Comparison of conventional chemotherapy regimens in adults with acute lymphoblastic leukemia: a systematic review and pooled survival analysis

Sheng-Feng Lin[1,2], Ping-Hsuan Hsieh[1], Yi-Ying Wu[3], Yu-Guang Chen[3,4]

1. School of Pharmacy, National Defense Medical Center, Taipei, Taiwan, R.O.C.
2. Department of Pharmacy, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.
3. Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, R.O.C.
4. School of Medicine, National Defense Medical Center, Taipei, Taiwan, R.O.C.

Background

- According to the information in National Comprehensive Cancer Network (NCCN) guidelines, traditional chemotherapy regimens are the primary treatment **for Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL)**. Acute lymphoblastic leukemia (ALL) primarily affects children, with an incidence rate of 75%, and treatment outcomes in children have shown significant success.
- Despite the availability of various treatment options for adult patients, treatment outcomes in adults remain unsatisfactory, and no comprehensive comparison of traditional chemotherapy regimens for adult ALL patients has been conducted in the past literature.
- This study aims to identify the **frontline chemotherapy regimen** that produces the best response in adult ALL patients. To achieve this goal, we conducted a **systematic review and pooled survival analysis** to evaluate the impact of various chemotherapy regimens on survival rates.

Methods

The systematic review and pooled survival analysis were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

- **Eligibility criteria** (i) patients: adults with Philadelphia chromosome-negative ALL, (ii) intervention: treatment with conventional chemotherapy regimens, and (iii) outcomes: data on complete remission (CR) rate, OS, event-free survival (EFS), and disease-free survival (DFS).
- **Search strategy and databases** Search filters were adapted to capture potentially relevant studies from OVID-Medline and PubMed until June 7, 2024.
- **Quality assessment** Clinical trials were assessed using the Downs and Black checklist, while randomized controlled trials (RCT) were evaluated using the Revised Cochrane risk-of-bias tool (RoB 2.0).
- **Pooled survival analysis** We used software to reconstruct individual patient data and analyzed the reconstructed data to calculate the variance, mean, and standard deviation of each treatment regimens. Therefore, effectiveness outcomes were summarized according to each treatment regimens.

Results

- **Study selection** Overall, 7 studies were included in the review (Figure 1). These studies consist of 6 clinical trials and 1 RCT. Five different traditional chemotherapy treatment regimens were reported, including CALGB 10403, CALGB 8811, Hyper-CVAD, GRAALL 2005, and GRAALL-2003.

