Tyrosine kinase inhibitors and reduced-dose chemotherapy for adult Philadelphia chromosome-positive acute lymphoblastic leukemia

Chunping Wu, Mengting Zeng, Yuanzhong Chen and Yong Wu

Department of Hematology, Fujian Institute of Hematology, Fujian Provincial Key Laboratory on Hematology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

ABSTRACT

Objectives: To compare the outcomes of tyrosine kinase inhibitors (TKIs) in combination with reduced-dose chemotherapy with those of standard induction chemotherapy, as well as the outcomes between chemotherapy and transplantation, in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

Methods: We retrospectively reviewed cases of Ph+ ALL treated with TKIs and combination chemotherapy. The patients were allocated to either the TKIs with reduced-dose chemotherapy group or the TKIs with standard chemotherapy group. In addition, patients were further stratified into either the transplant group or the non-transplant group.

Results: The complete remission rate (88.7% vs. 83.9%, p = 0.372), major molecular response (58.9% vs. 56.0%, p = 0.750), molecular complete response (20.5% vs. 22.0%, p = 0.891), and early mortality rate (3.2% vs. 3.5%, p = 0.922) were similar between the TKIs with reduced-dose chemotherapy group and the TKIs with standard chemotherapy group. The proportions of lung infections, bloodstream infections, patients with >21 days of hospitalization, the total costs, transfusion costs, and antimicrobial costs were higher in the standard chemotherapy group than in the TKIs with reduced-dose chemotherapy group. The 3-year overall survival rates (59.0% [95% CI, 46.6–74.7%] vs. 38.4% [95% CI, 29.9–49.4%]) and disease-free survival rates (48.6% [95% CI, 34.2–69.1%] vs. 32.0% [95% CI, 23.5–43.7%]) were significantly better in the transplant group than in the non-transplant group.

Conclusion: An induction regimen combining TKIs with reduced-dose chemotherapy and transplantation during the first complete remission remains a suitable and effective option for patients with Ph+ ALL.

Introduction

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) is a distinct subtype of acute lymphoblastic leukemia (ALL) associated with a poor prognosis. The incidence of Ph+ ALL increases with age, accounting for 3–5% of childhood ALL, 20–30% of adult ALL, and >50% of ALL cases in patients >50 years of age [1]. Before the advent of tyrosine kinase inhibitors (TKIs), the complete remission (CR) rate of patients with Ph+ ALL treated with standard chemotherapy regimens was at least 10% lower than the CR rate of patients with Ph- ALL, who have a median survival time of approximately 8 months. The use of TKIs has increased the CR rate and reduced the incidence of adverse events, allowing more opportunities for allogeneic hematopoietic stem cell transplantation (allo-HSCT), and significantly prolonging survival in patients who were unable to undergo transplantation [2]. Allo-HSCT may be the only available treatment option for achieving long-term survival after CR. However, the 5-year overall survival (OS) rate of Ph+ ALL is only approximately 50% [3,4]. The survival of patients with Ph+ ALL has improved greatly in recent years, with the 5-year OS rate increasing to 40–70%, and the efficacy of non-transplant treatment gradually approaching that of allo-HSCT with the use of TKIs [5].

Although the clinical efficacy of TKIs combined with chemotherapy has been confirmed, not all patients can tolerate chemotherapy, and high-dose chemotherapy often results in severe myelosuppression or complications, including infection and bleeding, leading to early death. To minimize toxicity, the combination of TKIs with low-dose chemotherapy has shown favorable results [6,7]. Data from the Italian Group for Hematologic Diseases in Adults (GIMEMA) suggested that elderly Ph+ ALL patients may benefit from an imatinib-steroids protocol (imatinib 800 mg/day in combination with prednisone), which does not require chemotherapy [8]. Nevertheless, very few data on adult ALL are available from developing countries, and whether intensive chemotherapy is needed at all is still controversial.
In response to this knowledge gap, we conducted a retrospective analysis aimed at exploring an effective and safe induction regimen for Ph+ ALL. We thus compare the effects of TKIs combined with either reduced-dose chemotherapy or standard induction chemotherapy, with or without Allo-HSCT, in patients with Ph+ ALL. We also explored other prognostic factors associated with outcome in our sample.

