Use of tyrosine kinase inhibitors for paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia: a systematic review and meta-analysis

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ABSTRACT

Objectives To investigate the effectiveness and safety of tyrosine kinase inhibitors (TKIs) in the management of paediatric Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL).

Design A systematic review and meta-analysis.

Data sources Electronic searches were conducted on CENTRAL, MEDLINE, EMBASE, SIOP, ASPHO, ASCO, ASH and four Chinese databases from inception to 8 March 2020. Language of publications was restricted in English and Chinese.

Eligibility criteria Prospective and retrospective comparative studies were included.

Data extraction and synthesis Two authors independently assessed and extracted data. Quality of studies was assessed by the Cochrane Collaboration’s tool and Newcastle-Ottawa Scale. Subgroup analysis was performed by comparing different types of TKIs. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results Two randomised controlled trials (RCTs) and four cohort studies enrolling 536 patients were included. For RCTs, the pooled HR was 0.68 (95% CI 0.26 to 1.78) in overall survival (OS), 0.63 (95% CI 0.28 to 1.42) in event-free survival (EFS), respectively, comparing TKI arm with non-TKI arm for treatment of paediatric Ph+ALL. There was significant difference in OS and EFS between imatinib arm and dasatinib arm (HR 2.26, 95% CI 1.02 to 5.01; HR 2.36; 95% CI 1.27 to 4.39, respectively). For cohort studies, the pooled HR was 0.25 (95% CI 0.14 to 0.47) in OS, 0.25 (95% CI 0.12 to 0.56) in EFS, respectively, comparing TKI arm with non-TKI arm. There was no significance difference in adverse drug reaction between TKI group and without TKI group (risk ratio (RR) 0.82, 95% CI 0.63 to 1.08 in RCT; RR 1.01, 95% CI 0.64 to 1.59 in cohort studies; respectively), and imatinib versus dasatinib (RR 0.97, 95% CI 0.77 to 1.23). The quality of evidence was rated as low for OS, EFS and adverse drug reaction (ADR).

Conclusions The combination of TKIs with chemotherapy is likely to improve the OS and EFS rates in paediatric Ph+ALL, and dasatinib is superior than imatinib. Large sample size and prospective controlled studies are warranted.

PROSPERO registration number CRD42018104107.

INTRODUCTION

Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ALL), which occurs in approximately 3%–5% of paediatric ALL patients, is recognised as a severe disease but leading to a dismal prognosis compared with those with Philadelphia chromosome-negative ALL.¹

In the past decades, intensive chemotherapy has been used in the treatment of paediatric Ph+ALL patients.² ³ Later, haematopoietic stem cell transplant (HSCT) in first complete remission (CR1) was considered the treatment of choice due to the improved rate of overall survival (OS) and event-free survival (EFS) than intensive chemotherapy alone. However, the mortality rate associated with transplantation was almost 50%.⁴ ⁵ Recent studies suggested that tyrosine kinase inhibitors (TKIs) targeting BCR-ABL fusion protein combined with chemotherapy may be an alternative effective therapy.⁶ In adult patients with Ph+ALL, the use of TKIs in combination with chemotherapy was capable to increase the CR and HSCT rates and improve the early outcome.⁷ In paediatric patients, the Children’s Oncology Group (COG) trial AALL0031 had shown 80% 3-year EFS for Ph+ALL patients treated with intensive chemotherapy plus continuous 340mg/
The addition of imatinib to chemotherapy has similar outcomes to HSCT, especially in patients who responded favourably. Long-term follow-up confirmed the favourable outcomes for these patients treated with imatinib plus intensive chemotherapy and HSCT seemed the favourable outcomes for these patients treated with imatinib trial. However, the trial was observational and confirmatory results are not yet available from the European intergroup study on post-induction treatment of Ph+ALL with imatinib trial.

Newer TKIs including dasatinib and nilotinib were developed for those patients with resistance to imatinib. The resistance mechanisms are commonly associated with acquiring kinase domain mutations, reduced drug availability and activation of other signalling pathways such as the SRC family kinases. Dasatinib is the more commonly used dual ABL/SRC kinase inhibitor. It can cross the blood–brain barrier to eradicate central nervous system leukaemia and play a role in most cases of imatinib resistance. For patients with BCR-ABL T315I mutation Ph+ALL, the third-generation TKI ponatinib was reported as a valuable alternative treatment option.

