


At three years, patients with acute lymphoblastic leukaemia are still at risk for relapse. Results of the international MRC UKALLXII/ECOG E2993 trial

Chezi Ganzel,^{1,2}  Xin V. Wang,³ Jacob M. Rowe,^{1,4} Susan M. Richards,⁵ Georgina Buck,⁵ David I. Marks,⁶ Mark R. Litzow,⁷ Elisabeth M. Paietta,⁸ Letizia Foroni,⁹ Selina M. Luger,¹⁰ Cheryl L. Willman,¹¹ Charles G. Mullighan,¹² Kathryn G. Roberts,¹² Peter H. Wiernik,¹³ Dan Douer,¹⁴ Hillard M. Lazarus,¹⁵ Martin S. Tallman¹⁴ and Anthony H. Goldstone¹⁶

¹Shaare Zedek Medical Center, ²Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel, ³Dana Farber Cancer Institute - ECOG-ACRIN Biostatistics Center, Boston, MA, USA, ⁴Rambam Medical Center, Haifa, Israel, ⁵Clinical Trial Service Unit, Oxford, ⁶University Hospitals Bristol National Health Service Foundation Trust, Bristol, UK, ⁷Mayo Clinic, Rochester, MN, ⁸Montefiore Medical Center, Bronx, NY, USA, ⁹Hammersmith Hospital, London, UK, ¹⁰University of Pennsylvania, Philadelphia, PA, ¹¹The University of New Mexico, Albuquerque, NM, ¹²St Jude Children's Research Hospital, Memphis, TN, ¹³Our Lady of Mercy Medical Center, Bronx, ¹⁴Memorial Sloan Kettering Cancer Center, New York, NY, ¹⁵Case Western Reserve University, Cleveland, OH, USA, and ¹⁶University College London, London, UK

Received 18 December 2019; revised 2 March 2020; accepted for publication 5 March 2020

Correspondence: Dr. Chezi Ganzel, Shaare Zedek Medical Center, Jerusalem, Israel and Faculty of Medicine, Hebrew University of Jerusalem, Israel.

E-mail: ganzelc@szmc.org.il

Summary

Late relapse [>3 years from complete remission (CR)] in acute lymphoblastic leukaemia (ALL), is unusual. Data from the MRC UKALLXII/ECOG E2993 trial are presented to evaluate the incidence and characteristics of late relapse in adult ALL. Of 1,909 patients, 1,752 (92%) achieved CR and among these 757 (43.2%) relapsed; 691 (91.3%) within three years and 66 (8.7%) beyond. Among these 66 patients, median time to relapse was 47 (37–144) months. Relapse beyond three years occurred in 3.8% of all who achieved CR. The cumulative risk of relapse was 40%, 43% and 45% at three, five and ten years respectively. Out of the 1752 patients who achieved CR, 11.7% underwent autologous and 40.6% allogeneic transplant, while in CR1. Of the autologous patients, 43.2% relapsed early and 3.4% relapsed late. However, among the allogeneic patients, 13.2% relapsed early and only 1.3% late. The five-year overall survival from relapse was 5.8% and 20% in the early and late relapse patients respectively. In conclusion, late relapse in adults with ALL is not uncommon, and is associated with better outcome after relapse compared to early relapse.

Keywords: acute lymphoblastic leukemia, late relapse.

Introduction

Late relapse in acute leukaemia is considered relatively uncommon. In acute myeloid leukaemia (AML), approximately 1% of all who achieved complete remission (CR) relapse after 3–5 years.^{1,2} In acute lymphoblastic leukaemia (ALL), data on late relapses are mostly reported in paediatrics.^{3,4} An Italian group⁵ reported that among 3 173 children with ALL and a median follow-up of 9.1 years, 93 (2.9%) had relapsed five years or more after achievement of CR with a median time from diagnosis to relapse of 6.1 years. The five-year survival after late relapse was 57%. In 2007, Fielding *et al.*⁶ reported on 609 relapsed patients who participated in the MRC UKALL-XII/ECOG E2993 study which is one of the largest prospective adult ALL studies⁷ with a median follow-up of 4.08 years. Now, with a longer follow-up (median follow-up of eight years), retrospectively analyzing the relapses of the patients in this study, allowed us to look at the question of the rate and characteristics of late relapses in adult ALL. We defined, arbitrarily, a late relapse as a first relapse occurring three years or more post achievement of CR and very late relapse as relapse beyond five years from CR.