Methods

Study design

This was a retrospective cohort study which analyzed the outcomes of patients aged >14 years with newly diagnosed Ph+ ALL treated at Fujian Union Hospital of Hematology, China, between January 2010 and December 2020. This study was approved by the ethics review board of the Fujian Medical University Union Hospital. The diagnosis of B-lymphoblastic leukemia was based on the World Health Organization criteria [9]. Patients with known severe cardiac, pulmonary, hepatic, or renal dysfunction; non-primary patients; patients who abandoned the treatment after diagnosis; and pregnant patients were excluded. Written informed consent for research participation was obtained from all patients.

Depending on the induction chemotherapy regimen, patients were non-randomly assigned to either the TKIs with reduced-dose chemotherapy group or the TKIs with standard chemotherapy group, based on the discretion of the treating physician. In cases where further treatment was required, patients were non-randomly assigned to either the transplant group or the TKIs + chemotherapy (non-transplant) group based on their individual preferences.

Chemotherapy regimens

Over a 10-year period, patients with newly diagnosed Ph+ ALL were treated with diverse protocols. Treatments are shown in Table 1. The standard chemotherapy regimens included hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) [10] and the protocol of Chinese Acute Lymphoblastic Leukemia Cooperative Group for adult ALL (CALLG2008) [11]. The reduced-dose chemotherapy regimens reduce the use of cyclophosphamide and doxorubicin during induction therapy compared to the protocol of CALLG2008. TKIs (imatinib 400 mg/d, dasatinib 140 mg/d, or nilotinib 400 mg/d) were administered concurrent with chemotherapy once the positive result for BCR-ABL1 was confirmed. Following the achievement of CR, allo-HSCT was recommended to all eligible patients.

Minimal residual disease monitoring and response definitions

Patients were monitored for the BCR-ABL1 transcript by reverse-transcription quantitative polymerase chain reaction (qRT-PCR) using bone marrow samples. BCR-ABL1 transcript levels were used for minimal residual disease (MRD) monitoring. Complete hematologic remission (CR) was defined as the absence of primitive cells in the peripheral blood, absence of extramedullary leukemia, blasts ≤5% in the bone marrow, neutrophil count ≥1.0×10^9/L, and platelet count ≥100×10^9/L. Major molecular response (MMR) was defined by a BCR-ABL1/ABL1 ratio ≤0.1%. Molecular CR (MCR) was defined by a BCR-ABL1/ABL1 ratio ≤0.01%. Early mortality was defined as death occurring during the induction treatment. Relapse was defined as >5% of leukemia cells in the bone marrow in patients who have achieved CR or had extramedullary disease. OS was defined as the time from the date of diagnosis until death or the final follow-up date. Disease-free survival (DFS) was measured from the date of complete remission to the date of disease relapse, death, or the final follow-up date.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (version 26.0) and R Studio (version 3.6.2) software packages. Categorical variables were compared between patient groups using a Fisher’s exact test or Chi-squared test. Continuous variables were compared between patient groups using the non-parametric Mann–Whitney U test. The cumulative incidence of relapse (CIR) was calculated considering death as a competitor and compared between groups using Grey’s test. The role of transplantation was assessed using the time-dependent Mantel–Byar method and visualized using Simon–Makuch plots [12]. Prognostic factors of survival were investigated using Cox proportional hazard models. Hazard ratios were obtained with 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant in all analyses.

Results

Patient characteristics

In this study, 234 patients were newly diagnosed with Ph+ ALL. In total, 29 patients were excluded because they received chemotherapy without TKIs. Therefore, 205 patients with Ph+ ALL enrolled between January 2010 and December 2020 were included in the present analysis. The median follow-up time was 33 months (range, 2–106 months). The median follow-up time was 37 months (range, 3–88 months) in the reduced-dose chemotherapy group and 32 months (range, 2–106 months) in the
standard chemotherapy group. The patient characteristics were well-balanced between the standard chemotherapy group and the reduced-dose chemotherapy group. The patients in the non-transplant group were significantly older than patients in the transplant group. No other significant between-group differences in patient characteristics were found. All patients were treated with a combination of TKIs in induction chemotherapy: imatinib (400–600 mg/d), dasatinib (100–140 mg/d), and nilotinib (400–800 mg/d) in 156, 47, and two patients, respectively. The patients who underwent allo-HSCT (n = 55) received a varying number of cycles until a transplant donor was identified. These patients underwent HSCT when their disease was in morphological CR1. The remaining patients were unable to undergo HSCT due to insufficient matching HSCT donors or personal reasons. The patient characteristics are shown in Table 2.

