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ORIGINAL ARTICLE

Nilotinib combined with multi-agent chemotherapy in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia: a single-center prospective study with long-term follow-up

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Abstract

The aim of this study is to investigate the efficacy and safety of nilotinib combined with multi-agent chemotherapy in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Thirty patients with Ph+ ALL were recruited. Standard induction chemotherapy was given for 4 weeks. Nilotinib was administered beginning on day 15 of induction. After achieving hematologic complete remission (HCR), patients received either seven courses of consolidation or hematopoietic cell transplantation (HCT). Nilotinib was continued 2 years after achieving HCR or before stem cell transplantation conditioning. HCR and molecular complete response (MCR), overall survival (OS), hematologic relapse-free survival (HRFS), molecular relapse-free survival (MRFS), toxicity, and nilotinib levels in the serum and cerebrospinal fluid were evaluated. All patients achieved HCR, and cumulative MCR rate was 83.3%. The median HRFS and OS were 18 and 47.5 months, respectively. Four-year HRFS and OS rates were 54% and 45%, respectively. The median MRFS and 4-year MRFS for the patients with MCR were 19 months and 45%, respectively. The molecular response of patients after induction cycle had no impact on HRFS, MRFS, or OS. The patients who achieved MCR after 3 and 6 months had superior HRFS. The HCT cohort in the first HCR had significantly lower rates of relapse and longer MRFS, HRFS, and OS. Most adverse events were reversible with dose reduction or transient interruption of nilotinib therapy. Only traces of nilotinib were detected in cerebrospinal fluid. Nilotinib combined with cytotoxic chemotherapy was effective and translated to a high HCR and MCR for patients with Ph+ ALL. It should be noted that nilotinib cannot cross the blood–brain barrier.

Keywords HRFS · MRFS · Nilotinib · OS · Ph+ ALL

Introduction

The Philadelphia chromosome (Ph) is present in approximately 25% of adults with acute lymphoblastic leukemia (ALL) [1]. Compared with patients with Ph-negative ALL, patients with Ph-positive ALL (Ph+ ALL) exhibit a comparatively poor prognosis, including inferior complete remission (CR) and lower survival rates following intensive combinatorial chemotherapy. Allogeneic hematopoietic cell transplantation (allo-HCT) is currently the only curative modality for patients with Ph+ ALL [2, 3].

Since the introduction of tyrosine kinase inhibitor (TKI) therapy to treatment regimens, significant improvements have been found in response rates, disease-free survival, and overall survival (OS) for patients with Ph+ ALL [3–9]. When the first-generation TKI agent known as imatinib was added to combinatorial chemotherapy in newly diagnosed Ph+ ALL, hematologic CR (HCR) rates increased to more than 90% and molecular CR (MCR) rates increased to 50%, the outcomes with significant improvements in prolonging the duration of CR duration [3–9]. However, approximately 30% of patients treated with imatinib-based multi-agent chemotherapy still experience disease recurrence [10]. In addition, cycles of chemotherapy for approximately 25% of patients were interrupted due to various treatment-associated side effects

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[11]. Nilotinib, a second-generation TKI, is approximately 30-fold more potent than imatinib and active in vitro against multiple BCR-ABL mutations resistant to the action of imatinib. Several studies have confirmed the efficacy and safety of nilotinib in relapsed patients presenting with Ph+ ALL following treatment with imatinib, dasatinib, or allo-HCT [9, 12–15].

We therefore hypothesized that the addition of nilotinib to combinatorial chemotherapy regimen would demonstrate greater efficacy compared with the prior use of imatinib in treating Ph+ ALL. This study explored the safety and efficacy of nilotinib when combined with multi-agent chemotherapy in patients with newly diagnosed Ph+ ALL.

Methods

Patients

Patients aged more than 15 years with newly diagnosed Ph+ ALL were potentially recruited between September 14, 2011, and November 21, 2013. The diagnosis was established according to morphology, immunology, cytogenetics, and molecular classification, including the presence of more than 25% bone marrow lymphoblasts as confirmed by immunophenotype, and cytogenetic (conventional analysis and/or fluorescence in situ hybridization (FISH) using BCR and ABL probe) and molecular genetic examination to confirm the expression of Philadelphia chromosome or BCR-ABL fusion gene [16]. Other inclusion criteria included the following: serum creatinine levels < 1.5 of the upper normal limit (ULN), serum bilirubin < 1.5 of the ULN, and serum transaminase < 3 of the ULN or < 5 of the ULN for patients with leukemia with hepatic involvement. In addition, patients had to demonstrate adequate performance (i.e., a need to demonstrate an Eastern Cooperative Oncology Group [17] performance status ≤ 2 and a heart color Doppler ejection fraction ≥ 45%). Also, patients needed to demonstrate acceptable electrolyte analyses in which the levels of potassium, magnesium, and sodium should not have been lower than the normal lower limit.

The exclusion criteria included the following: history of heart failure or other major heart diseases (including unstable angina, heart failure, uncontrolled hypertension, uncontrolled arrhythmia, and long QT syndrome) or family history of any of the aforementioned conditions; bradycardia (i.e., less than 50 beats/min); electrocardiogram QT interval greater than 450 ms; other serious or uncontrolled underlying diseases; pregnant or lactating women; confirmed human immunodeficiency-positive status; history of mental illness; and within 30 days of having been confirmed using other clinical trial therapeutics or having been enrolled in a study.

The patients provided the required written informed consent. All procedures were conducted according to the Declaration of Helsinki. The study was approved by the local ethics committee of the Chinese Academy of Medical Sciences and Blood Diseases Hospital (Approval Number: YL2011032201). This trial was registered as ChiCTR-ONC-12002469.