Materials and methods

UKALLXII/ECOG E2993 was an international ALL trial conducted jointly by the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States. All patients received identical induction therapy, followed by central nervous system (CNS) prophylaxis. Initially, patients aged under 50 years with a sibling donor [or a matched unrelated donor in Philadelphia chromosome-positive (Ph-pos) ALL] were assigned to receive an allogeneic haematopoietic stem cell transplant (HSCT); all others were randomized to undergo an autologous HSCT or protracted standard consolidation/maintenance therapy. In 2003 the protocol was modified to assign HSCT for patients aged up to 55 years. In addition, the tyrosine kinase inhibitor (TKI) imatinib, was introduced for Ph-pos patients and planned to be given following both phases of induction. In 2005 imatinib was added to the second phase of induction.⁸ The study accrued 2 109 patients from 1993 to 2006. In this report, the cohort of Ph-pos patients who received imatinib is reported separately.

Details of the study eligibility, diagnostic procedures and treatment were previously described.^{7,9}

Data collection after relapse

After relapse, following initial on-protocol therapy, patients were followed up, but choice of therapy was left to the discretion of physician and patient. Limited data were collected on therapy after relapse, but transplantations, subsequent relapses, and survival or date of death were recorded. Data on achievement of second or subsequent CR were not collected. The median duration of follow-up was based on

patients who have not died. The last update of the data was on December 2010.

Cytogenetic risk stratification

High-risk cytogenetics was defined as t(9;22), t(4;11), t(8;14), HoTr [low hypodiploidy (30–39 chromosomes), near triploidy (60–78 chromosomes)] or complex karyotype (five or more abnormalities in the absence of an established chromosomal or ploidy subgroup).¹⁰ All the others were part of the standard-risk cytogenetics group.

Identification of Philadelphia chromosome-like (Ph-like) ALL

RNA samples from 210 BCR/ABL-negative B-lineage cases of the E2993 cohort were analyzed, retrospectively, for the Ph-like phenotype using a 15-gene TaqMan® (Thermo Fisher Scientific, Waltham, MA, USA) low-density array (LDA) polymerase chain reaction (PCR) assay on a 384-well microfluidic card, as previously described.^{11,12} An integrated score between 0 and 1 was generated from the 15-gene assay, and any sample with a predictive score of ≥ 0.5 was considered to be Ph-like.

Minimal residual disease (MRD) status was not consistently measured during the period of the study.

Statistics

Descriptive statistics were used to describe patient characteristics. Cumulative incidence of relapse and death without relapse was estimated using the method developed by Gray.¹³ Competing risks regression was performed using the Fine and Gray method.¹⁴ The Kaplan–Meier method was used to construct the survival curve.

Results

The first and main cohort included 1 909 study patients; 1 440 (75.4%) Philadelphia chromosome negative (Ph-neg), 267 (14%) Ph-pos and 202 (10.6%) with unknown Philadelphia chromosome status (Ph-unknown). Altogether, 1 752 (92%) of the patients achieved CR. The median age of these patients was 30 years, 61.5% were male, 77.1% had B-lineage ALL, 46.2% had standard-risk cytogenetics, 22.8% high risk and 30.9% had unknown cytogenetics. As post-remission therapy, 711 patients (40.6% of those who achieved CR) underwent allogeneic HSCT in CR1, 206 (11.7%) underwent autologous transplant and all others received protracted chemotherapy, as consolidation-maintenance therapy. The median duration of follow-up among patients who achieved CR was 96.5 months (~8 years).

Relapse rate

Among the 1 752 patients who achieved CR, 757 (43.2%) had a documented relapse; 691 (91.3%) relapsed within three

years from achieving CR ('early relapse') and 66 (8.7%) relapsed beyond three years ('late relapse'). Among these 66 patients, 21 (2.8% of all relapses) relapsed after five years ('very late relapse'). Among 732 patients who survived three years, 9% experienced late relapse and 4% of the 528 patients who survived five years experienced very late relapse. The median time to relapse was nine months and 47 (37–144) months for the early and late relapses respectively. The relapse rate beyond three years of all those who achieved a CR was 3.8%. The cumulative risk of relapse increased to 40% after the first three years but thereafter slowed down, reaching 43% and 45% after five and ten years respectively. Of note, the cumulative risk of death without relapse after three years was 17% and it was increased to 18% and 20% at five and ten years respectively (Figure 1).