**Response to tyrosine kinase inhibitors with reduced-dose chemotherapy versus tyrosine kinase inhibitors with standard chemotherapy**

**Response and early mortality**

Table 3 summarizes the initial response to treatment in our patient sample. The use of standard chemotherapy versus reduced-dose chemotherapy was not associated with higher rates of early mortality (3.5% vs. 3.2%, p = 0.922) or hematologic CR (83.9% vs. 88.7%, p = 0.372) after induction. Among the 198 patients alive and in CR at the end-of-induction, 139 (67.8%) patients were tested for BCR-ABL. The MMR rate was similar in both groups (56.0% in the standard chemotherapy group and 58.9% in the reduced-dose chemotherapy group, p = 0.750). In total, 30 (21.6%) patients achieved molecular CR at the end-of-induction. The reduced-dose chemotherapy group (20.5%) was non-inferior to the standard chemotherapy group (22.0%) *(p = 0.891). Seven patients were considered refractory because of treatment failure at the end of the induction period. Infection was the major cause of death (5/7, 71%).

**Complications**

The reduced-dose chemotherapy group had a lower incidence of pulmonary infection (OR, 1.853 [95% CI, 1.003–3.422]) and blood-based infection (OR, 2.449 [95% CI, 1.108–5.412]) after the induction phase (Appendix Table A1). There was no significant difference in the use of granulocyte colony-stimulating factor during the induction phase between the standard chemotherapy group (29.4%) and the reduced-dose chemotherapy group (32.3%) (p = 0.679). The duration of neutropenia (neutrophil count <0.5

### Table 1. Chemotherapy regimens.

| Treatment phases       | Drugs | Doses       | Route | Schedules     |
|------------------------|-------|-------------|-------|---------------|
| Prephase               | Prednisone | 60 mg/d | PO    | D-3 to –1     |
|                        | Cyclophosphamide | 200 mg/m² | IV    | D-3 to –1     |
| **Frontline induction (4 weeks)** | Vincristine | 2 mg/d | IV    | D1,8,15,22    |
| Standard chemotherapy (VDCP) | Danuorubicin | 40 mg/m²/d | IV    | D1-3          |
|                        | Cyclophosphamide | 750 mg/m² | IV    | D1           |
| Reduced-dose chemotherapy (VP) | Prednisone | 1 mg/m²/d | PO    | D1-14,15-28/2/3dose |
|                        | Vincristine | 2 mg/d | IV    | D1,8,15,22    |
|                         | Prednisone | 1 mg/m²/d | PO    | D1-14,15-28/2/3dose |
| **Early-stage consolidation block** | Cyclophosphamide | 750 mg/m² | IV    | D1           |
| CAM                    | Cytarabine | 100 mg/m²/d | IV    | D1-3,8-10     |
|                         | Mercaptopurine | 60 mg/m²/d | PO    | D1-7         |
| HD-MTX + VP            | Methotrexate | 3 g/m² | IV    | D1          |
|                        | Vincristine | 2 mg/d | IV    | D8          |
|                         | Dexamethasone | 6 mg/m²/d | IV    | D8-15        |
| MA                     | Mitoxatrone | 8 mg/m²/d | IV    | D1-3         |
|                         | Cytarabine | 750 mg/m² | IV    | D1-3         |
| **Late-stage consolidation block** | Vincristine | 2 mg/d | IV    | D1,8,15,22   |
| VDCD                   | Danuorubicin* | 40 mg/m²/d | IV    | D1-3         |
|                        | Cyclophosphamide | 750 mg/m² | IV    | D1, D15      |
|                         | Dexamethasone | 8 mg/m²/d | PO    | D1-7, D15-21 |
| COAD                   | Cyclophosphamide | 750 mg/m² | IV    | D1           |
|                        | Vincristine | 2 mg/d | IV    | D1          |
|                         | Cytarabine | 100 mg/m²/d | IV    | D1-7         |
|                         | Teniposide | 100 mg/m²/d | IV    | D1-4         |
|                         | Dexamethasone | 8 mg/m²/d | IV    | D1-7         |
| HD-MTX                 | Methotrexate | 3 g/m² | IV    | D1          |
|                        | Vincristine | 2 mg/d | IV    | D8          |
|                         | Dexamethasone | 6 mg/m²/d | IV    | D8-15        |
| TA                     | Teniposide | 100 mg/m²/d | IV    | D1-4         |
|                         | Cytarabine | 100 mg/m²/d | IV    | D1-7         |
| Long-term maintenance (until 36 months) | Methotrexate | 2 mg/m²/week | PO | D8 for every 4 weeks |
|                         | 6-Mercaptopurine | 40 mg/m²/d | PO    | D1-7 for every 4 weeks |