Incorporation of TKIs into frontline regimens for patients with newly diagnosed Ph+ALL may be the current general consensus. However, this view may not be universally accepted. It will be helpful to analyse systematically to determine if it is truly beneficial to add TKIs to conventional chemotherapy. Therefore, our objective is to investigate the current available evidence on the effectiveness and safety of TKIs in the management of paediatric Ph+ALL.

METHODS
This protocol was registered in the international PROSPERO register of systematic reviews.

Patient and public involvement
Patients and the public were not be involved in this review.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) published in the Cochrane Library, MEDLINE in PubMed, EMBASE (Ovid), the Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals (VIP) and WANFANG for English and Chinese references. The full search strategies used in this study were detailed in online supplemental file 1. Retrieval time was from the inception of the database to 8 March 2020.

The following societies of conference proceedings of annual meetings (from the inception of TKIs treatment till 8 March 2020) were scanned: 1. International Society for Paediatric Oncology (SIOP). 2. American Society for Pediatric Hematology and Oncology (ASPHO). 3. American Society of Clinical Oncology (ASCO). 4. American Society of Hematology (ASH).

Inclusion and exclusion criteria

Study designs
There were limited randomised controlled trials (RCTs) in the treatment of paediatric patients with Ph+ALL; hence, we included retrospective and prospective cohort/case-control/randomised studies. Studies that did not include a comparative group of patients, duplicate studies, abstracts and historical control studies were excluded.

Participants
All patients aged 1–18 years with Ph positive status diagnosed by cytogenetic or molecular were included. Participants with Ph negative at diagnosis but positive at relapse, more than two types of malignant neoplasm, relapse or refractory Ph+ALL were excluded.

Interventions
TKIs alone, TKIs combined with other intervention.

Comparators
Treatment without TKIs.

Outcomes
1. OS, defined as time from start of treatment to death from any cause.
2. EFS, defined as time from start of treatment to an event, such as remission failure, relapse, death from any cause, abandonment of treatment, second malignancy or to the date of last follow-up contact.
3. Adverse drug reaction (ADR), collected and scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) or other criterion by investigators and clinical research coordinators.

Data extraction
Literature search results were uploaded to EndNote V.X7. Two authors independently screened the title and abstract of all studies identified by the search strategy and obtained full articles for all potentially relevant trials. Disagreements were resolved by consensus between authors or achieved final resolution using a third-party arbitrator.

Two authors independently used a predesigned data collection form to extract data from each study. The items included: characteristics of the trial (author, country, publication year, design, etc.), participants (age, sex, etc.), interventions (dose, regimen, etc.), outcomes and length of follow-up.

Risk of bias in individual studies
Two authors independently assessed the risk of bias using a standard form. For randomised trials, we used the domain-based evaluation recommended by the Cochrane Handbook for Systematic Reviews of Intervention to address the following domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data,
bias in measurement of the outcome and bias in selection of the reported result.\textsuperscript{17} Plots of ‘Risk of Bias’ assessment were created using Review Manager V.5 (RevMan V.5). For non-randomised trials, we used the Newcastle-Ottawa Scale (NOS) items that were categorised into three broad perspectives: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.\textsuperscript{18} The maximum total score of NOS is 9 points.

**Data analysis and synthesis**

**Strategy for data analysis**

For dichotomous data, we used the risk ratio (RR) with 95% CI as the effect measure. For time-to-event data, which take into account of the number and timing of events, we summarised and analysed data using HR with their corresponding 95% CI.\textsuperscript{17} We used Parmar’s method if HR was not explicitly presented in the research.\textsuperscript{19}

**Assessment of heterogeneity**

We quantified heterogeneity using the I\textsuperscript{2} statistic, which illustrated the percentage of the variability in effect estimates resulting from heterogeneity. In the absence of significant heterogeneity (I\textsuperscript{2} less than 50%), we used a fixed-effect model for the estimation of treatment effect.\textsuperscript{17} Otherwise, we explored possible reasons for the occurrence of heterogeneity and used random-effects model.

