Chemotherapy or Allogeneic Stem Cell Transplantation as Salvage Therapy for Patients with Refractory Acute Myeloid Leukemia: A Multicenter Analysis

Zhong-yu Wang, Wen-hui Gao, and Hui-jin Zhao contributed equally to the manuscript.

Abstract

Introduction: The overall outcome of patients with refractory AML (rAML) remains poor. Though allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered as the only curative therapy, it is routinely recommended only for patients after remission with salvage chemotherapy. Objective: In this study, we evaluated the impact of salvage chemotherapy or allo-HSCT on the overall outcome in rAML. Methods: We collected the clinical data of 220 patients from 4 medical centers and performed retrospective analysis of prognosis factors, including salvage chemotherapy, intensity of chemotherapy, and allo-HSCT. Results: A total of 29 patients received allo-HSCT directly without salvage chemotherapy, 26 patients achieved complete remission (CR) or complete remission with incomplete hematological recovery (CRi) after transplantation and 4-year leukemia-free survival (LFS) and overall survival (OS) were 45.0 ± 10.7 and 51.0 ± 10.6%, respectively. Another 191 patients received salvage chemotherapy and 81 (42.2%) achieved CR or CRi. Thirty-four patients among them underwent subsequent allo-HSCT with 4-year LFS and OS of 46.0 ± 8.8 and 46.2 ± 9.0%. The 4-year LFS and OS in 26 patients who failed to obtain CR or CRi but received allo-HSCT with active disease were 32.9 ±
10.0 and 36.9 ± 10.8%, respectively. For patients who received salvage chemotherapy but not allo-HSCT, few of them became long-term survivors. In multivariate analysis, salvage chemotherapy and the intensity of chemotherapy failed to have significant impact on both OS and LFS. Allo-HSCT was the only prognostic factor for improved OS and LFS in multivariate analysis. **Conclusions:** These results indicate the benefit of allo-HSCT in patients with rAML and direct allo-HSCT without salvage chemotherapy could be a treatment option.

**Introduction**

Patients with refractory AML (rAML) usually respond poorly to conventional chemotherapy and present with dismal outcomes [1–5]. Treatment options in the setting of refractory disease are limited [1]. Though there is no acceptable standard regimen as salvage chemotherapy, different trials with intensive salvage chemotherapy, such as dose escalation of daunorubicin within the “7 + 3” regimen [6–8], multiple combination of etoposide, cytarabine with mitoxantrone or idarubicin (MAC or ICE) [9, 10], or high-dose cytarabine (HiAC) containing regimen with fludarabine, cladribine with or without idarubicin, or mitoxantrone [11, 12], lead to complete remission (CR) rates of 20–40%, and few patients became long-term survivor. More recently, the clinical trials to add new agents such as gemtuzumab ozogamicin, all-trans retinoic acid, and molecular target agents, including FLT3 inhibitor as adjunct to intensive chemotherapy may increase the overall response rate, but still these trials offer almost no chance of cure [12–16].

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is considered as the only curative therapy for rAML [17]. Several reports suggest that immediate transplantation without salvage therapy is feasible for AML patients with primary induction failure (PIF) or at first relapse, if an available donor can be quickly identified [18, 19]. However, other reports show that achieving remission, through salvage chemotherapy, can lead to favorable outcomes and better survival suggesting that achieving remission may indicate intrinsically more responsive leukemia [20, 21]. Since allo-HSCT in rAML is associated with relative high non-relapse mortality and relapse rate, it is not regularly recommended in patients with rAML but mostly for patients achieved remission with salvage therapy.

### Materials and Methods

This retrospective analysis included patients with rAML receiving treatment between January 2008 to December 2017 from 4 different medical centers. The inclusion criteria were as following: (1) patients fulfilled one of the criteria of refractory AML, which including PIF after 2 or more cycles of chemotherapy, first early relapse after a remission duration of fewer than 6 months, late first relapse after a remission duration of 6–12 months and refractory to salvage chemotherapy, or multiple relapses; (2) age from 16 to 64; (3) the diagnostics and treatment at primary diagnosis of AML were performed at each center; (4) treatment outcome and subsequent follow-up data can be documented from patients charts or outpatients records. The risk stratification was based on the European LeukemiaNet 2017 recommendations with cytogenetic and molecular analysis outcome [22]. The study procedure including the collection and analysis of patients’ data were in accordance with the Helsinki Declaration. Written consent was obtained from patients for data use in clinical research. All patients gave informed consent and the institutional review board of participating centers approved allogeneic transplantation protocols and/or salvage chemotherapy regimens.

