Impact of timely \textit{BCR-ABL1} monitoring before allogeneic stem cell transplantation among patients with \textit{BCR-ABL1}-positive B-acute lymphoblastic leukemia

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Background
With the emergence of tyrosine kinase inhibitors and the incorporation of stringent measurable residual disease (MRD) monitoring, risk stratification for \textit{BCR-ABL1}-positive acute lymphoblastic leukemia (ALL) patients has changed significantly. However, whether this monitoring can replace conventional risk factors in determining whether patients need allogeneic stem cell transplantation is still unclear. This study aimed to determine the impact of \textit{BCR-ABL1} monitoring on the outcome of patients with \textit{BCR-ABL1}-positive ALL after allogeneic stem cell transplantation.

Methods
We retrospectively analyzed the survival outcome of patients with \textit{BCR-ABL1}-positive ALL based on the quantification of \textit{BCR-ABL1} at 3 timepoints: the end of induction (timepoint 1), post-consolidation week 16 (timepoint 2), and the end of treatment for patients who were either transplant-eligible or non-transplant eligible (timepoint 3).

Results
From 2006 to 2018, a total of 96 patients newly diagnosed with \textit{BCR-ABL1}-positive ALL were treated with chemotherapy and tyrosine kinase inhibitors. Thirty-eight (41.3\%) patients achieved complete remission, and 33 patients underwent allogeneic stem cell transplantation. Our data showed that pre-transplant MRD monitoring by real-time quantitative polymerase chain reaction had the highest correlation with survival in patients with \textit{BCR-ABL1}-positive ALL, especially for those who underwent allogeneic stem cell transplantation.

Conclusion
Patients without MRD pre-transplantation had superior survival compared with those who had MRD, and they had excellent long-term outcomes after allogeneic stem cell transplantation.

Key Words ALL, BCR-ABL1, Philadelphia, Survival, TKI
of BCR-ABL1 detected in cases of chronic myeloid leukemia, and the remainder harbor a translocation that produces the p190 protein. The incidence of BCR-ABL1-positive ALL increases with age, and it is identified in up to 50% of ALLs diagnosed in patients over 50 years old [3, 4]. This genetic alteration confers a poor prognosis that leads to shorter remission and decreased survival, in addition to increased resistance to standard chemotherapy [5-7]. The presence of this fusion gene also serves as a unique molecular signature, and it is an effective tool for monitoring measurable residual disease (MRD) to identify patients who would likely benefit from stem cell transplantation (SCT) [8-10]. Several studies have suggested that detection of BCR-ABL1 transcripts by quantitative real-time polymerase chain reaction (qRT-PCR) is associated with an increased risk of relapse, whereas deeper molecular responses have been associated with improved outcomes [9-11]. However, the effectiveness of MRD monitoring in BCR-ABL1-positive ALL has not been well defined [12, 13]. Further, the impact of achieving a complete molecular response (CMR) in BCR-ABL1-positive ALL remains undefined. A timepoint (TP) analysis for the quantitation of the BCR-ABL1 transcript could reveal its ability to predict CMR in these patients. Therefore, this study aimed to retrospectively investigate the prognostic impact of BCR-ABL1 molecular monitoring at different TPs on the survival of patients with BCR-ABL1-positive ALL from 2006 to 2018 in a major transplant center in Malaysia.