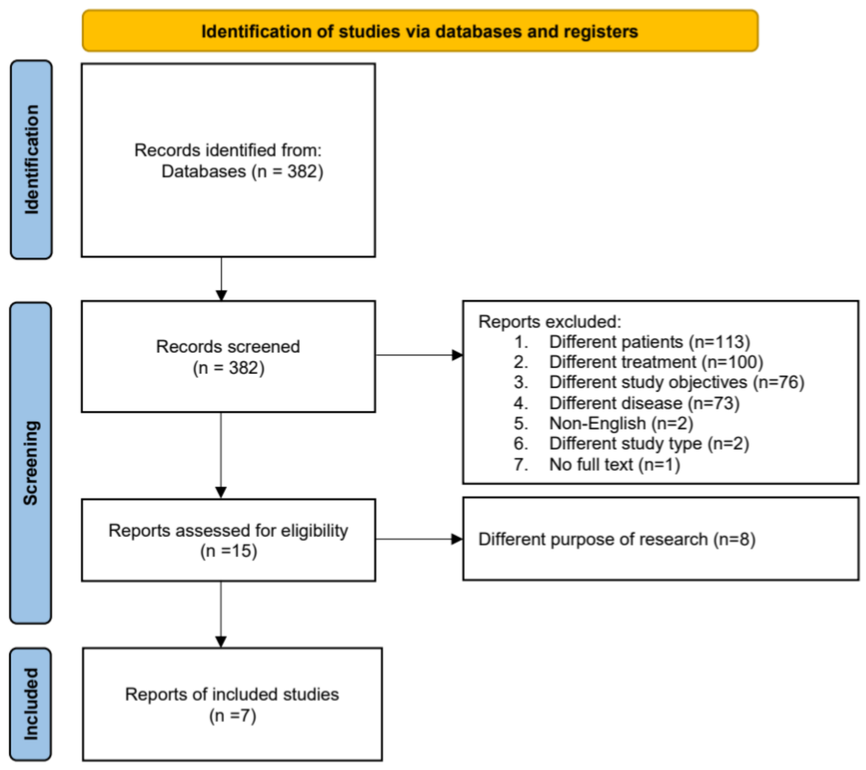

Figure 1. PRISMA flow diagram

- **Quality assessment**
  - Downs and Black quality checklist was used for clinical trials, while RoB 2.0 was applied to RCT.
  - Clinical trials: Five of these studies were deemed high quality (scores >21), and one study was considered moderate quality (score >14), as presented in Figure 2.

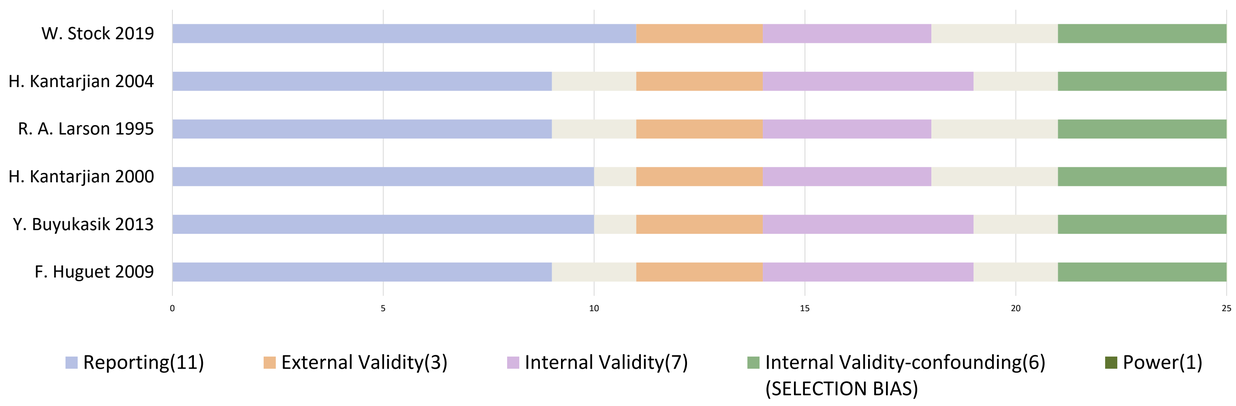

Figure 2. Bar chart illustrating quality assessment of clinical trials studies by using Downs and Black checklist

  - RCT: 12 out of the 16 questions in RoB 2.0 checklist were rated as low risk of bias, while the remaining 4 questions lacked sufficient information.

Based on these results, the study was deemed to have an overall low risk of bias for its outcomes.

- **Outcomes**
  - Complete remission (CR)

The CR rates for different regimens are as follows: Hyper-CVAD showed rates of 84% to 92% across three studies, CALGB 8811 had rates of 85% and 74% in different subsets, CALGB 10403 had 89%, and GRAALL-2005 and GRAALL-2003 achieved 92% and 93%, respectively.

Table 1. Complete remission rate among treatment regimens

Treatment Regimen	CR Rate (%)	Patient Count (No. of CR / Total)
Hyper-CVAD	84%	48/57
	92%	264/288
	91%	185/204
CALGB 8811	85%	167/197
	74%	48/65
CALGB 10403	89%	263/295
GRAALL-2005	92%	723/787
GRAALL-2003	93%	210/225

  - Overall survival (OS)

At 12 months, the highest OS rate is seen with CALGB 10403 (87.0%), followed by GRAALL 2005 (82.6%), GRAALL 2003 (81.8%), Hyper-CVAD (72.6%), and CALGB 8811 (71.4%). By 48 months, survival rates decline: CALGB 10403 remains the highest at 67.2%, followed by GRAALL 2005 (60.5%), GRAALL 2003 (58.2%), CALGB 8811 (44.7%), and Hyper-CVAD (43.1%).

