Published in final edited form as:
Am J Hematol. 2014 March ; 89(3): 282–287.

Phase II trial of HyperCVAD and Dasatinib in patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia or blast phase chronic myeloid leukemia

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Abstract

Dasatinib is a second generation tyrosine kinase inhibitor, with activity in imatinib resistant Ph-positive ALL. We have treated 34 patients with relapsed Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) (n=19) or lymphoid blast phase of chronic myelogenous leukemia (CML-LB) (n=15) with the combination of dasatinib and the hyperCVAD regimen. Prior regimens included hyperCVAD plus imatinib (n=11, 4 had transplant in first CR), other combination chemotherapy (n=12), monotherapy with kinase inhibitors other than dasatinib (n=9), and investigational agents (n=2). Pre-treatment *ABL* mutations were noted in 10 patients. The overall response rate was 91%, with 24 patients (71%) achieving complete response (CR), and 7(21%) CR with incomplete platelet recovery (CRp). Two patients died during induction and one had progressive disease. Twenty-six patients (84%) achieved complete cytogenetic remission after one cycle of therapy. Overall, 13 patients (42%) achieved complete molecular response, and 11 patients (35%) had major molecular response (*BCR-ABL/ABL*<0.1%). Nine patients proceeded to allogeneic transplantation. Grade 3 and 4 toxicities included hemorrhage, pleural and pericardial effusions and infections. The median follow-up for patients with CML-LB is 37.5 months (range, 7–70 months) with a 3-yr overall survival of 70%; 68% remained in CR at 3 years. For ALL patients, the median follow-up is 52 months (range, 45–59 months) with a 3-year survival of 26%; 30% remain in CR at 3 years. The combination of HyperCVAD regimen with dasatinib is effective in patients with relapsed Ph-positive ALL and CML-LB.

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DISCLOSURE

JC has received funding from Bristol Myers Squibb and has been member of advisory boards; EJ has received honoraria from Bristol Myers Squibb; HMK has received research funding from Bristol Myers Squibb; FR has received honoraria and research funding from Bristol Myers Squibb and has received honoraria from Bristol Myers Squibb.

Keywords

philadelphia; acute lymphoblastic leukemia; dasatinib; relapse

Introduction

The most common cytogenetic abnormality among adults with acute lymphoblastic leukemia (ALL) is the Philadelphia (Ph) chromosome, found in about 20% to 30% of all cases.[1–3] Incidence of Ph-positive ALL increases with age, occurring in up to 50% of patients over 50 years old.[4, 5] The disease in patients with Ph-positive ALL has a more aggressive clinical course and is associated with a higher incidence of central nervous system involvement.[6, 7] Prior to the advent of tyrosine kinase inhibitors (TKIs), patients with Ph-positive ALL treated with combination chemotherapy regimens were able to achieve complete response (CR) rates of 45% to 90%.[1, 8–15] However, most patients relapsed, with long-term disease-free survival less than 20% and a median disease-free survival of only about 10 months.

Allogeneic stem cell transplant (allo SCT) remains the only curative option for patients with available matched donors who are able to tolerate the procedure.[16] Survival rates improve to about 30–65% with an allo SCT, but transplantation is not universally available. The efficacy of allo SCT following achievement of CR after standard induction combination chemotherapy was evaluated by the UKALL XII/ECOG E2993 trial in the pre-imatinib era.[17] CR was achieved in 82% of the 267 patients included in this trial. The 5-yr overall survival, event-free survival and relapse-free survival rates were significantly better in those patients who underwent allo SCT, compared to those who received chemotherapy alone.

Incorporation of TKIs into frontline regimens for patients with newly diagnosed Ph-positive ALL is the current standard practice. Improvements in outcome with frontline imatinib in combination with chemotherapy have been reported by several groups.[17–28] However, resistance to imatinib may develop and is commonly associated with acquiring kinase domain mutations.[29, 30] Other mechanisms of resistance also include reduced drug availability and activation of other signaling pathways, such as the *Src* family kinases.[31, 32]

Dasatinib is a dual *Src* and *Abl* kinase inhibitor with ~325 times more potency against *BCR-ABL* than imatinib.[33] It is active against all imatinib-resistant kinase domain mutations, with the notable exception of T315I.[34, 35] In a phase 1 dose-escalation study of dasatinib in imatinib-resistant patients including 10 patients with Ph+ ALL, 7 patients were able to achieve complete hematologic remission and 8 patients had major cytogenetic response, though most relapsed (range, 1–8 months).[36] The phase 2 trial which led to the approval of dasatinib for second-line treatment of Ph-positive ALL included 46 patients, 96% of whom were imatinib-resistant, including 78% who were positive for *bcr-abl* kinase domain mutations (20% with T315I).[37] Response rate was high with a median time to response of 29 days. Furthermore, responses were durable, with a median duration of 6.3 months.