**Data synthesis**

We entered data into the RevMan 5 software and made analyses according to the guidance provided in the Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{20} We pooled results only if both treatment groups were comparable, including the outcome definition. Otherwise, we presented a narrative summary. If different analysis methods (such as intention-to-treat analysis, as-treated analysis) are used in the evaluation of benefits between groups, we adopt the results of the intention-to-treat analysis to reduce bias.

**Assessment of reporting biases**

If we include 10 or more trials, we use funnel plots to assess biases including publication bias and other reporting biases. If there are biases, the funnel plots may be asymmetrical.

**Subgroup analysis**

Considering that different types of TKIs might affect the outcomes, we conducted a subgroup analysis.

**Grading the evidence**

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the quality of evidence.\textsuperscript{21} In the GRADE approach, RCTs start as high-quality evidence. Five factors may lead to downgrading the quality of evidence. These factors include risk of bias, inconsistency, indirectness, imprecision and publication bias. Observational studies (including cohort and case-control studies) start as low-quality evidence. Three factors may lead to upgrading the quality of evidence, and these factors are large effect, dose response and all plausible residual confounding. The quality of the evidence was rated as high, moderate, low or very low. We used GRADEpro software (GRADEpro 2011) to create a ‘Summary of findings’ table for all three outcomes listed above.

**RESULTS**

**Study selection**

Our search strategy identified 2476 references from the electronic searches and 69 from other sources. Two hundred and fifty-two duplicate publications and 1928 articles were excluded after reviewing the title and abstract because they failed to meet the inclusion criteria such as type of article, study design, population or outcome of interest. Three hundred and sixty-five articles underwent full-text review and six literature were included in the final data analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of bibliographic search was illustrated in figure 1.

**Characteristics of included studies**

Six articles\textsuperscript{10,22–26} (two prospective randomised open-label controlled trials and four retrospective cohort studies) were included in our analysis. Five studies\textsuperscript{10,22–26} evaluated the efficacy and safety of TKIs in association with multidrug chemotherapy or chemotherapy alone in paediatric patients with Ph+ALL. Two of these studies\textsuperscript{25,26} came from the same research institution. Among them, one study\textsuperscript{25} retrospectively analysed 53 cases between 2008 and 2013. The other\textsuperscript{26} retrospectively analysed 92 cases between 2003 and 2012. One RCT\textsuperscript{22} compared the effect of dasatinib versus imatinib. Overall, 536 children aged 1–18 years with a confirmed diagnosis of Ph+ALL contributed to the analysis. The chemotherapy regimen was modelled on Berlin-Frankfurt-Munster high-risk arm, the Chinese Childhood Leukemia Group ALL high-risk arm and the Chinese Children’s Cancer Group ALL intermediate-risk arm. TKI drugs included first-generation imatinib and second-generation dasatinib. Patients were prescribed oral imatinib (260–340 mg/m\textsuperscript{2}/day) or dasatinib (40–80 mg/m\textsuperscript{2}/day) on day 8, day 22 of remission induction or the end of induction. The exposure of TKIs ranged from 56 days to the end of therapy. Table 1 described the detailed characteristics of the studies included in this meta-analysis.

**Risk of bias assessment in included studies**

Figure 2 provided quality assessment of RCTs and table 2 described quality assessment of non-RCTs. In the two prospective trials, stratified randomisation was done centrally with web-based randomisation system and both were open label. Therefore, the random sequence generation was low risk while the blindness was high risk. All studies had low risk bias in incomplete outcome
data, selective reporting and other issues. In four cohort studies, the NOS methodological score was 7–8 points. In the selection section, both exposed cohort and unexposed cohort were drawn from the same source of participant. Data was collected and retrospectively reviewed from medical records. Outcome was not present at the beginning of all studies. In the comparability section, the three studies did not describe important confounding factors, except for TKI treatment between exposed and unexposed cohorts among paediatric Ph+ALL. In the outcome section, one study was followed up for 2 years, which might not be long enough for outcomes to occur. One study did not describe the patient’s loss of follow-up. Overall, the retrospective research has high-quality NOS scores. Therefore, the risk of bias of RCTs was rated as moderate and the cohort studies were rated as low.

**TKI versus non-TKI**

**Overall survival**

Four studies (one RCT, three cohort studies) with a total of 294 patients were included in the meta-analysis of OS for paediatric Ph+ALL patients. The pooled HR of OS in patients with TKI use was 0.68 (95% CI 0.26 to 1.78, p=0.43) in RCT and 0.25 (95% CI 0.14 to 0.47, p<0.05) in cohort studies, respectively. Figure 3 showed the forest plot of the included studies.