Analysis according to patient characteristics at diagnosis

Table I shows patient characteristics comparing late and early relapses along with all patients in CR1. The cytogenetic abnormalities of both relapse groups are summarized in Table II. Among the late relapse patients 62% were males, median age was 32 years, median white blood cell (WBC) count was $6 \times 10^9/l$ and 87.9% had B-lineage ALL. In comparison, early relapse patients presented with a higher median WBC, for both B- and T-lineages ALLs. Among the 810 standard-risk patients, 35.4% relapsed early ($n = 287$) and 4.7% relapsed late ($n = 38$). In contrast, among the 400 high-risk patients, the rate of early relapse was higher (50.5%, $n = 202$) but the rate of late relapse was lower (1.25%, $n = 5$), compared to the standard-risk patients.

The cumulative incidence of relapse and death without relapse of each cytogenetic abnormality are summarized in Table SI.

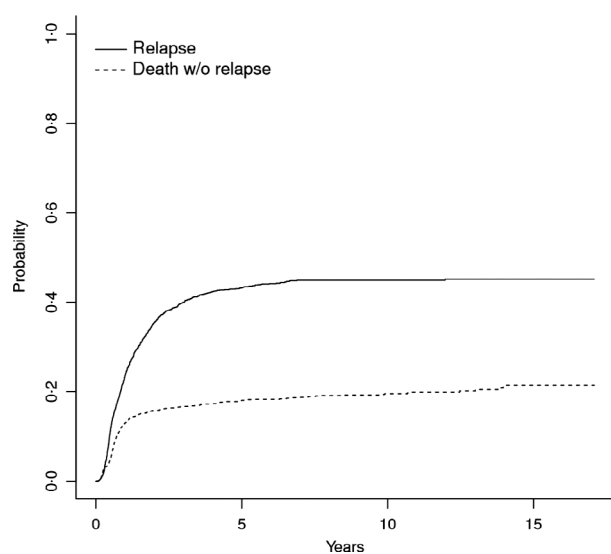


Fig 1. Cumulative incidence of relapse and death without relapse of all 1752 patients who achieved complete remission.

Among the subgroup of patients enrolled on the US ECOG (E2993) study, 210 BCR/ABL-negative patients who achieved CR were subsequently tested for the Ph-like phenotype. Of these 210 patients, 55 (26.2%) were identified as having the Ph-like phenotype. Of the 55 Ph-like patients, 30 relapsed early (four underwent allogeneic HSCT and seven autologous HSCT) and three relapsed late (one underwent allogeneic HSCT). To emphasize, these data were not available at the time of treatment and thus, did not influence decisions regarding treatment.

Analysis by HSCT in CR1

Of the 1752 patients who achieved CR, 206 (11.7%) underwent autologous HSCT and 711 (40.6%) underwent allogeneic HSCT. The other 835 (47.6%) patients received only chemotherapy as first-line treatment. The rate of early relapse was highest among those who received only chemotherapy ($n = 508$, 60.8%), lower among those who underwent auto-HSCT ($n = 89$, 43.2%) and lowest among the allo-HSCT patients ($n = 94$, 13.2%). Late relapse occurred in the same order; 5.9% ($n = 50$) among the chemotherapy patients, 3.4% ($n = 3$) among those who underwent auto-HSCT and only 1.3% ($n = 9$) among the allo-HSCT patients.

Analysis of Ph-positive patients by imatinib treatment

Of the 220 patients who achieved a CR and were treated in the pre-imatinib era, 124 (56.4%) relapsed but only two (1.6% of the relapses) relapsed beyond three years. Ph-positive patients who received imatinib included 175 eligible patients, of whom 159 (90.9%) achieved a CR, had remission date recorded and did not die within 56 days from start of treatment. Their baseline characteristics including additional cytogenetic abnormalities are summarized in Table SII. Among these 159 patients, 65 (40.9%) relapsed but only two patients (3% of the relapses) relapsed beyond three years. Of the 159 patients who achieved remission, 105 patients were assigned to receive the imatinib during induction and 54 started receiving it later. The hazard ratio for relapse-free survival (imatinib during induction vs. later) was 0.80 [95% confidence interval (CI) 0.54–1.2], P -value = 0.26.

