Ann Hematol (2016) 95:87–92
DOI 10.1007/s00277-015-2510-0

ORIGINAL ARTICLE

Meta-analysis and meta-regression analysis to compare the outcomes of chemotherapy for T- and B-lineage acute lymphoblastic leukemia (ALL): the use of dexamethasone, L-asparaginase, and/or methotrexate may improve the outcome of T-lineage ALL

Shinichi Kako[1] · Yu Akahoshi[1] · Naonori Harada[1] · Hirofumi Nakano[1] · Kazuaki Kameda[1] · Tomotaka Ugai[1] · Hidenori Wada[1] · Ryoko Yamasaki[1] · Yuko Ishihara[1] · Koji Kawamura[1] · Kana Sakamoto[1] · Miki Sato[1] · Masahiro Ashizawa[1] · Kiriko Terasako-Saito[1] · Shun-ichi Kimura[1] · Misato Kikuchi[1] · Hideki Nakasone[1] · Rie Yamazaki[1] · Junya Kanda[1] · Junji Nishida[1] · Yoshinobu Kanda[1]

Received: 30 June 2015 / Accepted: 16 September 2015 / Published online: 22 September 2015

Abstract The effects of intensive regimens and the roles of drugs used might differ between T- and B-lineage acute lymphoblastic leukemia (ALL). We performed a literature search for clinical studies published from January 1998 to March 2013. Studies were eligible for inclusion in the analyses if they included more than 80 patients with adult ALL who were treated with a uniform regimen and compared T- and B-lineage ALL. Studies that included only adolescent or elderly patients were excluded. We identified 11 clinical studies, which included a total of 381 and 1366 patients with T- and B-lineage ALL, respectively, and performed meta-analyses using the selected studies. Nine studies included patients with Philadelphia chromosome-positive (Ph+) ALL. A meta-analysis using the random-effect model demonstrated superior survival in patients with T-lineage ALL compared to those with B-lineage ALL (hazard ratio 1.78, 95 % confidence interval 1.50–2.11), though the inclusion of patients with Ph+ ALL in B-lineage ALL must have influenced this result strongly. We performed meta-regression analyses, adjusted according to whether or not patients with Ph+ ALL were included in each study. Use of dexamethasone (Dex), higher dose of methotrexate (MTX), and higher dose of L-asparaginase (L-asp) were associated with a significant trend toward a better outcome in T-lineage ALL. A meta-regression analysis including Dex and the dose of L-asp or MTX together as covariates showed that these factors were independently significant. In conclusion, the use of Dex and high-dose L-asp or MTX may improve the outcome of T-lineage ALL. This hypothesis should be tested in a prospective study including only patients with Ph-negative ALL.

Keywords Meta-analysis · Acute lymphoblastic leukemia · Dexamethasone · Methotrexate · L-asparaginase

Introduction

The biological and clinical features of T- and B-lineage adult acute lymphoblastic leukemia (ALL) are considered to be different [1–3]. In fact, several clinical studies have demonstrated this fact based on different results in T- and B-lineage ALL [4–12].

Intensive combination chemotherapy regimens have improved the outcome of pediatric patients with ALL [13]. Based on this success, intensive regimens have been adopted for the treatment of adult patients with ALL, and these have led to better outcomes [14–16]. With regard to pediatric regimens, clinical studies have examined the dose intensification of non-myelosuppressive drugs. A superior outcome is

✉ Yoshinobu Kanda
ycanda-tky@umin.ac.jp

[1] Division of Hematology, Department of Internal Medicine, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama-city, Saitama 330-8503, Japan

achieved with the use of dexamethasone, compared to predonisone [17, 18], and high-dose methotrexate has also been shown to be effective [19]. In addition, the intensified use of L-asparaginase could improve the outcome [20]. Moreover, studies in pediatric patients have suggested that the dose intensification of drugs, such as methotrexate and L-asparaginase, may have different effects in T- and B-lineage ALL [21, 22]. However, the role of each individual drug has not been well established in adult regimens.

Therefore, in the present study, we performed meta-analysis and meta-regression analysis to compare the outcomes of chemotherapy for T- and B-lineage ALL.