**Event-free survival**

The primary outcome in one RCT was disease-free survival (DFS) because the group only included good-risk patients in CR1 and poor-risk patients were not included. Therefore, in this meta-analysis, DFS was considered equivalent to EFS. Four studies (one RCT, three cohort studies) reported the EFS. Because Liu et al covered a longer period with larger number of patients, their results for EFS were included and those from Guo et al were excluded. Finally, a total of 200 patients were included. The pooled HR of EFS in Ph+ALL patients using TKI was 0.63 (95% CI 0.28 to 1.42, p=0.26) in RCT and 0.25 (95% CI 0.12 to 0.56, p<0.05) in cohort studies, respectively. Figure 4 showed the forest plot of the included studies.

**Adverse drug reaction**

Three studies (one RCT, two cohort studies) reported serious ADR in patients with Ph+ALL. Heterogeneity in the cohort studies was significant (I²=58%). We used a random-effect model for the estimation of treatment effect. In RCT, myelosuppression was the main cause of ADR. The proportions of patients with the most commonly reported serious ADR did not differ substantially between imatinib group and non-imatinib group (p=0.64). The most common serious ADR was infection, including fungal infection, localised infection and

**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. This flow diagram illustrated the results of search and the process of screening and selecting studies for inclusion and the reasons for exclusions in this review. Ph+ALL, Philadelphia chromosome-positive acute lymphoblastic leukaemia; TKI, tyrosine kinase inhibitor.

The pooled RR of serious ADR in patients with TKI use was 0.82 (95% CI 0.63 to 1.08, p=0.16) in RCT. Result of the cohort studies was consistent with RCT. The pooled RR was 1.01 (95% CI 0.64 to 1.59, p=0.12) (figure 5).

Different TKIs

One RCT22 with a total of 189 Ph+ALL children compared the OS, EFS and ADR of oral imatinib at a daily dosage of 300 mg/m² versus dasatinib at a daily dosage of 80 mg/m² in combination with an intensive chemotherapy backbone. The HR of OS was 2.26 (95% CI 1.27 to 4.01, p=0.01). There was no significant difference in the frequency of adverse events in each arm. Approximately 5% of the patients in each arm had disseminated fungal infections. The incidence of pleural effusion was 2% in the imatinib group and 4% in the dasatinib group. However, this difference was also not significant (p=0.44).

Table 1  Main characteristics of the studies included in this meta-analysis

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Setting</th>
<th>Time (years)</th>
<th>TKI start time</th>
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<tr>
<td>1 Biondi et al 201220</td>
<td>Europe</td>
<td>2004.1–2009.12</td>
<td>1–18</td>
<td>Post induction, good risk</td>
<td>46 Imatinib (300 mg/m²/day) + chemotherapy</td>
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<tr>
<td>2 Shen et al 202022</td>
<td>China</td>
<td>2015.1–2018.9</td>
<td>7.8 (0–18)</td>
<td>After diagnosis, usually on D8 of remission induction</td>
<td>97 Imatinib (300 mg/m²/day) + chemotherapy</td>
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<td>Cohort studies</td>
<td></td>
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<tr>
<td>1 Zhang et al 201937</td>
<td>China</td>
<td>2008.1–2012.12</td>
<td>8.26 (2–12)</td>
<td>Post induction</td>
<td>54 Imatinib (0.6 g/day) + chemotherapy</td>
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<tr>
<td>2 Wang and Jin 201624</td>
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<td>2008.10–2016.1</td>
<td>9 (3–15)</td>
<td>Post induction</td>
<td>9 Imatinib (260–340 mg/m²/day) or DAS (40–80 mg/m²/day) + chemotherapy</td>
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<td>4 Liu and Zhu 201326</td>
<td>China</td>
<td>2003.10–2012.12</td>
<td>11 (2–17)</td>
<td>D15 of remission induction</td>
<td>38 Imatinib (260–340 mg/m²/day) + chemotherapy</td>
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</table>

ADR, adverse drug reaction; EFS, event-free survival; OS, overall survival; TKI, tyrosine kinase inhibitors.