On the basis of significant activity of dasatinib against *BCR-ABL* and encouraging data in patients with relapsed or imatinib-resistant disease, we conducted this study to examine the efficacy and tolerability of dasatinib in combination with intensive chemotherapy in relapsed Ph-positive ALL or CML-LB. Herein, we report long term results of this study.

Methods

Eligibility

Patients ≥18 years of age with relapsed Ph+ ALL or CML-LB, identified by the presence of either t(9;22) karyotype or *BCR-ABL* fusion transcript were eligible to participate in the study. Other inclusion criteria included Eastern Cooperative Oncology Group performance status ≤2, adequate liver and kidney function (i.e. serum total bilirubin ≤3.0 mg/dL and serum creatinine ≤3.0 mg/dL, unless elevated levels were considered to be due to the disease); and an adequate cardiac function with left ventricular ejection fraction ≥ 45%. Patients were excluded if they had any of the following: an active serious infection not controlled by oral or intravenous antibiotics, clinical evidence of grade 3 or 4 heart failure as defined by the New York Heart Association criteria, any active second malignancy (except for non-melanoma skin cancer), and any prior treatment with dasatinib. Patients were also excluded if they were pregnant or breastfeeding, had a history of significant bleeding disorder unrelated to cancer, or if they had a documented significant pleural or pericardial effusion thought not to be related to underlying leukemia. All patients were asked to sign an informed consent form, in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the University of Texas M. D. Anderson Cancer Center. The study was registered on www.ClinicalTrials.gov (NCT00390793).

Treatment Schedule

Details of the hyper-CVAD regimen have been published previously.[38] Odd courses (1, 3, 5, and 7) of hyperfractionated cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and dexamethasone (Decadron) were given with alternating even courses (2, 4, 6, and 8) of high-dose cytarabine and methotrexate. During each even course, a chest radiograph was done to ensure the absence of development of significant pleural effusion prior to the administration of methotrexate. Dasatinib 50 mg orally twice daily was administered during the first 14 days of each of the above courses. Dasatinib dose was changed to 100 orally once daily after an amendment when further data on the best dose and schedule of dasatinib became available suggesting lower toxicity but similar efficacy for once daily dosing. The study was further amended to allow for the administration of dasatinib 100 mg orally once daily for the first 14 days of the first cycle of therapy followed by 70 mg orally once daily continuously from the second cycle onwards. Also, the amendment allowed patients with CD20 expression (>20% by flow cytometry) to receive rituximab at the dose of 375 mg/m^2 twice per cycle for the first 4 cycles of treatment. Central nervous system (CNS) prophylaxis was provided to all patients in the form of intrathecal chemotherapy with methotrexate and cytarabine administered alternately on days 2 and 7 of each cycle for a total of 6 or 8 doses, depending on the risk of CNS relapse (assessment based on serum lactate dehydrogenase and bone marrow proliferative index at the time of diagnosis). For those patients who presented with active CNS disease, confirmed

by cytologic examination of the cerebrospinal fluid (CSF), alternating doses of methotrexate and cytarabine were given intrathecally twice weekly until the CSF became clear of leukemic cells and the CSF cell count normalized. They then continued their intrathecal chemotherapy weekly for 4 more weeks or until initiation of the next cycle of systemic chemotherapy, when the above-stated prophylactic regimen was resumed. Cranial irradiation was not administered as prophylaxis, but was administered in patients who presented with or who developed cranial nerve palsies, in addition to the intrathecal chemotherapy.

Maintenance therapy was given for 2 years with monthly courses of intravenous vincristine and 5 days of prednisone 200mg orally daily. This was started after completion of the prescribed 8 courses of chemotherapy, or earlier, if intensive chemotherapy was poorly tolerated or if severe toxicities occurred. Dasatinib, 50 mg orally twice daily or 100 mg orally daily (after the amendment), was administered throughout the planned 2-year maintenance period, and was continued indefinitely thereafter. The antimetabolites 6-mercaptopurine and methotrexate were omitted during maintenance phase, to avoid compromising dasatinib dose, which was believed to be the most effective agent to prevent relapse. Maintenance phase could be interrupted in months 6 and 13 for intensification courses of hyper-CVAD and dasatinib. Patients with no evidence of minimal residual disease (MRD), who were considered poor candidate for such intensification continued on maintenance therapy. Dose reductions for cytotoxic agents according to the type and extent of side effects, and according to previously published measures were allowed. Dose reductions for dasatinib, both during initial therapy and the maintenance phase, to 70 mg or 50 mg orally once daily were allowed for significant drug-related toxicity, and dose escalation to 140 mg orally daily was permitted for inadequate response based on the level of BCR-ABL transcripts. At any given time during the intensive or maintenance treatment phases, patients had the option to proceed to an allogeneic stem cell transplant, if a suitable donor became available.