**MATERIALS AND METHODS**

**Patients**

This was a retrospective, single-center, observational study in the Department of Hematology at the Hospital Ampang, Selangor Malaysia, which is a national hematology referral center in Malaysia. A total of 176 patients with B-ALL underwent allogeneic SCT at the Hospital Ampang, Malaysia between 2006 and 2018. All patients diagnosed with BCR-ABL1-positive ALL were retrospectively analyzed to determine the impact of the BCR-ABL1 molecular response on overall survival (OS) and disease-free survival (DFS) after allogeneic transplantation. In brief, chemotherapy protocols were administered in 3 phases: induction, consolidation, and maintenance. The protocols used for the treatment of BCR-ABL1-positive ALL followed the modified GMALL 07/2003 [14], BFM [15], and Hyper-CVAD [16] regimens, which were administered depending on the patient’s clinical presentation. After the induction phase, the patients received a total of 3-4 courses of consolidation therapy before SCT. Central nervous system prophylaxis was also instituted for all patients, consisting of at least 4 doses of intrathecal chemotherapy. Tyrosine kinase inhibitors (TKIs) were only made available after 2011, when our national health program offered imatinib to patients with BCR-ABL1-positive ALL. Bone marrow assessment was performed at least 4 weeks before SCT to assess remission status. This included aspiration and trephine for morphological review, cytogenetics, and molecular studies. Because risk stratification based on genetic identification and MRD monitoring was not fully accessible in the past, our center offered SCT to all eligible ALL patients, even those with standard risk, if a matched sibling donor was available. Allogeneic SCT recipients received grafts from either a human leukocyte antigen-identical sibling or an unrelated donor. For transplantation, HLA-matching was determined by allelic typing using a resolution of 4 digits per allele. Matched sibling donors were assigned to siblings that demonstrated a 10/10 loci match. If a family-related donor was unavailable, a matched unrelated donor would be accepted with a 10/10, 9/10, or 8/10 loci match. If a suitable donor could not be identified by the methods above, a haploidentical match demonstrating a 5-8/10 loci match from a family-related donor was an option. Stem cell sources were either peripheral blood, bone marrow, or unrelated donor cord blood, whichever was available.

**Molecular monitoring strategy**

MRD evaluations at 3 different TPs were analyzed: post-induction (TP1), post-consolidation or week 16 (TP2), and end of treatment (TP3). BCR-ABL1 copies were quantified using qRT-PCR as previously described [17-20]. Any MRD-positive sample beyond the quantitative range was defined as below the limit of detection. A sample was defined as “negative” when all replicates were negative, with at least 1,000 ABL1 copies detected. The MRD value of each follow-up sample was calculated as the logarithmic reduction with respect to the diagnostic value.

**Definitions**

CMR was defined as the absence of detectable BCR-ABL1 transcripts with a sensitivity of 0.01%. The major molecular response (MMR) was defined as a BCR-ABL1:ABL1 ratio of ≤0.1% on IS for the major transcript of BCR-ABL1, p210, or a 3-log reduction in transcripts for the minor transcript of BCR-ABL1, p190, but not meeting the criteria for CMR. The first complete remission (CR1) referred to remission achieved during the first cycle of induction chemotherapy. OS was calculated from the time of treatment initiation until death, with patients alive at the time of the last follow-up being administratively censored. DFS was calculated from day 0 to any type of relapse or death during remission. Relapse was defined as the recurrence of ≥5% blasts in the bone marrow aspirate, presence of extramedullary disease, or a BCR-ABL1:ABL1 ratio > 0.1% on the IS for 2 consecutive analyses.

**Statistical analysis**

Continuous variables are summarized using the median and range. Categorical variables are summarized using the count (N) and proportion (%). Differences between subgroups were assessed with t-test, ANOVA, or Kruskal-Wallis test, depending on the sample size and distribution. Associations between categorical variables were analyzed using the chi-square test or Fisher’s exact test. Probabilities of OS and DFS were calculated using the Kaplan-Meier meth-
RESULTS

Patient demographics and characteristics
The study included a total of 96 patients (42 males and 54 females) with a median age of 37.5 years (range, 14-69 yr). Eight patients (8.3%) were in the adolescent age group of 12 to 19 years old, and 45 patients (46.9%) were young adults aged 20-39 years. The remaining 43 patients (44.8%) were aged 40 years and above. The most common ethnic group was Malay (50%, N=48), followed by Chinese (38.5%, N=37) and Indian (14%, N=19). Over half of the patients (53.1%) presented with a high white blood cell count (>30×10^9/L), with a median of 36×10^9/L. A total of 49 patients received the GMALL/BFM protocol (51%), whereas 47 patients (49%) received the HyperCVAD protocol. Of the 96 patients, 62 received TKIs, mostly imatinib, during chemotherapy and were still receiving TKIs as maintenance therapy at the time of SCT. All patients who underwent SCT received TKIs and chemotherapy (19 received imatinib, 13 received nilotinib, and 1 received dasatinib). Of the 38 patients who underwent SCT, 33 received allogeneic stem cells and 5 received autologous stem cells (Table 1).

