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Evidence Summary 12-16 ARCHIVED

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in Acute Lymphoblastic Leukemia

M. Sabloff, C. Agbassi, K. Howson-Jan

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Evidence Summary Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original June 22, 2016	2011 to Nov 2015	Full Report	Web publication	N.A.
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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated Programs is editorially independent from the OMHLTC.

OBJECTIVES AND RESEARCH QUESTIONS

The objective of this evidence summary is to systematically review the available evidence with respect to the following two topics in the treatment of acute lymphoblastic/lymphocytic leukemia (ALL):

- The use of pediatric-inspired regimens in the adolescent and young adult (AYA) population.
- The use of tyrosine kinase inhibitors (TKIs) in adult patients with Philadelphia chromosome-positive (Ph+) ALL.

From these objectives, the following research questions were derived to direct the search for available evidence to inform decision making:

1. Compared with adult regimens, is there a benefit in the use of pediatric-inspired regimens for the management of non-pediatric patients with ALL?
2. In the management of Ph+ ALL patients, does the addition of a TKI to the treatment regimen improve patient outcomes?

INTRODUCTION

Pediatric-Inspired Regimens in AYA

ALL is a cancer of the white blood cells (WBCs) primarily affecting the bone marrow. In ALL, the hematopoietic stem cells undergo malignant transformation into immature and poorly differentiated cells. The rapid proliferation of these immature cells obliterates the normal bone marrow resulting in suppression of normal hematopoiesis. Symptoms are usually nonspecific and result from the abnormal elevation or reduction of blood cell lines. The

immature cells also travel through the blood stream to infiltrate other organs such as the liver, spleen, lymph nodes, central nervous system (CNS), kidneys, and gonads. Although acute leukemia is a rare disease, it is the most common cancer in children and young adults. There are a number of identified risk factors, including environmental or occupational exposure to high dose ionizing radiation and benzene, prenatal radiation exposure and the presence of genetic conditions such as Down syndrome, Shwachman syndrome, Bloom syndrome, neurofibromatosis, and ataxia telangiectasia. ALL accounts for 80% of acute leukemia in the pediatric population [1,2]. ALL can occur at any age from neonates to the elderly, but the onset is usually before 20 years of age. The highest incidence of ALL occurs in Hispanic and Caucasian male children between the ages of two and three years.

The presence of the Philadelphia chromosome (Ph+) is the most common cytogenic abnormality found in ALL patients [3]. The proportion of Ph+ cases increases with age. It is less frequently detected in children, but the incidence is estimated to be 20% to 40% in adults [4,5]. The overall prognosis for Ph+ ALL is very poor and, because of the high-risk nature of the disease, the treatment strategy is usually considered separately from that of Ph- ALL patients. Ph+ patients are offered allogenic hematopoietic stem cell transplantation (HSCT) in first remission and in the past decade, TKIs have emerged as potent therapy agents in the management of these patients. Some trials have evaluated the efficacy of imatinib in patients with relapsed or refractory Ph+ ALL.

Among individuals 15 to 39 years of age, who are generally classified as the AYAs, ALL has been shown to be less prevalent [6]. Despite this, the AYAs have become an important population of interest, in part because they have been poorly represented in both the pediatric and adult literature, which has therefore created debate over the appropriate approach to the treatment of this group. Treatment options for patients with ALL are determined primarily by the patient's age, co-morbidities, and the karyotypic changes. Pediatric and adult regimens vary considerably in intensity. Pediatric regimens consist of delivering therapy over a long period of time whereas adult regimens consist of intensive administration of myelosuppressive agents and allogenic HSCT for the first remission [7]. Treatment outcomes in ALL have improved greatly from being universally fatal, to current survival rates of greater than 90% in pediatric patients. However, achieving comparable survival rates in older patients is still a challenge because of a number of factors including, but not limited to, co-morbidities, differential metabolism of medications, and poor tolerance to the intensity of pediatric regimens. The AYA population would be expected to be more tolerant to pediatric doses compared with the older cohort. However, due, in part, to community resources (i.e., proximity of an adult versus a pediatric hospital to the patient) the AYAs have been treated either under the supervision of a pediatric protocol or an adult protocol. The results of a number of retrospective studies comparing the outcomes of the AYAs treated either at an adult centre or a pediatric centre, have shown that treating this population with pediatric regimens presents a superior survival outcome, with a five-year event-free survival of 70% compared with 30% to 45% when adult regimens are used. Based on this premise, the authors developed this evidentiary base to help inform decision making for this patient population in clinical practice.

TARGET POPULATION

This is targeted to adult patients, defined as those 16 years and older, with ALL.

INTENDED PURPOSE

The purpose of this evidence summary is to inform care decisions regarding the use of ALL pediatric regimens in the treatment of AYAs with ALL.

INTENDED USERS

This evidence summary is targeted for all people involved in systemic therapy treatment of patients with ALL.

METHODS

This evidence summary was developed by a Working Group consisting of hematologists and a health research methodologist at the request of CCO's Specialized Services Oversight Program.

The Working Group was responsible for reviewing the identified evidence and drafting the summary. Conflict of interest declarations for all authors are summarized in Appendix I and were managed in accordance with the *PEBC Conflict of Interest Policy*.

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines (not otherwise considered suitable for adaptation or endorsement) were also considered eligible for inclusion. The Ovid interface was used to search MEDLINE and EMBASE for existing systematic reviews in this topic area. The Cochrane Database of Systematic Reviews was also searched, using a combination of search terms that included pediatric-inspired, adolescents and young adults (AYA), tyrosine kinase inhibitors (TKI), Philadelphia chromosome positive (Ph+), and ALL. The search was limited to systematic reviews published since January 2005 and up to September December 2015 because the authors believe that the use of pediatric-inspired therapy in the AYAs has only become popular within the past decade.

Identified systematic reviews were further evaluated based on their clinical content and their relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool [8] to determine their methodological quality.

Search for Primary Literature

Literature Search Strategy

In addition to the selection of suitable systematic reviews, a search for primary literature in MEDLINE and EMBASE was conducted. The original protocol suggested this search should go back to January 1995. However, after the search for systematic reviews (described above) was conducted, January 2011 was chosen as the earliest time point for inclusion. Existing systematic reviews were identified that covered the literature for pediatric-inspired regimens prior to 2011, and the Working Group agreed that it was very unlikely relevant studies of TKIs in PH+ ALL would have been published prior to 2011 as well. Details of the literature search strategy can be found in Appendix I. The Cochrane Library was also searched for potential randomized controlled trials (RCTs) in this topic area. The reference lists of studies deemed eligible for inclusion were also explored for additional citations. Abstracts of RCTs from conference proceedings were not searched based on the assumption that not many trials have been conducted in this topic area.

Study Selection Criteria and Process

A review of the titles and abstracts that resulted from the electronic searches was completed by one reviewer (CA). For those items that appeared to meet the inclusion

criteria, CA obtained and reviewed the full text. Since there was a predetermined assumption that there would be few or no RCTs in this topic area, the inclusion of studies was not limited by study type. However, the studies had to report at least one of the following outcomes: remission rates, survival rates, toxicity, or quality of life.

Exclusion Criteria

The following exclusion criteria were applied to the entire literature search:

- Case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies.
- Conference abstracts.
- Studies on cost-effectiveness, utility, and economics.
- Studies with fewer than 30 participants.
- Studied with a population median age of less than 10 years.
- Studies published in a language other than English, due to the lack of funding and resources for translation.

It is important to note that studies on the role of allogenic HSCT were not included in this review because they were considered outside its scope. Moreover, this topic has been addressed in the recommendation report SCT-6 developed by the CCO's Stem Cell Steering Committee group.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included studies were extracted by the project research methodologist (CA). The characteristics of the study population, including sample size, years of accrual, and duration of follow-up were extracted. Where reported, response, progression, and survival information were also extracted from the results of the included studies. In cases with more than one publication for the same study, only the most recent version of the data was extracted in the results. All the extracted data and information were audited by an independent auditor (TT).

Synthesizing the Evidence

The PEBC policy around evidence synthesis requires that when multiple RCTs with similar experimental and control arms are available, a meta-analysis is conducted using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration [9]. For all outcomes, the generic inverse variance model with random effects is used. For time-to-event outcomes, the hazard ratio (HR), rather than the number of events at a certain time point, is the preferred statistic for meta-analysis. If the HR and/or its standard error are not reported, they will be derived from other information reported in the study, using the methods described by Parmar et al. [10]. Statistical heterogeneity is calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% is considered indicative of statistical heterogeneity. Since the literature search did not find any suitable RCTs in this topic area, a meta-analysis was not conducted.

RESULTS

Search for Existing Guideline and Systematic Reviews

Pediatric-Inspired Regimens in AYA

No existing guidelines for this question were identified. The search for systematic reviews yielded 518 review articles published between 2005 and 2015. Out of these 518 reports, the full-text reports of 76 reviews were retrieved and reviewed. The majority of the excluded reviews were narrative reviews. After full-text review, two systematic reviews [11,12] were identified as relevant to the topic areas covered by this evidence summary. Both reviews scored highly on the AMSTAR assessment. The findings of these reviews are summarized below (Table 1).

Table 1: Characteristics of Included systematic Reviews

Author	Objectives (number of trial/ number of patients)	Relevant Studies Used	Conclusion
Ram et al. 2012 [11]	To evaluate the efficacy and safety of pediatric-inspired regimens given to AYAs (aged 16-39 years) with ALL. (11/2489)	Stock 2008, Boissel 2003, deBont 2004, Testi 2004, Ramanujachar 2007, Hallbook 2006, Haiat 2007, Usvasalo 2008, Alves 2008, Lopez-Hernandez 2008, Huguet 2009	Pediatric-inspired regimens are superior to conventional-adult chemotherapy in AYA ALL patients.
Ramanujachar et al 2006 [12]	To determine whether AYAs (15 –21 years) should be treated on pediatric or adult type protocols. (9/NR)	**Comparative Studies** Fiere1990, Boissel 2003, Stock 2000, Testi 2004, deBont 2004, **Parallel Studies** Larson 1995, Larsonn 1998, Annino 2002, Kantarjian 2000, Hoelzer 1993, Thiebaunt 2000, Hussein 1989, Petersdorf 2001, Durrant 2000	Adolescents appear to have a consistent survival advantage when treated on pediatric regimen.

Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; NR, not reported.

Ramanujachar et al

Ramanujachar et al [12] used an operational age of 15 to 21 years to define the AYA population and conducted a systematic review on all clinical trials published between 1980 and 2000 that included ALL patients in this age group. A total of 48 trials were included in this review. The included trials were grouped into four categories (comparative, pediatric, adult, and parallel trial groups) and were analyzed based on the protocol used in treating the AYAs. Although the percentages and results of the AYAs included in the pediatric and adult trial groups were reported in the review, they were not included in this review because they were not comparative – the target of analysis was only pediatric or adult population with a small percentage of AYA. However, the Working Group believes that these results may provide insight into which regimens are better. For the purpose of this evidence review, only the results from the comparative and parallel trials, as classified by Ramanujachar et al, were used as an evidence base in this evidence summary. The pediatriac and adult trials included

in the Ramanujachar et al paper had too small proportions of AYA to be used to answer the research questions of this evidence review.

The included comparative studies are retrospective studies that reported the results of 891 patients treated with either a pediatric protocol or an adult protocol. In the pediatric trial group, the French ALL Cooperative Group 83 (FRALLE83) trial used more asparaginase and anthracyclines compared with the Leucemie Aigue Lymphoblastque de L'Adult (LALA) 85 trial. Prednisolone, vincristine, and asparaginase were respectively used five, three, and 20 times more in the FRALLE93 trial compared with the adult regimen used in the LALA94. The outcomes reported were complete remission (CR), event-free survival (EFS), and overall survival (OS). Although the results of these trials were not pooled, the comparative analyses demonstrated a 15% to 35% difference in EFS in favour of the pediatric regimens. The parallel trials evaluated the effect of a similar regimen in patients younger than 15 years compared with those 15 years and older and demonstrated that age is an important prognostic factor with the risk of treatment failure doubling after 10 years.