Supportive Care

Supportive care and symptom management were provided according to institutional standards of care. Prophylaxis for tumor lysis syndrome with allopurinol or other alternatives (e.g. rasburicase) and intravenous hydration was provided in the first course of therapy to all patients. Appropriate prophylaxis with antibiotics, antifungals and antivirals were also provided to all patients during periods of neutropenia. Appropriate blood products were transfused to alleviate symptoms and to support periods of profound cytopenias or coagulopathy. Granulocyte colony stimulating factors were also administered during each course of intensive chemotherapy to provide growth factor support.

Patient Assessments

Baseline evaluation was performed in all patients, including history and physical examination, complete blood counts with differentials, chemistry profile (including liver and kidney function tests), bone marrow aspiration for histology, flow cytometry, cytogenetics, fluorescent in situ hybridization (FISH), quantitative reverse transcription polymerase chain reaction (qRT-PCR) for *BCR-ABL* transcripts, and DNA PCR for immunoglobulin heavy-chain (*IGH*) gene rearrangements.

Complete blood counts with differentials, electrolytes, hepatic and renal indices were obtained at least on a weekly basis during the intensive courses of chemotherapy. Bone marrow aspiration was repeated on approximately day 14 and 21 of the first treatment course to assess response. Thereafter, it was repeated every 2 to 3 cycles for assessment of MRD. All specimens were assessed for evidence of disease by morphology, cytogenetics, flow cytometry and qRT-PCR for *BCR-ABL* transcripts as well as consensus PCR for *IGH*.

Lumbar puncture was done on day 2 of the induction course together with administration of first intrathecal chemotherapy dose. Cardiac function was evaluated at baseline with a multigated radionuclide ventriculography (MUGA) scan or a 2-D Doppler echocardiogram. Repeat cardiac assessment was done when clinically indicated.

MRD monitoring techniques

Molecular monitoring—qRT-PCR for *BCR-ABL* transcripts was done on total RNA extracted from leukocytes after red blood cell lysis. Reverse transcription was done with random hexamers, and PCR was performed with TaqMan primer/probes for the e1a2, e13a2 (b2a2), and e14a2 (b3a2) *BCR-ABL* transcripts in a single tube with normalization to total *ABL* transcripts. Post-PCR capillary electrophoresis was then used to type splice form, with the method having a sensitivity of approximately 1 in 10,000 *BCR-ABL*–expressing cells, as established by periodic dilution studies.[39] Major molecular response was defined as a *BCR-ABL/ABL* ratio of less than 0.1%. *BCR-ABL* kinase domain mutation analysis that covered codons 221 to 500 was performed on cDNA with a nested PCR strategy.[40] For subjects with a T315I mutation, quantitation of mutation levels was performed with a pyrosequencing-based strategy with a sensitivity detection rate of 1%.[40] *IGH* clonality studies were done on extracted genomic DNA with separate FR1, FR2, and FR3 PCR reactions with a consensus J primer. The sensitivity of detection of this method in samples with low numbers of polyclonal B cells (such as post-treatment bone marrow and CSF) is approximately 0.2% to 1%. [41]

Multiparameter flow cytometry—MRD assessment by flow cytometry was performed on bone marrow specimens by use of a standard stain-lyse-wash procedure. A total of 1×10^6 cells were stained for each analysis tube, and data were acquired on 2×10^5 cells when specimen quality and quantity permitted. In the initial part of the study, data on 4-color staining combinations were acquired on FACS Calibur cytometers with CellQuest software (Version 6.0; BD Biosciences) and analyzed with FlowJo (Version 8.8.6; TreeStar). Beginning in March 2009, data on 6-color stains were acquired on FACSCanto cytometers with FACSDiva software (Version 6.1.2; BD Biosciences) and analyzed with FCS Express (Clinical edition, Version 3; De Novo Software). Four-color combinations contained CD19 conjugated to peridinin chlorophyll protein–cyanine 5.5 (PerCP-Cy5.5) and CD34 conjugated to allophycocyanin (APC) in all tubes, with additional antigens conjugated to fluorescein isothiocyanate (FITC) and phycoerythrin (PE), including CD10, CD13, CD15, CD20, CD22, CD25, CD33, CD38, CD45, CD58, CD66c, and CD81 (all antibodies from BD Biosciences, except CD10 from Beckman Coulter and CD66c from Immunotech). Six-color combinations included CD34-PerCP-Cy5.5, CD10-PE-Cy7, and CD19-APC-H7 in each tube, with the additional antigens listed above conjugated to FITC, PE, and APC. MRD