Figure 2  The quality assessment of randomised clinical trials. This plot is created by the software of RevMan V.5.3. It illustrated the quality of included randomised clinical trials with each of the judgement (low risk, high risk or unclear risk of bias).

Table 1  Main characteristics of the studies included in this meta-analysis
GRADE assessment
The evidence provided by the RCTs was low quality for both comparison of TKI-based chemotherapy regimens versus chemotherapy alone, and the comparison of imatinib and dasatinib. The quality was downgraded by the risk of bias and imprecision due to high risk in blindness and wide 95% CI for effect estimates. Meanwhile, the evidence that the cohort studies provided to this review was of moderate quality. It was upgraded by the large magnitude of treatment effect. A summary of the GRADE assessment was shown in online supplemental file 2.

DISCUSSION
TKIs have revolutionised the management of Ph+ALL patients. The National Comprehensive Cancer Network has recommended the use of TKI-based chemotherapy regimens for the adolescents and adults with Ph+ALL.7 Systematic review by Warraich et al comprising 18 prospective and retrospective studies with 462 participants showed that utilisation of TKI (all generations) post allo-HSCT for adults patients in CR1 improved OS when given as prophylactic or pre-emptive regimen.27 However, it is unclear whether this observed improvement of TKIs is significant in children. To our knowledge, our research is the first systematic review to investigate whether adding TKIs to conventional chemotherapy is indeed beneficial in paediatric Ph+ALL. Our research applied strict inclusion criteria and only those studies had comparative group of patients. Eventually, a meta-analysis was performed including one RCT and four non-RCTs with or without TKI treatment, and one RCT comparing dasatinib and imatinib in paediatric Ph+ALL.

TKI versus non-TKI
The included randomised trial EsPhALL 200410 demonstrated that imatinib in conjunction with intensive chemotherapy might be beneficial for treating children with Ph+ALL. The 4-year DFS in good-risk patients who received intensive chemotherapy and discontinuous post-induction imatinib 300 mg/m2/day increased by approximately 20% compared with patients receiving chemotherapy alone (75.2% vs 55.9%). The long-term follow-up outcome showed 5-year DFS in the imatinib arm of 75.5% vs 61.4% in the no imatinib arm (p=0.20).28 However, the benefit was not significant. The pooled

Table 2 The quality assessment in cohort studies

<table>
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<tr>
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<th>Zhang et al23</th>
<th>Wang and Jin24</th>
<th>Guo et al25</th>
<th>Liu and Zhu26</th>
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<td>Demonstration that outcome of interest was not present at start of study</td>
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<td>Assessment of outcome</td>
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<tr>
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</table>

NOS score 8 8 8 7
NOS, Newcastle-Ottawa Scale.

Figure 3 Meta-analysis of the effectiveness of tyrosine kinase inhibitors (TKIs) on overall survival, TKI versus non-TKI. The square data markers represent HR; horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using fixed-effects meta-analysis. A diamond data marker represents the overall HR and 95% CI for the outcome of interest. RCT, randomised controlled trial.
HR was 0.68 (95% CI 0.26 to 1.78) in OS, 0.63 (95% CI 0.28 to 1.42) in EFS, respectively, comparing TKI arm with non-TKI arm in combination with intensive chemotherapy. But the results were reversed by the meta-analysis including four high-quality cohort studies (NOS score ≥7). In these cohort studies, the pooled HR was 0.25 (95% CI 0.14 to 0.47) in OS, 0.25 (95% CI 0.12 to 0.56) in EFS, respectively, comparing TKI arm with non-TKI arm. The different results may be owing to the various regimen of timing and dosage of TKIs and the interference of HSCT during treatment.