| Table 1. Baseline clinical characteristics of all patients with BCR-ABL1-positive ALL. |
|---------------------------------------------------------------|
| **Parameter** | **Total (N=96)** |
| **Age, years** | **15–39 (AYA)** | **40–59 (adult)** | **≥ 60 (elderly)** |
| N (%) | 53 (55.2) | 38 (39.6) | 5 (5.2) |
| Median (range) | 37.5 (14–59) |
| **Sex** | **Male** | **Female** |
| N (%) | 42 (43.8) | 54 (56.3) |
| **Ethnicity** | **Malay** | **Chinese** | **Indian** | **Others** |
| N (%) | 48 (50.0) | 37 (38.5) | 9 (9.4) | 2 (2.1) |
| WCC, at diagnosis | >30×10^9/L | <30×10^9/L |
| N (%) | 51 (53.1) | 45 (46.9) |
| Median (range), 10^9/L | 36 (2–500) |
| **MRD status** | **TP1** | **TP2** | **TP3** |
| ≥0.1% | <0.1% | ≥0.1% | <0.1% | ≥0.1% | <0.1% |
| N | 31 | 40 | 25 | 25 | 40 | 13 | 36 |
| Missing | 40 | 31 | 47 |
| **Treatment modalities** | **GMALL/BFM** | **Hyper-CVAD** | **TKIs** |
| N (%) | 49 (51) | 47 (49) | 62 (64.6) | 34 (35.4) |
| **Treatment response** | **Remission post-induction** | **Overall remission** | **Relapse** | **Refractory** | **Induction death** |
| N (%) | 80 (83.3) | 38 (41.3) | 34 (37.0) | 10 (10.9) | 4 (4.3) |
| **Transplant** | **Yes** | **No** |
| N (%) | 38 (39.6) | (33-Allogeneic; 5-Autologous) | 58 (60.4) |