Ram et al

Ram et al [11] defined AYAs as ALL patients between the ages of 16 and 39 years of age and evaluated the use of a pediatric-inspired regimen in this population. In their review, trials conducted between 1979 and 2011 were considered for inclusion and a meta-analysis was conducted on the results of 11 comparative studies published between 2003 and 2009. The total number of patients included was 2489. Three-year all-cause mortality, CR, EFS, and relapse rates were among the outcomes evaluated. All-cause mortality (relative risk [RR], 0.58; 95% confidence interval [CI], 0.51 to 0.67) and relapse (RR, 0.51; 95% CI, 0.39 to 0.66) were significantly reduced in patients treated with the pediatric-inspired regimens compared with those treated with the adult regimens, but there was no difference in non-relapse mortality (NRM) between the groups. The absolute risk reduction for all-cause mortality at three years was 0.20. A statistically significant increase in post-induction CR (RR, 1.05; 95% CI, 1.01 to 1.10) and EFS (RR, 1.66; 95% CI, 1.39 to 1.99) in favour of the pediatric-inspired regimens was also reported. Although heterogeneity was demonstrated in the meta-analysis for all-cause mortality, the identification and removal of the contributing study did not change the results.

TKIs in Ph+ ALL

No existing guidelines or systematic reviews were identified for this question.

Systematic Review of Primary Literature

The search strategy outlined in Appendix I retrieved 2630 articles from MEDLINE and EMBASE after the removal of duplicates. As noted in the Methods, the earliest time point covered by the search was 2011. The title and abstracts screening of the remaining publications retained 80 reports for full-text review. After full-text review, 20 studies were eligible for inclusion overall. Table 2 shows the details and primary results for the pediatric-inspired regimens question; Table 3 shows the details and primary results for the TKIs in PH+ ALL question.

Table 2: Included Studies published after 2010 on the use Pediatric-inspired Regimens in AYAs

Author [Ref] Study Name (Years of Accrual)	Regimen Base	Study Objective & Median Duration of Follow-up	Population	Results (95% CI)
Non-comparative Studies				
Marks et al. 2013 [13] UKALLXII/ECOG2993 (1993-2006)		To describe the outcome and delineate prognostic factors and optimal post-remission therapy in a sub-analysis of	t(4;11)-positive BCP-ALL Med age: 38	**CR:** 93% **NRM:** 32% (21 to 46) **OS:** 35% (25 to 45) at 5 yr

		UKALLXII/ECOG2993 Med F/U: 64.8 mo	N=85	**Relapse**: 45% (33 to 58)
Rijneveld et al. 2011 [14] HOVON 70 (2005-2007)	FRALLE-93	To evaluate the effectiveness of a pediatric regimen in adult patients under the age of 40 Med F/U: 32 mo	Previously untreated ALL Med age: 26 N=54	**CR:** 91% **EFS:** 66% (52 to 77) **OS:** 72% (58 to 82) at 2 yr
DeAngelo et al. 2015 [15] (2002-2008)	DFCI ALL Consortium Protocol 01-175	To evaluate the feasibility of treating adult ALL patients aged 18-50 years with the DFCI Pediatric ALL Consortium regimen utilizing a 30-week course of pharmacokinetically dose-adjusted *E. coli* L-asparaginase during consolidation Med F/U: 54 mo	Newly diagnosed ALL Med age: 28 N=92	**CR:** 85% **DFS:** 69% (56 to 78) at 4 yr for patients achieving CR **OS:** 67% (56 to 76) at 4 yr
Hayakawa et al. 2014 [16] JALSG-ALL202-U (2002-2009)	JALSG-ALL202	To examine the efficacy and feasibility of a pediatric protocol in AYAs with *BCR-ABL*-negative ALL Med F/U: 61.2 mo	*BCR-ABL*-negative ALL Age: 15-24 N=139	**CR:** 94% (88 to 97) **DFS:** 67% (58 to 75) at 5 yr **OS:** 73% (64 to 80) at 5 yr
Hassan et al. 2013 [17] (2000-2009)	UKALLXII/ECOGE2993	To examine the outcome of ALL patients treated at Tawam Hospital Med F/U: 11.8 mo	Newly diagnosed ALL Med age: 28 N=99	**CR:** 86.7% **EFS:** 28.7% at 3 yr for 91 patients **OS:** 50.6% at 3 yr for 91 patients
Hocking et al. 2014 [18] (2004-2011)	FRALLE-93	To assess the progress and outcomes of adolescents and adults up to the age of 45 treated on the FRALLE-93 pediatric protocol Med F/U: 37.2 mo	Diagnosed ALL Med age: 23 N=40	**CR:** 97.5% **EFS:** 70% at 3 yr **OS:** 70% at 3 yr
Rytting et al. 2014 [19] (2006-2012)	ABFM	To evaluate the pediatric ABFM regimen in AYA patients up to the age of 40 Med F/U: 40 mo	Newly diagnosed, Ph- ALL Med age: 21 N=85	**CR:** 94% **DFS:** 70% at 3 yr **OS:** 74% at 3 yr **Relapse**: 29.4%
Stock et al. 2013 [20] CALGB 19802 (1999-2001)		To evaluate whether dose intensification of daunorubicin and cytarabine could improve DFS in adults with ALL Med F/U: 124.8 mo	Previously untreated ALL Med age: 40 N=161	**CR:** 80% (72 to 85) **DFS:** 25% (18 to 33) at 5 yr **OS:** 30% (23 to 37) at 5 yr **TRM:** 13%
Comparative Studies				
Seftel et al. 2014 [21] [ABSTRACT] Seftel et al. 2016 [22] (2002-2011)		HSCT vs Chemotherapy Med F/U: 65 mo vs 48 mo	HSCT vs Chemotherapy Med age: 34 vs 30; p=0.001 T-cell ALL: 14% vs 22%; p=0.03 CNS disease at diagnosis: 6% vs 11%; p<0.001 N=422 vs N=108	HSCT vs Chemotherapy **DFS**: 40% (35 to 45) vs 71% (60 to 79); p<0.0001 **OS**: 45% (40 to 50) vs 73% (63 to 81); p<0.0001 **TRM**: 37% (31 to 42) vs 6% (3 to 12); p<0.0001 **Relapse**: 24% (19 to 28) vs 23% (15 to 32); p=0.97

Abbreviations: ABFM, augmented Berlin-Frankfurt-Münster therapy; ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; BCP, B-cell precursor; BCR-ABL, BCR-ABL oncogene; CALGB, Cancer and Leukemia Group B; CI, confidence interval; CNS, central nervous system; CR, complete remission rate; DFCI, Dana-Farber Cancer Institute; DFS, disease-free survival rate; ECOG, Eastern Cooperative Oncology Group; FRALLE, French Group for Childhood Acute Lymphoblastic Leukemia; F/U, follow-up; GCS-F, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; HOVON, Dutch-Belgian cooperative trial group for Hematology Oncology; JALSG, Japan Adult Leukemia Study Group; Med, median; mo, months; N, number enrolled; OS, overall survival rate; Ph-, Philadelphia chromosome-negative; TRM, treatment-related mortality rate; UKALL, United Kingdom Acute Lymphoblastic Leukemia; yr, years.

Table 3: Included Studies on the use of TKI in Ph+ ALL

Author [Ref] Study Name (Years of Accrual)	Study Objective & Median Duration of Follow-up	Population	Results (95% CI)
Non-comparative Studies			
Foa et al. 2011 [23] GIMEMA LAL1205 (2006-NR)	To assess the activity of first-line induction treatment with dasatinib without systemic chemotherapy Med F/U: 24.8 mo	Newly diagnosed patients of any age Med age: 53.6 N=53	**CR:** 100% **DFS:** 51.1% (44.4% to 58.7%) at 20 mo **RFS:** 42.9% (41.9% to 43.9%) at 20 mo **OS:** 69.2% (60.7% to 79.0%) at 20 mo
Lim et al. 2015 [24] (2005-2009)	To evaluate the effects of imatinib plus chemotherapy Med F/U: 68.9 mo	Newly diagnosed adults Med age: 41 N=87	**CR:** 94% **RFS**: 39% at 5 yr **OS:** 33% at 5 yr **NRM:** 44.8
Ravandi et al. 2015 [25] (2006-2012)	To evaluate the long-term efficacy of a combination of chemotherapy and dasatinib Med F/U: 67 mo	Newly diagnosed patients over the age of 18 Med age: 55 N=72	**CR:** 96% **DFS:** 44% at 5 yr **EFS:** 42% at 5 yr **OS:** 46% at 5 yr **Relapse**: 31%
Kim et al. 2015 [26] (2009-2012)	To investigate the effects of nilotinib plus multiagent chemotherapy followed by consolidation therapy or alloHSCT Med F/U: NR	Newly diagnosed adults Med age: 47.0 N=90	**CR:** 91% **RFS:** 72% at 2 yr **OS:** 72% at 2 yr **NRM:** 25% (18 to 37) **Relapse**: 24% among patients achieving CR
Thyagu et al. 2012 [27] (2001-2008)	To evaluate the clinical course associated with treatment using a pediatric –based protocol plus imatinib Med F/U: 85 mo (alloHSCT) vs. 59 mo (chemotherapy)	Med age: 46 N=32	**CR:** 94% **EFS:** 50% (31% to 66%) at 3 yr **Med EFS:** 30.1 mo **OS:** 53% (34% to 68%) at 3 yr **Med OS:** 40.7 mo
Lee et al. 2012 [28] (2000-2009)	To describe the effect of MRD kinetics during imatinib-based treatment on long-term allogeneic transplantation outcome Med F/U: 61 mo	Newly diagnosed adults Med age: 34 N=95	**CR:** 94.7% **DFS:** 61.5% at 5 yr **OS:** 63.7% at 5 yr
Comparative Studies			
Chalandon et al. 2015 [29] GRAAPH-2005 (2006-2011)	High dose imatinib plus reduced-intensity chemotherapy (Arm A) vs. standard dose imatinib plus hyperCVAD (Arm B) Med F/U: 57.6 mo	Newly diagnosed Med age: 47 <u>Arm A vs. Arm B</u> N=135 vs. N=133	<u>Arm A vs Arm B</u> **CR:** 98% vs. 91%; p=0.006 **EFS:** HR=1.27 (0.93 to 1.72) at 5 yr; p=0.13 **OS:** HR=1.17 (0.84 to 1.62) at 5 yr; p=0.37 **NRM:** 23.7% (17.3% to 32.0%) vs. 22.6% (16.1% to 31.2%) at 5 yr; p=0.90
Chen et al. 2012 [30] (2005-2010)	Imatinib vs. no imatinib post-alloHSCT Med F/U: 31 mo vs. 24.5 mo	Diagnosed patients who received myeloablative alloHSCT and are in CR prior to imatinib therapy Imatinib vs no imatinib Med age: 29 vs. 27.5 N=62 vs. N=20	**CR:** 100% Imatinib vs. no imatinib **DFS:** 81.5% vs. 33.5% at 5 yr; p=0.000 **OS:** 86.7% vs. 34.3% at 5 yr; p=0.000 **NRM:** 6.66% vs. 37.19%; p=0.0006 **Relapse**: 10.18% vs. 33.05% at 5 yr; p=0.016
Fielding et al. 2014 [31] UKALLXII/ECOG2993 (1993-2003)	Pre-imatinib vs. imatinib Med F/U: 54 mo vs. 57 mo	Newly diagnosed <u>Pre-imatinib vs imatinib</u> Med age: 40 vs. 42 N=266 vs. N=175	<u>Pre-imatinib vs imatinib</u> **CR:** 82% vs. 92%; p=0.004 **EFS:** 18% (13% to 22%) vs. 33% (26% to 40%) at 4 yr; OR=0.65 (0.52 to 0.80); p=0.0001 **RFS:** 33% (26% to 41%) vs. 50% (41% to 58%) at 4 yr; OR=0.59 (0.46 to 0.79); p=0.0003**OS:** 22% (17% to 27%) vs. 38% (31% to 45%) at 4 yr; OR=0.67 (0.53 to 0.83); p=0.0003
Mizuta et al. 2014 [32] (1990-2010)	Imatinib vs. no imatinib prior to alloHSCT	Newly diagnosed patients who received alloHSCT during their first CR	**CR:** 100% <u>Imatinib vs. no imatinib</u>