In the EsPhALL 2004 study, imatinib was used at a dose of 300 mg/m² for 126 days after induction. In cohort studies, imatinib 260–340 mg/m² was started after induction or earlier on day 15 of remission induction. Most of the cohort studies have continued to use TKIs throughout chemotherapy unless severe infections, intolerance to TKIs or neutropenia with fever. Early and continuous exposure of imatinib may improve outcomes of OS and EFS. However, a prospective, open-label, single-arm clinical trial EsPhALL2010, the successor of EsPhALL 2004, administrated imatinib 300 mg/m²/day continuously from day 15 of induction, displayed similar results to EsPhALL2004.29

The outcome of comparison between TKIs with chemotherapy versus HSCT treatment was limited in the current studies. The investigators from the COG reported the long-term outcome of paediatric Ph+ALL, showing the equivalent efficacy between the patients who received at least 280 continuous days of imatinib and those who underwent HSCT.9 Two other retrospective studies indicated that there was no significant difference in OS or EFS between HSCT and chemotherapy with TKI treatment, which was consistent with COG study.30 31 In the included study EsPhALL 2004,10 about 80% of the patients had HSCT, 37 out of 46 in the imatinib group and 32 out of 44 in the non-imatinib group. This might lead to no statistical difference between the two groups of results in this RCT. However, the difference in the treatment outcomes of TKI combined with chemotherapy and HSCT for paediatric Ph+ALL has not been proven.

Different TKIs

In previous studies of imatinib, EFS was approximately 60% at 5 years, but resistance and relapse was common. Disappointingly, COG trial (AALL0622) for treatment of paediatric Ph+ALL did not prove the superior of dasatinib over imatinib. OS and EFS were similar in the...
preceding trials using imatinib.32 Another COG trial (AALL1122) using dasatinib 60 mg/m^2/day is ongoing.33 Now, Shen et al22 reported different outcomes from the first randomised trial directly comparing dasatinib with imatinib. The 4-year OS rate in the dasatinib group was significantly higher than in the imatinib group (88.4% vs 69.2%; p=0.04). The 4-year EFS rate for the 92 dasatinib-treated patients was 71.0%, significantly better than the 48.9% for the 97 imatinib-treated patients (p=0.005). In these 189 eligible patients, there was significant difference in OS and EFS between dasatinib arm and imatinib arm (HR 2.26, 95% CI 1.02 to 5.01; HR 2.36, 95% CI 1.27 to 4.39; respectively). It is worth noting that the dose of dasatinib is higher than COG trials and longer follow-up is required to assess whether they represent significant improvement.

Adverse drug reaction
The dosing of imatinib (260–570 mg/m^2/day) and dasatinib (50–110 mg/m^2/day) is well tolerated in children and adolescents with leukaemia.34 35 In the included studies, the daily dose of imatinib and dasatinib 260–340 mg/m^2 and 40–80 mg/m^2 did not increase the chemotherapy-related toxicity and side effects such as cytopenia and pleural effusions, suggesting that imatinib or dasatinib combined with intensive chemotherapy was well tolerated.36 There was no significance difference in severe ADR between TKI arm and without TKI arm (RR 0.82, 95% CI 0.63 to 1.08 in RCT; RR 1.01, 95% CI 0.64 to 1.59 in cohort studies; respectively). Similarly, no significant difference in the frequency of severe ADR was detected between dasatinib and imatinib arm (RR 0.97, 95% CI 0.77 to 1.25).

Quality of the evidence
The overall quality of the evidence assessed by the GRADE approach was low. Due to the rarity of Ph+ALL in this age group and the dramatic improvement in survival with TKIs reported in observational researches, data from blinded controlled studies are very scarce. In addition, the sample size was small, making the 95% CIs wide. For this reason, we limited confidence in the estimation of effect values. Further studies are likely to have an important impact on our confidence in the estimated effect and may change our estimate.

Limitations
This meta-analysis has the following limitations. First, the included studies are limited by the small sample size. In addition, HSCT is also a very important factor that needs to be taken into consideration. Even though the addition of the TKIs had improved the 5-year EFS and OS rates, but about 40–80% patients received transplant. Lastly, this is a meta-analysis of prospective and retrospective studies, which has its inherent limitations. Therefore, we did not combine the results of different types of studies.

CONCLUSIONS
Overall, low-quality studies suggested that TKIs combined with intensive chemotherapy were likely to improve the OS and EFS rates in paediatric Ph+ALL, and the second-generation TKI dasatinib was superior to first-generation imatinib. The ADRs of TKIs could be tolerated.

This review highlights the need for future large sample size research for the use of TKIs in the treatment of paediatric Ph+ALL. Further prospective controlled studies are warranted to address remaining questions relating to the appropriate time to use TKIs during chemotherapy, as well as the role of HSCT in the management of these patients.