**Treatment**

A total of 220 patients were included in the final analysis with median age of 42 (16–64). The salvage therapy included intensified chemotherapy ($n = 81$, 36.8%), non-intensive chemotherapy ($n = 110$, 50%) and direct allogeneic HCT without salvage chemotherapy ($n = 29$, 13.2%). The intensified chemotherapy included HiAC (3 g/m² b.i.d., days 1–3), FLAG-based regimens (FLAG or FLAG-IDA with cytarabine 2 g/m² for 5 days, FLAG-Mito with cytarabine 1 g/m² b.i.d. days 1–5), and CHA regimen (cytarabine 2 g/m² together with cladribine 10 mg and homoharringtonine 4 mg from day 1–5). Non-intensified chemotherapy, including MAC regimen (mitoxantrone 8–10 mg/m², day 1–3 with cytarabine 100 mg/m² day 1–7 and cyclophosphamide 400 mg/m², day 2 and day 5) or CAG regimen (aclacinomycin 20 mg day 1–4 with Ara-C 15 mg/m² bid, day 1–14 and G-CSF 5 μg/kg, day 1–14). Among these 191 patients, 60 patients underwent allo-HSCT (34 in remission and 26 in active disease) after salvage chemotherapy. No patients received non-myeloablative conditioning regimens. The common conditioning regimens used were standard myeloablative regimen (MAC) with busulfan and cyclophosphamide (Bu-Cy), fludarabine, cytarabine, and busulfan (Flu-Bu-Ara-C) and an intensified conditioning with sequential cytoreductive chemotherapy with fludarabine, cytarabine, and idarubicin (FLAG-IDA) followed by a reduced toxicity conditioning with fludarabine and 3-day busulfan (Flu-Bu3) at the hematological nadir of chemotherapy-induced aplasia. After allo-HSCT, the early tapering and/or stop of immunosuppression and prophylactic donor lymphocyte infusion were carried out based on the protocols of participating centers.

**Response Criteria and Survival End Point**

The response criteria were established according to revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [23]. CR was defined as <5% blasts in the bone marrow with normal peripheral and differential counts (granulocytes >1,000/mm³ and platelets >100,000/mm³) without extramedullary dis-
Allogeneic Stem Cell Transplantation for Patients with Refractory AML

Response to Therapy and Overall Outcome

For those patients receiving salvage chemotherapy, 81 (42.4%) achieved CR or CRi, 19 (9.9%) obtained only partial remission, and 91 (47.6%) with no response. In those patients who directly underwent allo-HSCT without salvage chemotherapy, 26 out of 29 (89.7%) achieved CR/CRi, which was significantly higher than the salvage chemotherapy group (p < 0.001).

At the last follow-up with a median follow-up of 24.4 months, a total of 72 patients remained alive with an over-
all median OS of 10.0 months, while only 56 patients remain alive in CR/CRi with a median LFS of 8.9 months. The 4-year estimated OS and LFS were 20.9 ± 3.8 and 18.4 ± 3.3%, respectively, as shown in Figure 1.

Overall Outcome Analysis Based on Allo-HSCT

According to the treatment received, we identified several groups of patients. For patients directly undergoing allo-HSCT, the estimated 4-year OS and LFS were 51.5 ± 10.6 and 45.0 ± 10.7%, respectively. For 81 patients who obtained CR/CRi after salvage chemotherapy, 38 (46.9%) received subsequent allo-HSCT and 47 failed to undergo allo-HSCT. The 4-year OS/LFS for these 2 groups were 46.2 ± 9.0/46.0 ± 8.8 and 11.0 ± 8.9%/9.6 ± 4.0%, respectively. Among 110 patients who failed to obtain CR/CRi after salvage chemotherapy, only 26 eventually underwent rescuing allo-HSCT with active disease. The 4-year OS and LFS were 36.9 ± 10.8 and 32.9 ± 10.0% for patients in the allo-HSCT group with only 3.6 ± 3.0 and 1.8 ± 1.6% in 84 patients who did not receive allo-HSCT (as shown in Fig. 1).

Prognostic Factors via Univariate/Multivariate Analysis

In univariate analysis, we analyzed the impact of intensity of salvage chemotherapy on the treatment outcome. Of the 81 intensively treated patients, the 4-year LFS and OS were 21.1 ± 9.6% (median 2.8 months) and 23.2 ± 5.1% (median 8.8 months), respectively. For patients treated with non-intensive chemotherapy, the 4-year LFS and OS were 9.6 ± 4.0% (median 2.1 months) and 14.4 ± 4.8% (median 9.4 months) as shown in Figure 2. The p values were 0.68 and 0.72 for OS and LFS, respectively. Of interest, patients treated with allo-HSCT directly without salvage chemotherapy had significantly improved OS and LFS (as shown in Figure 2 and Table 2). Secondary, we evaluated the impact of allo-HSCT on the overall outcome. The 4-year OS of the HSCT group (including direct allo-HSCT) was overwhelmingly better than patients who did not receive HSCT group (43.8 ± 6.1 vs. 8.0 ± 3.6%, p < 0.001, as shown in Fig. 3). Besides these 2 factors, younger patients (<40 vs. ≥40, as shown in Fig. 4) tended to have improved OS. All other factors such as risk stratification by cytogenetic/molecular profiling and disease stage were not associated with OS (as shown in Table 2). Using a Cox regression model for multivariate analysis, patients receiving allo-HSCT was the only factor associated with a better OS (RR = 2.38, p < 0.001, as shown in Table 3).

