18 days (range 14-26), and 21 days (range 17-32), respectively. Among the patients who achieved CR, cytogenetic CR was identified in 34 of the 39 (87%) patients who had a cytogenetic evaluation after one course of therapy. Overall, 40 (95%) patients went on to achieve cytogenetic CR. Among the patients who achieved CR, complete or major molecular response was achieved in 15 of the 29 (52%) patients who had RT-PCR evaluation after one course of therapy. Overall, 83% of the patients who achieved CR went on to have a molecular response (complete or major): 19 (45%) achieved complete molecular remission at a median of 12 weeks (range 2.4-87.6 weeks), and 16 (38%) achieved major molecular response at a median of 10 weeks (range 2.9-51.4 weeks). Minimal residual disease (MRD) assessment by multiplanar flow cytometry was available in 32 patients: 28 (88%) achieved MRD-negative status at a median of 4.1 weeks (range 2.1-138.1).

As noted, one patient achieved CRp and another patient achieved PR after the first course, both with a time to response of 22 days. One patient died on day 20 of induction from pneumonia and sepsis. Bone marrow examination performed on day 14 showed persistent disease.

Remission duration and survival

With a median follow up of 130 months (range 73-149), 19 patients are alive and 18 are in CR. The median OS for the entire group is 31 months (range 0.6-149) with an estimated 2-year and 5-year OS rate of 57% and 43%, respectively (Figure 1A). The median DFS for 51 patients in CR is 22.0 months (range 3.0-148.2) with an estimated 2-year and 5-year DFS of 49% and 43%, respectively (Figure 1B). The median OS censored for ASCT was 27 months (Figure 1C). A total of 18 patients remain alive in CR, including 10 who received imatinib and hyperCVAD alone and 8 who received imatinib and hyperCVAD followed by ASCT. The only significant predictors of OS on univariate analysis were age at initiation of protocol therapy (>60 years), type of molecular transcript, and disease status at enrollment (Table 2). On multivariate analysis, the only factor that remained significant was age over 60 years. The OS and DFS by disease status at study entry are shown in Figure 2A and B. The OS, DFS, and OS censored for ASCT among the 36 *de novo* patients are shown in Figure 2C-E.

All patients in CR had the option to proceed to ASCT with matched sibling donor, matched unrelated donor or alternate donors (haploidentical or umbilical cord). Sixteen (30%) of the 54 patients underwent ASCT, including matched sibling (n=10), matched unrelated donor (n=5), and umbilical cord donor (n=1). Of the 14 patients aged over 60 years, no one proceeded to ASCT. Therefore, patients aged over 60 years were excluded from the ASCT versus no ASCT analysis: six patients were not referred to the ASCT service due to older age and 8 were evaluated by the ASCT service but were unable to proceed with ASCT due to lack of a suitable donor (n=4), not being unfit for ASCT (n=3), or patient refusal (n=1). Of the 40 patients aged 60 years or under, 16 underwent ASCT. The remaining 24 patients aged 60 years or under were referred to the ASCT service but were unable to proceed with ASCT due to lack of a suitable donor (n=7), patient refusal (n=8), being unfit for ASCT (n=3), MRD-negative and the decision was to proceed to ASCT if they became MRD-positive (n=3), financial constraints (n=2), and relapse prior to ASCT (n=1). Median time from start of therapy to ASCT was 4.9 months (range 1.1-12.3). RT-PCR was detectable in 11 patients prior to ASCT (up to 60 days pre-transplant) including 4 patients with a BCR-ABL/ABL ratio of greater than 0.5% (no major molecular response). Of these, 8 patients became RT-PCR negative after ASCT.

There was no significant difference in 5-year DFS for patients who received imatinib and hyperCVAD alone versus patients who received imatinib and hyperCVAD followed by ASCT (43% *vs.* 63%; P=0.52) (Figure 3A). There was no significant difference in 5-year DFS for patients aged 41-60 years who received imatinib and hyperCVAD alone as compared to those who received imatinib and hyperCVAD followed by ASCT (47% vs. 20%; P=0.19). Similarly, patients aged 40 years or under who received imatinib and hyperCVAD followed by ASCT did not have a significantly different 5-year DFS as compared to those who received imatinib and hyperCVAD alone (82% *vs.* 33%; P=0.16) (Figure 3B). It must be noted that the numbers for comparison are small in these small subsets. Patients who did not achieve a deep molecular remission at three months from initiation of therapy had a significantly inferior DFS as compared to those who achieved a deep remission (25% *vs.* 60%; P=0.05) (Figure 4A). The addition of ASCT did not significantly improve the 5-year DFS in patients who did not achieve a deep molecular remission at three months, although the numbers are small (50% *vs.* 0; P=0.22).