was identified in comparison with the known patterns of antigen expression by normal maturing $CD19^+$ B cells by an approach similar to that described by Weir et al.[42] A distinct cluster of at least 20 cells that showed altered antigen expression was regarded as an aberrant population, which yielded a sensitivity for both 4- and 6-color assays of 1 in 10 000 cells (for adequate specimens in which 2×10^5 cells could be collected). Aberrant expression of at least 2 antigens required to make a diagnosis of MRD.

Response and outcome definitions

Complete remission (CR) was defined as the presence of less than 5% blasts in the bone marrow, with $\geq 1 \times 10^9$/L neutrophils, and $\geq 100 \times 10^9$/L platelets in the peripheral blood, and the absence of extramedullary disease. Relapse was defined by the recurrence of more than 5% lymphoblasts in a bone marrow aspirate, or by the occurrence of extramedullary disease in the absence of bone marrow disease. Overall survival (OS) was calculated from the time of diagnosis until death. Complete remission duration (CRD) was calculated from the time of CR until relapse.

Statistical Methods

Survival curves were plotted by the Kaplan-Meier method and compared with the log-rank test. Differences in subgroups by different covariates were evaluated with the χ^2 test for nominal values and the Mann-Whitney *U* and Fisher exact tests for continuous variables.

Results

Patients and treatment

From September 28, 2006 to October 21, 2011, a total of 34 patients with relapsed Ph-positive ALL (n=19) and CML-LB (n=15) were enrolled and treated in the study. Baseline patient characteristics are given in Table I. The median age at presentation for the 19 patients with ALL was 52 years (range, 21–77 years). The median white blood cell count at diagnosis was 10.4×10^9/L (range, 1.2–295.5×10^9/L) and the median bone marrow blast percentage was 71% (range, 3–97%). Three (16%) had CNS involvement at presentation. Fusion transcripts detected included: p190 in 15 patients (79%) and p210 in 4 patients (21%). The median age at presentation for the 15 patients with CML-BP was 47 years (range, 26–71). The median white blood cell count at diagnosis was 9.5×10^9/L (range, 0.3–60.8×10^9/L), and the median bone marrow blast percentage was 81% (range, 0–96%). Six patients (40%) had CNS involvement at presentation; one with solitary CNS relapse. Fusion transcripts detected included p210 in all patients. Overall, the median number of prior therapies was 1 (range 1–2); it included: hyperCVAD plus imatinib (n=11, 4 had transplant in first CR), combination chemotherapy other than hyperCVAD (n=12), monotherapy with TKI other than dasatinib (n=9), and investigational agents (n=2). Thirteen pretreatment *ABL* mutations found in 10 patients included the following: Y253H (n=4), Y253F (n=1), M351T (n=1), L298V (n=1), F317L (n=1), T315I (n=1), F359V (n=1), E459K (n=1), and E255K (n=2).

Response to Induction

All but two patients that died from overwhelming sepsis were evaluable for assessment of response to induction, as shown in Table II. One patient did not respond to induction chemotherapy and had progressive disease. Overall, median time to achievement of CR was 24 days (range, 17–44 days). Among the 31 patients who achieved CR, 26 patients (83%) achieved complete cytogenetic remission after first course of therapy, 3 patients (10%) had persistent Ph-positive metaphases, in one patient (3%) karyotype analysis was not done and one (3%) had insufficient metaphases. Molecular testing done on the 31 patients who were able to achieve CR showed that 13 patients (42%) achieved complete molecular remission at a median of 11 weeks (range, 2–46 weeks), while 11 additional patients (35%) achieved major molecular remission at a median of 4 weeks (range, 2–26 weeks). MRD assessment by multiparameter flow cytometry was negative in 23 of 31 patients (74%) at a median of 4 weeks (range, 2–19). Figure 1 shows overall MRD response by *BCR-ABL/ABL* qRT-PCR monitoring.

Follow-up and outcome

These 34 patients received a total of 114 courses of therapy; the median number of chemotherapy cycles administered per patient was 3 (range, 1–8). All patients were able to start at the prescribed dose of dasatinib at 100mg orally daily. Nine patients proceeded to allogeneic stem cell transplantation (ALL n=2; CML-LB n=7). One previously transplanted patient with ALL received donor lymphocyte infusion.