Values are presented as mean, median (range), or number (%). Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; MRD, measurable residual disease; TKI, tyrosine kinase inhibitor; TP1, timepoint 1; TP2, timepoint 2; TP3, timepoint 3; WCC, white cell count.
| Parameter                                      | Total (N=33) | Age, years | Parameter                                      | Total (N=33) |
|------------------------------------------------|--------------|------------|------------------------------------------------|--------------|
| N (%)                                         | 20 (60.6)    | 40-59 (adult) | 13 (39.4)                                       | 0 (0)        |
| Median (range)                                 | 20 (60.6)    | 37 (15-59)  |                                                |              |
| Sex                                            | Male         | Female     |                                                |              |
| N (%)                                         | 16 (48.5)    | 17 (51.5)  |                                                |              |
| Ethnicity                                      | Malay        | Chinese    | Indian                                         | Others       |
| N (%)                                         | 15 (45.5)    | 15 (45.5)  | 3 (9.0)                                        | 0 (0)        |
| Disease status at transplant                   | CR1          | CR>1       |                                                |              |
| N (%)                                         | 28 (84.8)    | 5 (15.2)   |                                                |              |
| Pre-transplant BCR-ABL1 level                 | <0.1%        | ≥0.1%      |                                                |              |
| N (%)                                         | 25 (75.8)    | 8 (24.2)   |                                                |              |
| WCC at diagnosis                              | >30×10⁹/L    | <30×10⁹/L  |                                                |              |
| N (%)                                         | 21 (63.6)    | 12 (36.4)  |                                                |              |
| Blood type mismatch                            | None         | Minor      | Major                                          | Bidirectional |
| N (%)                                         | 25 (75.8)    | 4 (12.1)   | 3 (9.1)                                        | 1 (3.0)      |
| Gender mismatch (donor-recipient)             | Female to male | Male to female | Male to male                          | Female to female |
| N (%)                                         | 4 (12.1)     | 8 (24.2)   | 10 (30.3)                                       | 10 (30.3)    |
| CMV status                                    | Recipient negative | Recipient positive | Missing |
| N (%)                                         | 3 (9.1)      | 2 (6.1)    | 5 (15.1)                                        |              |
| Donor negative                                 | 3 (9.1)      | 2 (6.1)    | 5 (15.1)                                        |              |
| Donor positive                                 | 1 (3.0)      | 22 (66.7)  |                                                |              |
| Type of allogeneic transplant                  | Matched-sibling | Matched-unrelated | Haplo-matched | Cord blood |
| N (%)                                         | 27 (81.8)    | 3 (9.1)    | 2 (6.1)                                        | 1 (3.0)      |
| Stem cell source                               | Peripheral blood | Bone marrow | Umbilical cord | |
| N (%)                                         | 32 (97.0)    | 0          | 1 (3.0)                                        |              |
| Median stem cell dose (×10⁶/kg)                | 5.0 (3.0-11) | 1 (3.0)   |                                                |              |
| Conditioning regimen                           | Myeloablative | RIC        | TBI-based                                      | Non-TBI      |
| N (%)                                         | 29 (87.9)    | 4 (12.1)   | 22 (66.7)                                       | 11 (33.3)    |
| Post-transplant response                       | Remission    | Relapse/death |                                                |              |
| N (%)                                         | 23 (69.7)    | 10 (30.3)  |                                                |              |
| GVHD                                           | Acute        | Chronic    |                                                |              |
| N (%)                                         | 13 (44.8)    | 14 (50.0)  |                                                |              |
| Grade I                                       | 4 | Limited | 7 | |
| Grade II                                      | 6 | Extensive | 7 | |
| Grade III                                     | 3 | 0 | |
| Grade IV                                      | 0 | | |
| Missing                                       | 4 | | 5 | |
| No GVHD                                        | 16 (55.2)    | 14 (50.0)  |                                                |              |
| Mortality rate                                 | Alive        | Dead       |                                                |              |
| N (%)                                         | 20 (60.6)    | 13 (39.4)  | Relapse/disease progression                     | 6            |
| Infection/transplant-related mortality         | 7            | |

Values are presented as mean, median (range), or number (%).
Abbreviations: AYA, adolescent and young adult; CR, complete remission; GVHD, graft-versus-host disease; RIC, reduced intensity conditioning; TBI, total body irradiation; GVHD, graft-versus-host disease; WCC, white cell count.
Fig. 1. OS and DFS after stem cell transplantation according to BCR-ABL1 transcript level at certain timepoints. Post-induction MRD (A). Post-consolidation week 16 (B). End of treatment (C). The overall cohort (D).

Abbreviations: DFS, disease-free survival; MRD, measurable residual disease; OS, overall survival.
CMR prediction using BCR-ABL transcript levels at different TPs

A total of 33 patients (34.4%) who completed chemotherapy were transplant-eligible and underwent allogeneic SCT. The median age of transplant recipients was 37 years (range, 15–59 yr). All patients received allografts, with the majority being from a matched-sibling donor (N=27) (Table 2). Most patients (87.9%, N=29) underwent myeloablative conditioning chemotherapy, with a total body irradiation-based protocol being the main conditioning regimen (66.7%). Thirteen patients (44.8%) developed acute graft-versus-host disease (GVHD) and 14 (50.0%) developed chronic GVHD. MRD status based on the pre-transplant BCR-ABL transcript levels was better able to predict OS (P=0.005) and DFS (P=0.002) than the post-induction (P=0.70 and P=0.75, respectively) and post-consolidation (P=0.138 and P=0.078, respectively) BCR-ABL transcript levels (Fig. 1). The univariate analysis of the factors predictive of OS is shown in Table 3. Multivariate analysis showed that being in the high-risk group and transplantation in CR>1 were independent prognostic factors for inferior OS [pre-transplant BCR-ABL1 levels: hazard ratio (HR), 4.358; P=0.017; CR > 1; HR, 4.582; P=0.016] and DFS (pre-transplant BCR-ABL1 levels: HR, 4.106; P=0.002; CR > 1; HR, 3.787; P=0.033) (Table 4, Fig. 1).