REFERENCES


Appendix 1: Search strategies for English databases

<table>
<thead>
<tr>
<th>Databases</th>
<th>Search strategies</th>
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<tr>
<td>PubMed</td>
<td>#1 &quot;Philadelphia Chromosome&quot;[Mesh]) OR &quot;Ph Chromosome positive&quot; OR &quot;Philadelphia Chromosome positive&quot; #2 &quot;Precursor Cell Lymphoblastic Leukemia-Lymphoma&quot;[Mesh] OR &quot;Acute Lymphoblastic Leukemia&quot; OR &quot;Acute Lymphocytic Leukemia&quot; OR &quot;Acute Lymphoid Leukemia&quot; OR &quot;Acute Lymphoblastic Lymphoma&quot; #3 &quot;Imatinib Mesylate&quot;[mesh] OR &quot;imatinib&quot;[mesh] OR &quot;Imatinib&quot; OR &quot;Dasatinib&quot; OR &quot;nilotinib&quot; OR &quot;ponatinib&quot; OR &quot;tyrosine kinase inhibitor&quot; OR &quot;TKI&quot; #4 #1 AND #2 AND #3</td>
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<td>EMBASE</td>
<td>#1 &quot;Philadelphia 1 chromosome&quot;[thesaurus] OR &quot;Philadelphia 1 chromosome positive&quot; OR &quot;Philadelphia Chromosome positive&quot; #2 &quot;acute lymphoblastic leukemia&quot;[thesaurus] OR &quot;Acute Lymphoblastic Leukemia&quot; OR &quot;Acute Lymphocytic Leukemia&quot; OR &quot;Acute Lymphoid Leukemia&quot; OR &quot;Acute Lymphoblastic Lymphoma&quot; #3 &quot;protein tyrosine kinase inhibitor&quot;[thesaurus] OR &quot;Imatinib&quot; OR &quot;Imatinib Mesylate&quot; OR &quot;Dasatinib&quot; OR &quot;nilotinib&quot; OR &quot;ponatinib&quot; OR &quot;tyrosine kinase inhibitor&quot; OR &quot;TKI&quot; #4 #1 AND #2</td>
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<tr>
<td>Cochrane library</td>
<td>#1 &quot;Philadelphia Chromosome&quot;[Mesh]) OR &quot;Ph1 Chromosome positive&quot; OR &quot;Philadelphia Chromosome positive&quot; #2 &quot;Precursor Cell Lymphoblastic Leukemia-Lymphoma&quot;[Mesh] OR &quot;Acute Lymphoblastic Leukemia&quot; OR &quot;Acute Lymphocytic Leukemia&quot; OR &quot;Acute Lymphoid Leukemia&quot; OR &quot;Acute Lymphoblastic Lymphoma&quot; #3 &quot;Imatinib Mesylate&quot;[mesh] OR &quot;imatinib&quot;[mesh] OR &quot;Imatinib&quot; OR &quot;Dasatinib&quot; OR &quot;nilotinib&quot; OR &quot;ponatinib&quot; OR &quot;tyrosine kinase inhibitor&quot; OR &quot;TKI&quot; #4 #1 AND #2 AND #3</td>
</tr>
</tbody>
</table>

Appendix 2: Search strategies for Chinese databases

<table>
<thead>
<tr>
<th>Databases</th>
<th>Search strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBM</td>
<td>全部字段&quot;费城染色体&quot;and&quot;急性淋巴细胞白血病&quot;</td>
</tr>
<tr>
<td>CNKI</td>
<td>FT=&quot;费城染色体&quot; and FT=&quot;TKI&quot;+&quot;酪氨酸激酶抑制剂&quot;+&quot;伊马替尼&quot;+&quot;尼洛替尼&quot;+&quot;达沙替尼&quot;+&quot;帕纳替尼&quot;and FT=&quot;ALL&quot;+&quot;急性淋巴细胞白血病&quot;+&quot;急淋&quot;</td>
</tr>
<tr>
<td>VIP</td>
<td>U=&quot;费城染色体&quot;and&quot;急性淋巴细胞白血病&quot;</td>
</tr>
<tr>
<td>WANFANG</td>
<td>全部字段&quot;费城染色体&quot;and&quot;急性淋巴细胞白血病&quot;</td>
</tr>
</tbody>
</table>
Appendix 3: Summary of findings for the main outcomes.