Fifteen patients relapsed after median response duration of 31 weeks (range, 5–170) (Figure 2). Six patients had acquired *ABL* kinase mutations; one patient lost the baseline Y253H mutation and acquired T315I and E450G mutations. Another patient lost the Y253H, F359V and E459K baseline mutation and acquired a T351I mutation other 4 patients acquired T315I, G303fs, F317L and T315I and F317I, respectively. Twelve patients died after disease relapse: 3 died post-transplant after achieving second CR, 2 died during salvage induction,2 died with inadequate response, and 4 died in CR/CRp (all from infectious complications).

Overall, with a median follow-up of 45 months (range 7–70), a total of 13 patients (38%) are alive, with 10 patients (29%) in CR/CRp. Among the patients with ALL, with a median follow-up of 52 months (range, 45 – 59 months), 2 patients (11%) are alive. Thirty percent remain in CR at 3 years (median CRD = 8.8 months) with a 3-yr OS of 26% (median = 9 months). (Figure 2A, 2B) For patients with CML-LB, the median follow-up is 37.6 months (range, 7 – 70) and 11 patients (73%) are alive. The 3-yr CR is 68% (median not reached) with 3-yr OS of 70% (median not reached). (Figure 2A, 2B) To date, 15 patients have received maintenance. Four patients (ALL n=2; CML-LB n=2) are continuing on maintenance only with dasatinib. Their median time on maintenance dasatinib is 31 months (range 9 – 44 months).

Toxicities

During the first induction course, the median time to neutrophil recovery was 18 days (range, 14–32 days) and the median time to platelet recovery was 26 days (range, 17–41). With subsequent courses, the median times to neutrophil and platelet recovery were 17 and

23 days, respectively (ranges, 0–21 and 0–52 days, respectively). Grade 3 and 4 toxicities included 12 episodes of bleeding (5 gastro-intestinal, 3 subdural hematomas, 2 genito-urinary, and 2 diffuse alveolar hemorrhages). A total of 5 episodes of pleural effusion and 2 episodes of pericardial effusion were noted, all of which were of Grade 3/4 severity (Table III). Other serious (Grade 3/4) adverse events included episodes of neutropenic infections, diarrhea, acute renal failure, increased liver function tests, hyperbilirubinemia, hypocalcemia, hypophosphatemia and hypokalemia (Table III).

Discussion

The introduction of TKIs together with chemotherapy markedly improved the treatment outcome of patients with Ph-positive ALL.[43] About 95% of patients treated with imatinib combined with chemotherapy will attain CR. In pediatric population imatinib plus intensive chemotherapy was not inferior to allo SCT.[44] In young adults, the use of imatinib in remission induction therapy and post-remission therapy has increased the number of patients who can undergo allo SCT.[45] Despite these promising results of imatinib together with chemotherapy, most adults with Ph-positive ALL will eventually relapse. The outcome of adults with relapsed or refractory Ph-positive ALL and CML–BL is extremely poor. Attainment of second CR is possible in about half of the patients and the median survival after relapse is less than 6 months.[46]

In this study, we report the long term results of 34 patients with Ph-positive ALL (19 patients) or CML-LB (15 patients) treated with hyperCVAD plus dasatinib regimen after relapse. Half of the patients failed previous TKI therapy. Of 31 patients that achieved CR, 71% of patients had CMR (42%) or at least MMR (35%) after induction assessed by qRT-PCR. Only one patient did not respond to the induction regimen. Nine patients (26%) proceeded to allo SCT and one of previously transplanted patient received donor lymphocyte infusion.

With a median follow-up of 45 months, 13 patients (38%) patients are alive, with 10 patients (29%) in CR/CRp. For the patients with relapsed Ph-positive ALL, with a median follow-up of (52 months), 2 patients (11%) are alive.