Therapy

Chemotherapy regimens followed the CALLG2008 protocol with certain modifications as detailed in the chemotherapeutic regimen shown in Table 1. Nilotinib was given orally twice a day at a dose of 400 mg commencing from day 15 of the induction cycle and continuing for 2 years after achieving HCR and as an integral component of consolidation and maintenance therapy. Patients could receive allogeneic or autologous HCT (allo- or auto-HCT) whenever possible during their first HCR. Nilotinib would be terminated at the beginning of conditioning. The trail had no mandatory recommendation on the using of TKI (including when and which to use) after HCT. Those who lacked donor or had contraindications or were reluctant to transplant could continue consolidation and maintenance chemotherapy. Full details of the treatment phases (including a specific chemotherapeutic agent, dose, and scheduling) are given in Table 1.

For central nervous system (CNS) leukemia prophylaxis, intrathecal injection with triple-agent therapy (i.e., 10 mg methotrexate (MTX), 50 mg cytarabine, and 10 mg dexamethasone) was performed after peripheral blood cell count recovery (i.e., a total neutrophil count > 1000/μL and a total platelet count > 50,000/μL) in the induction and consolidation cycles of chemotherapy. Prophylactic cranial irradiation was recommended but not obligatory for this cohort. Patients who did not receive HCT were treated with cranial irradiation at 18–20 Gy. Patients who did not receive cranial irradiation were treated with intrathecal injection once or twice during every consolidation cycle of chemotherapy (i.e., 8–12 doses in total). The initial diagnostic lumbar puncture before hematological remission was not mandatorily required.

The patients were dropped off the present study for the following reasons: hematological relapse (HREL), molecular relapse (MREL), withdrawal of consent, transplantation, change of TKI for any reason, or death from any cause. The patients were considered to complete the trial when starting the conditioning for transplantation, involving 2 years of consolidation and maintenance therapy. All the patients were followed up for survival analysis till death or October 31, 2017, whichever came first.

Responses and outcomes

The conventional morphological response and residual disease (i.e., detecting transcriptional expression of BCR-ABL by quantitative real-time polymerase chain

Table 1 Induction, consolidation, and maintenance treatment

Treatment phase	Drug	Dose	Schedules
Induction			
VDCP	VCR	2 mg	d1, d8, d15, and d22
	DNR	30 mg/m^2	d1–3
		30 mg/m^2	d15–16 (withdrawn if bone marrow blast cell frequency less than 5% on d14)
	CTX	750 mg/m^2	d1 and d15
	PDN	1 mg/kg	d1–14
		0.5 mg/kg	d15–28
Consolidation			
CAM	CTX	750 mg/m^2	d1
	Ara-c	75 mg/m^2	d1–3, d8–10
	6-MP	60 mg/m^2	d1–7
HD-MTX	MTX	3 g/m^2	d1
MA	MTZ	8 mg/m^2	d1–3
	Ara-c	100 mg/m^2	d1–5
COATD	CTX	750 mg/m^2	d1
	VCR	2 mg	d1
	Ara-c	100 mg/m^2	d1–5
	VM-26	100 mg/m^2	d1–3
	DEX	6 mg/m^2	d1–7
VDCD	VCR	2 mg	d1, d8, d15, and d22
	DNR	40 mg/m^2	d1–3
	CTX	750 mg/m^2	d1 and d15
	DEX	6 mg/m^2	d1–7, d15–21
HD-MTX	MTX	3000 mg/m^2	d1
TA	VM26	100 mg/m^2	d1–3
	Ara-c	100 mg/m^2	d1–5
Maintenance	Nilotinib	800 mg/day	Continuing 2 years after achievement of HCR

Nilotinib was continuously administered from day 15 of induction chemotherapy

Ara-c Cytarabine, *CTX* cyclophosphamide, *DEX* dexamethasone, *DNR* daunorubicin, *MTX* methotrexate, *MTZ* mitoxantrone, *PDN* prednisone, *6MP* purinethol, *VCR* vincristine, *VM-26* teniposide

reaction assay and blast cells by multiparameter flow cytometry) were evaluated at diagnosis, at the time of completing induction, before each consolidation cycle, and then every 3 months during maintenance therapy. For patients who had undergone HCT, response evaluation was completed at the initiation of conditioning therapy, and then every 3 months for the first 2 years.

The conventional HCR response was defined as normal cellular bone marrow and adequate blood count recovery with less than 5% marrow lymphoblasts detected in the absence of circulating lymphoblasts or any evidence of extramedullary leukemia.

Major molecular response (MMR) was defined as the BCR-ABL transcript expression levels decreasing at least three logs compared with baseline levels in addition to HCR.

MCR was defined as the undetectable BCR-ABL transcript levels in addition to HCR.

HREL was defined as the reappearance of lymphoblasts at a level of more than 5% in the bone marrow, peripheral blood, or extramedullary sites.

MREL was defined as the BCR-ABL transcript being detected again in patients who previously achieved MCR, and at least one log increasing in the expression of the BCR-ABL transcript for patients not in MCR.

Survival was defined as HRFS that was effective from the date of the first HCR to the time of death or HREL.

Molecular relapse-free survival (MRFS) was measured from the date of the first MCR to the time of death, HREL, or MREL.

OS was defined as the date from the time of diagnosis to the date of the final follow-up or death.

Detection of nilotinib levels in the serum and cerebrospinal fluid

For measuring serum concentration, the fasting serum samples were drawn before administering nilotinib on days 1, 8, 15, and 28 after nilotinib initiation. For measuring cerebrospinal fluid (CSF) levels of nilotinib, the CSF samples were collected 3 h after nilotinib administration, at which time the serum controls were also drawn.

Adverse event evaluation

Side effects that might have resulted from combinatorial therapy were monitored and described according to the Common Toxicity Criteria, Version 3.0, as published by the National Cancer Institute, National Institutes of Health, MD, USA [18].

Statistical analysis

Continuous data were expressed as median and range, whereas categorical data were expressed as number and percentage. RFS and OS were estimated by the Kaplan–Meier method. All statistical analyses were performed using SPSS version 21 statistical analysis software (IBM Corporation, NY, USA).