Methods

Study selection

In April 2013, we performed a literature search for clinical studies published in English from January 1998 to March 2013 through PubMed by using key words, "acute lymphoblastic leukemia OR acute lymphocytic leukemia OR acute lymphoid leukemia AND adult AND chemotherapy". In addition, the studies were restricted to those in humans. The titles and abstracts of the identified articles were reviewed. Studies were eligible for inclusion in the analyses if they included more than 80 patients with adult ALL who received the primary treatment with a uniform regimen, and if a hazard ratio (HR) and its 95 % confidence interval (CI) comparing overall survival (OS), disease-free survival (DFS), or event-free survival (EFS) between patients with T- and B-lineage ALL were either reported or could be calculated. Studies that included only adolescent or elderly patients were excluded.

Outcome measures and data extraction

The primary outcome measure was OS. However, if OS was not reported in the identified studies, DFS or EFS was substituted for OS. Characteristics that were extracted from each study were the name of the first author, study title, year of publication, numbers of total patients, patients with T-lineage ALL, and those with B-lineage ALL, age of included patients, inclusion of Philadelphia chromosome-positive (Ph+) ALL, the rate of achieving first complete remission (CR1), the rate of transplantation in CR1, and HR and its 95 % CI for the primary outcome measure. In addition, the use of dexamethasone (Dex), total dose of cytosine arabinoside (AraC), total dose of methotrexate (MTX), and total dose of L-asparaginase (L-asp) during induction and consolidation regimens was collected. The dose of L-asp was calculated according to the International Union of Biochemistry (I.U.), and one unit or one Kyowa Unit (K.U.) was considered to be equal to 0.86 I.U.

If the HR and/or its 95 % CI of the primary outcome measure could not be extracted directly, the numbers of patients with T-lineage and those with B-lineage ALL, the total number of events of the primary outcome measure, and the *P* value were extracted. The HR and its 95 % CI were then calculated from these data [23].

Statistical analyses

We used the fixed-effect model and random-effect model to combine the HR in each study. Interstudy heterogeneity was tested by using the Cochran *Q* statistic (chi-square value), with a *P* value of less than 0.1 considered to be significant, and was quantified by using the I^2 statistic, where a value of 50 % or greater indicates substantial heterogeneity. Meta-regression analyses were performed using the factors extracted from each study, and factors with a *P* value of equal to or less than 0.1 were considered to be significant. We also performed a multivariate meta-regression analysis using significant factors. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University) [24], which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria). It uses a "meta" package for meta-analysis and a "metatest" package for meta-regression analysis [25].

Results

The primary literature search yielded 2870 articles, most of which could be excluded by screening their titles. The abstracts of the remaining 134 articles were reviewed. Finally, 11 clinical studies that were published between 1998 and 2013 were included in the following meta-analysis [7–10, 14, 16, 26–30].

The study characteristics are summarized in Table 1. These studies included a total of 381 patients with T-lineage ALL and 1366 patients with B-lineage ALL. Nine studies included patients with Ph+ ALL, but no study used tyrosine kinase inhibitors (TKIs) for those with Ph+ ALL. The primary outcome measure was OS in seven studies, DFS in two, and EFS in two.

Meta-analyses using the fixed-effect model and the random-effect model demonstrated superior survival in patients with T-lineage ALL compared to those with B-lineage ALL (HR 1.88, 95 % CI 1.73–2.05, and HR 1.78, 95 % CI 1.50–2.11, respectively), though there was significant heterogeneity among studies ($P<0.0001$) (Fig 1). We thought that this heterogeneity was attributed to whether or not patients with Ph+ ALL were included in each study, and therefore, we performed a meta-regression analysis regarding Ph+ ALL. The inclusion of patients with Ph+ ALL in a study showed a significant and positive correlation with superior