For the patients with CML-LB, with a median follow-up of more than 37.6 months, 11 patients (73%) are still alive. Single agent imatinib for previously treated relapsed or refractory Ph-positive ALL and CML-BL was associated with objective response in less than half of the patients with low CR rates of 5% to 7% and median survival of 2 to 5 months.[47–49] Resistance to imatinib occurs in 70 – 90% of patients with CML-BL. The emergence of BCR-ABL mutations is the most important mechanism of resistance to TKIs. At relapse approximately 80 to 90% of patients with Ph-positive ALL treated with imatinib are found to have ABL mutations, predominantly in the P-loop and T315I mutations.[40] Resistance may develop in response to TKI driven selective pressure giving rise to competing sub-clones.[50] Second generation TKIs possess a broader spectrum of kinase inhibition activity than imatinib. Dasatinib is a second generation TKI with activity against more than 100 ABL kinase mutations known to confer resistance to imatinib that have been tested to date, including many in the p-loop region, with the important exception of the

catalytic domain (T315I mutation) and a few other mutations (V299L, F317L/V, and T315A).[51]

In relapsed Ph-positive ALL nilotinib with or without chemotherapy was tolerable and feasible, yet with short survival rates.[47, 52]

Several groups reported their favorable results with the use of dasatinib with steroids or chemotherapy.[53–56] In recent study by Foa et al, dasatinib as single agent combined with steroids obtained complete hematologic remission in all 53 evaluable patients, however after 20 months of follow up 43% of the patients relapsed.[55] Relapse rate was 70% in patients who received only TKI as post induction treatment or no further treatment, compared with 17% in patients that received TKI plus chemotherapy or allograft.[55] In mouse model resistance to dasatinib was effectively circumvented by the addition of chemotherapy.[57] We have recently proven that the addition of dasatinib to cytotoxic chemotherapy is more effective in achieving longer-term remissions with 69% of the patients free of leukemia after median follow up of 14 months. [56]

In our study, 9 patients (26%) had CNS disease at relapse. The CNS is regarded as sanctuary site in Ph-positive ALL and CML-BL and 20% to 30% of patients will have CNS involvement at relapse.[58, 59] Imatinib poorly penetrates the blood-brain barrier and as a single agent does not reach therapeutic levels in the CSF.[60] Dsatinib is particularly attractive for Ph-positive ALL treatment, given its better CNS penetration compared to Imatinib and Nilotinib.[61]

Overall, the treatment regimen was tolerated well. Grade 3 and 4 toxicities included episodes of bleeding, pleural or pericardial effusions and neutropenic fever. These required temporary treatment discontinuation and dose reductions, along with other supportive therapy such as steroids and antibiotics. The median time to neutrophil and platelet recovery was 17 and 23 days, (ranges, 0–21 and 0–52, respectively). In August 2009, because of these episodes of prolonged cytopenias in some patients, we modified the dose of dasatinib to 70 mg orally daily continuously. This was associated with a better regimen tolerance.

Reduction of disease burden as measured by qRT-PCR was demonstrated in our cohort of patients. The detection of MRD is an important factor in prediction of survival in Ph-positive ALL.[62] Either by qRT-PCR of BCR-ABL1 or by multiparameter flow cytometry (MFC), the interpretation of the results in the context of time and different treatment regimens is largely unclear. We have recently shown that achieving MMR and negative MFC status at ≥ 3 months after treatment with HyperCAVD and imatinib or dasatinib were associated with decrease likelihood of relapse and longer OS.[63] In this study, the achievement of high rate of MMR at CR is promising yet the results of studies on post induction molecular remission are conflicting.[63–65]

We have demonstrated that the combination of the hyperCVAD regimen with dasatinib is effective in patients with relapsed Ph-positive ALL and CML-LB. Achieving long-term leukemia-free survival even without allo SCT in second CR may be possible in patients without a suitable donor, particularly in patients with CML-LB. Acquired mutations conferring resistance, in particular T315I is an important mechanism of treatment failure,

therapy with third generation tyrosine kinase inhibitors such as ponatinib would be of significant interest; this is the subject of ongoing clinical trials.