Outcome after relapse

The median survival and the 5-year OS after relapse for the late relapse patients were low; 11.3 months (95% CI 9.2–22.5) and 20% (95% CI 11–35%), respectively, but longer than of those who relapsed within three years; 5.4 months (95% CI 4.9–6.0) and 5.8% (95% CI 4.3–7.9%) respectively (Figure 2).

Discussion

Based on the current study, relapse three years beyond CR among adults with Ph-neg ALL is not uncommon; ~9% of

Table I. Baseline characteristics of the patients who achieved CR and their modality of treatment.

		All patients who achieved CR	Relapse < 3 years	Relapse ≥ 3 years
<i>n</i>		1 752	691	66
Age	Median	30	32	32
Gender (%)	Male	61.5	62.4	62.1
Lineage (%)	B	77.1	79.2	87.9
	T	19.6	17.1	10.6
WBC (10/l)	Median	13	18	6
	B-ALL (median)	10	15	6
	T-ALL (median)	38	40	15
Cytogenetic risk group	Standard, <i>n</i> (%)	810 (46.2)*	287 (35.4)†	38 (4.7%)†
	High, <i>n</i> (%)	400 (22.8)*	202 (50.5)†	5 (1.25)†
	Unknown, <i>n</i> (%)	542 (30.9)*	202 (37.3)†	23 (4.2)†
Days to CR	Median	30	31	34
Haematopoietic stem cell transplant, at CR1	Autologous, <i>n</i> (%)	206 (11.7)*	89 (43.2)‡	7 (3.4)‡
	Allogeneic, <i>n</i> (%)	711 (40.6)*	94 (13.2)‡	9 (1.3)‡
	No (chemotherapy only), <i>n</i> (%)	835 (47.6)*	508 (60.8)‡	50 (5.9)‡

CR, complete remission; WBC, white blood cells.

*Percentage of the 1 752 patients who achieved CR.

†Percentage of patients with the same cytogenetic risk group.

‡Percentage of the patients who received the same modality of treatment as first-line therapy (autologous transplant, allogeneic transplant or chemotherapy only).

all relapses or ~4% of all who achieved CR. Survival after relapse is poor but longer for late relapses.

Among the standard-risk patients, the rate of early and late relapse was 35% and 5%, respectively, compared to 50% and 1% among the high-risk patients. Nevertheless, for patients who survived three years or longer (28% of the high-risk cytogenetics and 49% of the standard-risk), the rate of late relapse was similar among the two groups (8% of the high-risk patients and 11% of the standard-risk ones). Thus, although a lower percentage of high-risk patients survived three years, those who actually survived had a similar risk of subsequent late relapse, compared to the standard-risk

patients. Taken together, adult ALL patients in CR in all cytogenetic risk groups should be followed carefully for a longer duration of time.

The current analysis, with its long follow-up, shows the impact of transplant on relapse rate. The majority of the relapses after allogeneic or autologous HSCT occurred early. We can confirm our early report⁹ that the overall relapse rate after allogeneic transplantation in first CR remains low (14.5%) and now show that after three years relapses rarely occur (1.3%). On the other hand, the overall relapse rate after autologous transplant in CR1 is high (46.6%), but only 3.4% relapsed late.

Table II. Cytogenetic abnormalities. The last line represent the second and different cohort of Ph-positive patients who received imatinib.

	<i>n</i> (% of 1 752 patients who achieved CR)	Relapse < 3 years <i>n</i> (% of patients with the same abnormality)	Relapse ≥ 3 years <i>n</i> (% of patients with the same abnormality)
t(1;19)†	31 (1.8)	10 (32)	0
Hyperdiploidy†	132 (7.5)	37 (28)	5 (3.8)
t(8;14)†	18 (1)	10 (55.6)	0
Ho-Tr†	34 (1.9)	15 (44.1)	2 (5.9)
Complex†	56 (3.2)	28 (50)	1 (1.8)
t(4;11)†	78 (4.5)	29 (37.2)	0
Ph-positive*	220 (12.6)	122 (55.5)	2 (0.9)
<i>Ph-positive – imatinib cohort</i>	159	63 (39.6)	2 (1.2)

Complex, complex karyotype (five or more abnormalities in the absence of an established chromosomal or ploidy subgroup); CR, complete remission; Ho-Tr, low hypodiploidy (30–39 chromosomes) and near triploidy (60–78 chromosomes); hyperdiploidy, high hyperdiploidy (51–65 chromosomes); Ph, Philadelphia chromosome.