Table 1 Study characteristics

Reference	Study title	Published year	Primary outcome measure	No. of total Pts	No. of T-ALL Pts	No. of B-ALL Pts	Median age (range)	Ph+ ALL	Dex use	AraC total dose (g/m^2)[a]	MTX total dose (g/m^2)[a]	L-asp total dose (1000 IU/m^2)[a]	HR of primary outcome measure (B/T) (95 % CI)	CR rate (%)	Transplant rate in CR1 (%)
Larson et al. [7]	CALGB 9111	1998	DFS	185	29	115	35(16–79)	+	+	1.2	0.1	52	2.33(1.80–3.01)	85	N.M.
Ueda et al. [26]	JALSG ALL90	1998	DFS	180	20	121	43(15–78)	+	–	0	0.4	22	1.72(1.33–2.22)	69	19
Ribera et al. [10]	PETHEMA ALL93	2002	OS	86	17	69	33(19–50)	+	+	24	12	215	2.88(2.31–3.59)	79	N.M.
Kantarjian et al. [14]	MDACC	2004	OS	288	38	250	40(15–92)	+	+	48	4	0	1.90(1.55–2.33)	92	4
Tobinai et al. [27]	JCOG 9004	2007	OS	143	41	102	41(15–69)	+	–	0.48	0	60	1.43(0.90–2.27)	83	30
Bajel et al. [9]	modified GMALL(India)	2007	EFS	210	71	129	23(15–66)	+	–	1.35	0	63	1.63(1.29–2.06)	82	3
Wetzler et al. [28]	CALGB 9511	2007	OS	85	12	50	N.M.	+	–	0.6	0	N.M.[b]	1.91(0.86–4.28)	84	17
Huguet et al. [16]	GRALL	2009	EFS	225	76	149	31(15–60)	–	+	24	9.075	144	1.46(1.13–1.88)	93	34
Jinnai et al. [29]	JALSG ALL97	2010	OS	256	35	199	30(15–64)	–	+	0.8	1	18	0.83(0.52–1.32)	81	28
Azuma et al. [30]	JCOG 9402	2012	OS	108	23	85	34(15–69)	+	–	221	0.12	90	1.56(0.87–2.79)	81	36
Stock et al. [8]	CALGB 19802	2013	OS	161	19	97	40(16–82)	+	–	12	6.6	72	2.01(1.62–2.49)	80	11

Pts patients, *Ph+* Philadelphia chromosome-positive, *ALL* acute lymphoblastic leukemia, *Dex* dexamethasone, *AraC* cytosine arabinoside, *MTX* methotrexate, *L-asp* L-asparaginase, *HR* hazard ratio, *CI* confidence interval, *CR* complete remission, *DFS* disease-free survival, *OS* overall survival, *EFS* event-free survival, *N.M.* not mentioned

[a] Total dose of each drug was calculated by adding the doses used in induction and consolidation regimens

[b] Pegasparaginase was used in this study

survival in patients with T-lineage ALL (coefficient 0.49, P= 0.007), although superior survival in patients with T-lineage ALL was preserved at least in the fixed-effect model, even if studies that did not include patients with Ph+ ALL were separately analyzed (HR 1.28, 95 % CI 1.03–1.60 in the fixed-effect model and HR 1.14, 95 % CI 0.66–1.97 in the random-effect model). Next, we performed meta-regression analyses, adjusted for whether or not patients with Ph+ ALL were included in each study. Use of Dex, higher total dose of MTX, and higher total dose of L-asp in induction and consolidation regimens were associated with a significant trend toward a better outcome in T-lineage ALL compared to that in B-lineage ALL (Table 2). A meta-regression analysis including Dex and the dose of L-asp together as covariates showed that the effects of these factors were independently significant (P=0.023 and P=0.002, respectively) (Table 3a), and a meta-regression analysis including Dex and the dose of MTX together as covariates also showed that the effects of these factors were independently significant (P=0.102 and P=0.003, respectively) (Table 3b). We could not compare the effects of the doses of MTX and L-asp to avoid multicollinearity, since there was a strong correlation between these doses (data not shown).

Discussion

Many clinical studies have compared T- and B-lineage ALL [4–12]. However, the results of these comparisons have been inconsistent, partially because the studies included only a limited number of patients with T-lineage ALL, due to the relative rarity of T-lineage ALL in adult patients. Therefore, we performed a meta-analysis that included 381 patients with T-lineage ALL and found a superior outcome for T-lineage ALL.