Results

Patient characteristics

A total of 30 patients (19 males and 11 females) were enrolled. Only two subjects withdrew informed consent after the third and fourth cycles of consolidation therapy. Table 2 shows the baseline characteristics of the patients. All the patients expressed the BCR-ABL transcripts. Two patients predominantly expressed the P210 transcript that was also associated with minimal levels of expression of the P190 transcript at 0.02%. Nine of the 10 patients with normal chromosome and 1 of the 2 patients without metaphase by conventional cytogenetic analysis were confirmed the reciprocal translocation between chromosome 9 and 22FISH analysis.

Response to induction therapy

All 30 patients achieved HCR after 4-week induction therapy. No patient died during induction. Figure 1 shows the response and residual disease as measured by flow cytometry and expression of the BCR-ABL transcript after the induction cycle. Chromosome karyotype was analyzed in all of the patients after induction therapy. Twenty-eight patients had a normal karyotype, and one patient had no evidence of metaphases. All of these 29 patients confirmed the evanishment of Ph+ metaphases after induction by FISH analysis. One patient had 6.25% Ph+ metaphases after induction cycle and achieved cytogenetic CR after the first consolidation cycle.

Table 2 Baseline characteristics of the patients

Characteristic	Value
Patients (*N*)	30
Sex, male/female	19/11
Median age, year (range)	40 (21–59)
Median WBC, 10^9/L (range)	36.9 (0.91–548)
Cytogenetics	
Normal, *n* (%)	10 (33.3)
Ph+, *n* (%)	8 (26.7)
Ph+ plus other, *n* (%)	9 (30)
Other, *n* (%)	1 (3.3)
No metaphases, *n* (%)	2 (6.7)
BCR-ABL transcript type	
P190, *n* (%)	24 (80.0)
Median transcript level, L (range)	136 (53.5–314.71)
P210, *n* (%)	6 (20.0)
Median transcript level, L (range)	26.5 (4.09–71.0)
Myeloid antigen expression on blasts, *n* (%)	29 (96.7)

Consolidation therapy

Figure 2 shows the treatment regimens for all patients. Three patients received auto-HCT, and 13 patients received allo-HCT in the first HCR. The donors included six matched sibling donors, four fully matched unrelated donors, and three haploidentical familial donors. The remaining 14 patients continued combinatorial chemotherapeutic consolidation therapy and nilotinib maintenance therapy due to no donor being available or a reluctance to receive HCT.

Survival outcomes

The median follow-up duration was 56.5 months (range 49–72 months) for the surviving patients. The median HRFS and OS were 18 months (range 2–70 months) and 47.5 months (range 5–71 months), respectively. The median MRFS for the patients who ever achieved MCR was 19 months (range 2–66 months). The 4-year HRFS and OS rates were 54% and 45%, respectively, while the 4-year MRFS for the patients who achieved MCR was 45%. Figure 3 shows the outcomes of this cohort. Up to the time of the final follow-up, 17 patients had died.

Among the 14 patients who did not receive HCT in the first HCR, and with a median follow-up of 24.5 months, 11 experienced HREL with a median HRFS duration of 13 months (range 2–62 months), and all the 11 patients died from disease progression. In addition, two patients experienced MREL 26

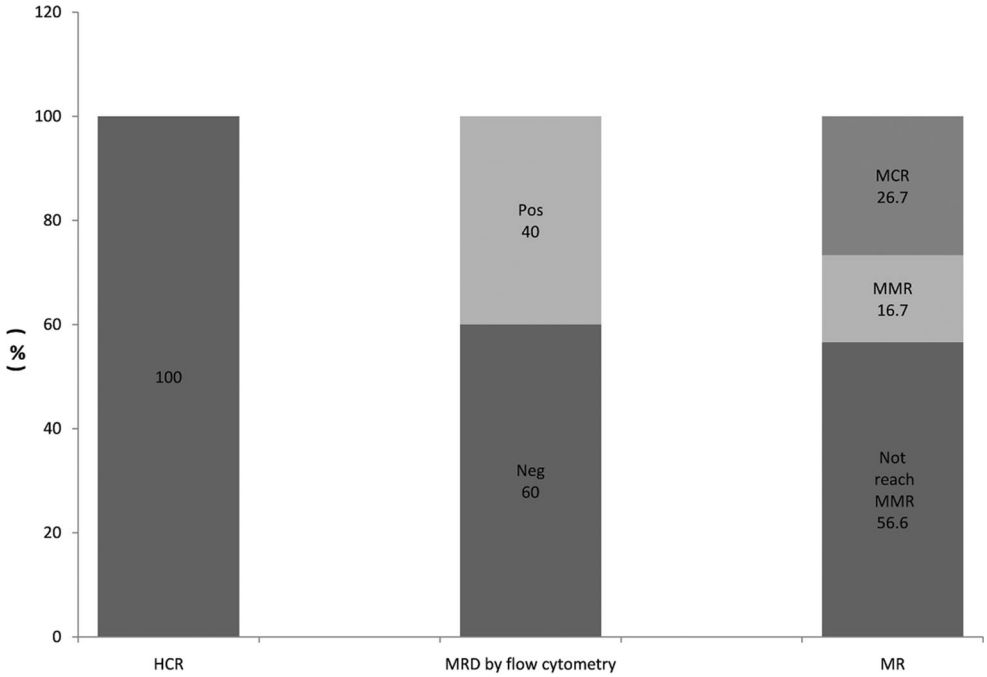

Fig. 1 Response after induction cycle

and 27 months after the first HCR, which are 1 and 2 months following the cessation of nilotinib maintenance therapy.

Sixteen patients received HCT in the first HCR, including three patients with auto-HCT (Fig. 3). The median follow-up was 56 months for these patients. Four patients who received allo-HCT died without leukemic relapse 4–12 months after HCT, and one patient died of a car accident in MCR 39 months after allo-HCT. Three patients experienced HREL.