Author [Ref] Study Name (Years of Accrual)	Study Objective & Median Duration of Follow-up	Population	Results (95% CI)
	Med F/U: 60 mo	Imatinib vs. no imatinib Med age: 42 vs. 39 N=542 vs. N=196	**DFS:** 58% (41.8% to 70.9%) vs. 37% (28.5% to 45.6%) at 3 yr; p=0.039 **OS:** 59% (54% to 63%) vs. 38% (31% to 45%) at 5 yr; p<0.001 HR=0.56 [0.45 to 0.70]; p<0.001) HR=0.52 [0.39-0.71]; p<0.001) **NRM:** 22% (18% to 26%) vs. 30% (24% to 37%) at 3 yr; HR=0.65 (0.49 to 0.88); p<0.001 **Relapse**: 23% (20% to27%) vs. 39% (31% to 47%) at 3 yr; p<0.001
Mizuta et al. 2011 [33] 2002-2005	Imatinib vs. no imatinib prior to alloHSCT Med F/U: 36 mo	Newly diagnosed patients who received alloHSCT during their first CR Imatinib vs. no imatinib Med age: 42 vs. 39 N=52 vs. N=122	**CR:** 97% <u>Imatinib vs. no imatinib</u> **DFS:** 58% (41.8% to 70.9%) vs. 37% (28.5% to 45.6%) at 3 yr; p=0.03 **OS:** 65% (49% to 78%) vs. 44% (35% to 52%) at 3 yr; p=0.014. **NRM:** 28% (20% to 36%) vs. 21% (11% to 33%) at 3 yr; p=0.26 **Relapse**: 15% (6.6% to26.7%) vs. 50.4% (39.6% to 60.2%) at 3 yr; p=0.002

Abbreviations: ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; CR, complete remission; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; F/U, follow-up; GIMEMA, Gruppo Italiano Malatti EMatologiche dell'Adulto; GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia Philadelphia positive; HR, hazard ratio; hyperCVAD, intense cyclophosphamide/vincristine/doxorubicin/dexamethasone; LAL, Spanish abbreviation for acute lymphoblastic leukemia; Med, median; mo, months; MRD, minimal residual disease; N, number enrolled; NR, not reported; NRM, nonrelapse mortality; OR, odds ratio; OS, overall survival; Ph+, Philadelphia chromosome-positive; RFS, relapse-free survival; TKI, tyrosine kinase inhibitor; UKALL, United Kingdom Acute Lymphoblastic Leukemia; yr, years.

Study Design and Quality

The studies included for pediatric-inspired regimen question and TKIs in Ph+ ALL questions were non-randomized studies conducted between 1993 and 2012 with sample sizes ranging from 40 to 530 participants. Patients were accrued between 1993 and 2012 from centres located in Asia, Australia, Europe, and North America. Since the majority of the studies were non-comparative retrospective studies, quality assessment was not performed. However, some quality features such as the follow-up rate were considered while reviewing the articles. In all the studies, the enrolled patients were all accounted for during analysis and toxicity outcomes were graded based on the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events.

Pediatric-Inspired Regimens in AYA

The majority of the included patients were classified as standard- or intermediate-risk patients. Risk classification, where reported, was based on age, WBC count, karyotype, and CNS involvement prior to treatment. Although the definition of the high-risk population varied slightly across the studies, the presence of CNS involvement and/or Ph+ karyotype were consistent criteria for a high-risk classification. Cytogenetic translocation involving chromosomes (8;14), (4;11) or one of the fusion genes (e.g., *MLL-AF4*) was also used to classify high-risk groups. WBC greater than 30×10^9/L in B-cell ALL or greater than 100×10^9/L in T-cell ALL was also used to identify high-risk patients. Patients who did not achieve CR after induction were also considered high-risk and were given alternative treatment from the protocol under study. Patients with mature B-cell ALL were excluded in some of the studies [14-16].

The regimens used in all the studies were based on a slight modification in dosage or schedule of previously known pediatric regimens. For instance, some studies modified the type, dosage, and timing of administration of asparaginase. Steroid use and vincristine were

also modified in some studies. See Appendix II for more details on the regimens. Treatment intensification was carried out either during induction, consolidation, or maintenance, or in all three phases. Post-induction remission therapy was similar across the studies and included HSCT, continuation with chemotherapy alone, or continuation with chemotherapy in combination with allogeneic HSCT. In one study [13], a subanalysis of the UKALLXII/ECOG2993 study, patients were randomized to either receive an autograft or continue on chemotherapy alone. As previously mentioned, the role of allogeneic HSCT is beyond the scope of this evidence review.

TKI

The studies investigated the use of a TKI plus multiagent chemotherapy in Ph+ ALL. One study [23] included biphenotypic acute leukemia and another study [25] Included patients treated with one or two courses of chemotherapy before the Ph+ status was known. In most of the studies, the TKI was started on day 8 of induction therapy until transplantation. Patients that were not qualified for transplantation continued on TKI until the end of consolidation, which was up to two years in one study [24]. The comparative studies [29-33] evaluated the effect of imatinib on Ph+ ALL patients pre-transplantation [32,33] and post-transplantation [30]. In one study [30], the Imatinib was administered post-transplantation and another randomized study [29] evaluated the impact of imatinib administration duration. Both arms received the same dose of imatinib in combination with either standard or reduced intensity chemotherapy. In the reduced intensity arm, imatinib was given for 28 days versus 14 days in the standard arm.

Outcomes

In this evidence review, remission and survival outcomes as they relate to the use of intensified chemotherapy in the AYA population and the use of TKI in the adult population were the key outcomes of interest. Minimal residual disease (MRD) analysis, where reported, was also included as one of the prognostic outcomes.

Pediatric-Inspired Regimens in AYA

Remission and Post-Remission Relapse

The results of the two systematic reviews described above suggest better outcomes for the AYAs with consistent survival advantages. AYAs had a significantly lower all-cause mortality rate at three years when treated with pediatric-inspired regimen. In Table 2, complete remission, as reported by the authors of the non-comparative studies [13-20], ranged from 80% to 97.5%. This was shown to be comparable to that of the total population of patients in the UKALLXII/ECOG 2993A study. Hassan et al [17] conducted additional analysis based on ALL subtype. The results of pre-B ALL patients treated with low intensity protocols prior to 2002 were compared with those treated with intensified protocols after June 2002. A significantly better CR rate (50% vs. 91%; p=0.02) in favour of intensified protocol was found [17]. WBC count at diagnosis, pregnancy, and CNS involvement significantly worsened the CR rate, and this finding was consistent in all studies. In DeAngelo et al. [15], 20.5% of those that achieved CR underwent allogeneic HSCT, and 69% of those that received allogenic HSCT remained in CR. For Ph+ and Ph- patients, the CR rates were reported as 78% and 86%, respectively [15]. Using registry data obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), Seftel et al. [22] compared the Dana-Farber Consortium pediatric-inspired chemotherapy protocol to allogeneic HSCT in adults with Ph-ALL in first CR. The relapse rate after first CR did not differ between the two groups, but the median time to achieve CR in the HSCT arm was twice that of the chemotherapy group

(p<0.001). Marks et al. [13] also reported that patients who were treated with an allograft, especially a sibling allograft, had a very low relapse rate. Data on post-treatment MRD as a predictor of relapse were not reported in most of the studies.

Survival

The survival rates for AYAs treated with pediatric-inspired regimen ranged from 30% to 74% for OS and 28.7% to 81% for DFS (Table 2). These rates were significantly higher (p<0.001) for patients who achieved CR [17]. Hayakawa et al. [16] compared the survival rates in the JALSG-ALL202-U study with the findings of another study (JALSG-ALL97-U) that used an adult protocol in a comparable population. DFS and OS were markedly better with the pediatric protocol compared with the adult protocol (67% vs. 44% and 73% vs. 45%, respectively). Age at diagnosis was repeatedly shown to be a strong predictor of survival outcome in all the studies. Hassan et al. [17] showed that the three-year OS for those 20 to 35 years old (p=0.04) and those older than 35 years (p=0.012) were significantly worse compared with the OS for patients younger than 20 years. The three-year EFS for patients older than 35 years of age was also significantly worse (p=0.018). In the subgroup analysis of the UKALLXII/ECOG2993 study, Marks et al. [13] examined the effect of age and post-remission treatment among adult patients with t(4;11) ALL and found that the risk of death increased with increasing age (HR, 1.03; 95% CI, 1.01 to 1.06; p=0.002). Other factors found to be predictive of better OS included standard risk status and karyotype.

In Seftel et al. [22], a recently published analysis comparing post-remission HSCT with pediatric-inspired chemotherapy, treatment-related mortality (TRM) was shown to be significantly higher in the HSCT arm (p<0.0001). While relapse accounted for more deaths in the chemotherapy arm, 70% of deaths in the HSCT arm were caused by HSCT-related toxicities. OS and DFS were also in favour of chemotherapy. Being older than 30 years (HR, 1.69; 95% CI, 1.16 to 2.44; p<0.01) and having a B-cell phenotype (HR, 2.26; 95% CI, 1.30 to 3.93; p<0.01) were both shown to be associated with a higher TRM. Marks et al. [13] also reported that allografting was not significantly superior to chemotherapy for survival outcomes.

Toxicity

Toxicity was graded based on the NCI-CTC for adverse effect. Severe adverse events included neutropenia, thrombocytopenia, febrile neutropenia, sepsis, hepatic toxicity, pancreatitis, and neuropathy. Intensification of asparaginase was one of the major causes of adverse events. One study reported using an *Escherichia coli* asparaginase at a median dose of 15,000 IU/m^2 (range, 6000 IU/m^2 to 25,000 IU/m^2) [15]. In the absence of *E. coli* asparaginase, *Erwinia*-derived or polyethylene glycol asparaginase was used.

Although toxicity assessment was performed in all phases of treatment, the majority of the toxic events were experienced during the induction phase. Febrile neutropenia had the highest incidence ranging from 33% to 70% [14-17]. DeAngelo et al. [16] reported that during induction, 99% of patients developed grade 4 neutropenia, although this was difficult to distinguish from other hematopoietic disorders due to the leukemia. Other toxic events reported during induction were liver enzyme disorders, pancreatitis, ileus, disseminated intravascular coagulopathy, gastrointestinal bleeding, hyperglycemia, neuropathy, and tumour lysis syndrome. Severe adverse effects did occur during post-remission therapy but were not as frequent as in the induction phase.

Increasing the dosage of asparaginase, steroids, methotrexate, and vincristine were the key sources of grades 3-4 toxic effects. Other than toxic deaths due to pulmonary embolism and septic shock, allergic reactions to asparagine, grade 4 thromboembolic events, and severe liver diseases were also reported. Tolerance to intensification of asparaginase in

the first 30 weeks of treatment was the primary focus of one of the studies [15], and the reported toxicities included allergic reactions (5%), pancreatitis (11%), and thrombosis (17%). In other studies, toxicity to asparaginase was reported to be tolerable during induction and uneventful in the other treatment phases [14,18]. Intensified steroid use also presented some toxic effects such as susceptibility to infection and avascular bone necrosis. Most of the infections were classified as febrile neutropenia. In some cases, methotrexate caused renal failure that eventually resolved completely [14]. Liver enzyme abnormalities were encountered in 55% of patients during the maintenance phase and were attributed to transient hepatotoxicity caused by methotrexate [14]. Severe mucositis was also reported after methotrexate administration. Long-term toxicities such as peripheral neuropathy due to vincristine were also reported [16,18].