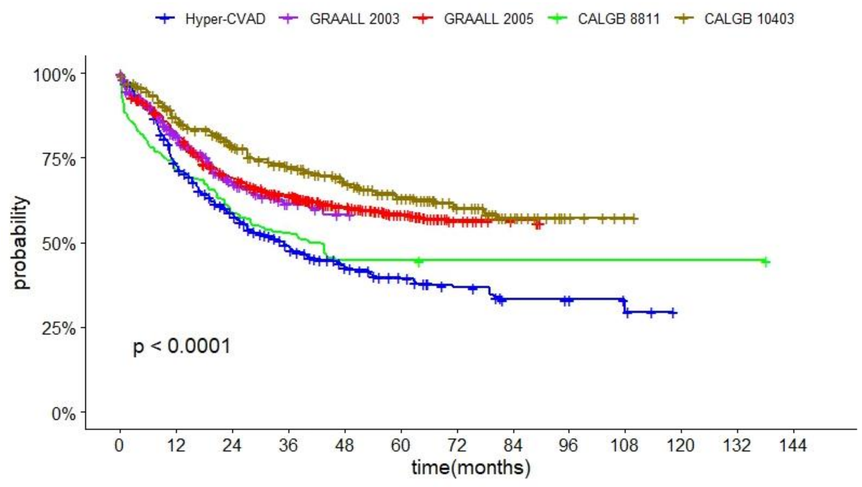

Figure 3. Kaplan-Meier curves of overall survival between five treatment regimens

  - Event-free survival (EFS)

At 12 months, the highest EFS is seen with CALGB 8811 (84.6%), followed by CALGB 10403 (76.7%), GRAALL 2005 (73.0%), GRAALL 2003 (70.7%), and Hyper-CVAD (52.6%). At 48 months, CALGB 8811 and CALGB 10403 maintain strong EFS rates of 58.5% and 53.0%, while GRAALL 2005 and GRAALL 2003 show 54.4% and 55.7%. Hyper-CVAD drops to 24.6%.

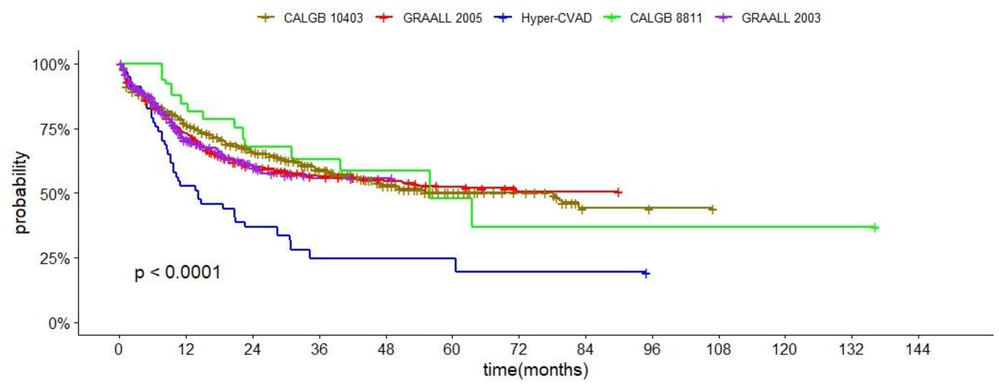

Figure 4. Kaplan-Meier curves of event-free survival between five treatment regimens

Conclusions

The comprehensive synthesis shows that the CALGB 10403 regimen has the best overall survival rate and superior long-term event-free rate. If patients do not experience serious side effects, CALGB 10403 can be recommended for long-term treatment for adults with ALL.

Correspondent to: Sheng-Feng Lin. Email: jd960403@gmail.com