Molecular response

All 30 patients were evaluated for molecular response at the end of the induction cycle and 3 months post-treatment initiation. However, 29 patients were evaluated for molecular response 6 months post-treatment initiation. Figure 4 shows the molecular response at different time points. A total of 22 patients (75.9%) achieved MCR after 6 months (i.e., the patients who had received HCT were evaluated before conditioning). The median time to achieving MMR and MCR was 3 months (MMR range 1–10 months; MCR range 1–17 months) from treatment initiation. The median duration of maintaining MCR for those who had achieved it was 19 months (range 2–66 months). In addition, two patients achieved and maintained MCR after allo-HCT.

Details of HCT

Sixteen subjects received HCT in the first HCR. Three patients received auto-HCT at 3.5, 7, and 7.5 months after the first HCR. All of them began imatinib treatment when blood cell recovery after HCT and continued for 1.5 years.

Thirteen patients received allo-HCT at a median 5.5 (range 3.5–9.5) months after the first HCR and with a median 4 (range 3–5) consolidation cycles. All the 13 patients achieved neutrophil engraftment with the median 15 (range 11–21) days. Twelve patients achieved platelet engraftment with median 20 (range 13–30) days, and only 1 patient was platelet transfusion dependence after SCT till to death (4 months after HCT). Seven of 13 (53.8%) patients experienced acute graft-versus-host disease (GVHD), 1 with grade 4 involved in the

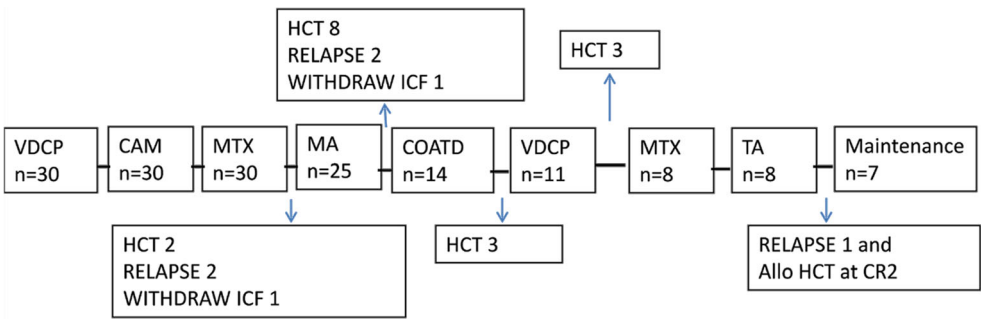

Fig. 2 Flow diagram of treatment for the cohort

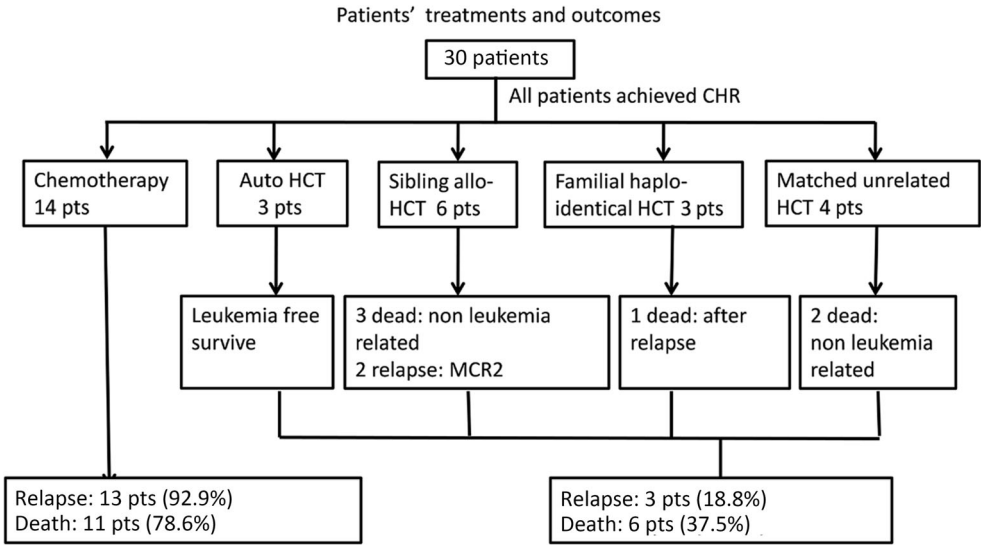

Fig. 3 Survival outcomes of the patients

skin and intestinal tract, 1 with grade 3 involved in the mouth and liver, and 5 with grade 1 involved in the intestinal tract, skin, and bladder. Eight of 13 (61.5%) patients had chronic GVHD, one of whom had extensive chronic GVHD. Three patients received continuous imatinib for 1 year after allo-HCT for leukemia prophylaxis; the other 10 patients did not use any TKI if no molecular or hematologic relapse was confirmed.

Subgroup analysis

Patients assessed for minimal residual disease (MRD) were stratified into subgroups of MRD levels after induction and 3 and 6 months post-treatment initiation. The patients who achieved MCR after 3 months had the best median HRFS compared with those with MMR and less than MMR (MCR vs MMR: not reached vs 24 months, $P = 0.12$; MCR vs less MMR: not reached vs 11 months, $P = 0.007$; MMR vs less MMR: 24 vs 11 months, $P = 0.385$) (Fig. 5a). Further, the molecular response was evaluated in 29 patients after 6 months, and only 1 patient was found with MMR. Hence, the patients were grouped into MCR or no MCR according to the molecular response after 6 months. The result showed that the group with MCR after 6 months had significantly longer median HRFS compared with those without MCR (not reached vs 11 months, $P = 0.019$, Fig. 5b). Further analysis showed that the patients who ever achieved MCR (including those after HCT) had superior HRFS (60 vs 5 months, $P = 0.008$, Fig. 5c) and OS (70 vs 9 months, $P = 0.0027$, Fig. 5d). The molecular response after induction had no impact on survival.