TKIs in Ph+ ALL

Remission

Table 3 shows the results of the studies relevant to the use of TKIs in Ph+ ALL. The addition of imatinib to remission, induction, and consolidation chemotherapy regimens resulted in 91% to 100% of patients achieving their first CR. A significant difference in favour of imatinib was found to be consistent in all the studies that compared the results with those of pre-imatinib regimens [23-25,29-31]. In the UKALLXII/ECOG2993 study [31], the difference in early versus late administration of imatinib in the course of induction therapy was not significant. However, Lim et al. [24] demonstrated that the intensity of imatinib in the first seven weeks of treatment was shown to be associated with a longer median CR duration ($p<0.0001$), but did not have a significant impact on molecular response. Kim et al. [26] demonstrated that Ph+ patients treated with nilotinib that failed to achieve a *BCR-ABL1/G6PDH* ratio $\leq 10^{-3}$ were 9.1 times more likely to relapse ($p=0.004$). Molecular response was also better in patients that received allogeneic HSCT than in those that did not receive allogeneic HSCT (89% vs. 56%) [26]. One RCT [29] compared the combination of high-dose imatinib plus reduced-intensity chemotherapy with a combination of standard-dose imatinib plus hyperCVAD (intense cyclophosphamide/vincristine/doxorubicin/dexamethasone). The imatinib dose was the same in both arms, except it was given for 28 days in the high-dose arm and for 14 days in the other. High-dose imatinib demonstrated a significantly higher CR rate compared with normal-dose imatinib (98% vs. 91%; $p=0.006$). A significant difference was not found between the two treatments, however, in the five-year DFS and OS rates.

The impact of TKI on post-remission outcomes was confounded by the variations in post-remission therapy. There was a considerable reduction in relapse risk in the imatinib group; (OR, 59; 95% CI, 0.46 to 0.79) [23]. Mizuta et al. [32,33] evaluated the impact of imatinib on the outcomes of allogeneic HSCT and compared the results with a historic cohort that did not receive imatinib. The results favoured the imatinib group. Three-year cumulative incidence of relapse incidence was significantly lower in the imatinib cohort (23% vs. 39%; $p<0.001$) [32,33]. Risk of relapse was also found to be significantly reduced by the administration of imatinib (HR, 0.52; 95% CI, 0.39 to 0.71; $p<0.001$), as was the rate of NRM (HR, 0.65; 95% CI, 0.49 to 0.88; $p<0.001$) [32,33].

Survival

The DFS and OS rates demonstrated in the non-comparative studies ranged from 39% to 51% and 33% to 72%, respectively. In the comparative studies, the addition of imatinib at any time was associated with a significantly better survival outcome than when no imatinib was added. The five-year OS for those treated with imatinib prior to allogeneic HSCT was 59% (95% CI, 54% to 63%) compared with 38% (95% CI, 31% to 45%) in the non-imatinib cohort

(p<0.001) [32,33]. Imatinib administration before allogeneic HSCT also significantly reduced the risk of death (HR, 0.56; 95% CI, 0.45 to 0.70; p<0.001) [32,33]. The three-year DFS was also significantly better in the imatinib cohort (58% vs. 37%; p=0.039) [32,33]. Foa et al. [23] demonstrated that a molecular response involving a reduction of *BCR-ABL* levels to $<10^{-3}$ during induction was predictive of better DFS. Patients' age at transplant and the length of time between diagnosis and HSCT were among the prognostic factors that had a significant impact on survival outcomes. The most prominent cause of death was relapse from primary disease, while the major causes of TRM included infection, organ failure, and interstitial pneumonia [32,33]. The intensity of imatinib in the first seven weeks of treatment was associated with better OS (p=0.002) [24]. Furthermore, an initial dose intensity of ≥90% resulted in a longer median duration of relapse-free survival compared with an initial dose intensity <90% (70.5 months vs. 14.2 months) [24].

Toxicities

Toxicities occurred mainly during induction and were easily reversible. The majority of patients (80%-100%) experienced grade 4 neutropenia or thrombocytopenia in the studies.

Ongoing, Unpublished, or Incomplete Studies

The search for ongoing trials was conducted on March 25, 2016, and the included trials were first initiated between the years 2011 and 2016. Table 4 presents the list of ongoing trials identified from clinicaltrials.gov.

Table 4: Ongoing Trials

Official Title	Status	Protocol ID
Pediatric-Inspired Regimens in AYAs		
A Novel "Pediatric-Inspired" Regimen With Reduced Myelosuppressive Drugs for Adults (Aged 18-60) With Newly Diagnosed Ph Negative Acute Lymphoblastic Leukemia Date trial summary last modified: January 13, 2016	Recruiting	NCT01920737
Combination Chemotherapy in Treating Young Patients With Newly Diagnosed High-Risk Acute Lymphoblastic Leukemia Date trial summary last modified: February 3, 2016	Recruiting	NCT01406756
Combination Chemotherapy in Treating Young Patients With Newly Diagnosed Acute Lymphoblastic Leukemia Date trial summary last modified: July 31, 2015	Active, not Recruiting	NCT00558519
Augmented Berlin-Frankfurt-Munster (BFM) Therapy for Adolescent/Young Adults With Acute Lymphoblastic Leukemia or Acute Lymphoblastic Lymphoma Date trial summary last modified: November 5, 2015	Active, not Recruiting	NCT00866749
TKIs in Ph+ ALL		
Low-dose Chemotherapy Combine With Tyrosine Kinase Inhibitor to Treat ph+ Acute Lymphoblastic Leukemia Patients (TCLDCWTTNDPP)	Not yet Recruiting	NCT02690922

Official Title	Status	Protocol ID
Date trial summary last modified: February 23, 2016		
Dasatinib Combined With Chemotherapy in Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia Date trial summary last modified: August 13, 2015	Not yet Recruiting	NCT02523976
TKI Therapy Based on Molecular Monitoring in Allogeneic-HSCT Recipients With Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia Date trial summary last modified: June 23, 2013	Recruiting	NCT01883219
Phase II Front-line Ponatinib in Adult Philadelphia+/BCR-ABL+ Acute Lymphoblastic Leukemia. (LAL1811) Date trial summary last modified: July 29, 2015	Recruiting	NCT01641107

DISCUSSION

Pediatric-Inspired Regimens in AYA

Historically, chemotherapy has improved the prognosis for patients with ALL. A variety of treatment regimens have been developed over the past 35 years but no two regimens are the same. The intensification of chemotherapy to improve survival rates has been tested in many non-comparative and non-randomized comparative studies. However, the AYAs with ALL respond differently to treatment compared with younger children. The differences between younger and older patients have been attributed to a variety of factors including the biology of these populations in relation to ALL disease. Hence, the interpretation of the results of the included trials was made in consideration of the impact of advancing age. A median age of less than 10 years was used to exclude studies involving younger patents. Although some studies defined the upper limit of age for AYAs to be 39 years, in this review there was no restriction for the upper limit of age. The cohorts in the comparative studies were also matched for age.

Achievement of CR was shown to be one of the good prognostic factors for better survival outcome in these patients. Despite the remarkable improvement in CR rates due to dose intensification, using a standardized method to monitor MRD was shown to be one way of predicting relapse and survival. Unfortunately, a widely available standardized method of monitoring MRD is not readily available so this is not currently possible at many centres in Ontario. Analysis of the outcomes based on post-remission treatment was confounded by a number of factors including the variability in the upper age limit of AYAs.

Significant reduction in all-cause mortality was also demonstrated in the included systematic reviews and the comparative studies. Age was one of the factors that significantly affected survival and toxicity outcomes. Patients 15 to 24 years of age have very encouraging survival rates, which could be attributed to the fact that the younger age group is more tolerant to treatment-related adverse effects, as was demonstrated in the studies.

One limitation of this review was the limited quality of evidence, which was due to a lack of randomized trials in this topic area. Another challenge was making a reasonable conclusion regarding the best regimen or component of a regimen that was responsible for the reported benefits during induction and post-remission. Since the majority of the studies

were single-arm studies with slight modifications in schedule and dosage, drawing comparisons among regimens was not feasible. However, it is worth noting that all the regimens contained asparaginase, methotrexate, and a steroid in the induction phase.

Overall, the use of a pediatric-inspired regimen in the AYA population has shown a remarkable improvement in the outcomes of these patients. While the challenge of defining an upper limit of age for the AYA population remains, better results have been reported for patients younger than 40 years of age compared with older patients.

TKIs in Ph+ ALL

For Ph+ patients, the administration of a TKI at any time during the course of treatment significantly increased CR rates. Imatinib administration pre-allogeneic HSCT also had a significantly favourable effect on relapse and OS rates. Despite this significant impact of TKI on allogeneic HSCT, monitoring MRD kinetics during the course of treatment is a good way of predicting the risk of treatment failure. Patients' age at transplant and the interval between diagnosis and HSCT were among the prognostic factors that had a significant impact on survival outcomes. Although imatinib is the most common TKI in use, second- and third-generation TKIs such as dasatinib and nilotinib have shown promising results in overcoming imatinib resistance and inducing better responses in patients that have failed imatinib.

For Ph+ ALL patients, the addition of a TKI to the chemotherapy regimen improves outcomes even in the absence of allogeneic HSCT. The duration of administration of a TKI may be more important for CR than intensity of chemotherapy.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. With evidence summaries, this review is conducted by the Director of the PEBC. The Working Group is responsible for considering the changes, and if those changes could be made without substantially altering the conclusions, the altered draft would not need to be resubmitted for approval.

Report Review by the Director of the PEBC

The purpose of the review by the Director of the PEBC is to ensure the methodological rigour and quality of PEBC evidence summaries. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the conclusions, the altered draft would not need to be resubmitted for approval again.

The Director of the PEBC reviewed the document in May 2016. During this review the Director provided the following key feedback and the Working Group made some changes.

- It was not clear if the patient populations were pediatric ALL patients becoming AYAs and wanting to stay on pediatric regimens, or new ALL patients being diagnosed at AYA ages and wanting pediatric regiments, or regular adult regimen or post-AYA aged patients who wanted pediatric regimens or a combination of both.
  - The Working Group specified the definition as newly diagnosed AYA patients.
- It appears there are more data reported in the text than in the table.
  - The Working Group made some statements to clarify that the extra information represents the results of some extra analysis conducted in the studies.
- It seems to also include aspects of those who received transplant.
  - Since this is usually part of the treatment in ALL, no changes were made. However, in the Ph+ population, the Working Group decided to focus on pre-transplant.
- Since the document is about the use of pediatric-inspired regimen in AYAs and the use of TKI in a particular type of ALL patients (Ph+), make sure throughout the paper you

either keep the evidence differentiated between these two issues or provide a narrative about where the discussion is combined.
    - The Working Group added some explanatory phrases and subheadings to differentiate the two.

