



Clinical Study on Flumatinib Mesylate Combined with Chemotherapy Followed by Autologous Hematopoietic Cell Transplantation in Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia

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Objective: To investigate the clinical efficacy and safety of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph⁺ALL) patients treated with second-generation tyrosine kinase inhibitor (TKI) flumatinib mesylate combined with chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HSCT).

Methods: From September 2020 to March 2022, clinical information of Ph⁺ALL patients who received flumatinib mesylate, chemotherapy and auto-HSCT were collected and analyzed.

Results: Of the 8 patients who were enrolled, a median age was 43 years old. The BCR-ABL transcript type was P190 in patients with the exception of one P210. It was determined that 2 patients suffered from tuberculosis (TB), and 1 patient developed central nervous system leukemia (CNSL). All patients got clinical remissions after the chemotherapy. A total of 4 patients (50%) received auto-HSCT in major molecular response (MMR). However, 1 patient (12.5%) relapsed following auto-HSCT and was switched to dasatinib therapy. Flumatinib was used during the induction and consolidation chemotherapy except the period of HSCT. Myelosuppression and infection were the most common side effects. At a median follow-up of 19.22 months, the 1-year OS rate was 75%.

Conclusion: Flumatinib combined with chemotherapy followed by auto-HSCT in Ph⁺ALL achieved a great remission rate and safety.

Keywords: Philadelphia chromosome; Acute lymphoblastic leukemia; Flumatinib mesylate; Autologous hematopoietic stem cell transplantation.

Introduction

The Philadelphia chromosome-positive acute lymphoblastic leukemia is the primary subtype of adult acute lymphoblastic leukemia^[1]. It occurs in approximately 15% to 50% of cases of adult acute lymphoblastic leukemia, with the long-time survival of conventional chemotherapy only accounting for 10%^[2]. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) has improved patient cure rate and prognosis^[3], long-term survival is still only approximately 30%^[4]. Only 30% of patients are able to obtain HLA-matched sibling donors, and the possibility of recurrence and graft-versus-host disease (GVHD) would affect the quality of life^[5,6].

The effectivity of TKIs has been presented in the Ph⁺ALL patients^[7,8]. However, some patients treated with the first and second-generation TKIs like imatinib and dasatinib acquire resistance or adverse events such as hepatic dysfunction, fluid retention and cardiovascular events^[9]. Flumatinib is a new second-generation TKI independently developed in China. Its inhibitory ef-

fect is twice as great as nilotinib in vitro cell studies^[10]. Compared with imatinib and nilotinib, flumatinib has more activity and fewer side effects^[11]. Regarding safety, flumatinib carries a lower risk of pleural effusion and liver injury^[10,12]. Due to its success, the China Food and Drug Administration (CFDA) has approved flumatinib mesylate to be the front-line therapy for newly diagnosed chronic myelogenous leukemia (CML) patients in the chronic phase^[13]. The treatment-related mortality (TRM) after auto-HSCT is better than allo-HSCT, despite the fact that auto-HSCT has a greater relapse rate than allo-HSCT^[14]. In general, most scholars have reached similar conclusions in Ph⁺ALL: auto-HSCT has better overall survival (OS) and recurrence-free survival (RFS) than chemotherapy and is similar to allo-HSCT. At the same time, auto-HSCT has the advantages of no donor limitation, no graft versus host disease, and fast immune system recovery^[15]. Autologous stem cell transplantation is a potential alternative therapy if there is no suitable donor^[15]. So, the combination of flumatinib mesylate with auto-HSCT may enhance the clinical efficacy of Ph⁺ALL while minimizing the side effects. In this study, we will verify the clinical efficacy and safety of flumatinib mesylate combined with chemotherapy followed by Auto-HSCT in Ph⁺ALL patients.

Methods

Eligibility

ALL patients aged 18 to 60 with Ph chromosome or BCR-ABL

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fusion gene, were included in the study. Patients were excluded if they suffered from other malignant tumors, had severe liver, kidney and other primary organs dysfunction. Patients with known CML in blast phase, severe mental disease and pregnancy were unqualified to be enrolled. The exclusion criteria also included patients who were secondary to the proliferative diseases of the lymphatic system, MDS and MPN. All patients signed the informed consent forms.