We have to be careful about the significant interstudy heterogeneity in our meta-analysis. This heterogeneity might be attributed to the difference regarding whether or not each study included patients with Ph+ ALL. The inclusion of patients with Ph+ ALL in a study was positively related to superior survival in patients with T-lineage ALL. Although the inclusion of tyrosine kinase inhibitors (TKIs) in the present treatment of patients with Ph+ ALL has dramatically improved the outcomes of these patients [31], TKIs were not used in patients with Ph+ ALL in the studies that we included, since we chose clinical studies, in which uniform regimens were used in patients with T- and B-lineage ALL and we could not obtain the clinical data regarding patients limited to those with Ph-negative ALL from published articles. This fact must have influenced the results of the meta-analysis strongly. Superior survival in patients with T-lineage ALL was preserved at least in a fixed-effect model even if studies that did not include patients with Ph+ ALL were analyzed separately.

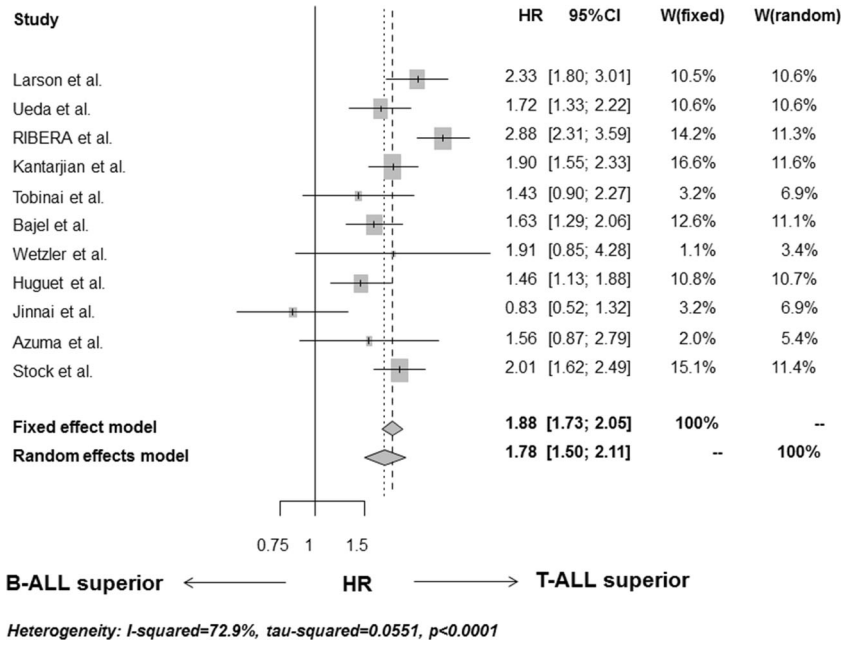

Fig. 1 Forest plot of the hazard ratio (HR) and 95 % confidence interval (CI) for survival in each study and the entire study. Meta-analyses using the fixed-effect model and the random-effect model demonstrated superior survival in patients with T-lineage acute lymphoblastic leukemia (ALL) compared to those with B-lineage ALL, though there was significant heterogeneity

In addition, we should be cautious, since we only included studies that made it possible to determine a HR and its 95 % CI for the comparison of survival between patients with T- and B-lineage ALL. It is possible that the authors who found a difference between T- and B-lineage ALL were more likely to provide detailed results, and this could have led to a reporting bias.

Through our meta-regression analyses, we demonstrated that the use of Dex, a higher total dose of MTX, or a higher total dose of L-asp might improve the outcome of adult patients with T-lineage ALL. Dose intensification of non-myelosuppressive drugs, such as MTX and L-asp, has been used in pediatric regimens and has led to excellent results, especially in pediatric patients with T-lineage ALL [21, 22]. The efficacy of dose intensification of non-myelosuppressive drugs, especially for T-lineage ALL, seems to be a common feature, independent of patient's age, although we have to confirm this result through clinical data regarding patients limited to those with Ph-negative ALL. Intensified chemotherapy based on pediatric regimens is now being extended to adolescents and young adults [32], and even to older patients in recent trials [16], and this treatment strategy might be considered more favorably for T-lineage ALL, even in adult patients.