IV, Intravenous; IM, Intramuscular; PO, Oral. *Or idarubicin 8 mg/m²/d. Intrathecal (IT) chemotherapy: cytarabine (50 mg) and/or methotrexate (10 mg), and dexamethasone (5 mg). Patients received at least 8 intrathecal chemotherapy treatments administered during the consolidation courses as a prophylactic for relapse in the CNS.
\( \times 10^9/L \) was significantly shorter in the reduced-dose chemotherapy group (12 days, range 7–22 days) compared to the standard chemotherapy group (18 days, range 14–31 days) \( (p < 0.001) \).

**Healthcare utilization**

The mean duration of in-hospital care was 23 ± 7 days in 27 ± 8 days the reduced-dose chemotherapy group and the standard chemotherapy group. In the reduced-dose chemotherapy group \( (n = 62) \), 33 (52.4%) patients were hospitalized for >21 days. In the standard chemotherapy group \( (n = 143) \), 115 (80.4%) patients were hospitalized for >21 days. This difference between the two groups was significant \( (p < 0.001) \).

The reduced-dose chemotherapy group had lower red blood cell counts and platelet transfusion burden during the induction phase, which are associated with lower hematologic toxicity. Expectedly, the total cost, transfusion cost, and antimicrobial cost were significantly lower in the reduced-dose chemotherapy group compared to the standard chemotherapy group (Appendix Table A2).

**Antibiotic use in induction chemotherapy**

In total, 14.6% (30/205) of patients received fluoroquinolone prophylaxis during the induction phase, which occurred mainly during the latter 3 years of the study. There was no significant difference in antibiotic use between the reduced-dose chemotherapy group (12.6%) and the standard chemotherapy group (19.3%) \( (p = 0.208) \).

Most patients were prescribed antibiotics for infections. The types and dosages of antibiotics used to control infections during hospitalization are recorded (Appendix Table A3). There was a significant difference in the number of patients who received more than four antibiotics between the reduced-dose chemotherapy group (14/62, 22.6%) and the standard chemotherapy group (64/143, 44.8%) \( (p = 0.003) \). The use of antifungal drugs, carbapenems, and the restricted class of anti-gram-positive drugs (tigecycline, vancomycin, and linezolid) were similar between the two groups. However, the rates of use of restricted tigecycline and/or polymyxin were significantly higher in the standard chemotherapy group compared to the reduced-dose chemotherapy group \( (p = 0.031) \).

**Survival outcomes in the transplant group versus the non-transplant group**

Among the 175 patients in CR, 55 (31%) were transplanted in CR1, including 28 sibling donors, nine