At the time of analysis, 20 patients were alive (60.6%), whereas 13 died (39.4%), as shown in Table 2. With a median follow-up of 25 months, the median OS was not reached. With a median follow-up of 9 months, the median DFS was not reached. Six (46.2%) of 13 patients with MMR experienced relapse, with a median time to relapse of 14 months (range, 8–104). The 2-year, 3-year, and 5-year OS rates were 66.3%, 58.7%, and 53.4%, respectively, and the 2-year, 3-year, and 5-year DFS rates were 63.7%, 59.9%, and 54.5%, respectively (Fig. 1D).

**DISCUSSION**

It is widely accepted that MRD monitoring is paramount when considering the best treatment options for patients with BCR-ABL1-positive ALL [21, 22]. However, MRD monitoring requires high laboratory expertise and is costly in developing nations. Further, unlike chronic myeloid leukemia, the effect of MRD response to chemotherapy on long-term outcomes in BCR-ABL1-positive ALL has not been clearly defined.

With our low non-relapse mortality rate in matched-sib-

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**Table 3. Univariable analysis of factors predictive for OS.**

| Characteristic                        | All BCR-ABL1-positive ALL patients | Transplanted BCR-ABL1-positive ALL patients |
|---------------------------------------|-----------------------------------|---------------------------------------------|
|                                       | 3-year OS (%) | P   | 3-year OS (%) | P   |
| Age group                             |                  |     |               |     |
| AYA                                   | 39.0             | 0.064 | 52.9           | 0.690 |
| Adult and elderly                     | 19.6             |      | 55.0           |      |
| Sex                                   |                  |     |               |     |
| Male                                  | 33.6             | 0.876 | 54.2           | 0.906 |
| Female                                | 26.8             |      | 52.9           |      |
| WCC at diagnosis                      |                  |     |               |     |
| > 30×10^9/L                           | 25.5             | 0.585 | 52.3           | 0.684 |
| < 30×10^9/L                           | 35.9             |      | 63.6           |      |
| MRD status (%)                        |                  |     |               |     |
| ≥ 0.1                                 | 36.7             | 0.974 | 36.1           | 0.974 |
| < 0.1                                 | 23.5             | 0.077 | 53.1           | 0.077 |
| TP1                                   | 11.5             | 0.005 | 65.4           | 0.005 |
| Chemotherapy                          |                  |     |               |     |
| GMALL/BFM                             | 25.7             | 0.081 | 25.0           | 0.081 |
| Hyper-CVAD                            | 33.7             |      | 73.9           |      |
| TKI                                   |                  |     |               |     |
| Yes (2012–2018)                       | 33.7             | 0.390 | 23.5           | 0.390 |
| No (2006–2011)                        | 23.5             |      | 33.7           |      |
| Transplant                            |                  |     |               |     |
| Yes                                   | 58.9             | < 0.001 | 58.9           | < 0.001 |
| No                                    | 10.6             |      | 10.6           |      |
| Disease status at transplant          |                  |     |               |     |
| CR1                                   | 65.9             | 0.003 | 16.7           | 0.003 |
| CR > 1                                | 16.7             |      | 16.7           |      |

Significant P_value < 0.05.

Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; CR, complete remission; MRD, measurable residual disease; OS, overall survival; TKI, tyrosine kinase inhibitor; TP1, timepoint 1; TP2, timepoint 2; TP3, timepoint 3; WCC, white cell count.
Residual disease in B-ALL with BCR-ABL1

Table 4. Multivariable analysis of factors predictive of OS and DFS in transplant recipients.

| Characteristic                                      | Risk of relapse or death | Risk of death |
|----------------------------------------------------|--------------------------|---------------|
|                                                    | HR  | 95% CI | P   | HR  | 95% CI | P   |
| Pre-transplant BCR-ABL1 level ≥ 0.1%               | 4.106 | 1.226-13.752 | 0.022 | 4.358 | 1.301-14.597 | 0.017 |
| Transplant in CR >1                                | 3.787 | 1.113-11.520 | 0.033 | 4.582 | 1.352-15.528 | 0.016 |

P-value < 0.05.