The HCT cohort in the first HCR had a significantly lower rate of HREL/MREL (Fig. 6a) and superior MRFS (not reached vs 15 months, Fig. 6b), HRFS (not reached vs 12 months, Fig. 6c), and OS (not reached vs 24 months, Fig. 6d).

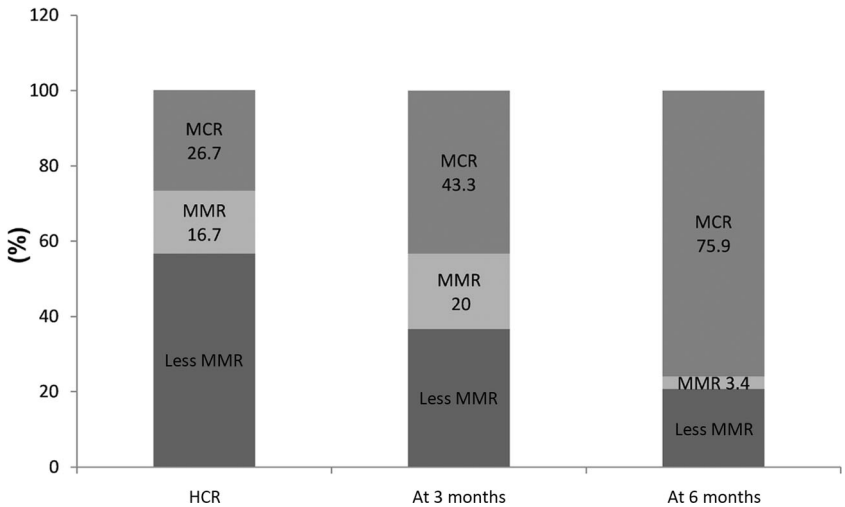

Fig. 4 Molecular response rates at different time points

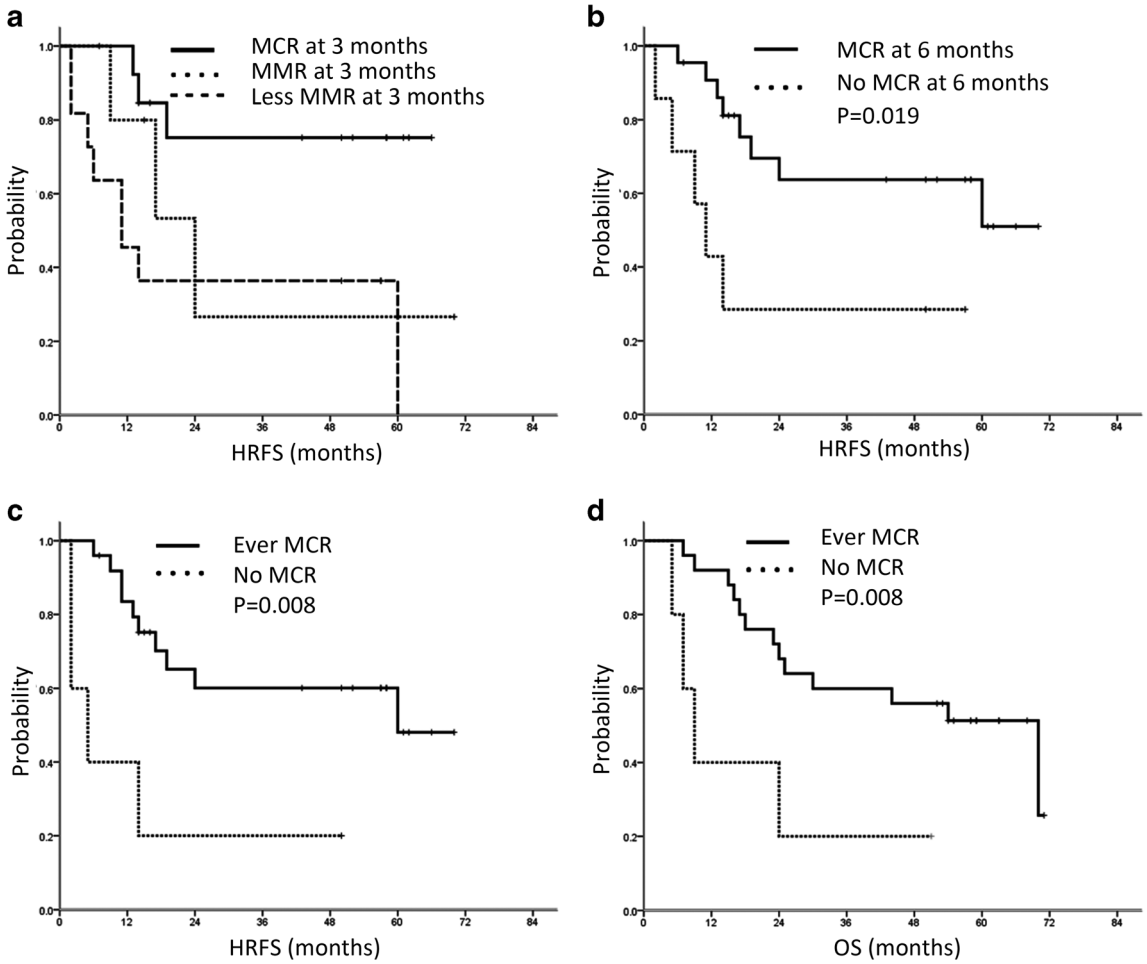

Fig. 5 **a**–**d** Impact of molecular response on survival

Mutation analysis and post-relapse therapy

The details of the 16 relapsed patients are shown in Table 3. Thirteen patients showed detectable mutations in ABL on relapsing from their disease. In addition, five patients showed detectable T315I mutations, of which four patients failed to respond to salvage therapy. Further, two patients achieved and maintained MCR by intensive salvage chemotherapy and a second donor stem cell transfusion. One patient lost his best molecular response (MCR) without evidence of mutation before conditioning therapy and achieved transient MCR after the first allo-HCT. However, HREL with the evidence of T315I mutation occurred 4 months after the first allo-HCT. Most patients without the T315I mutation received dasatinib-based combinatorial chemotherapy with a good response.