### Table 2. Patient characteristics.

| Group                      | Standard chemotherapy group \( (n = 143) \) | Reduced-dose chemotherapy group \( (n = 62) \) | \( P \) | Transplant group \( (n = 55) \) | Non-transplant group \( (n = 143) \) | \( P \) |
|----------------------------|---------------------------------------------|-----------------------------------------------|-------|---------------------------------|-----------------------------------|-------|
| Gender, \( n \) (%)        |                                             |                                               | 0.176 | 0.307                           |                                   |       |
| Male                       | 77 (53.8)                                  | 27 (43.5)                                     |       |                                 |                                   |       |
| Female                     | 66 (46.2)                                  | 35 (56.5)                                     |       |                                 |                                   |       |
| Age (years), mean (range)  |                                             |                                               | 0.467 | 0.001                           |                                   |       |
| WBC count \( \times 10^9/L \) | 89.93 (1.50–504.64)                        | 78.17 (1.10–974.82)                           | 0.515 |                                 |                                   |       |
| HB (g/L)                   | 91 (32–160)                                | 90 (43–161)                                   | 0.921 |                                 |                                   |       |
| PLT count \( \times 10^9/L \) | 59 (1–356)                                | 52 (3–329)                                    | 0.525 |                                 |                                   |       |
| Chromosome type, \( n \) (%) |                                             |                                               | 0.208 | 0.888                           |                                   |       |
| Ph+ only                   | 40 (28.0)                                  | 12 (19.4)                                     | 12 (21.8) | 39 (27.3)              |                                   |       |
| Ph+ plus additional changes| 30 (21.0)                                  | 21 (33.9)                                     | 14 (25.5) | 35 (24.5)              |                                   |       |
| Normal karyotype           | 44 (30.8)                                  | 19 (30.6)                                     | 18 (32.7) | 43 (30.1)              |                                   |       |
| Unknown                    | 29 (20.2)                                  | 10 (16.1)                                     | 11 (20.0) | 26 (18.2)              |                                   |       |
| BCR-ABL1, \( n \) (%)      |                                             |                                               | 0.244 | 0.675                           |                                   |       |
| P190                       | 59 (41.3)                                  | 24 (38.7)                                     | 21 (38.2) | 58 (40.6)              |                                   |       |
| P210                       | 31 (21.7)                                  | 20 (32.3)                                     | 16 (29.1) | 33 (23.1)              |                                   |       |
| Unknown                    | 53 (37.0)                                  | 18 (29.0)                                     | 18 (32.7) | 52 (36.4)              |                                   |       |
| TKIs received              |                                             |                                               | 0.315 | 0.822                           |                                   |       |
| First-generation           | 106 (74.1)                                 | 50 (80.7)                                     | 42 (76.4) | 107 (74.8)             |                                   |       |
| Second-generation          | 37 (25.9)                                  | 12 (19.3)                                     | 14 (25.4) | 35 (24.5)              |                                   |       |
| Year of initial diagnosis  |                                             |                                               | 0.128 | <0.001                          |                                   |       |
| 2010–2015                  | 50 (35.0)                                  | 27 (43.5)                                     | 15 (27.3) | 60 (42.0)              |                                   |       |
| 2015–2020                  | 93 (65.0)                                  | 35 (56.5)                                     | 40 (72.7) | 83 (58.0)              |                                   |       |

### Table 3. Response at the end-of-induction.

|                              | All patients \( n = 205 \) | Standard chemotherapy group \( n = 143 \) | Reduced-dose chemotherapy group \( n = 62 \) | \( P \) |
|------------------------------|-----------------------------|---------------------------------------------|-----------------------------------------------|-------|
| Hematologic CR, \( n \) (%) | 175 (83.4)                  | 120 (83.9)                                  | 55 (88.7)                                     | 0.375 |
| MMR, \( n/\text{tested} \) (%) | 79/139 (56.8)              | 56/100 (56.0)                              | 23/39 (58.0)                                  | 0.750 |
| MCR, \( n/\text{tested} \) (%) | 30/139 (21.6)              | 22/100 (22.0)                               | 8/39 (20.5)                                   | 0.891 |
| Early mortality, \( n \) (%) | 7 (3.4)                    | 5 (3.5)                                     | 2 (3.2)                                       | 0.922 |
unrelated donors, and 18 cord blood transplantations (Appendix Table A4). No patient received an autograft. As illustrated in Figure 1A–B, the 3-year DFS in the allo-HSCT group (48.6% [95% CI, 34.2–69.1%]) was significantly higher than that in the non-HSCT group (32.0% [95% CI, 23.5–43.7%]). The 3-year OS in the allo-HSCT group (59.0% [95% CI, 46.6–74.7%]) was significantly higher than that in the non-HSCT group (38.4% [95% CI, 29.9–49.4%]).

**Relapses and deaths**

Of the 205 (85%) patients, 175 achieved CR. Thirty patients failed to obtain CR; 23 were refractory and obtained CR after salvage therapy, and seven died during the induction phase. Among the 175 patients in CR after induction, 46 (26.3%) relapsed. Thirteen patients obtained a second CR (28%), six (46.1%) of whom had a secondary relapse event. In total, 120 (58.5%) patients died, including 65 deaths in those with relapse or refractory disease. Non-relapse related mortality (NRM) was reported in 55 patients. There was no significant difference in NRM between the reduced-dose chemotherapy group (30.6% [95% CI, 19.9–43.8%]) and the standard chemotherapy group (25.2% [95% CI, 18.5–33.2%]) (p = 0.417). In considering non-relapse mortality as a competitor event, the 5-year CIR was 43.4% (95% CI, 36.6–50.5%), while the 5-year non-relapse mortality was 30.7% (95% CI, 24.8–37.6%) (Figure 2).