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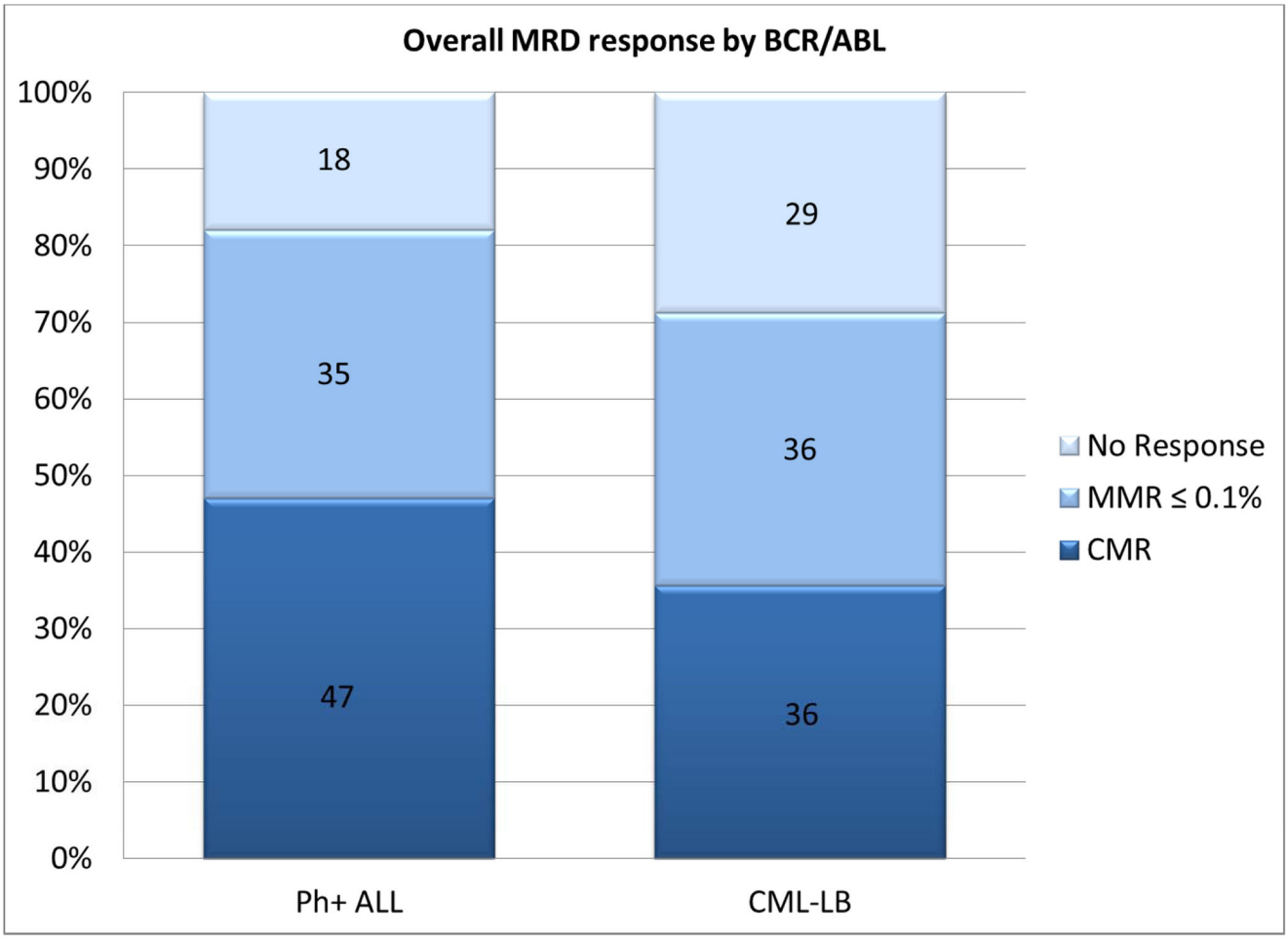

Figure 1.

Level of residual disease after one cycle of HyperCVAD plus dasatinib assessed by qRT-PCR for BCR-ABL/ABL in patients with (A) Ph-positive ALL and (B) CML-BL. MMR, major molecular response; BCR-ABL/ABL ≤ 0.1%, CMR, complete molecular response; BCR-ABL/ABL ≤ 0.001% from baseline.