Treatment regime

Treatments schedules are shown in Table 1. Pretreatment (Prednisolone or cyclophosphamide) was administered to patients with high tumor burden ($WBC \geq 50 \times 10^9/L$, spleen, liver and lymph nodes markedly enlarged) at first visit. To determine whether they had extramedullary infiltration, all patients received the evaluation. Central nervous system (CNS) lumbar punctures were performed after induction therapy when platelet was greater than or equal to $50 \times 10^9/L$. Intrathecal therapy was administered every four weeks during the consolidation and reinforcing phase for CNSL prevention. Patients with diagnosed central nerve system leukemia (CNSL) received intrathecal therapy twice a week. A response evaluation was carried out at the end of each cycle. Patients who achieved a complete or partial response (CR/PR) can continued the following treatment. Major molecular remission (MMR) was an essential requirement for conducting the auto-HSCT. If remission was not achieved in the first induction therapy or MMR was not achieved after consolidation therapy, the patients would withdrew from the trial and underwent salvage treatment. Flumatinib was administered throughout our treatment until two years following auto-HSCT, at a dosage of 600 mg/d.

Assessment

A complete remission (CR) was defined as 5% bone marrow blasts or less, the absence of blasts in the peripheral blood, no extramedullary involvement and a full recovery of the peripheral blood count. A major molecular remission (MMR) was defined as the copy-number decreased by 3 log steps from baseline (or qualification $\leq 0.1\%$). Overall survival was determined from the time of diagnosis until death.

Statistical Analysis

We analyzed the data from September 2020 to March 2022. All statistic tests were adopted using a two-sided test. SPSS25.0 software was used for statistical analysis. Kaplan-Meier method was used for survival analysis, and Log-rank method for comparison between groups, with $P < 0.05$ indicating significance.

Results

Patient characteristics

Eight patients were enrolled (7 men and 1 female), with a median age of 43 years old (range, 28–60). The BCR-ABL transcript type analysis was performed in all patients while Philadelphia chromosome was evidenced. 7 cases expressed P190, with 1 case expressed P210. A patient's blood routine on admission suggests a white blood cell greater than 50×10^9 . Central nervous system leukemia was discovered in one male.

The treatment before transplantation

Before transplantation, flumatinib was administered to 7 patients.

Table 1. Therapeutic scheme for Ph⁺ALL patients.

Treatment phases	Drugs	Doses	Schedules
Cycle 1	DNR	40 mg/m ² ivgtt	D1–3
	VCR	2 mg ivgtt	D1,8,14,22
	Pred	40–60 mg/m ² PO	D1–21, dose gradually reduced to 0 from d22 to d28
	Flumatinib	600 mg PO qd	D1–28
Cycle 2	CTX	1000 mg/m ² ivgtt	D1,8
	Ara-C	75 mg/m ² ivgtt	D1–4, 8–11
	6-MP	60 mg/m ² PO	D1–7
	Flumatinib	600 mg PO qd	D1–11
Cycle 3	MTX	1 g/m ² ivgtt	D1
	VCR	2 mg ivgtt	D8
	DEX	6 mg/m ² ivgtt	D8–15
	Flumatinib	600 mg PO qd	D1–15
Cycle 4	Ara-C	1 g/m ² ivgtt q12h	D1–3
	Flumatinib	600 mg PO qd	D1–3
Intrathecal therapy	MTX	30 mg	
	Ara-C	15 mg	
	DEX	5 mg	

DNR: Daunorubicin; VCR: Vincristine; Pred: Prednisolone; CTX: Cytosine arabinoside; Ara-C: Cytosine arabinoside; 6-MP:6-mercaptopurine; MTX: Methotrexate; DEX: Dexamethasone.

In the trial, 1 (14.2%) changed flumatinib to ponatinib because of T315I gene mutation. One patient originally used imatinib and later switched to flumatinib due to nausea and vomiting. To treat the CNSL, the patient successfully completed intrathecal therapy twice a week before auto-HSCT. In order to consolidate, it is then reduced to once a month. Pretreatment (Prednisolone) was used by patients with an initial WBC $> 50 \times 10^9/L$ to decrease the leukemia cells. All patients reached objective remission, including 7 cases CR and 1 PR. In the end, 5 patients reached MMR to achieve the transplantation.