Abbreviations: CI, confidence interval; CR, complete remission; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

ling donor transplants, it was justifiable to perform SCT in ALL patients with standard risk in CR1, given the significantly higher rate of relapse and lower DFS among patients who did not undergo SCT. This echoed earlier observations of the UKALL/RCOG 2993 studies, which showed significant differences in survival between the transplanted and non-transplanted cohorts, even in ALL patients with standard risk [23], and they did not perform MRD monitoring or identification of high-risk genetic markers. Reports showing successful transplants in CR2 with a curative potential of 25–30% have been reported [24, 25]. However, these reports were highly selective and did not influence decisions against earlier transplants. In our retrospective observation, other factors, such as age, sex, and BCR-ABL1 status, did not affect OS or DFS. However, patients who underwent SCT between 2012 and 2018 had superior 3-year OS compared to those who underwent SCT between 2006 and 2011 (Table 3). This was most likely due to the better selection of patients, improved supportive care, and availability of TKIs for patients with BCR-ABL1-positive ALL in the later cohort.

We showed that pre-transplant BCR-ABL1 quantitation had a significant prognostic ability. This finding suggests that patients treated with chemotherapy and TKIs who achieve end-of-treatment MMR in CR1 have excellent long-term survival. The optimal timing of MRD assessment may vary based on the TKI; however, end-of-treatment and pre-transplant quantitation have proven to be extremely informative, and the results should be factored into the decision-making and counseling processes. Conversely, quantitation at earlier TPs did not retain statistical power in the multivariate analyses.

Patients who achieved CMR at 3 months had better OS and DFS than those who did not, regardless of whether they received chemotherapy or allogeneic SCT. Although there was a trend for better survival among patients treated with chemotherapy, the difference was not statistically significant. However, the relapse rate was higher in the chemotherapy group. The higher non-relapse mortality in patients who underwent allogeneic SCT may have contributed to this discrepancy. Therefore, chemotherapy plus TKIs may be an option for patients who achieve early CMR but are unwilling to undergo SCT.

Relapse or disease progression post-SCT remains a problem [26], as these patients have an extremely poor prognosis. Novel immunotherapies such as inotuzumab and blinatumomab, as well as chimeric antigen receptor T-cell therapy, have provided an opportunity for patients with relapsed or refractory ALL [25, 27]. Blinatumomab has been shown to eliminate MRD in ALL patients and has led to better survival outcomes post-SCT [28]. In this study, 6 patients with BCR-ABL1 transcripts < 0.1% at TP3 either declined SCT or were not eligible. Only 1 patient remained alive at the time of the census; 3 patients died, and 2 refused follow-up.

Our study focused on allogeneic SCT in the largest cohort of adult BCR-ABL1-positive B-ALL patients in Malaysia. Its retrospective nature makes it a true reflection of real-world practices in this part of the world. This is also one of the few studies to include a multi-ethnic group of patients. However, this study design also has inherent limitations, in which variables related to disease characteristics and cytogenetic profiles were missing or unavailable. The MRD data were also incomplete in earlier patient datasets. Patients were also unable to be further classified based on additional genetic mutations. A multicenter approach and collaboration are required to determine a more precise survival outcome.