*Data are missing in around 10% of the patients.

†Data are missing in 25–35% of the patients.

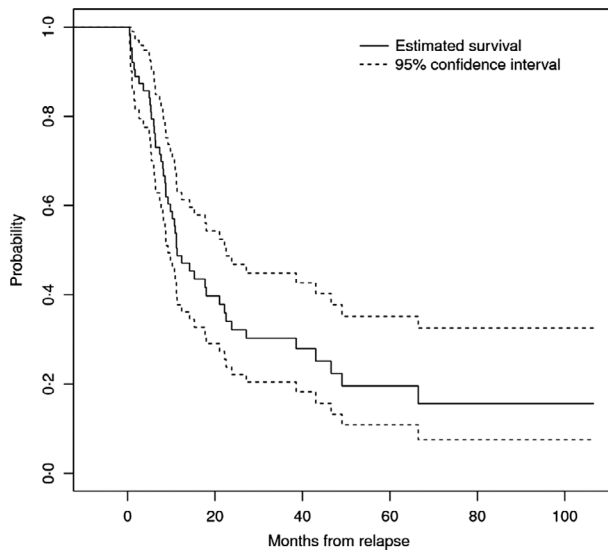


Fig 2. Survival from relapse date for all patients who relapsed after 3 years from complete remission ($n = 66$).

While the study was conducted, imatinib was introduced as standard therapy in Philadelphia-positive ALL. A retrospective comparison demonstrated a reduction in the rate of relapse among the imatinib cohort compared to pre-imatinib (40.9% vs. 56.4% of the patients who achieved CR in each cohort respectively) but the rate of late relapses among the relapses of each cohort was comparable (3% vs. 1.6% respectively).

The concept of Ph-like ALL was not known during the conduct of the study. Retrospective analysis of 210 BCR/ABL-negative patients who achieved CR revealed that a quarter of them were Ph-like ALL (unpublished data). A similar rate was reported in a large study which included 798 samples from different clinical trials (including this one); 27.9% of young adults (age 21–39 years) and 20.4% of adults (age 40–59 years).¹² Ph-like patients are known to have an unfavourable prognosis¹⁵ and in the current study, most Ph-like ALL patients relapsed early and only two of them relapsed late. More data regarding this group of patients will be subsequently published.

Prior studies showed that adults with ALL who relapse later have a relatively more favourable outcome than early relapses. The PETHEMA group with 263 adults with ALL, reported a higher five year OS rate of 31% (95% CI, 21–41%) among patients relapsing after two years in CR1 compared to 1.8% (95% CI 0–4%), among those relapsing within the first year of achieving first CR and 15% (95% CI 7–23%) for patients relapsing between one and two years.¹⁶ The German Multicenter Study Group for Adult Acute Lymphoblastic Leukaemia reported in 291 adult patients with relapsed ALL that those who relapsed after 18 months had a median OS of 19.7 months, compared to 8.3 months for those who relapsed earlier.¹⁷ In comparison, our study with more patients and longer follow-up showed that the outcome of

even later relapses — beyond three years — remains dismal with median survival of only 11 months and a five years OS of 20%, although slightly longer than earlier relapses.

The reason for patients relapsing late is not clear. The original leukaemic stem cells or different subclones¹⁸ might be protected in the bone marrow niche¹⁹ and eventually progress due to a change in the microenvironment²⁰ or to the cessation of long continuous chemotherapy pressure when a patient completes the maintenance therapy. Hogan *et al.*²¹ demonstrated a different gene expression signature of early versus late relapse ALL in children. Furthermore, they showed that the late relapse patients had up-regulation of genes involved in nucleotide biosynthesis and folate metabolism and speculated that this is related to the methotrexate and mercaptopurine that are basic components of maintenance therapy.