In conclusion, the use of Dex and high-dose L-asp or MTX may improve the outcome of T-lineage ALL. This hypothesis should be tested in a prospective study including only patients with Ph-negative ALL.

Table 2 Meta-regression analysis adjusted for whether or not patients with Philadelphia chromosome-positive acute lymphoblastic leukemia were included

	Regression coefficient	Standard error	*P* value
Median age	−0.001	0.012	0.931
CR rate	0.756	1.070	0.478
Transplant rate in CR1	−0.264	0.608	0.664
Dex use	0.288	0.116	0.013
AraC total dose (g/m^2)	0.005	0.004	0.182
MTX total dose (g/m^2)	0.039	0.010	0.0001
L-Asp total dose (1000 IU/m^2)	0.002	0.001	0.0002

CR complete remission, *Dex* dexamethasone, *AraC* cytosine arabinoside, *MTX* methotrexate, *L-asp* L-asparaginase

Table 3 Multivariate meta-regression analysis including significant factors

	Regression coefficient	Standard error	*P* value
A			
Ph+ ALL	0.635	0.132	0.000002
Dex use	0.161	0.099	0.102
MTX total dose (g/m^2)	0.032	0.011	0.003
B			
Ph+ ALL	0.645	0.132	0.000001
Dex use	0.213	0.094	0.023
L-Asp total dose (1000 IU/m^2)	0.002	0.0006	0.002

Ph+ Philadelphia chromosome-positive, *ALL* acute lymphoblastic leukemia, *Dex* dexamethasone, *MTX* methotrexate, *L-asp* L-asparaginase

Compliance with ethical standards

Conflict of interest Kako S. reports grants and/or honoraria from MSD K.K., Kyowa Hakko Kirin Co., Ltd., and Nippon Shinyaku Co., Ltd. with regard to this study. Harada N. reports honoraria from Kyowa Hakko Kirin Co., Ltd. to this study. Kimura S. reports honoraria from Pfizer K.K. and Kyowa Hakko Kirin Co., Ltd. to this study. Misato Kikuchi reports grant from MSD K.K. to this study. Kanda J. reports grants and/or honoraria from Kyowa Hakko Kirin Co., Ltd., and Nippon Shinyaku Co., Ltd. with regard to this study. Kanda Y. reports grants and/or honoraria from MSD K.K., Pfizer K.K., Kyowa Hakko Kirin Co., Ltd., and Nippon Shinyaku Co., Ltd. with regard to this study.

Ethical approval Since this study was meta-analyses using published articles, an approval by an ethics committee and statement of informed consent were not applicable.