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Appendix 1: Members of the acute lymphoblastic lymphoma working group

Name	Affiliation(s)	COI
Mitchell Sabloff Assistant Professor	Ottawa Hospital, University of Ottawa Faculty of Medicine, Ottawa Hospital Research Institute Ottawa, Ontario	No
Kang Howson-Jan Interim Chief/Chair, Division of Hematology	London Health Science Centre, London Regional Cancer Centre, London, Ontario	No
Chika Agbassi Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	No

Appendix 2: Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, ALL Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

Appendix 3A: Literature search strategy- MEDLINE

MEDLINE Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to November Week 3 2015**, Ovid MEDLINE(R) Daily Update** November 18, 2015**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** December 02, 2015

#	Searches	Results
1	(acute lymphocytic leukemia or acute lymphoblastic leukemia).mp. or exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/	42393
2	(Cyclophosphamide or Carloxan or Ciclofosfamida or Ciclofosfamide or Cicloxal or Clafen or Claphene or CP monohydrate or CTX or CYCLO-cell or Cycloblastin or Cycloblastine or Cyclophospham or Cyclophosphamid monohydrate or Cyclophosphamidum or Cyclophosphan or Cyclophosphane or Cyclophosphanum or Cyclostin or Cyclostine Cytophosphan or Cytophosphane or Cytoxan or Fosfaseron or Genoxal or Genuxal ro Ledoxina or Mitoxan or Neosar or Revimmune or Syklofosfamid or WR138719).tw.	49261
3	(Cytarabine or Alexan or Ara C or ARA cell or Arabine or Arabinofuranosylcytosine or Arabinosylcytosine or Aracytidine or Aracytin or Aracytine or Beta Cytosine Arabinoside or CHX 3311 or Cytarabinum or Cytarbel or Cytosar or Cytosar U or Cytosine Arabinoside or Cytosine beta arabinoside or Cytosine beta arabinoside or Erpalfa or Starasid or Tarabine PFS or U 19920 or U19920 or Udicil or WR28453).tw.	11247
4	(Daunorubicin Hydrochloride or Cerubidin or Cerubidine or Cloridrato de or Daunorubicina or Daunoblastinor Daunoblastina or Daunoblastine or Daunomycin Hydrochloride or Daunorubicin HCl or Daunorubicini hydrochloridum or FI 6339 or Ondena or RP 13057 or Rubidomycin Hydrochloride or Rubilem).tw.	192
5	(ADM or Adriacin or Adriamycin or Adriamycin Hydrochloride or Adriamycin PFS or Adriamycin RDF or Adriamycine or Adriblastina or Adriblastine or Adrimedac or Chloridrato de Doxorrubicina or DOX or DOXOCELL or Doxolem or Doxorubicin HCl or Doxorubin or Farmiblastina or FI 106 or hydroxydaunorubicin or Rubex).tw.	23353
6	(Leucovorin Calcium or Adinepar or Calcifolin or Calcium 6S Folinate or Calcium Folinate or Calcium Leucovorin or Calfolex or Calinat or Cehafolin or Citofolin or Citrec or Citrovorum Factor or Cromatonbic Folinico or Dalisol or Disintox or Divical or Ecofol or Emovis or Factor, Citrovorum or Flynoken A or Folaren or Folaxin or FOLI cell or Foliben or Folidan or Folidar or Folinac or Folinate Calcium or folinic acid or Folinic Acid Calcium Salt Pentahydrate or Folinoral or Folinvit or Foliplus or Folix or Imo or Lederfolat or Lederfolin or Leucosar or Leucovorin or Rescufolin or Rescuvolin or Tonofolin or Wellcovorin).tw.	8558
7	(Mercaptopurine or 3H Purine 6 thiol or 6 MP or 6 Thiohypoxanthine or 6 Thiopurine or 6 Mercaptopurine or 6 Mercaptopurine Monohydrate or 6 MP or 6 Purinethiol or 6 Thioxopurine or 6H Purine thione or 7 Mercapto tetrazaindene or Alti Mercaptopurine or Azathiopurine or Flocofil or Ismipur or Leukerin or Leupurin or Mercaleukim or Mercaleukin or Mercaptina or Mercaptopurinum or Mercapurin or Mern or NCI C04886 or PuriNethol or Purimethol or Purine 6 mercaptoPurine 6 thiol or Purine6thiol monohydrate or Purinethiol or Purinethol).tw.	3799
8	(Methotrexate or Abitrexate or AlphaMethopterin or Amethopterin or Brimexate or CL 14377 or CL14377 or Emtexate or Emthexat or Emthexate or Farmitrexat or Fauldexato or Folex or Folex PFS or Lantarel or Ledertrexate or Lumexon or Maxtrex or Medsatrexate or Metex or Methoblastin or Methotrexate LPF or Methotrexate Methylaminopterin or Methotrexatum or Metotrexato or Metrotex or Mexate or Mexate AQ or MTX or Novatrex or Rheumatrex or Texate or Tremetex or Trexeron or Trixilem or WR19039).tw.	37688
9	(Pegaspargase or L Asparaginase with Polyethylene Glycol or Oncaspar or PEG Asparaginase or PEG L Asparaginase or PEGLA or Polyethylene Glycol L Asparaginase or Polyethylene Glycol L Asparaginase).tw.	451
10	(ASP1 or Cristanaspase or L Asnase or Asparaginase II or Colaspase or Elspar or Kidrolase or L Asnase or L ASP or L Asparaginase or L Asparagine Amidohydrolase or Laspar or Lcf ASP or Leucogen or Leunase or Paronal or Serasa).tw.	2332
11	(Prednisone or delta1Cortisone or Dehydrocortisone or Adasone or Cortancyl or Dacortin or DeCortin or Decortisyl or Decorton or Delta-Dome or Deltacortene or Deltacortisone or Deltadehydrocortisone or Deltasone or Deltison or Deltra or Econosone or Lisacort or Meprosona-F or Metacortandracin or Meticorten or Ofisolona or Orasone or Panafcort or Panasol or Paracort or PRED or Predicor or Predicorten or Prednicen or Prednicort or Prednidib or Prednilonga or Predniment or Prednisonum or Prednitone or Promifen or Servisone).tw.	27637
12	(Vincristine Sulfate or Kyocristine or Leurocristine Sulfate or Leurocristine sulfate or Oncovin or Vincasar or Vincosid or Vincrex or Vincristine sulfate).tw.	1398
13	(idarubicin or zavedos or idamycin or IDR or idarubicin hydrochloride or 4demethoxydaunorubicin or 4DMDR or IMI30).tw.	2591
14	(lenograstim or lenograstim$).tw.	738
15	or/2-14	146769
16	(Afatinib or gilotrif or Apatinib or YN968D1 or Axitinib or Bosutinib or Bosulif or Cabozantinib or Canertinib or Cediranib or Crenolanib or Crizotinib or CYT387 or Damnacanthal or Dasatinib or Sprycel or Erlotinib or Filgotinib or Foretinib or Fostamatinib or Gefitinib or Grandinin or Ibrutinib or Icotinib or Imatinib or Gleevec or Lapatinib or Lestaurtinib or Lestaurtinib or Linifanib or Motesanib or Mubritinib or Neratinib or Nilotinib or Tasigna or Nintedanib or Pacritinib or Pazopanib or Ponatinib or iclusig or Quizartinib or Radotinib or Regorafenib or Ruxolitinib or Saracatinib or Semaxanib or Sorafenib or Sunitinib or Tivozanib or Toceranib or Tofacitinib or Vandetanib or Vatalanib or Vemurafe or Angiokinase inhibitors).tw.	57088
17	exp stem cell transplantation/ or exp allotransplantation/ or exp transplantation/ or exp hematopoietic stem cell	625630

	transplantation/ or allogenic transplant.mp.	
18	16 and 17	5001
19	15 or 18	151310
20	1 and 19	5901
21	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/	3855648
22	Animal/ not Human/	519794
23	21 or 22	4358273
24	20 not 23	4031
25	limit 24 to (human and english language and yr="2005 - 2015")	2255

Appendix 3B: Literature search strategy- EMBASE (1996 to 2015 Week 48)

#	Searches	Results
1	(acute lymphocytic leukemia or acute lymphoblastic leukemia).mp. or exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/	21849
2	(Cyclophosphamide or Carloxan or Ciclofosfamida or Ciclofosfamide or Cicloxal or Clafen or Claphene or CP monohydrate or CTX or CYCLO-cell or Cycloblastin or Cycloblastine or Cyclophospham or Cyclophosphamid monohydrate or Cyclophosphamidum or Cyclophosphan or Cyclophosphane or Cyclophosphanum or Cyclostin or Cyclostine Cytophosphan or Cytophosphane or Cytoxan or Fosfaseron or Genoxal or Genuxal ro Ledoxina or Mitoxan or Neosar or Revimmune or Syklofosfamid or WR138719).tw.	29628
3	(Cytarabine or Alexan or Ara C or ARA cell or Arabine or Arabinofuranosylcytosine or Arabinosylcytosine or Aracytidine or Aracytin or Aracytine or Beta Cytosine Arabinoside or CHX 3311 or Cytarabinum or Cytarbel or Cytosar or Cytosar U or Cytosine Arabinoside or Cytosine beta arabinoside or Cytosine beta arabinoside or Erpalfa or Starasid or Tarabine PFS or U 19920 or U19920 or Udicil or WR28453).tw.	6064
4	(Daunorubicin Hydrochloride or Cerubidin or Cerubidine or Cloridrato de or Daunorubicina or Daunoblastinor Daunoblastina or Daunoblastine or Daunomycin Hydrochloride or Daunorubicin HCl or Daunorubicini hydrochloridum or FI 6339 or Ondena or RP 13057 or Rubidomycin Hydrochloride or Rubilem).tw.	27
5	(ADM or Adriacin or Adriamycin or Adriamycin Hydrochloride or Adriamycin PFS or Adriamycin RDF or Adriamycine or Adriblastina or Adriblastine or Adrimedac or Chloridrato de Doxorrubicina or DOX or DOXOCELL or Doxolem or Doxorubicin HCl or Doxorubin or Farmiblastina or FI 106 or hydroxydaunorubicin or Rubex).tw.	13243
6	(Leucovorin Calcium or Adinepar or Calcifolin or Calcium 6S Folinate or Calcium Folinate or Calcium Leucovorin or Calfolex or Calinat or Cehafolin or Citofolin or Citrec or Citrovorum Factor or Cromatonbic Folinico or Dalisol or Disintox or Divical or Ecofol or Emovis or Factor, Citrovorum or Flynoken A or Folaren or Folaxin or FOLI cell or Foliben or Folidan or Folidar or Folinac or Folinate Calcium or folinic acid or Folinic Acid Calcium Salt Pentahydrate or Folinoral or Folinvit or Foliplus or Folix or Imo or Lederfolat or Lederfolin or Leucosar or Leucovorin or Rescufolin or Rescuvolin or Tonofolin or Wellcovorin).tw.	5782
7	(Mercaptopurine or 3H Purine 6 thiol or 6 MP or 6 Thiohypoxanthine or 6 Thiopurine or 6 Mercaptopurine or 6 Mercaptopurine Monohydrate or 6 MP or 6 Purinethiol or 6 Thioxopurine or 6H Purine thione or 7 Mercapto tetrazaindene or Alti Mercaptopurine or Azathiopurine or Flocofil or Ismipur or Leukerin or Leupurin or Mercaleukim or Mercaleukin or Mercaptina or Mercaptopurinum or Mercapurin or Mern or NCI C04886 or PuriNethol or Purimethol or Purine 6 mercaptoPurine 6 thiol or Purine6thiol monohydrate or Purinethiol or Purinethol).tw.	2144
8	(Methotrexate or Abitrexate or AlphaMethopterin or Amethopterin or Brimexate or CL 14377 or CL14377 or Emtexate or Emthexat or Emthexate or Farmitrexat or Fauldexato or Folex or Folex PFS or Lantarel or Ledertrexate or Lumexon or Maxtrex or Medsatrexate or Metex or Methoblastin or Methotrexate LPF or Methotrexate Methylaminopterin or Methotrexatum or Metotrexato or Metrotex or Mexate or Mexate AQ or MTX or Novatrex or Rheumatrex or Texate or Tremetex or Trexeron or Trixilem or WR19039).tw.	21426
9	(Pegaspargase or L Asparaginase with Polyethylene Glycol or Oncaspar or PEG Asparaginase or PEG L Asparaginase or PEGLA or Polyethylene Glycol L Asparaginase or Polyethylene Glycol L Asparaginase).tw.	126
10	(ASP1 or Cristanaspase or L Asnase or Asparaginase II or Colaspase or Elspar or Kidrolase or L Asnase or L ASP or L Asparaginase or L Asparagine Amidohydrolase or Laspar or Lcf ASP or Leucogen or Leunase or Paronal or Serasa).tw.	1483
11	(Prednisone or delta1Cortisone or Dehydrocortisone or Adasone or Cortancyl or Dacortin or DeCortin or Decortisyl or Decorton or Delta-Dome or Deltacortene or Deltacortisone or Deltadehydrocortisone or Deltasone or Deltison or Deltra or Econosone or Lisacort or Meprosona-F or Metacortandracin or Meticorten or Ofisolona or Orasone or Panafcort or Panasol or Paracort or PRED or Predicor or Predicorten or Prednicen or Prednicort or Prednidib or Prednilonga or Predniment or Prednisonum or Prednitone or Promifen or Servisone).tw.	14267
12	(Vincristine Sulfate or Kyocristine or Leurocristine Sulfate or Leurocristine sulfate or Oncovin or Vincasar or Vincosid or Vincrex or Vincristine sulfate).tw.	365
13	(idarubicin or zavedos or idamycin or IDR or idarubicin hydrochloride or 4demethoxydaunorubicin or 4DMDR or IMI30).tw.	1570
14	(lenograstim or lenograstim$).tw.	231