Other etiologies for late relapse need to be considered. True secondary ALL, as has been well described in AML,^{22–24} is very uncommon and its existence is, in fact, uncertain.²⁵ However, a second de novo ALL has been suggested in some cases of relapsed ALL.²⁶ The current study could not determine whether the late relapses are true recurrences rather than second leukaemias, but it remains a likely assumption. Future molecular studies comparing the original clones with the relapsed cells may shed light on this question as well the association of late relapse and better outcome.^{27,28}

The basis for better survival from relapse of the late relapse patients is also unclear, but is reminiscent to late relapse of AML,²⁹ chronic lymphocytic leukaemia³⁰ and other lymphoproliferative diseases, where the outcome after relapse is dependent on the duration of first remission. Patient-related factors, such as the ability to tolerate more aggressive treatment after being off treatment for longer time, probably have some influence on the survival. But disease-related factors, such as the ability of the dormant cells to not acquire new mutations or other biological changes causing treatment resistance, probably play a bigger role.

Finally, one of the limitations of this analysis is that patients went off study after relapse and continued to be followed mainly for survival and not for subsequent treatments. Thus, we could not address the important question of whether new drugs, such as blinatumumab and inotuzumab, and new modalities of treatment, such as CAR-T cell therapy, that may have been used in several patients, influenced the survival of the patients. It is likely, that these new strategies will in the future become part of the first-line treatment and then it will be very important to study the impact of these novel strategies on late relapse.

In conclusion, relapses three years beyond CR among adults with ALL are not uncommon. Adult patients with ALL cannot be considered as cured after three years and need to be closely followed up to five years and even beyond. The rate of late relapse after allo-HSCT in first CR is very low. Survival of patients after late relapse is longer than among early relapse, but is still short.

Author contributions

CG designed the research, analyzed data and wrote the paper. XVW analyzed data and wrote the paper. JMR designed the research and wrote the paper. SMR analyzed data. GB analyzed data. DIM performed research. MRL performed research. EMP analyzed data and wrote the paper. LF performed research and analyzed data. SML performed research. CLW analyzed data. CGM analyzed data. KGR analyzed data. PHW performed research. DD designed the research and wrote the paper. HML performed research. MST designed the research and wrote the paper. AHG performed research.

Conflicts of interest

There are no conflicts of interest for any of the co-authors.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Cumulative incidence of relapse and death without relapse, by cytogenetic abnormality.

Table SII. Characteristics of eligible Ph-pos patients from the imatinib cohort who achieved CR ($n = 159$).