In conclusion, end-of-treatment MMR was associated with a lower relapse rate and higher DFS among patients with BCR-ABL1-positive ALL who underwent allogeneic SCT. This suggests that, although frequent molecular monitoring and intervention are required for patients who do not show a reduction in BCR-ABL1 transcript levels, only end-of-treatment levels are highly predictive of the post-transplant outcome. However, future prospective trials are needed to evaluate the effectiveness of MRD monitoring for risk stratification of patients with BCR-ABL1-positive ALL. The impact of different generations of TKIs on patient outcomes also warrants further evaluation. The current work may be used to guide surveillance plans for patients in Asian countries and could potentially be used as a platform or reference point to design future prospective trials.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Loghavi S, Kutz JL, Jorgensen JL. B-acute lymphoblastic leukemia/lymphoblastic lymphoma. Am J Clin Pathol 2015;144:393-410.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-90.
3. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALL XII/ECOG2993. Blood 2009;113:4489-96.
4. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood 2004;103:4396-407.
5. Preti HA, O’Brien S, Giralt S, Beran M, Pierce S, Kantarjian HM. Philadelphia-chromosome-positive adult acute lymphocytic leukemia: characteristics, treatment results, and prognosis in 41 patients. Am J Med 1994;97:60-5.
6. Faderl S, Kantarjian HM, Talpaz M, Estrov Z. Clinical significance of cytogenetic abnormalities in adult acute lymphoblastic leukemia. Blood 1998;91:3995-4019.
7. Moorman AV, Harrison CJ, Buck GA, 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.
8. Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact on relapse and long-term outcome. Biol Blood Marrow Transplant 2016;22:1868-76.
9. Dhédin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood 2015;125:2486-96.
10. Dhédin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood 2015;125:2486-96.
11. Nashed AL, Rao KW, Gulley ML. Clinical applications of BCR-ABL molecular testing in acute leukemia. J Mol Diagn 2003;5:63-72.
12. Short NJ, Jabbour E, Sasaki K, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2016;128:504-7.
13. Fielding AK. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia in adults: a broader range of options, improved outcomes, and more therapeutic dilemmas. Am Soc Clin Oncol Educ Book 2015:e352-9.
14. Scherrer R, Bettelheim P, Geissler K, et al. High efficacy of the German multicenter ALL (GMLA) protocol for treatment of adult acute lymphoblastic leukemia (ALL)--a single-institution study. Ann Hematol 1994;69:181-8.
15. Henze G, Langemann HJ, Brämswig J, et al. The BFM 76/79 acute lymphoblastic leukemia therapy study (author’s transl). Klin Padiatr 1981;193:145-54.
16. Garcia-Manero G, Kantarjian HM. The hyper-CVAD regimen in adult acute lymphocytic leukemia. Hematol Oncol Clin North Am 2000;14:1381-96. x-xi.
17. Gabert J, Beillard E, van der Velden VH, et al. Standardization and quality control studies of ‘real-time’ quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia—a Europe Against Cancer program. Leukemia 2003;17:2318-57.
18. Mocellin S, Rossi CR, Pilati P, Nitti D, Marincola FM. Quantitative real-time PCR: a powerful ally in cancer research. Trends Mol Med 2003;9:189-95.
19. Yu S, Cui M, He X, Jing R, Wang H. A review of the challenge in measuring and standardizing BCR-ABL1. Clin Chem Lab Med 2017;55:1465-73.
20. Arora R, Press RD. Measurement of BCR-ABL1 transcripts on the International Scale in the United States: current status and best practices. Leuk Lymphoma 2017;58:8-16.
21. Holowiecki J, Krawczyk-Kulis M, Giebel S, et al. Status of minimal residual disease after induction predicts outcome in both standard and high-risk Ph-negative adult acute lymphoblastic leukaemia. The Polish Adult Leukemia Group ALL 4-2002 MRD Study. Br J Haematol 2008;142:227-37.
22. Lussana F, Intermesoli T, Gianni F, et al. Achieving molecular remission before allogeneic stem cell transplantation in adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: impact on relapse and long-term outcome. Biol Blood Marrow Transplant 2016;22:1983-7.
23. Goldstone AH, Richards SM, Lazarus HM, 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.
24. Gupta V, Richards S, Rowe J. Acute Leukemia Stem Cell Transplantation Trialists’ Collaborative Group. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. Blood 2013;121:339-50.
25. Terveillenger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J 2017;7:e577.
26. Socié G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med 1999;341:14-21.
27. Jabbour E, Pui CH, Kantarjian H. Progress and innovations in the management of adult acute lymphoblastic leukemia. JAMA Oncol 2018;4:1413-20.
28. Topp MS, Kufer P, Gökbüget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011;29:2493-8.