15	or/2-14	84632
16	(Afatinib or gilotrif or Apatinib or YN968D1 or Axitinib or Bosutinib or Bosulif or Cabozantinib or Canertinib or Cediranib or Crenolanib or Crizotinib or CYT387 or Damnacanthal or Dasatinib or Sprycel or Erlotinib or Filgotinib or Foretinib or Fostamatinib or Gefitinib or Grandinin or Ibrutinib or Icotinib or Imatinib or Gleevec or Lapatinib or Lestaurtinib or Lestaurtinib or Linifanib or Motesanib or Mubritinib or Neratinib or Nilotinib or Tasigna or Nintedanib or Pacritinib or Pazopanib or Ponatinib or iclusig or Quizartinib or Radotinib or Regorafenib or Ruxolitinib or Saracatinib or Semaxanib or Sorafenib or Sunitinib or Tivozanib or Toceranib or Tofacitinib or Vandetanib or Vatalanib or Vemurafe or Angiokinase inhibitors).tw.	28052
17	exp stem cell transplantation/ or exp allotransplantation/ or exp transplantation/ or exp hematopoietic stem cell transplantation/ or allogenic transplant.mp.	268544
18	16 and 17	965
19	15 or 18	85521
20	1 and 19	2828
21	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/	1714202
22	Animal/ not Human/	1932396
23	21 or 22	3602652
24	20 not 23	2286
25	limit 24 to (human and english language and yr="2005 - 2015")	1069

Appendix 4A: DFCI regimen used in DeAngelo et al [15]

Time Frame	*Treatment*
Induction	Vincristine 2 mg weekly, days 1, 8, 15 and 22
4 Weeks	Prednisone 40 mg/m^2/day, days 1–28
	Doxorubicin 30 mg/m^2/dose, days 1and 2
	Methotrexate 4 g/m^2 (8–24 h after doxorubicin) with leucovorin rescue on day 3
	E coli L-asparaginase 25 000 IU/m^2 IM × 1 dose, day 5
	IT cytarabine 50 mg, day 0[a] (prior to initiation of systemic therapy)
	IT methotrexate/cytarabine/hydrocortisone,[b] days 15 and 29
CNS therapy	Vincristine 2 mg × 1 dose
3 Weeks	6-mercaptopurine (6-MP) 50 mg/m^2/day orally, × 14 consecutive days
	Doxorubicin 30 mg/m^2 × 1 dose
	IT methotrexate/cytarabine twice weekly × 4 doses
	Cranial radiation[c]
Intensification	*Every 3-week cycles:*
30 Weeks	Vincristine 2 mg, day 1
	Dexamethasone 18 mg/m^2/day b.i.d., orally, days 1–5
	Doxorubicin 30 mg/m^2, day 1 of each cycle to a (cumulative dose 300 mg/m^2)
	6-MP 50 mg/m^2/day orally × 14 consecutive days
	E. coli asparaginase
	Individualized dosing: 12 500 IU/m^2/dose (starting dose)[d]
	Methotrexate 30 mg/m^2 i.v. or IM weekly, 1 day after asparaginase (no weekly methotrexate until doxorubicin completed).
	IT methotrexate/cytarabine/hydrocortisone at start of a cycle
	IT therapy consisting of methotrexate/cytarabine at start of a cycle every 18 weeks
Continuation	*Every 3-week cycles:* Same as intensification except no asparaginase and dexamethasone dose reduced to
74 weeks	6 mg/m^2/day

Abbreviations: ALL, acute lymphoblastic leukemia; CSF, cerebrospinal fluid; CNS, central nervous system; DFCI, Dana-Farber Cancer Institute; IM, intramuscular; IT, intrathecal.

[a] Patients with CNS leukemia at diagnosis (CNS-2 and CNS-3) received twice weekly doses of IT cytarabine until CSF was clear of blast cells on three consecutive examinations.

[b] IT methotrexate 12 mg; cytarabine 40 mg; hydrocortisone 50 mg.

[c] Patients received cranial radiation 1800 cGy delivered as 180 cGy fractions daily for 10 days. The dose was 24 Gy for patients with CNS-2 or CNS-3, regardless of CNS signs or symptoms.

[d] Asparaginase dose adjustments based on nadir serum asparaginase activity measurements.

Appendix 4B: JALSG-ALL202-U schedule used in Hawayaka et al [16]

Phases/drugs	*Route*	*Doses*	*Days*
Induction therapy (weeks 1-5)			
Methotrexate	IT	12 mg/body	1
Prednisolone	PO/IV	60 mg/m^2	1–7
Dexamethasone	IV	10 mg/m^2	8–14
Vincristine	IV	1.5 mg/m^2 [a]	8, 15, 22, 29
THP-adriamycin	IV	25 mg/m^2	8, 9
Cyclophosphamide	IV	1200 mg/m^2	10
L-asparaginase	IV/IM	6000 U/m^2	15, 17, 19, 21, 23, 25, 27, 29
Prednisolone	PO	40 mg/m^2	15–28
IT-triple[b]	IT		8, 22[c]
Consolidation thrapy (weeks 6-9)			
Cyclophosphamide	IV	750 mg/m^2	1, 8

Phases/drugs	*Route*	*Doses*	*Days*
THP-adriamycin	IV	25 mg/m^2	1, 2
Cytarabine	IV	75 mg/body	1–6, 8–13[d]
Mercaptopurine	PO	50 mg/m^2	1–14
IT-triple[b]	IT		1, 8
Sanctuary therapy (weeks 10–11)			
Methotrexate[e]	IV (24 h)	3 g/m^2	1, 8
IT-triple[b]	IT		2, 9
Reinduction therapy (weeks 12–15)			
Vincristine	IV	1.5 mg/m^2 [a]	1, 8, 15
THP-adriamycin	IV	25 mg/m^2	1, 8
Cyclophosphamide	IV	500 mg/m^2	1, 8
L-asparaginase	IM	6000 U/m^2	1, 3, 5, 8, 10, 12
Prednisolone	PO	40 mg/m^2	1–14
IT-triple[b]	IT		1
Reconsolidation therapy (weeks 16–19)			
Same as consolidation therapy			
Maintenance therapy 1-A (weeks 20–25) for CNS-invasion-negative cases			
Methotrexate	IV	150 mg/m^2	1, 15, 29
Mercaptopurine	PO	50 mg/m^2 [f]	1–28
IT-triple[b]	IT		29
Maintenance therapy 1-B (weeks 20–25) for CNS-invasion-positive cases			
Cranial irradiation		1.5 Gry × 8	1–12[g]
Methotrexate	IV	150 mg/m^2	29
Mercaptopurine	PO	50 mg/m^2 [f]	1–28
IT-triple[b]	IT		1, 8
Maintenance therapy 2 (weeks 26–29, 46–49, 66–69, 86–89)			
Vincristine	IV	1.5 mg/m^2 [a]	1, 8, 15
Cyclophosphamide	IV	600 mg/m^2	8
L-asparaginase	IM	10000 U/m^2	1, 8, 15
Prednisolone	PO	40 mg/m^2	1–14
Maintenance therapy 3 (weeks 30–35, 40–45, 50–55, 60–65, 70–75, 80–85, 90–95)			
Methotrexate	IV	150 mg/m^2	1, 15, 29
Mercaptopurine	PO	50 mg/m^2 [f]	1–28
IT-triple[b]	IT		29[hi]
Maintenance therapy 4 (weeks 36–39, 56–59, 76–79, 96–98)			
Vincristine	IV	1.5 mg/m^2 [a]	1, 8, 15
THP-adriamycin	IV	25 mg/m^2	8
L-asparaginase	IM	10 000 U/m^2	1, 8, 15
Prednisolone	PO	40 mg/m^2	1–14

Abbreviations: CNS, central nervous system; JALSG, Japan Adult Leukemia Study Group; IM, intramuscularly; IT, intrathecally; IV, intravenously; PO, per os; WBC, while blood cell.

[a] Maximum dose was 2 mg per body.

[b] IT-triple consisted of methotrexate 12 mg, cytarabine 30 mg and hydrocortisone 25 mg.

[c] On days 8, 11, 15, and 22, when CNS invasion was positive.

[d] Administration was stopped, when neutrophil count went down to 0/l.

[e] With folinic acid rescue (15 mg/m^2, IV, six times every 6 h), beginning 42 h after the start of methotrexate infusion.

[f] Dose should be adjusted to keep WBC count from 2000 to 3000/ul.

[g] Eight times during this period.

[h] For CNS-invasion-negative cases.

[i] Not on weeks 74 and 94.

Appendix 4C: Hovon-70 protocol used in Rijneveld et al [14]

Drug	*Dose*	*Days*
Pre-phase		
Prednisone (PO)	60 mg/m^2 divided in two doses	1–7
Methotrexate (IT)	15 mg	1
Induction		
Prednisone (PO)	40 mg/m^2 divided in two doses	8–28
Vincristine (IV)	1.5 mg/m^2	8, 15, 22, 29
Daunorubicin (IV)	40 mg/m^2	8, 15, 22
Cyclophosphamide (IV)	1000 mg/m^2	8
L-asparaginase (IV)	6000 IU/m^2	8, 10, 12, 15, 17, 19, 22, 24, 26
Methotrexate (IT)	15 mg	8, 15 (22 when CNS pos)
Consolidation A (scheduled before day 45)		
6-thioguanine (PO)	60 mg/m^2	1–21
Cyclophosphamide (IV)	1000 mg/m^2	1, 15
Cytarabine (SC)	60 mg/m^2	1, 2, 8, 9, 15, 16
Methotrexate (IT)	15 mg	1, 15
Consolidation B (scheduled before day 75)		
Prednisone (PO)	40 mg/m^2	29–35
Vincristine (IV)	1.5 mg/m^2	29, 43
6-mercaptopurine (PO)	50 mg/m^2	29–49
Methotrexate (IV)	5000 mg/m^2	29, 43
Methotrexate (PO)	25 mg/m^2	36
Methotrexate (IT)	15 mg	29, 43
Intensification IA (scheduled before day 105)		
Dexamethason (PO)	10 mg/m^2	1–14, taper in 1 week
Vindesine (IV)	3 mg/m^2	1, 8, 15
Adriamycine (IV)	25 mg/m^2	1, 8, 15
L-asparaginase (IV)	6000 IU/m^2	4, 6, 8, 10, 12, 15
Methotrexate (IT)	15 mg	1 (15 when CNS pos)
Intensification IB (scheduled before day 135)		
6-thioguanine (PO)	60 mg/m^2	29–49
Etoposide (IV)	150 mg/m^2	29, 36, 43
Cytarabine (SC)	60 mg/m^2 in two doses	29, 30, 36, 37, 43, 44
Methotrexate (IT)	15 mg	29
Interphase A (scheduled before day 165)		
Prednisone (PO)	40 mg/m^2	1–7
Vincristine (IV)	1.5 mg/m^2	1, 15
6-mercaptopurine (PO)	50 mg/m^2	1–22
Methotrexate (IV)	5000 mg/m^2	1, 15
Methotrexate (PO)	25 mg/m^2	8, 22
Methotrexate (IT)	15 mg	1, 15
Interphase B (scheduled before day 195)		
Prednisone	40 mg/m^2	29–35
Vincristine	1.5 mg/m^2	29, 43
6-mercaptopurine	50 mg/m^2	29–49
Methotrexate (IV)	5000 mg/m^2	29, 43
Methotrexate (PO)	25 mg/m^2	36