TKI versus Non-TKI for pediatric Ph+ALL in randomized controlled trial

**Patient or population:** patients with pediatric Ph+ALL  
**Intervention:** TKI with chemotherapy  
**Comparison:** chemotherapy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk chemotherapy</td>
<td>Corresponding risk TKI with chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall survival</td>
<td>727 per 1000 (287 to 901)</td>
<td>587 per 1000 (234 to 741)</td>
<td>HR 0.68 (0.26 to 1.78)</td>
<td>90 (1 study)</td>
<td>⊕⊕ ⊥⊥⊥⊥ ⊗⊥⊥ ⊥⊥ ⊗ ⊥</td>
</tr>
<tr>
<td>Follow-up: mean 3.1 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>event free survival</td>
<td>614 per 1000 (234 to 741)</td>
<td>451 per 1000 (234 to 741)</td>
<td>HR 0.63 (0.28 to 1.42)</td>
<td>90 (1 study)</td>
<td>⊕ ⊤ ⊤ ⊤ ⊤ ⊤ ⊤ ⊤</td>
</tr>
<tr>
<td>Follow-up: mean 3.1 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse drug reaction</td>
<td>774 per 1000 (488 to 836)</td>
<td>635 per 1000 (488 to 836)</td>
<td>RR 0.82 (0.63 to 1.08)</td>
<td>89 (1 study)</td>
<td>⊤ ⊤ ⊤ ⊤ ⊤ ⊤ ⊤</td>
</tr>
<tr>
<td>Follow-up: mean 3.1 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1 blindness was high risk
2 not applicable
### TKI versus Non-TKI for pediatric Ph+ALL in cohort studies

**Patient or population:** patients with pediatric Ph+ALL  
**Intervention:** TKIs  
**Comparison:** Non-TKIs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall survival</td>
<td>Non-TKIs 340 per 1000 (56 to 177)</td>
<td>TKIs 99 per 1000</td>
<td>HR 0.25 (0.14 to 0.47)</td>
<td>204 (3 studies)</td>
<td>moderate</td>
</tr>
<tr>
<td>event free survival</td>
<td>Non-TKIs 95 per 1000 (12 to 55)</td>
<td>TKIs 25 per 1000</td>
<td>HR 0.25 (0.12 to 0.56)</td>
<td>110 (2 studies)</td>
<td>moderate</td>
</tr>
<tr>
<td>adverse drug reaction</td>
<td>Non-TKIs 561 per 1000 (359 to 891)</td>
<td>TKIs 566 per 1000</td>
<td>RR 1.01 (0.64 to 1.59)</td>
<td>147 (2 studies)</td>
<td>moderate</td>
</tr>
</tbody>
</table>

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio.

---

**GRADE Working Group grades of evidence**

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- **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
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- **Very low quality:** We are very uncertain about the estimate.
the magnitude of the treatment effect is large

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk Imatinib</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall survival</td>
<td>880 per 1000 (885 to 1000)</td>
<td>992 per 1000 (885 to 1000)</td>
<td>HR 2.26 (1.02 to 5.01)</td>
<td>189 (1 study)</td>
<td>⊕ ⊕ ⊝ ⊝ low1,2,3</td>
</tr>
<tr>
<td>Follow-up: mean 26.4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>event free survival</td>
<td>707 per 1000 (789 to 995)</td>
<td>945 per 1000 (789 to 995)</td>
<td>HR 2.36 (1.27 to 4.39)</td>
<td>189 (1 study)</td>
<td>⊕ ⊕ ⊝ ⊝ low1,2,3</td>
</tr>
<tr>
<td>Follow-up: mean 26.4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse drug reaction</td>
<td>596 per 1000 (459 to 733)</td>
<td>578 per 1000 (459 to 733)</td>
<td>RR 0.97 (0.77 to 1.23)</td>
<td>189 (1 study)</td>
<td>⊕ ⊕ ⊝ ⊝ low1,2,4</td>
</tr>
<tr>
<td>Follow-up: mean 26.4 months</td>
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</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

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- **Very low quality:** We are very uncertain about the estimate.
Supplemental material

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1 the blindness was high risk
2 not applicable
3 the 95% CI includes appreciable benefit or harm
4 the 95% CI for effect estimates were wide