**Prognostic factors**

In a univariable analysis, age, hematologic CR, MMR, MCR, and transplantation were significant predictors of OS. Gender, white blood cell (WBC) count, the presence of additional cytogenetic alterations (ACAs), and BCRABL1 transcript were not significantly associated with OS. In a multivariate analysis modelling the effects of age, hematologic CR, MMR, MCR, and transplantation, only MMR (HR, 2.33 [95% CI, 1.35–4.0; p = 0.002] and MCR (HR, 7.13 [95% CI, 2.58–19.7; p < 0.001]) remained significant predictors of OS during the induction phase (Figure 3).

**Discussion**

Over the last decade, TKIs have revolutionized the treatment and prognosis of patients with Ph+ ALL. TKIs combined with chemotherapy have become the first-line induction chemotherapy regimen for patients newly diagnosed with Ph+ ALL, improving the CR rate and OS and DFS rates, while reducing treatment-related mortality [13,14]. The intolerance to intensive chemotherapy for older patients has led to consideration of whether this approach is still needed, especially in older patients who are at greater risk of early death by infections after intensive chemotherapy. Hence, several international clinical studies of TKIs with reduced-dose chemotherapy have been conducted.

The European Working Group on Adult ALL examined the clinical efficacy of dasatinib combined with low-dose chemotherapy in 71 elderly patients with CR, CMR, and MMR rates of 96%, 24%, and 65%, respectively. Moreover, only 10% of patients underwent allo-HSCT, with 5-year relapse-free survival and OS rates of 28% and 36%, respectively [6]. Similar results were obtained in other clinical trials [15–17].

In the present study, patients with reduced-dose chemotherapy had CR, MMR, and CMR rates of 88.7%, 58.9%, and 23.0%, respectively. We did not find differences in achievement of molecular remission when we de-escalated chemotherapy. Rather, the reduced intensity of chemotherapy allowed patients to achieve high rates of CR while significantly reducing treatment-related toxic side-effects. Our sample had a lower CR rate than samples from studies conducted in developed countries [15–17], but a significantly higher CR rate compared to a study conducted in Brazil, which is also a developing country, with a CR rate of 77.3%–84.6% [18]. Second- and third-generation TKIs combined with chemotherapy are associated

![Figure 1](image1.png)

**Figure 1.** Simon–Makuch plots for overall survival (A) and disease-free survival (B) in all Ph-positive ALL.
**Figure 2.** Cumulative incidence curves for relapse and non-relapse mortality (NRM) in all Ph-positive ALL.

**Figure 3.** Forest plot summarizing the multivariable model for OS in all Ph-positive ALL.
with a decreased MRD [19]. Most (76%) of the patients enrolled in this study were treated with the first-generation TKI imatinib, which could explain the worse outcomes found in our sample. A recent randomized clinical trial performed in pediatric patients with Ph+ ALL showed that dasatinib in the frontline treatment of pediatric Ph+ ALL is associated with better survival and fewer central nervous system (CNS) relapses [20].

Ph+ ALL is a hematological malignancy and a chronic disease that requires repeated hospitalization, resulting in high hospitalization costs and serious threats to the quality of life of affected patients. We found that the financial burden faced by Chinese families with a patient with ALL was tremendous, as it is one of the most significant factors affecting compliance, as well as a direct impact on the willingness of the patient to be treated. However, research determining the costs associated with ALL in developing countries is rare. This study provided a breakdown of the direct medical costs and in-depth understanding of financial burden to families. A cost-analysis shows that the mean total treatment cost of childhood ALL per patient was 17,647.5 United States dollars (USD). The important drivers of overall costs were hospital admissions (36.2%) and drug expenditures (31.4%), especially expenditure on antibiotics/antifungals [21], which were the main contributors to high medical cost [22–26]. In the low-intensity chemotherapy group, due to the reduced intensity of chemotherapy, the degree and duration of bone marrow suppression was reduced. In turn, life-threatening infections were also reduced, as evidenced by the reduction of serious infections and the use of fewer types and lower intensity of antibiotics. The number of hospital days was thus shortened, and the cost of antibiotics and total healthcare costs reduced. Therefore, the use of low-intensity chemotherapy in induction may be one of the important ways to lower the treatment costs of Ph+ ALL. Currently, there is a paucity of literature on the comprehensive cost analysis of ALL treatment. Most studies to date have examined the cost-effectiveness of different treatment methods; however, few have analyzed the impact of this financial burden on patient survival.