Drug	*Dose*	*Days*
Methotrexate (IT)	15 mg	29, 43
Cranial irradiation (only when CNS pos)	24 Gy	
Intensification IIA (scheduled before day 225)		
Prednisone (PO)	40 mg/m^2	1–14
Vincristine (IV)	1.5 mg/m^2	1, 8, 15
Daunorubicin (IV)	30 mg/m^2	1, 8, 15
L-asparaginase (IV)	6000 IU/m^2	4, 6, 8, 10, 12, 15
Methotrexate (IT)	15 mg	1
Intensification IIB (scheduled before day 255)		
6-thioguanine (PO)	60 mg/m^2	29–49
Cyclophosphamide (IV)	1000 mg/m^2	29
Cytarabine (SC)	60 mg/m^2 in two doses	29, 30, 36, 37, 43, 44
Methotrexate (IT)	15 mg	29
Maintenance (scheduled before day 285)		
6-mercaptopurine (PO)	75 mg/m^2	1–21
Methotrexate (PO)	25 mg/m^2	1, 8, 15
***Re-induction courses (× 12) (scheduled before** day 415)*	15 mg	
Prednisone (PO)	40 mg/m^2	1–7
Vincristine (IV)	1.5 mg/m^2	1
Methotrexate (IT)	15 mg	1

Abbreviations: CNS, central nervous system; HOVON, Dutch-Belgian cooperative trial group for Hematology Oncology; IV, intravenous; IT, intrathecal; PO, per os; pos, positive.
Cumulative doses: L-asparaginase 126.000 IU/m^2, methotrexate 30.000 g/m^2, prednisone 7280 mg/m^2, vincristine 42 mg/m^2.

Appendix 4D: Tawam protocal used in Hassan et al [17]

Phase and therapy	Dosage	Route of administration	Days administered
Phase 1, weeks 1–4			
Idarubicin	10 mg/m^2	IV	1–3
Vincristine	1.4 mg/m^2	IV	1, 8, 15, 22
Cyclophosphamide	1,200/m^2	IV	1
Dexamethasone	10 mg/m^2	PO	1–5
Intensification, weeks 5–8			
Cyclophosphamide	1,500 mg/m^2	IV	1, 15
Adriamycin	50 mg/m^2	IV	1, 15
Vincristine	1.4 mg/m^2	IV	1, 15
Dexamethasone	10 mg/m^2	PO	1–5 and 15–19
Consolidation (one course)			
AraC	3,000 mg/m^2	IV	1, 3, 5
CNS therapy			
Methotrexate	10 mg/m^2	IT	
Hydrocortisone	50 mg	IT	
Maintenance (2 years)			
Vincristine	1.4 mg/m^2	IV	1 (monthly)
Dexamethasone	10 mg/m^2	PO	1–5 (monthly)
Methotrexate	20 mg/m^2	PO	Weekly
6-Mercaptopurine	75 mg/m^2	PO	Daily

IV, intravenously; PO, by mouth; IT, intrathecally

Appendix 4E: FRALLE protocol used in Hocking et al [18]

Drug	*Dose*	*Days*
Induction		
Prednisolone	30 mg/m^2 O, BD 1-7	
Prednisolone	13.35 mg/m^2 O, TDS	8-21
Daunorubicin	40 mg/m^2 IV	8, 15, 22
*For patients with high risk disease	40 mg/m^2 IV	8, 9, 10, 15
Vincristine	1.5 mg/m^2 IV	8, 15, 22, 29
Asparaginase	10,000 IU/m^2 IV	22, 24, 26, 28, 30, 32
CNS		1, 8, 15
- Methotrexate	15 mg IT	
- Cytarabine	40 mg IT	
- Hydrocortisone	50 mg IT	
Consolidation		
Etoposide	150 mg/m^2 IV	1, 8, 15
Cytarabine	30 mg/m^2 SC, BD	1, 2, 8, 9, 15, 16
6-Thioguanine	60 mg/m^2 O	1-21
Prednisolone	13.3 mg/m^2 O, TDS	26-28
Vincristine	1.5 mg/m^2 IV	29
6-Mercaptopurine	50 mg/m^2 O	29-50
Methotrexate	25 mg/m^2 O, TDS	29, 36, 43
CNS		1, 15, 29, 43
Delayed Intensification 1		
Vindseine	3 mg/m^2 IV	1, 8, 15
Doxorubicin	25 mg/m^2 IV	1, 8, 15
Asparaginase	6,000 IU/m^2	1, 3, 5, 8, 10, 12
Dexemethasone	3.3 mg/m^2	1-7
Etoposide	150 mg/m^2 IV	29, 36, 43
Cytarabine	30 mg/m^2 SC, BD	29, 30, 34, 36, 37, 44
6-Thioguanine	60 mg/m^2 O	29-49
CNS		1, 15, 29, 43
Interim Maintenance		
Vincristine	1.5 mg/m^2 IV	1
Prednisolone	13.3 mg/m^2 O, TDS	1-8, 29-36
Methotrexate	25 mg/m^2 O, TDS	1, 8, 15, 22, 29, 36
6-Mercaptopurine	50 mg/m^2 O	1-49
CNS		1
Cranial RT	1800 cGy	40-55
Delayed Intensification 2		
Vindesine	3 mg/m^2 IV	1, 8, 15
Daunorubicin	30 mg/m^2 IV	1, 8, 15
Asparaginase	6,000 IU/m^2	1, 3, 5, 8, 10, 12
Prednisolone	13.3 mg/m^2 O, TDS	1-14
Etoposide	150 mg/m^2 IV	29, 43
Cytarabine	30 mg/m^2 SC, BD	29, 30, 43, 44
6-Thioguanine	60 mg/m^2 O	29-49
Maintenance		
Vincristine	1.5 mg/m^2	1, 29, 57, 85, 113, 141
Prednisolone	13.3 mg/m^2 O, TDS	1-7, 29-35, 57-63, 85-91, 113-119, 141-147

Drug	*Dose*	*Days*
6-Mercaptopurine	50 mg/m^2	8-28 each month for 18 months
Methotrexate	25 mg/m^2	Weekly from D8 for 18 months

O, oral; IV, intravenous; SC, subcutaneous; IT, intrathecal; BD, twice daily; TDS, three times daily; cGy, centigray.

Ontario Health
Cancer Care Ontario

Evidence Summary 12-16

Systemic Therapy in Acute Lymphoblastic Leukemia

Document Review Summary

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February 16, 2021

The 2016 evidence review is

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes

OVERVIEW

The original version of this evidence summary was released by the OH (CCO) Program in Evidence-based Care on June 22, 2016.

In November 2018, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature in July 2020. Clinicians from the Hematology Disease Site Group and the Stem Cell Transplantation Advisory Committee determined that the scope of the topic had changed and a literature review based on the search strategy of the original document had failed to retrieve known relevant studies. They agreed that the evidence summary should be archived.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Compared with adult regimens, is there a benefit in the use of pediatric-inspired regimens for the management of non-pediatric patients with ALL?
2. In the management of Ph+ ALL patients, does the addition of a TKI to the treatment regimen improve patient outcomes?

Target Population
This is targeted to adult patients, defined as those 16 years and older, with ALL.

Study Selection Criteria
Studies had to report at least one of the following outcomes: remission rates, survival rates, toxicity, or quality of life.
Exclusion Criteria
The following exclusion criteria were applied to the entire literature search:

- Case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies.
- Conference abstracts.
- Studies on cost-effectiveness, utility, and economics.
- Studies with fewer than 30 participants.
- Studied with a population median age of less than 10 years.
- Studies published in a language other than English, due to the lack of funding and resources for translation.

Search Details

- 2015 to July 2020 (Cochrane Database of Systematic Reviews)
- November 2015 to July 2020 (Medline and Embase)
- November 2015 to July 2020 (Medline and Embase)

Summary of new evidence
Out of 1311 hits from the search of Medline, Embase, and the Cochrane Database for systematic reviews, 25 publications were included. Three articles reported only QoL/toxicity outcomes. No guidelines or systematic reviews were identified. Most of the identified primary studies were non-comparative studies. See the evidence table for the results.

Evidence Tables

Author [Ref] Study Name	Regimen Base (Modified Regimen)	Study Objective & Median Duration of Follow-up	Population	Results (95% CI)
Pediatric-inspired regimens for the management of non-pediatric patients with ALL				
NON-COMPARATIVE STUDIES				
Sasaki et al 2020 [1]	Hyper-CMAD + Liposomal Vincristine	To evaluate toxicity and response outcomes of using liposomal rather than regular vincristine Med F/U: 59 mo (range, 0.3-70 months)	Newly diagnosed adults with B-cell with CD +ve (42%) & Ph+ve (68%) Med age: 53 N=31	In newly diagnosed ALL, the combination of Hyper CMAD with liposomal vincristine is safe **CR:** 97% **CRD:** 73%% (44.4% to 58.7%) at 5yr **OS:** 61% (60.7% to 79.0%) at 5yr
Hanbali et al 2019[2]	**Children's Cancer Group 1900 protocol** (AYA-15 ALL protocol)	To assess efficacy and tolerability of using a pediatric-inspired protocol in AYA patients Med F/U: 5yr	newly diagnosed high--risk Ph-ve ALL patients Med Age =18 (14-34) N=40	Pediatric inspired regimen for the treatment high risk AYA patients improved survival outcomes. The side effects were tolerable. **CR:** 93% **DFS:** 72% at 5yr **EFS:** 60% at 5yr **OS:** 75%% at 5yr
Li et al 2019[3]	Modified BFM-ALL-95	To evaluate the outcomes by using the modified regimen Med F/U = 34mo	Newly diagnosed Chinese adults with standard-risk ALL treated with the modified ALL-BFM 95 regimen PH-VE Med Age 27 (range 19-34) N=46	**The modified regimen was well tolerated as no toxicity related death was recorded.** **HCR 91.3%** **MCR: 76.1%** **EFS: 58% (95% CI, 42.1-73.9%) at 5yr:** **OS: 66.7% (95% CI, 51.4-82.0%) at 5yr:**
Huguet et al 2018\[4] GRAALL-2005	Std-CT vs. HyperC	To evaluate randomly the role of hyper-C dose intensification and to determine the upper age limit for treatment tolerability. Med F/U = 5.2yr	Adults with newly diagnosed Ph negative ALL Med Age = 36.1yr N=787	**Std-CT vs. HyperC @ 5yr** CR: 90.2% vs. 93.6% EFS: 50.1(44.9 to 55.1) vs. 54.2(49.0 to 59.2), P = 0.25 OS: 57.4(52.2 to 62.3) vs. 59.5 (54.2 to 64.3) p= 0.45 Note: 55yrs was found to be a good cut off age for treatment tolerability
Guzauskas et al 2017[5]	hyper-CVAD + protocol	To estimate the risk–benefit trade-off of a pediatric-inspired regimen for first-line treatment of AYA	AYA with Ph-ve ALL	**After 10 years of follow up, pediatric-inspired protocols was associated with a 0.32 (95% credible range 18-0.49) and 0.24 24 (95% credible range 0.09-0.42) increase in life-years and QALYs respectively.**
Burke et al 2018[6]	six planned pegaspargase doses, 2000 IU/m2/dose intravenously	We studied the frequency and characteristics of high-grade pegaspargase-related hepatotoxicity	newly diagnosed adults on a pediatric-in-spired regimen that	**Pegaspargase at this dose and interval is associated with high hepatotoxicity rates, but patients can be rechallenged despite earlier pegaspargase-related hepatotoxicity.**