Safety

Twenty-one (70%) patients experienced nilotinib interruption due to intestinal obstruction or grades 3–4 non-hematologic toxicity. During the study, 10 (33.3%) patients interrupted nilotinib once, 7 (23.3%) patients with two times, and 4 (13.3%) patients with three times. The top 3 reasons for nilotinib interruption were infection (7/21 patients), intestinal obstruction (7/21 patients), and rash and increased creatinine (both were 4/21 patients). Thirteen (43.3%) patients reduced the dose of nilotinib to 400 mg/day temporarily for combination therapy with triazol antifungal (9/13 patients) or recurrence of toxicity (4/13 patients). The mean dose for each patient was from 335 to 800 mg/day during the study, and the median dose for the cohort was 760 mg/day. The termination of nilotinib occurred in 8 patients due to molecular/hematologic relapse and in 2 patients due to withdrawal of informed consent.

The median time to neutrophil and platelet recovery at cell densities of 0.5×10^9/L and 20×10^9/L was 22.5 (range 0–35) and 10.5 (range 0–26) days respectively during the induction cycle of chemotherapy. The median number of transfused units of blood products for red blood cells (RBCs) was four and for platelets was three.

Febrile infection was the most common adverse event in this trial with an incidence of 76.7% (23/30) during the induction cycle and 52.6% during the consolidation cycle (i.e., 61

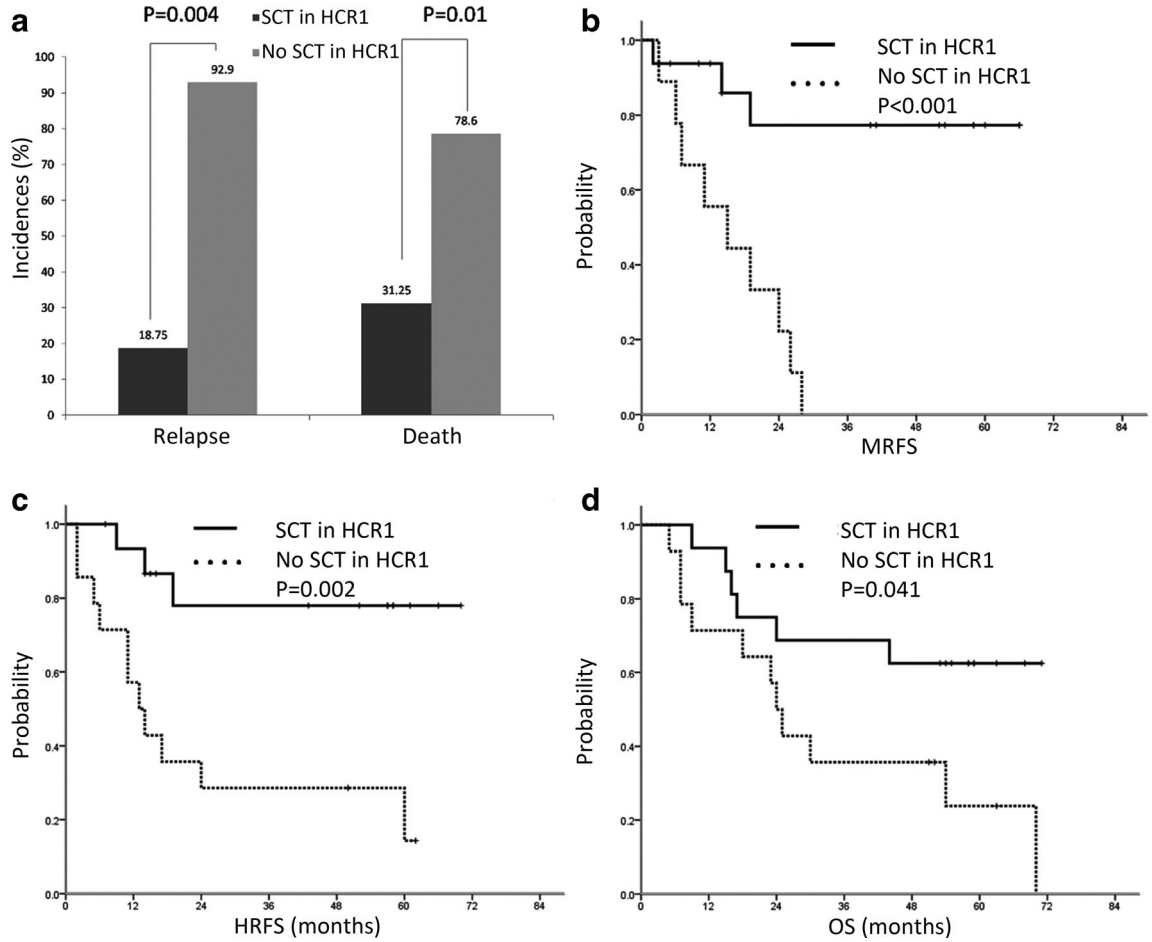

Fig. 6 **a**–**d** Impact of stem cell transplantation on patient survival

episodes in 116 treatment cycles before HCT). The most frequent infection sites during therapy were the respiratory system, including upper respiratory tract infection and pneumonia (both of which were 25 episodes in 146 treatment cycles, 25/146, or 17.1%). In addition, febrile neutropenia (22/146, 15.1%), perianal infections (12/146, 8.2%), intestinal infections (7/146, 4.8%), and gingivitis (7/146, 4.8%) were common reasons for using antibiotics. Three patients experienced septicemia, two of which were during the induction cycle and one was during the consolidation cycle. Six patients received antifungal therapy for pneumonia in the induction phase of the chemotherapy cycle. Eighteen episodes of clinically probable fungal pneumonia occurred during 116 consolidation cycles. Moreover, intestinal obstruction occurred in seven patients, of which six showed this condition in the induction cycle and the remaining patient showed this condition in the consolidation cycle with COATD regimen. Intestinal obstruction was relieved after transient interruption of nilotinib therapy.