References

- Verma D, Kantarjian H, Faderl S, O'Brien S, Pierce S, Vu K, et al. Late relapses in acute myeloid leukemia: analysis of characteristics and outcome. *Leuk Lymphoma*. 2010;51:778–82.
- Watts JM, Wang XV, Litzow MR, Luger SM, Lazarus HM, Cassileth PA, et al. Younger adults with acute myeloid leukemia in remission for ≥ 3 years have a high likelihood of cure: the ECOG experience in over 1200 patients. *Leuk Res*. 2014;38:901–6.
- Kato M, Manabe A, Saito AM, Koh K, Inukai T, Ogawa C, et al. Outcome of pediatric acute lymphoblastic leukemia with very late relapse: a retrospective analysis by the Tokyo Children's Cancer Study Group (TCCSG). *Int J Hematol*. 2015;101:52–7.
- Nygaard R, Moe PJ, Brincker H, Clausen N, Nyman R, Perkkio M, et al. Late relapses after treatment for acute lymphoblastic leukemia in childhood: a population-based study from the Nordic countries. *Med Pediatr Oncol*. 1989;17:45–7.
- Rizzari C, Valsecchi MG, Arico M, Miniero R, Messina C, De Rossi G, et al. Outcome of very late relapse in children with acute lymphoblastic leukemia. *Haematologica*. 2004;89:427–34.
- Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007;109:944–50.
- Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, et al. 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*. 2005;106:3760–7.
- Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood*. 2014;123:843–50.
- Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008;111:1827–33.
- Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALL-XII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007;109:3189–97.
- Reshmi SC, Harvey RC, Roberts KG, Stonerock E, Smith A, Jenkins H, et al. Targetable kinase gene fusions in high-risk B-ALL: a study from the Children's Oncology Group. *Blood*. 2017;129:3352–61.
- Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Chen IM, et al. High frequency and poor outcome of Philadelphia chromosome-like acute lymphoblastic leukemia in adults. *J Clin Oncol*. 2017;35:394–401.
- Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16:1141–54.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Statist Assoc*. 1999;94:496–509.
- Tasian SK, Loh ML, Hunger SP. Philadelphia chromosome-like acute lymphoblastic leukemia. *Blood*. 2017;130:2064–72.
- Oriol A, Vives S, Hernandez-Rivas JM, Tormo M, Heras I, Rivas C, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica*. 2010;95:589–96.
- Gokbuget N, Stanze D, Beck J, Diedrich H, Horst HA, Huttman A, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*. 2012;120:2032–41.
- Konrad M, Metzler M, Panzer S, Ostreicher I, Peham M, Repp R, et al. Late relapses evolve from slow-responding subclones in t(12;21)-positive acute lymphoblastic leukemia: evidence for the persistence of a preleukemic clone. *Blood*. 2003;101:3635–40.
- Lane SW, Scadden DT, Gilliland DG. The leukemic stem cell niche: current concepts and therapeutic opportunities. *Blood*. 2009;114:1150–7.
- Indraccolo S, Stievano L, Minuzzo S, Tosello V, Esposito G, Piovan E, et al. Interruption of tumor dormancy by a transient angiogenic burst within the tumor microenvironment. *Proc Natl Acad Sci U S A*. 2006;103:4216–21.
- Hogan LE, Meyer JA, Yang J, Wang J, Wong N, Yang W, et al. Integrated genomic analysis of relapsed childhood acute lymphoblastic leukemia reveals therapeutic strategies. *Blood*. 2011;118:5218–26.
- Bacher U, Schnittger S, Kern W, Trenn G, Weissner M, Haferlach T, et al. Acute myeloid leukemia (AML) with t(8;21)(q22;q22) relapsing as AML with t(3;21)(q26;q22). *Cancer Genet Cytogenet*. 2006;168:172–4.
- Roulston D, Anastasi J, Rudinsky R, Nucifora G, Zeleznik-Le N, Rowley JD, et al. Therapy-related acute leukemia associated with t(11q23) after primary acute myeloid leukemia with t(8;21): a report of two cases. *Blood*. 1995;86:3613–4.
- Seiter K, Feldman EJ, Sreekantaiah C, Pozzuoli M, Weisberger J, Liu D, et al. Secondary acute myelogenous leukemia and myelodysplasia without abnormalities of chromosome 11q23 following treatment of acute leukemia with topoisomerase II-based chemotherapy. *Leukemia*. 2001;15:963–70.
- Ganzel C, Devlin S, Douer D, Rowe JM, Stein EM, Tallman MS. Secondary acute lymphoblastic leukaemia is constitutional and probably not related to prior therapy. *Br J Haematol*. 2015;170:50–5.
- Szczepanski T, van der Velden VH, Waanders E, Kuiper RP, Van Vlierberghe P, Gruhn B, et al. Late recurrence of childhood T-cell acute lymphoblastic leukemia frequently represents a second leukemia rather than a relapse: first evidence for genetic predisposition. *J Clin Oncol*. 2011;29:1643–9.

27. Babor F, Manser AR, Fischer JC, Scherenschlich N, Enczmann J, Chazara O, et al. KIR ligand C2 is associated with increased susceptibility to childhood ALL and confers an elevated risk for late relapse. *Blood*. 2014;**124**:2248–51.
28. Gandemer V, Chevret S, Petit A, Vermeylen C, Leblanc T, Michel G, et al. Excellent prognosis of late relapses of ETV6/RUNX1-positive childhood acute lymphoblastic leukemia: lessons from the FRALLE 93 protocol. *Haematologica*. 2012;**97**:1743–50.
29. Stahnke K, Boos J, Bender-Gotze C, Ritter J, Zimmermann M, Creutzig U. Duration of first remission predicts remission rates and long-term survival in children with relapsed acute myelogenous leukemia. *Leukemia*. 1998;**12**:1534–8.
30. Tam CS, O'Brien S, Plunkett W, Wierda W, Ferrajoli A, Wang X, et al. Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). *Blood*. 2014;**124**:3059–64.