At two years, the molecular status of the 15 patients who were alive and in CR and did not go for ASCT was as follows: 9 were in CMR, 2 were in MMR, one had positive molecular disease, and molecular analysis was not carried out in 3 patients. At five years, the molecular status of the 12 patients who were alive and in CR and did not go for ASCT was as follows: 8 were in CMR, one was in MMR, and molecular analysis was not carried out in 3 patients. Patients aged over 60 years had inferior outcomes. Among patients aged over 60 years, 5 of 14 (36%)

were alive at two years and only 2 of 14 (14%) at five years from initiation of therapy. At this time, 13 of 14 patients aged over 60 years of age have died. The cause of death included sepsis during induction (n=1), refractory disease/partial response (n=1), relapse (n=4), infectious complications during maintenance/post-maintenance (n=4), congestive heart failure (n=1), and unknown cause (n=2).

The median OS for patients who remain in CR was 94 months (range 3.7-148.9). A total of 17 patients have relapsed with a median CR duration of 14.1 months (range 7.9-92.7). One or more ABL-kinase mutations were identified in 5 of 8 patients with relapsed disease in whom mutational analysis was performed. The mutations identified were F359V, E459K, V338, P309A, Y253F, and Y253H. No ABL-kinase mutations were detected in 3 patients. The relapsed patients received a median of one salvage regimen (range 1-4) and 4 have undergone ASCT with a median OS for relapsed patients of 23 months (range 11-98). One of the relapsed patients remains alive but is not in remission at this time. Of the 35 deaths, 10 deaths occurred in patients in CR (infectious complication=7, myocardial infarction=1, and unknown causes=2), 17 deaths were related to ALL-relapse, 6 deaths were due to post-transplant complications, one patient died during induction, and another patient died in PR.

In the presence of limited data supporting the use of imatinib post-ASCT, a common policy of administration of tyrosine kinase inhibitors after transplantation was not adopted. The decision to continue imatinib post ASCT and the duration of imatinib post ASCT was left to the discretion of the individual ASCT physician. Imatinib was administered as maintenance therapy post ASCT in 7 of 16 (44%) patients. These 7 patients received post-transplant imatinib for a median of 36 months (range 1-96). Six of the 7 patients are still alive and are currently not receiving a TKI. There are 6 non-ASCT patients who are alive in CR and still on imatinib: 3 at imatinib 400 mg/day, 2 at imatinib 600 mg/day, and 1 at imatinib 800 mg/day.

Toxicity

The median time to hematologic recovery and severe toxicities (including febrile episodes and documented infections) associated with the hyperCVAD and imatinib combination were not significantly different from those observed with conventional chemotherapy in adult patients with Ph$^+$ ALL. Grade 3/4 toxicities on-protocol irrespective of attribution included: infections (52% in induction and 70% in consolidation); metabolic (hyperglycemia 43%, hypophosphatemia 59%, hyperbilirubinemia 17%); cardiac (fluid retention 2%, left ventricular dysfunction 2%, arrythmia 4%, myocardial infarction 4%); neurological (peripheral neuropathy 4%, confusion 2%, syncope 4%); gastrointestinal (constipation 2%, diarrhea 9%, nausea 6%); and vascular (deep vein thrombosis 7%, pulmonary embolus 2%).

One induction death occurred on day 20. As mentioned above, only 36 patients were able to start maintenance. In addition, one of the patients withdrew from the study immediately after starting maintenance due to persistent pleural effusion and was switched to an alternated TKI. The daily imatinib dose at the start of maintenance for the remaining 35 patients was: 800 mg (n=11), 600 mg (n=19), and 400 mg (n=5). Of the 11 patients who started maintenance at 800 mg daily dose, 7 (64%) decreased their dose to 600 mg after a median of two maintenance courses (range 1-4) due to rash (n=2), cytopenias (n=3), and persistent fluid retention in the form of pulmonary and periorbital edema (n=2). Of the 19 patients who started maintenance at 600 mg daily dose, 5 (26%) decreased their dose to 400 mg due to cytopenias (n=3), rash (n=1), and persistent fluid retention (n=1).

Discussion

Imatinib is a signal transduction inhibitor that selectively inhibits the *bcr-abl* tyrosine kinase, *c-kit*, platelet-derived growth factor (PDGF) and stem cell factor (SCF).[34] Single agent imatinib produced high response rates in patients with relapsed or refractory Ph$^+$ ALL.[35-37] However, the responses with imatinib were short-lived and were followed by disease progression within weeks due to emergence of resistance. These results suggest that, unlike CML, single agent imatinib is not sufficient to produce long-term remissions in patients with Ph$^+$ ALL.