Autologous hematopoietic stem cell transplantation

BU/CY conditioning regimens are commonly used prior to auto-HSCT. Hematopoietic stem cells were collected. The average of mononuclear cells (MNC) and CD34⁺ cells were $4.76 \times 10^8 \text{ kg}^{-1}$ and $8.67 \times 10^6 \text{ kg}^{-1}$, respectively (Table 2).

Table 2. Clinical data of autologous stem cells of patients.

Patient	MNC (mononuclear cell)	CD34 ⁺ cell
1	$2.85 \times 10^8 \text{ kg}^{-1}$	$3.68 \times 10^6 \text{ kg}^{-1}$
2	$6.02 \times 10^8 \text{ kg}^{-1}$	$22.13 \times 10^6 \text{ kg}^{-1}$
3	$2.75 \times 10^8 \text{ kg}^{-1}$	$3.96 \times 10^6 \text{ kg}^{-1}$
4	$7.40 \times 10^8 \text{ kg}^{-1}$	$4.91 \times 10^6 \text{ kg}^{-1}$
Average	$4.76 \times 10^8 \text{ kg}^{-1}$	$8.67 \times 10^6 \text{ kg}^{-1}$

The use of flumatinib after transplantation

Flumatinib was out of use during the transplantation and continued after that for up to 2 years. All patients in the study group took oral administration 14 days after transplantation.

Overall survival and follow-up period

The median follow-up was 19.22 months (range, 8.23–26.33). Among the 8 patients, 3 cases relapsed, 1 withdrew from the study and none died. Compared to 14.13 months (range, 12.53–26.33) for those who did not receive a transplant, the median OS for individuals who underwent auto-HSCT was 24.15 months (range, 8.23–25.53). The 1-year OS rate of transplanted patients and the untransplanted were both 75% (3/4).

Toxicities of flumatinib

The toxicities of flumatinib are shown in Table 3. The grade IV toxicity was the hematological toxicity, including leukopenia, anemia and thrombopenia. Other toxicities were infection, digestive tract symptoms, rash and liver dysfunction. All patients had myelosuppression and infection during the whole cycle. After transplantation, there were fewer 3–4 grade severe adverse events. All adverse effects were effectively controlled after treatment interruption. The relapsed patient left our research after changing flumatinib to dasatinib. And the hepatic dysfunction still existed without any extra adverse events.

Discussion

Philadelphia chromosome (Ph)/BCR-ABL fusion gene positive

Table 3. Treatment-related toxicities of patients treated with flumatinib.

	Patient before transplantation n = 8		Patient after transplantation n = 4	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Myelosuppression	0	8	0	2
Anemia	0	7	0	2
Thrombocytopenia	1	4	0	2
Neutropenia	1	6	0	2
Leukopenia	0	7	0	2
Infection	0	8	0	2
Rash	3	0	0	0
Diarrhea	4	0	2	0
Liver dysfunction	7	1	3	0

acute lymphoblastic leukemia is the largest genetically-defined subtype in adult ALL and until recently, the one with the most unfavorable prognosis^[16–18]. The advent of TKIs targeting BCR-ABL1 led to major changes in the outcome of Ph⁺ALL^[7,13]. Imatinib, the first-generation tyrosine kinase inhibitor, has significantly improved the way Ph⁺ALL patients are managed. Combined with conventional chemotherapy, imatinib enhanced the 3-year overall survival rate (OS) from 15% to 54%^[18]. Some patients treated with imatinib developed drug resistance and the BCR-ABL gene mutated, resulting in a change in the enzyme structure^[19]. Consequently, imatinib is unable to attach to the enzyme, which results in disease relapse, particularly in the central nervous system, and therapy failure^[19]. The effect was greatly enhanced by the second-generation TKI, but the negative effects were clear. The secondary-generation TKI like nilotinib and dasatinib had several side effects, which include fluid retention, liver damage and adverse cardiac events, which may limit their clinical use to a certain extent^[20–23].