References

1. Armstrong SA, Look AT (2005) Molecular genetics of acute lymphoblastic leukemia. J Clin Oncol 23(26):6306–15. doi:10.1200/JCO.2005.05.047
2. Mullighan CG (2012) The molecular genetic makeup of acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2012:389–96. doi:10.1182/asheducation-2012.1.389
3. Riley RS, Massey D, Jackson-Cook C, Idowu M, Romagnoli G (2002) Immunophenotypic analysis of acute lymphocytic leukemia. Hematol Oncol Clin North Am 16(2):245–99, **v**
4. Boucheix C, David B, Sebban C, Racadot E, Bene MC, Bernard A, Campos L, Jouault H, Sigaux F, Lepage E et al (1994) Immunophenotype of adult acute lymphoblastic leukemia, clinical parameters, and outcome: an analysis of a prospective trial including 562 tested patients (LALA87). French Group on Therapy for Adult Acute Lymphoblastic Leukemia. Blood 84(5):1603–12
5. Czuczman MS, Dodge RK, Stewart CC, Frankel SR, Davey FR, Powell BL, Szatrowski TP, Schiffer CA, Larson RA, Bloomfield CD (1999) Value of immunophenotype in intensively treated adult acute lymphoblastic leukemia: cancer and leukemia Group B study 8364. Blood 93(11):3931–9
6. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, Lazarus HM, Franklin IM, Litzow MR, Ciobanu N, Prentice HG, Durrant J, Tallman MS, Goldstone AH (2005) Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 106(12):3760–7
7. Larson RA, Dodge RK, Linker CA, Stone RM, Powell BL, Lee EJ, Schulman P, Davey FR, Frankel SR, Bloomfield CD, George SL, Schiffer CA (1998) A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood 92(5):1556–64
8. Stock W, Johnson JL, Stone RM, Kolitz JE, Powell BL, Wetzler M, Westervelt P, Marcucci G, DeAngelo DJ, Vardiman JW, McDonnell D, Mrozek K, Bloomfield CD, Larson RA (2013) Dose intensification of daunorubicin and cytarabine during treatment of adult acute lymphoblastic leukemia: results of Cancer and Leukemia Group B Study 19802. Cancer 119(1):90–8. doi:10.1002/cncr.27617
9. Bajel A, George B, Mathews V, Viswabandya A, Kavitha ML, Srivastava A, Chandy M (2007) Adult ALL: treatment outcome and prognostic factors in an Indian population using a modified German ALL (GMALL) protocol. Leukemia 21(10):2230–3. doi:10.1038/sj.leu.2404785
10. Ribera JM, Ortega JJ, Oriol A, Granada I, Hernandez-Rivas JM, Parody R, Bethencourt C, Rivas C, Bastida P, del Potro E, Gonzalez-Valentin ME, Moreno MJ, Besalduch J, Fernandez-Calvo J, Tormo M, Arias J, Molines A, Sanz MA, Maldonado J, Milla F, Feliu E, San Miguel JF (2002) Prognostic value of karyotypic analysis in children and adults with high-risk acute lymphoblastic leukemia included in the PETHEMA ALL-93 trial. Haematologica 87(2):154–66
11. Larson RA, Dodge RK, Burns CP, Lee EJ, Stone RM, Schulman P, Duggan D, Davey FR, Sobol RE, Frankel SR et al (1995) A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 85(8):2025–37
12. Hunault M, Harousseau JL, Delain M, Truchan-Graczyk M, Cahn JY, Witz F, Lamy T, Pignon B, Jouet JP, Garidi R, Caillot D, Berthou C, Guyotat D, Sadoun A, Sotto JJ, Lioure B, Casassus P, Solal-Celigny P, Stalnikiewicz L, Audhuy B, Blanchet O, Baranger L, Bene MC, Ifrah N (2004) Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood 104(10):3028–37
13. Pui CH, Relling MV, Downing JR (2004) Acute lymphoblastic leukemia. N Engl J Med 350(15):1535–48. doi:10.1056/NEJMra023001
14. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, Bueso-Ramos CE, Pierce S, Shan J, Koller C, Beran M, Keating M, Freireich EJ (2004) Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 101(12):2788–801
15. Linker C, Damon L, Ries C, Navarro W (2002) Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin Oncol 20(10):2464–71
16. Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Delabesse E, Chevallier P, Buzyn A, Delannoy A, Chalandon Y, Vernant JP, Lafage-Pochitaloff M, Chassevent A, Lheritier V, Macintyre E, Bene MC, Ifrah N, Dombret H (2009) Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol 27(6):911–8
17. Bostrom BC, Sensel MR, Sather HN, Gaynon PS, La MK, Johnston K, Erdmann GR, Gold S, Heerema NA, Hutchinson RJ, Provisor AJ, Trigg ME (2003) Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. Blood 101(10):3809–17. doi:10.1182/blood-2002-08-2454
18. Schwartz CL, Thompson EB, Gelber RD, Young ML, Chilton D, Cohen HJ, Sallan SE (2001) Improved response with higher corticosteroid dose in children with acute lymphoblastic leukemia. J Clin Oncol 19(4):1040–6
19. Niemeyer CM, Gelber RD, Tarbell NJ, Donnelly M, Clavell LA, Blattner SR, Donahue K, Cohen HJ, Sallan SE (1991) Low-dose versus high-dose methotrexate during remission induction in childhood acute lymphoblastic leukemia (protocol 81-01 update). Blood 78(10):2514–9
20. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, Hurwitz CA, Moghrabi A, Samson Y, Schorin MA, Arkin S, Declerck L, Cohen HJ, Sallan SE (2001) Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 97(5):1211–8
21. Reiter A, Schrappe M, Ludwig WD, Hiddemann W, Sauter S, Henze G, Zimmermann M, Lampert F, Havers W, Niethammer D et al (1994) Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood 84(9):3122–33