Infections are a major cause of mortality and morbidity in patients with ALL. In our study, induction mortality (7/205, 3.4%) was mainly accounted for by infections. The major cause of treatment-related mortality in patients with Ph+ ALL is infections, especially occurring during the induction period [27,28]. Although some studies have shown a reduction in the incidence of infection, bacterial resistance often hampers treatment implementation in clinical settings [29,30]. The role of antibacterial prophylaxis during induction chemotherapy is still controversial. In this study, only 14.6% (30/205 patients) received fluoroquinolone prophylaxis during induction chemotherapy. Most patients received antibiotics while developing fever and/or infections, so the efficacy and safety of antibacterial prophylaxis could not be confirmed. Large randomized controlled trials are needed to confirm the validity of the approach to induction chemotherapy for ALL described in the present study.

Patients with Ph+ ALL are mostly older, have a high WBC count, are at risk of CNS involvement, and are more likely to relapse with chemotherapy alone [31]. Therefore, allo-HSCT is recommended for patients with Ph+ ALL who have achieved CR when possible. Although the advent of TKIs has changed the management of patients with Ph+ ALL, chemotherapy combined with TKIs has been widely used to treat these patients, improving the CR and long-term survival time and reducing the risk of relapse [32], bringing into question the status of allo-HSCT in the treatment of Ph+ ALL. However, several national and international studies still demonstrate the survival benefit of allo-HSCT compared to combination chemotherapy in both the pre- and post-TKIs eras [33,34]. In an analysis of 145 patients (median age, 37; range, 14–65 years) with Ph+ ALL at the Peking University People’s Hospital treated with imatinib in combination with chemotherapy during the induction phase, 57.9% (n = 77) of patients underwent allo-HSCT after remission, and the 4-year cumulative relapse, DFS, and OS rates in the transplant groups were 29.4%, 60.9%, and 69.2%, respectively, a significant advantage over the non-transplant group, especially in those with persistent minimal residual disease level [35]. In our study, OS and DFS were significantly better in the transplant group than in the non-transplant group. Only 27.8% of patients underwent allo-HSCT, of whom six (10.9%) died of relapse, further suggesting that allo-HSCT should be the treatment of choice.

This study had some limitations. According to Anderson et al. [7,36,37], more potent TKIs, for example, nilotinib and ponatinib, used as frontline therapy together with chemotherapy to reduce minimal residual disease, significantly prolong patient survival. However, considering the small sample size of our study, the roles of second- and third-generation TKIs in combination chemotherapy were not analyzed. Moreover, patients in the transplant group were younger than patients in the non-transplant group, and the non-transplant group included more patients with advanced disease, including those with poor systemic status or refractory relapses, who were often lost to transplantation, and may have masked the efficacy of some TKIs combined with chemotherapy regimens. Taken together, TKIs combined with reduced-dose chemotherapy is a practical treatment option for patients with Ph+ ALL, since it reduces chemotherapy-related adverse effects, lowers hospital costs,
reduces the financial burden of patients, and improves patient compliance, all without affecting the effectiveness of the therapy. Moreover, this study showed that HSCT in CR1 remains a good treatment option for patients with Ph+ ALL. These findings need to be further validated by multi-center, prospective clinical studies with larger sample sizes. Additionally, the treatment of Ph+ ALL continues to face serious problems of disease relapse and drug resistance, and further studies of novel biologic agents and antileukemic regimens, including immunotherapy, will improve the outcome and prognosis of patients with Ph+ ALL.

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Data availability statement:
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data and materials support the published claims and comply with field standards. All the content has not been published elsewhere, nor is it under consideration for publication anywhere else.

ORCID
Chunping Wu http://orcid.org/0000-0002-5386-3278
Mengting Zeng http://orcid.org/0000-0001-8433-3563
Yuanzhong Chen http://orcid.org/0000-0003-1298-6391
Yong Wu http://orcid.org/0000-0002-2873-0334

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