Additional AEs that occurred with an incidence of 5% or more during induction and consolidation cycles are shown in Table 4. Episodes of jaundice and rash were common AEs in this trial with an incidence of 63.3% and 46.7%, respectively. Most AEs were of grades 1–2. Adverse events above grade 3 were rarely seen, and most were reversed when nilotinib therapy was reduced to a lower dose or transiently discontinued. Except for arrhythmia that was seen in two patients (one presented with sinus tachycardia and another one presented with atrial and ventricular premature heart beat). No other AE related to the cardiovascular system and no evidence of QTc prolongation were found to occur.

Pharmacokinetics of nilotinib

The steady-state concentration of nilotinib was achieved after approximately 2 weeks of nilotinib treatment with the mean level of 1780 ± 660 ng/mL. The CSF samples were obtained 3 h post-administration of nilotinib. Only traces of nilotinib were found in the CSF, while the plasma levels of nilotinib were in the steady state.

Delayed clearance of MTX

All patients completed the first cycle of MTX consolidation therapy combined with nilotinib. Twenty (66.7%) patients

Table 3 Characteristics and outcomes of relapsed patients

Patient number	Best response before relapse	Duration of CR1	Relapse status	SCT before relapse	Mutation	Salvage treatment	Response to salvage	Outcome
1	MCR	35	MREL	No	L278V	Dasatinib-based regimen	MCR2	HREL2, died
8	HCR	2	HREL	No	T315I	Chemotherapy	No	Died
9	MCR	24	HREL	No	ND	No		Died
11	MCR	27	MREL	No	No	Imatinib	MCR2	Alive
13	MCR	11	HREL	No	No	Dasatinib	MCR2	HREL2, died
14	MMR	2	HREL	No	T315I	Chemo	No	Died
15	MCR	11	HREL	No	No	Dasatinib	HCR2	SCT, died
18	MCR	6	HREL	No	ND	No		Died
20	MCR	19	HREL	Yes	No	Dasatinib	MCR2	Died of infection
22	MCR	14	HREL	No	T315I	Chemo	No	Died
23	MMR	5	HREL	No	T315I	Chemo	No	Died
24	MCR	17	HREL	No	ND	No		Died
25	MCR	14	HREL	Yes	No	Dasatinib/2nd SCT	MCR2	Alive
26	MMR	4	MREL1/HREL2	No/Yes	No/T315I	Chemo/2nd SCT	MCR2	Alive
28	MCR	25	MREL	No	No	Dasatinib	UK	Alive
30	MCR	13	HREL1/HREL2	No	Y253H/T315I	Dasatinib/chemo	HCR2	HREL2, died

ND not detected, *UK* unknown

experienced delayed MTX elimination with the MTX serum level > 0.1 μmol/L 72 h after the initiation of MTX. The median time to MTX serum level < 0.1 μmol/L in the cohort was 5 (range 3–23) days. Increasing levels of serum creatinine were found in seven patients including three patients with grade 3 and one patient needing emergency dialysis. All seven patients recovered from renal injury after transiently discontinuing nilotinib therapy.

Discussion

In the present study, it was originally hypothesized that including nilotinib in a combinatorial chemotherapeutic regimen would offer improved efficacy compared with the prior use of imatinib in treating patients presenting with Ph+ ALL. The study successfully reported the safety and efficacy of nilotinib combined with multi-agent chemotherapy in patients with newly diagnosed Ph+ ALL. Nilotinib in combination with multi-agent chemotherapy was both well tolerated and clinically beneficial in patients with newly diagnosed Ph+ ALL, thus supporting the original working hypothesis. Moreover, the clinical significance of this study showed that when nilotinib was combined with cytotoxic chemotherapy, it was highly effective; it not only translated to a higher hematological CR rate but also enhanced the response rates of molecular CR in Ph+ ALL.

Table 4 Non-hematologic adverse events

Adverse events	All, *n* (%)	1–2, *n* (%)	3–4, *n* (%)
Jaundice	19 (63.3)	12 (43.3)	7 (23.3)
Rash	14 (46.7)	10 (33.3)	4 (13.3)
Nausea	7 (23.3)	6 (20)	1 (13.3)
Intestinal obstruction	7 (23.3)	7 (23.3)	0
AST/ALT increase	7 (23.3)	6 (20)	1 (13.3)
Creatinine increase	7 (23.3)	4 (13.3)	3 (10)
Bone pain	6 (20)	4 (13.3)	2 (6.7)
Headache	5 (16.7)	5 (16.7)	0
Myalgia	4 (13.3)	2 (6.7)	2 (6.7)
Palpitation	3 (10)	3 (10)	0

Historically, treatment outcomes for adult patients with Ph+ ALL were extremely poor. Imatinib combined with chemotherapy led to substantial improvements in outcomes compared with chemotherapy alone and is now considered front-line therapy for Ph+ ALL [3–9, 19]. However, the resistance to imatinib poses a challenge for patients with primary refractory disease or following relapse after receiving an initial treatment with imatinib-containing regimens. Second-generation TKIs, such as dasatinib and nilotinib presented as an effective option for patients resistant to imatinib. Several studies have shown the promising activity of dasatinib when incorporated into front-line or second-line regimens for patients with Ph+ ALLs [20–23]. The activity of dasatinib against most imatinib-resistant *BCR-ABL* mutants has been demonstrated, and its greater penetration into the CNS has been shown [24]. Therefore, it was recommended for newly diagnosed or

relapsed patients resistant to imatinib [25]. In contrast, relatively few data are available on the use of nilotinib in patients with Ph+ ALL, especially in the context of studying its role in the front-line therapy of Ph+ ALL [26]. A previous study showed that nilotinib, compared with imatinib, had a high in vitro affinity for BCR-ABL1 tyrosine kinase, improved molecular response rates, and improved tolerance in patients with chronic-phase CML [27].