Author [Ref] Study Name	Regimen Base (Modified Regimen)	Study Objective & Median Duration of Follow-up	Population	Results (95% CI)
			Age = 18 to 57 N= 51	
COMPARATIVE				
Kim et al. 2020[7]	Pediatric-inspired protocol: median of 14 doses of L-asparaginase	to investigate the relationship between treatment patterns and outcomes in Korean AYA diagnosed with ALL	Age = 10 to 29 N = 1168	**Treatment with pediatric inspired protocol showed significan survival benefit compared to adult protocol.** **Five year OS: 53·3% vs. 40·4%; P < 0·0001**
Liang et al 2018[8]	CT + E. coli or PEG asparaginase + TKI for PH+ patients (Hyper CVAD)	To investigate the efficacy and safety of PEG asparaginase compared to E-coli asp	newly diagnosed ALL Med Age = 27.4 (14 to 62) N = 122	CR: 95.65 vs. 90.79% RFS: 10.00 vs. 8.57m OS: 14.07 vs. 16.29m PEG asparaginase showed a comparable efficacy with E-coli asparaginase. However, PEG was significantly better in the e prevention of central nervous system leukemia in AYAs
Sakura et al 2018[9] JALSG ALL202-O (ALL202-O)	Hd-MTX vs. Id-MTX	Comparing Hd-MTX therapy with intermediate-dose (Id)-MTX therapy.	Philadelphia chromosome (Ph)-negative ALL patients Med Age = 43yr N = 232	**CR:** 86% **DFS:** 58% **(95% CI, 45% to 58%)** Vs. 32%(95% CI, 22% to 43%) : P = 0 .0218 **OS:** 64% **(95% CI, 51% to 74%) vs.** 48% **(95% CI, 37 to 59%)** : P=0.2381 The 5yrs survival benefits were significantly better in the high dose compared to the intermediate MTX dose in treating AYAs.
Liu et al 2016[10]	CT + E. coli asparaginase vs. CT + PEG asparaginase UKALLXII/ECOG E2993-based regimen	compared with E. coli-asparaginase Med F/U = 42.4 mos 41.2 (17.7-86.8) and 43.6 (18.4-85.2)	adult patients with newly diagnosed standard-risk ALL Med Age = 26 (16 to 35) N = 122	**CR: 44% vs. 67%% (P = 0.032)** **EFS: 46.9% vs. 43.6% (P = 0.632)** **OS: 48.1 vs. 46.2% (P = 0.769)** **PEG-A did not show significant improvement in survival and asparaginase-related toxicity over E-coli-A**
Rytting et al 2016[11]	ABFM vs Hyper CVAD	To investigated the use of ABFM regimen in AYA.	AYA with Ph negative ALL Med age 22 vs 27	**CR: 93% vs. 98%** **OS: 60% vs. 60%** **Both regimen showed comparative survival and response benefits.**
El-Cheikh et al [12]	Hyper CVAD vs ABFM-like	Med F/U 29mos	adult ALL patients treated with either hyper-CVAD or a BFM like therapy	**CR: 74% vs. 75%** **DFS: 54.7% vs. 76.4% (P = 0.435)** **OS: 71.9% vs. 76.9% (P = 0.808** **There was no survival benefit between the two arms.**

TKI in the management of Ph-positive acute lymphoblastic leukemia				
NON-COMPARATIVE STUDIES				
Shin et al [13]	Ct + imatinib	To analyzed the outcomes and prognostic factors	children with Ph+ ALL. All patients received HCT post diagnosis. Med Age = 12.7 N = 31	**CR:** 100% **EFS:** 64.5% at 5yr **OS:** 75%. at 5yr **Continuation of TKI into the consolidation Phase may be beneficial in optimizing post-HCT**
Liu et al 2019[14]	Induction CT + nilotinib followed by Consolidation CT or HCT	to investigate the efficacy and safety of nilotinib combined with multi-agent chemotherapy in newly diagnosed Ph+ ALL	newly diagnosed Ph+ ALL Age > 15 N= 30	**HCR 100%** **MCR: 83.3%** **HRFS: 54% at 4yr: Med = 18mo** **MRFS: 53% at 4yr: Med = 19mo** **OS: 45% at 4yr: Med= 47.5mo** **The addition of nilotinib to a cytotocix CT was effective.**
Akahoshi et al 2019[15]	TKI followed by HSTC	whether TKI prophylaxis for –ve MRD after HSCT would improve patient outcomes Med F/U = 7yr	Ph+ ALL patients who received TKI before undergoing allo-HSCT Age: >15yr N=850	**OS: 72.1%** (95% CI, 68.7%-75.3%) at 4yr TKI prophylaxis before HSTC was not associated with a decreased risk of relapse.
Lou et al [16] CALLG2008	imatinib + CT (CALLG2008 protocol)	Med F/U = 24.2	newly diagnosed adult patients with Ph+ ALL Med Age = 40(range, 18–68 N=153	**HCR 96.7%%** **EFS: 49.2% (95% CI, 38.3%-59.2%) at 3yr:** **OS: 49.5% (95% CI, 38.5%-59.5%) at 3yr:** **Imitamib in combination with the CALLG2008 was effective in treaing Ph+ve ALL**
Jabbour et al 2018[17]	hyper-CVAD + ponatinib	to evaluate the long-term efficacy and safety of combination Med F/U = 36mo	newly diagnosed previously untreated Ph+ ALL Med Age 47 N=76	**CR: 83% (95% CI 69-91)** **EFS: 67% (95% CI 53-78) @ 5yr** **OS: 71% (95% CI 57-81) @5yr** **At a median follow up of 36 months, panatinib in combination with Hyper-CVAD showed sustained remission and survival outcome with a 5yr continuous CR, EFS and OS of 83% (95% CI 69-91), 67% (53-78), and 71% (57-81) respectively.**
Fujisawa et al 2017[18]	imatinib + CT	To investigate the efficacy of imatinib-based therapy with intensified consolidation therapy in patients with Ph+ ALL in the prevention of early relapse. Med F/U = 34mo	newly diagnosed BCR-ABL-positive ALL in adults Age = 49 N= 68	**CR: 95.6%eDFS: 52% (95% CI: 37%-66%) at 3yr** **OS: 62% (95% CI, 49%-72%) at 3yr**
Yoon et al 2016[19]	dasatinib + CT	To assess the MRD-based effect and long-term outcome of first-	Adults with Ph+ve ALL.	CR: 98% DFS: 52% (95% Cl, 37.4%–64.7%) at 4yr

		line TKI into chemotherapy	Med age: 46yr N= 51	OS: 51% (95% Cl, 36.6%–63.6%) at 4yr
Kuang et al[20]	Imatinib +interferon-α + CT	integrating imatinib and interferon-α into maintenance therapy Med F/U = 32 months	Adult Ph+ ALL patients with ineligible for allo-HSCT) Med Age = 36 N=41	CR: 98% DFS: 42.7% (95% Cl, 34.1%–51.3%) at 3yr OS: 57.9% (95% Cl, 49.5%–66.3%) at 3yr The combination of imatinib and interferon α improved survival in adult Ph+ ALL patients
Ravandi et al 2016[21]	Hyper CVAD + igh-dose cytarabine and methotrexate with dasatinib.	To determine the feasibility of addition of dasatinib to CT before HCT is feasible Med F/U = 36 mos	newly diagnosed Ph+ ALL med Age = 44 N = 94	CR: 88% EFS: 55% (95% Cl, 46% to 66%) at 3yr RFS: 62% (95% Cl 52% to 74%;%) at 3yr OS: 69% (95% Cl, 52% to 79%) at 3yr Dasatinib to CT and HCT isa feasible treatment option in in younger patients with Ph+ve ALL
Rousselot et al[22] EWALL-PH-1 Study	Dasatinib + CT	To investigate dasatinib in combination with low-intensity chemotherapy.	Elderly Ph+ ALL Med Age = 69 N = 71	CR: 96% EFS: 27% (95% CI, 17-37) at 5yr; Med = 18.9 mos RFS: 28% (95% CI, 18-39) at 5yr; Med = 19.1mos OS: 36% (95% CI, 25-47) at 5yr; Med = 25.8mos Dasatinib, combined with low-intensity chemotherapy, gave 36% 5-year overall survival in Ph+ ALL patients older than age 55 years.
COMPARATIVE STUDIES				
Wang et al 2018[23]	Imatinib +CT Vs. Allo-HSCT	to compare the outcomes of the combination of TKIs and chemotherapy versus Allo-HSCT in patients with Ph+ ALL. Med F/U = 41.5mo	patients diagnosed with Ph+ ALL Med age: 37yr N= 145	**TKI vs. HCT** **CR:** 98% vs. 96% CIR: 41.4% (95% CI, 34.9% to 47.9%) vs. 19.8% (95% CI, **15.3% to 24.3%,**): P < .001 **DFS:** 43.9% **(95% CI, 39% to 52.2%)** Vs. 71.3%(95% CI, 66.2% to 76.4%) : P < .001 **OS:** 45.6% **(95% CI, 39.2% to 52%) vs**. 82.6% **(95% CI, 78.2 to 87%)** : P < .001 Allo-HSCT shows significantly better survival benefit in patients with Ph+ ALL compared with TKIs + CT especially in intermediate- and high-risk patients.
Hatta et al 2018 [24] JALSGPh+ALL202	Imatinib +CT vs. CT	To investigate the survival benefits of imatinib for Ph+ALL patients. Med F/U = 4.5yr	newly diagnosed Ph+ ALL Med Age = 45 N = 99	**CR:** 97% vs 59%. P < 0.001 **DFS:** 43% (95% CI, 33–53%) vs.19% (95% CI, 11–29%) P = 0.001 **OS:** 50% (95% CI, 40–60%) vs. 15% (95%CI, 10–21%); P < 0.001
Sasaki et al 2016[25]	Hyper CVAD + panatinib vs. Hyper CVAD + dasatinib	To compare the efficacy of two TKI in Ph+ve ALL patients		**EFS: 69% vs. 46% (p= 0.04)** **OS: 83% vs. 56% (p= 0.-3)** **Adition of ponatinib to Hyper CVAD demonstrated significantly better survival benefits compared to dasatinib.**

ABFM: Augmented Berlin–Frankfurt–Münster; ALL: acute lymphoblastic leukemia; Allo: allogeneic; AYA: adolescents and young adults; BFM: Berlin-Frankfurt-Muster; CD +ve: percentage of CD20 expression 20% or above; CI: confidence interval; CIR: cumulative incidence of relapse; CMR: complete molecular response; CR: complete remission; CRD:

complete remission duration; CT: chemotherapy; DFS; disease free survival; E. coli: Escherichia coli; EFS: event free survival; HCR: hematologic complete remission; HCT: hematopoietic cell transplantation; Hd: high dose; HRFS: hematologic relapse free survival; HSCT: hematopoietic stem cell transplantation; Hyper-C: hyperfractionated cyclophosphamide; Hyper-CMAD: cyclophosphamide and liposomal vincristine; Hyper-CVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; Ld: low dose; MCR: molecular complete remission; Med: median; Med F/U: median follow up; Mo(s): month(s); MRD: minimal residual disease; MRFS: molecular relapse free survival; MTX: methotrexate; OS: overall survival; PEG: polyethylene glycol-conjugated; Ph+ve: Philadelphia chromosome positive; QALY: quality-adjusted life years; RFS: relapse free survival; Std-C: standard dose of cyclosphosphamide; TKI: tyrosine kinase inhibitors; Yr: year

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