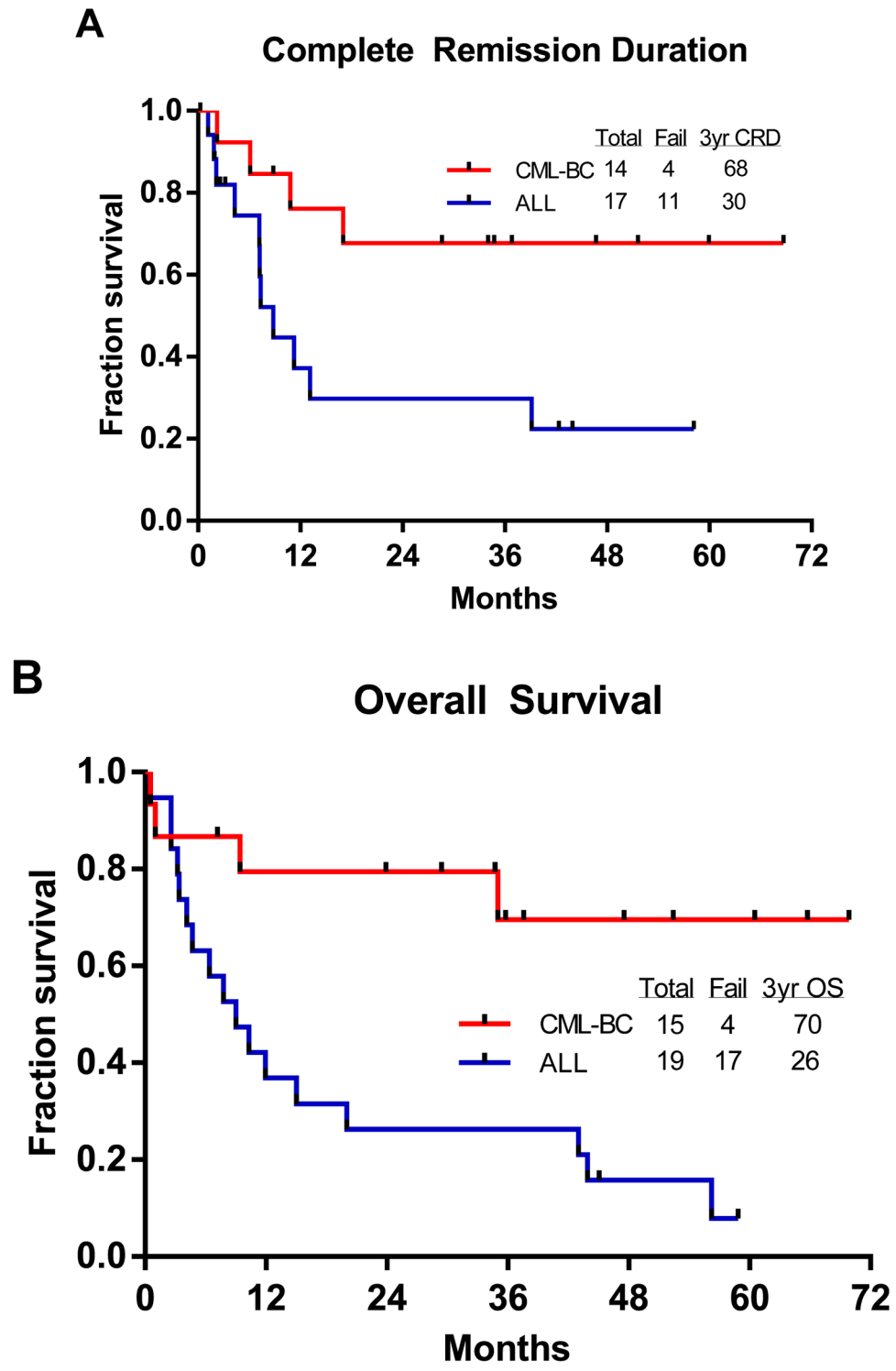

Figure 2.

A. complete remission duration from response date of patients with Ph-positive ALL and CML-BL B. Overall survival from induction with HyperCVAD plus dasatinib.

TABLE I

Pretreatment Patients' Characteristics

	Median (range) or No. (%)	
Parameter	**Ph+ ALL *n* = 19**	**CML-LB *n* = 15**
Age at induction	52 (21–77)	47 (26–71)
Bone marrow blasts	71 (3–97)	81 (0–96)
WBC on presentation	10.4 (1.2–295.5)	9.5 (0.3–60.8)
CNS Disease	3 (16)	6 (40)

WBC indicates white blood cells 1000/μL; CNS, central nervous system.

TABLE II

Response Assessed After Induction Cycle

	No. (%)	
Parameter	**ALL *n* = 19**	**CML-LB *n* = 15**
Complete hematological response	13 (68)	11 (73)
Complete Response with Incomplete Platelet Recovery (CRp)	4 (21)	3 (20)
Complete cytogenetic response	16 (94)	10 (71)
Major cytogenetic response	0 (0)	2 (14)
Complete molecular response	8 (47)	5 (36)
Major molecular response	6 (35)	5 (36)

TABLE III

Grade 3–4 Toxicity Associated with HyperCVAD Plus Dasatinib in Relapsed Ph-Positive ALL or CML BL

Toxicity	***N* = 34 (100%)**
Bleeding	
Gastrointestinal	5 (15)
Subdural hematoma	3 (9)
Genitourinary	2 (6)
Diffuse alveolar hemorrhage	2 (6)
Epistaxis	1 (3)
Pleural effusion	5 (15)
Pericardial effusion	2 (6)
Neutropenic infection (≥one episode)	32 (94)
Diarrhea	7 (21)
Acute renal failure	7 (21)
Increased liver function tests	2 (6)
Hyperbilirubinemia	6 (18)
Hypocalcemia	20 (59)
Hypophosphatemia	22 (65)
Hypokalemia	24 (71)