Overall, the combination of VDCP and nilotinib showed excellent induction responsiveness with a 100% HCR rate, coupled with long-term survival outcomes comparable to those shown for dasatinib-, nilotinib-, or imatinib-based regimens for Ph+ ALL. The molecular MRD levels were also previously shown to be correlated with the rates of relapse and outcomes [22, 26, 28–30]. In the present study, the molecular MRD after induction cycle had no impact on RFS and OS. The negative molecular MRD 3 and 6 months after the initiation of therapy had a positive effect on survival. The patients who had achieved MCR 3 or 6 months after the initiation of therapy had a superior HRFS. In addition, achieving MCR indicated longer OS. These results supported the notion that the early stable molecular responder had improved survival.

The role of allo-HCT in the first complete remission (CR1) has been challenged by the hypothesis that the use of TKIs as front-line therapy might improve the outcome in patients with Ph+ ALL, especially in older patients [31, 32]. After a median follow-up of 56 months for surviving patients in this study, 13 of the 14 patients (92.9%) who did not receive HCT relapsed with a median time of 13.5 (range 2–35) months after the first HCR and 11 patients died from leukemic progression. In contrast, only 3 of 16 patients (18.8%) relapsed after HCT in the first HCR and only 1 patient died. Two patients with minimal MRD achieved durable MCR after allo-HCT, of which one patient experienced MREL and one patient experienced persistent molecular disease prior to HCT. Despite 25% nonrelapse mortality in the transplanted patients and high efficiency of salvage therapy following relapse, the patients who received SCT in the first HCR still had a lower relapse rate and superior survival. The present study with long-term follow-up showed that it was challenging to achieve a durable remission for patients treated with nilotinib-based intensive chemotherapy alone without incorporating SCT. It should also be noted that three patients received auto-HCT after achieving MCR and maintained durable MCR till the cutoff day. The results suggested that patients achieving early stable MCR had a favorable survival outcome. The early and stable molecular response rates that favored RFS or OS in patients with Ph+ ALL have also been demonstrated by many studies [24, 26, 28–30]. Rvandi et al. [21] suggested that only patients younger than 40 years would benefit from allo-HCT. Thus, auto-HCT is a good choice for post-inductive therapy for patients with early MCR, especially for older patients or those deemed unsuitable for allo-HCT.

The results also indicated that the combination of chemotherapy and nilotinib could induce an acceptable level of myelosuppression. Besides, all patients who achieved HCR and did not die in the early stage (e.g., during the inductive cycle and the first 3 months of treatment) showed superior outcomes compared with other previously published studies of TKI-based intensive chemotherapy [7, 22, 26]. The recovery time of platelets and neutrophils in the induction course of therapy was similar to that found in imatinib combined with intensive chemotherapy [33]. In addition, the incidence of infectious events in the inductive cycle of therapy was similar to that in previously published reports of nilotinib- or dasatinib-based multi-agent chemotherapy and was comparable to that in imatinib-based intensive chemotherapy [22, 26, 33]. The excellent response to the inductive cycle of therapy in this cohort might have been due to the limited number of patients and the highly effective local care that could be afforded at a single center.

In the present study, most of the AEs associated with nilotinib-based multidrug regimens were reversible after dose reduction or interruption of nilotinib therapy. Intestinal obstruction and delayed clearance of MTX were rarely reported in the study of the use of TKIs in Ph+ ALL. All instances of intestinal obstruction occurred only during the cycles of nilotinib combined with vincristine. Thus, it was presumed that nilotinib increased vincristine serum levels or delayed vincristine clearance, which might enhance peripheral neurotoxicity of vincristine.

A previous study about MTX clearance showed that the MTX serum level > 0.1 μmol/L after 72 h was 40.1% [34], and the median time to the MTX serum level < 0.1 μmol/L was 3 days in MTX treatment alone. Compared with a previous study, more patients experienced delayed MTX clearance when given nilotinib therapy. A delayed clearance of MTX and especially the consequence of renal injury required additional attention during nilotinib administration. Shortening the intravenous infusion time of MTX and earlier use of calcium folinate could reduce the observed damage.

The steady-state serological levels of nilotinib at doses of 400 mg twice daily was reached in 2 weeks post-therapy, which was similar to that previously reported [12]. In addition, a previous case report of a patient with Ph+ ALL experiencing CNS relapse during nilotinib maintenance therapy suggested that nilotinib might be incapable of achieving efficacious levels in the CSF to prevent the onset or occurrence of CNS leukemia [35]. The present data provided direct evidence that nilotinib could not penetrate the blood–brain barrier.

The small sample size was clearly one of the limitations of the present analysis, which might restrict better evaluating the efficacy and toxicity of nilotinib therapy, besides the confounding contributions of added statistical bias to the analyses.

Conclusions

The study found that combinatorial therapy with nilotinib and cytotoxic chemotherapy was both effective and well tolerated for adult patients with Ph+ ALL. In addition, it is important of course to note that nilotinib could not penetrate the blood–brain barrier.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interest.

Research involving human participants The patients provided the required written informed consent. All procedures were conducted according to the Declaration of Helsinki. The study was approved by the local ethics committee of the Chinese Academy of Medical Sciences and Blood Diseases Hospital (Approval Number: YL2011032201). This trial was registered as ChiCTR-ONC-12002469.

Informed consent Informed consent was obtained from all individual participants included in the study.

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