Flumatinib is a novel TKI, which has a higher potency and fewer adverse events than other TKIs^[11]. It outperforms imatinib as a BCR-ABL inhibitor and effectively overcomes imatinib resistance conferred by BCR-ABL point mutations^[9]. Li Zhang et al reported that the MMR rate in the intention-to-treat CML patients was significantly higher in patients receiving flumatinib than in those receiving imatinib (33.7% vs 18.3%)^[24]. The frequencies of side effects such as edema, discomfort in the limbs, rash, neutropenia, anemia, and hypophosphatemia were much lower in patients with flumatinib. Therefore, flumatinib is a low toxic effective drug targeted to the BCR-ABL fusion gene^[24]. The effectiveness of flumatinib was discovered by a researcher who gave it to individuals with newly diagnosed/relapsed Ph⁺ALL^[25]. The authors reported that 9 patients (100%) reached CR within 28 days, then 2 (22.2%) reached MMR, consistent with the results of nilotinib combined with chemotherapy^[25]. As a result, flumatinib may be a suitable and alternative option for patients because its efficacy.

Although it has severe side effects, allogeneic hematopoietic stem cell transplantation is still an effective post-remission therapy in patients with acute lymphoblastic leukemia^[26]. Allogeneic hematopoietic stem cell transplantation has improved the survival

al of Ph⁺ALL, but its widespread use was restricted by high transplant-related mortality and a lack of donors^[27]. Autologous hematopoietic stem cell transplantation was an alternative, less toxic treatment option, particularly for those who lacked appropriate donors and were unfit for allo-HSCT^[28]. Haichen Wei et.al. found auto-HSCT was superior to allo-HSCT in overall survival, whereas there was no difference between the two treatments in terms of relapse-free survival or relapse rate^[27]. Therefore, We may attempt to employ auto-HSCT in place of allo-HSCT for patients who has no access to it. In our study, all patients achieved remission while receiving chemotherapy. Then 4 patients completed the auto-HSCT within one relapsed after HSCT.

In a present study of dasatinib and chemotherapy followed by allo-HSCT, 17 patients (89.5%) got MMR and 15 patients (78.9%) got complete molecular remission before allo-HSCT. 13 patients (68.4%) kept taking dasatinib after the allo-HSCT. However, due to its significant adverse effects, such as headache and emesis, 7 patients (36.2%) had quit using dasatinib^[28]. Although the TKI combined with allo-HSCT can achieve good results, serious adverse events existed^[29]. The Japan Adult Leukemia Study Group treated Ph⁺ALL patients with chemotherapy and imatinib^[27]. The group reported a 1-year OS rate of 73% among patients who underwent allogeneic HCT, compared with 85% for those who did not^[30]. Adverse events increased with allo-HSCT. We may speculate from the above results that allo-HSCT may not be the optimal option for patients receiving chemotherapy and TKI.

Additionally, we discovered that following the first cycle of chemotherapy, 100% of patients achieved CR/PR. 6 patients (75%) got MMR prior to HSCT, and 4 of them have successfully undergone auto-HSCT. The median follow-up was 19.22 months, and the 1-year OS rate was 75% till the deadline. During the period of treatment, 1 patient changed flumatinib to dasatinib owing to relapse. No extra severe adverse events appeared after changing the TKI. In one patient, imatinib was utilized during chemotherapy, but flumatinib was substituted following auto-HSCT due to side effects. For the adverse reactions of flumatinib, we could find that the probability after transplantation was significantly reduced. It means that flumatinib are better tolerated. The severity of hepatic damage are lower than imatinib and dasatinib. Therefore, we can assume that the side effects of fumatinib are relatively small.

In a conclusion, flumatinib combined with chemotherapy followed by auto-HSCT is essential in the treatment of diagnosed Ph⁺ALL, which produced a high rate of remission and safety. Meanwhile, our study supports the effect and safety of flumatinib. Although there are other TKIs now being used in clinical settings, flumatinib is also a great choice for treatment planning. Through the data on adverse effects, we can conclude that auto-HSCT reduces the adverse effects of flumatinib to a certain extent. Therefore, the Ph⁺ALL patients who were unfit for allo-HSCT can benefit from flumatinib and auto-HSCT. To get more certain findings, the sample size still has to be increased.

Abbreviations

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; Auto-HSCT, autologous hematopoietic stem cell transplantation.

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Conflict of interest

The authors declare no conflicts of interest.

Authors' contributions

YS, SJC, as the principal investigators, were responsible for the design and writing of the study. XYT, JCD, QY, JY were responsible for the case study; NZ were responsible for the data curation.

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