22. Amylon MD, Shuster J, Pullen J, Berard C, Link MP, Wharam M, Katz J, Yu A, Laver J, Ravindranath Y, Kurtzberg J, Desai S, Camitta B, Murphy SB (1999) Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: a Pediatric Oncology Group study. Leukemia 13(3): 335–42
23. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17(24):2815–34
24. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48(3):452–8. doi:10.1038/bmt.2012.244
25. Huizenga HM, Visser I, Dolan CV (2011) Testing overall and moderator effects in random effects meta-regression. Br J Math Stat Psychol 64(Pt 1):1–19. doi:10.1348/000711010X522687
26. Ueda T, Miyawaki S, Asou N, Kuraishi Y, Hiraoka A, Kuriyama K, Minami S, Ohshima T, Ino T, Tamura J, Kanamaru A, Nishikawa K, Tanimoto M, Oh H, Saito K, Nagata K, Naoe T, Yamada O, Urasaki Y, Sakura T, Ohno R (1998) Response-oriented individualized induction therapy with six drugs followed by four courses of intensive consolidation, 1 year maintenance and intensification therapy: the ALL90 study of the Japan Adult Leukemia Study Group. Int J Hematol 68(3):279–89
27. Tobinai K, Takeyama K, Arima F, Aikawa K, Kobayashi T, Hanada S, Kasai M, Ogura M, Sueoka E, Mukai K, Tajima K, Fukuda H, Shirakawa S, Hotta T, Masanori S (2007) Phase II study of chemotherapy and stem cell transplantation for adult acute lymphoblastic leukemia or lymphoblastic lymphoma: Japan Clinical Oncology Group Study 9004. Cancer Sci 98(9):1350–7. doi:10.1111/j.1349-7006.2007.00556.x
28. Wetzler M, Sanford BL, Kurtzberg J, DeOliveira D, Frankel SR, Powell BL, Kolitz JE, Bloomfield CD, Larson RA (2007) Effective asparagine depletion with pegylated asparaginase results in improved outcomes in adult acute lymphoblastic leukemia: Cancer and Leukemia Group B Study 9511. Blood 109(10):4164–7. doi: 10.1182/blood-2006-09-045351
29. Jinnai I, Sakura T, Tsuzuki M, Maeda Y, Usui N, Kato M, Okumura H, Kyo T, Ueda Y, Kishimoto Y, Yagasaki F, Tsuboi K, Horiike S, Takeuchi J, Iwanaga M, Miyazaki Y, Miyawaki S, Ohnishi K, Naoe T, Ohno R (2010) Intensified consolidation therapy with dose-escalated doxorubicin did not improve the prognosis of adults with acute lymphoblastic leukemia: the JALSG-ALL97 study. Int J Hematol 92(3):490–502
30. Azuma T, Tobinai K, Takeyama K, Shibata T, Hidaka M, Kurosawa M, Kasai M, Chou T, Fukushima N, Mukai K, Tsukasaki K, Shimoyama M (2012) Phase II study of intensive post-remission chemotherapy and stem cell transplantation for adult acute lymphoblastic leukemia and lymphoblastic lymphoma: Japan Clinical Oncology Group Study, JCOG9402. Jpn J Clin Oncol 42(5):394–404. doi:10.1093/jjco/hys029
31. Fielding AK (2011) Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2011:231–7. doi:10.1182/asheducation-2011.1.231
32. Stock W (2010) Adolescents and young adults with acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010:21–9. doi:10.1182/asheducation-2010.1.21