In vitro studies demonstrated synergistic effects against Ph$^+$ cell lines when imatinib was combined with cytotoxic chemotherapeutic agents including anthracyclines, vincristine and cytarabine.[38,39] Subsequently, several studies explored the efficacy of incorporating imatinib into frontline chemotherapy regimens.[15,16,19,40-44] In one of the first clinical trials combining imatinib with chemotherapy (the hyperCVAD regimen), we reported a complete remission rate of 100% in patients treated with active disease and a 2-year DFS rate of 85%.[17] There were no unexpected toxicities from the addition of imatinib mesylate to the regimen and the outcomes were superior to historical outcomes with chemotherapy alone. Furthermore, there was no significant difference in OS and DFS between patients who underwent ASCT and those who received imatinib-combined chemotherapy alone. With a 13-year follow up our initial observations have been confirmed; the CR rate is 95% and the imatinib-combination regimen continues to be well tolerated. Time to hematopoietic recovery was not prolonged and most of the imatinib related toxicities, including fluid retention, transaminitis, hyperbilirubinemia, cytopenia, diarrhea, rash, abdominal pain and nausea, were manageable with adequate supportive care and dose adjustments.

Similarly, other groups have reported CR rates between 82% and 96% when imatinib was incorporated into frontline chemotherapy regimens for patients with Ph$^+$ ALL.[15,16,19,40-42] The responses appear to be durable in a majority of the patients. The relapse rate ranged from a low of 9% to a high of 37%. One of the major mechanisms of resistance to imatinib is via the occurrence of point mutations in the kinase domain or amplification of the BCR-ABL signal.[45,46] BCR-ABL kinase point mutations may be present at the time of diagnosis conferring primary resistance or may be acquired during therapy with imatinib. We identified point mutations in 5 of 8 patients who relapsed and had mutational analysis performed. BCR-ABL independent mechanisms may have contributed to the acquisition of resistance in the other patients. BCR-ABL independent mechanisms that are known to induce resistance include reduced bioavailability of imatinib within Ph$^+$ cells and activation of alternative signaling pathways that promote cell survival and proliferation such as Src-kinase pathways.[47,48] The 2nd-generation TKIs are capable of overcoming resistance to imatinib.

Furthermore, the 2nd-generation TKIs are active against commonly occurring imatinib-resistant BCR-ABL mutants with the exception of T315I.[49] Both dasatinib and nilotinib have been used in combination with chemotherapy for the front-line treatment of *de novo* Ph+ ALL.[18,20,50]

Prior to the advent of TKIs, combination chemotherapy regimens were not durable. Myeloablative ASCT was considered to be the only curative option and was offered to all patients with Ph+ ALL in first CR who had a suitable donor.[10-13] However, the older age of patients with Ph+ ALL, the limited availability of donors, and the occurrence of treatment-related toxicities and mortality make ASCT a less than ideal approach. The question remains as to whether ASCT is necessary in all patients with Ph+ ALL. There is a dearth of data in the adult literature comparing the outcomes of patients with Ph+ ALL treated with ASCT versus those treated with chemotherapy in combination with TKI. COG reported that ASCT provides no benefit compared with treatment with intensive continuous imatinib. This finding, albeit from a small number of patients, holds true with longer follow up. In contrast, in the European Intergroup study on post-induction treatment of Ph+ ALL (EsPhALL), the few patients who received imatinib but not stem-cell transplantation had a poorer outcome. However, this finding is limited by the fact that a majority (approx. 80%) of enrolled patients in EsPhALL underwent ASCT.[44] The EsPhALL group suggested that the concomitant use of TKI therapy earlier, more continuously, and for longer may further improve outcomes, resulting in no need for ASCT. At the time of conception of our study, the ideal dose, frequency and duration of TKI administration in combination with chemotherapy was undefined. Based on the experience in CML and preliminary reports suggesting improved outcomes with early initiation and continuous exposure to TKIs, we recommended that imatinib be administered early and be continued without interruption during the consolidation and maintenance therapy followed by imatinib indefinitely. The results of our study were similar to the COG study wherein outcomes with ASCT were no better than among patients who received HyperCVAD in combination with imatinib.

The presence of residual molecular disease (less than major or complete molecular response) three months after initiation of therapy is a known high-risk feature for relapse in patients with Ph+ ALL.[32] Intensification with ASCT may be considered for patients with residual molecular disease at three months. The EsPhALL group has suggested that the serial analysis of minimal residual disease might help identify patients who can be treated with chemotherapy in combination with TKI without the need for ASCT.[44] Along the same lines, patients in our study with residual molecular disease at three months had a trend towards inferior OS. The addition of ASCT clearly improved the CR duration in these patients. We recommend regular monitoring of minimal residual disease and early consideration of ASCT for slow responders (≥3 months).

The newer TKIs (dasatinib, nilotinib, bosutinib, and ponatinib) may further reduce the incidence of relapse resulting in improved overall survival. Frontline combinations incorporating these TKIs in the treatment of ALL are ongoing.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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