As to the LFS, in univariate analysis, younger age and direct allo-HSCT without salvage chemotherapy and re-
receiving allo-HSCT at any time were associated with improved LFS (Table 2). In multivariate analysis, the only factor significantly associated with improved LFS was allo-HSCT (RR = 2.83, \( p < 0.001 \), Table 3).

**Impact of Timing of Allo-HSCT, Disease Status, and Conditioning Regimens in Patients Undergoing Allo-HSCT**

In our series, a total of 89 patients underwent allo-HSCT directly without chemotherapy (\( n = 29 \)) or after salvage chemotherapy either in remission (\( n = 34 \)) or with active disease (\( n = 26 \)). The 4-year OS and LFS were both around 45% for patients underwent allo-HSCT up-front or in CR after salvage chemotherapy. For those patients who underwent allo-HSCT with active disease after salvage chemotherapy, the OS and LFS decreased to 36.9 and 32.9%, respectively, but not significant different from the previous groups perhaps due to limited statistical power as shown in Table 4. For patients with primary refractory disease, the OS and LFS were similar to all other patients with relapsed disease after first remission. As to the conditioning regimens, 50 patients received standard regimens and 39 patients received sequential conditioning regimens. The OS and LFS were similar between the 2 sets of conditioning as shown in Table 4.
Discussion

Refractory AML remains a clinical challenge. A limited proportion of patients may respond to salvage chemotherapy such as MAC or combination of HiAC with Fludarabine or cladribine, while the remission duration is usually short and most patients die of subsequent disease relapse [8–11]. Even though multiple clinical trials carried out with new therapeutic agents, the overall remission rates reported are low with few long-term survivors [12–16]. Allogeneic HSCT is considered as the only therapeutic option, and the retrospective analysis demonstrated that ∼70% patients can obtain clinical remission and 2- to 3-year OS and DFS may vary between 15 and 40% [24, 25].

Table 2. Univariate analysis of patients and treatment-related factors associated with OS and LFS

| Parameters                        | 4-year OS, % | p value | 4-year LFS, % | p value |
|-----------------------------------|--------------|---------|---------------|---------|
| Age                               |              |         |               |         |
| <40 years                         | 30.2±5.5     | 0.071   | 27.7±4.8      | 0.015   |
| ≥40 years                         | 19.1±4.6     |         | 8.2±4.3       |         |
| BM blasts at diagnosis, %         |              |         |               |         |
| <50                               | 28.2±4.6     | 0.503   | 23.2±4.6      | 0.300   |
| ≥50                               | 19.0±4.9     |         | 17.1±4.3      |         |
| Salvage chemotherapy (Y/N)        |              |         |               |         |
| Yes                               | 20.2±3.6     | 0.03    | 17.0±3.1      | 0.003   |
| No                                | 51.5±10.6    |         | 45.0±10.7     |         |
| Salvage chemo intensity           |              |         |               |         |
| Intensive salvage chemo           | 23.2±5.1     | 0.68    | 21.1±9.6      | 0.72    |
| Non-intensive salvage chemo       | 14.4±4.8     |         | 9.6±4.0       |         |
| Cyto/mol (n = 166)                |              |         |               |         |
| Favorable (n = 30)                | 24.2±9.4     |         | 20.8±7.8      |         |
| Intermediate (n = 81)             | 16.7±7.8     | 0.513   | 9.1±6.9       | 0.455   |
| Adverse (n = 55)                  | 20.0±6.5     |         | 18.9±5.9      |         |
| Stage                             |              |         |               |         |
| PIF                              | 33.4±6.1     |         | 31.2±5.4      |         |
| 1st rel: CR1 <6 months            | 31.2±6.8     |         | 30.9±6.7      | 0.137   |
| 1st rel: CR1 ≥6 months            | 11.2±4.9     | 0.238   | 7.0±4.5       |         |
| 2nd rel or beyond                 | 0            |         | 0             |         |
| Allo-HSCT (Y/N)                   |              |         |               |         |
| Yes                               | 8.0±3.6      | <0.001  | 2.5±2.3       | <0.001  |
| No                                | 43.8±6.1     |         | 41.5±5.8      |         |

PIF, primary induction failure; LFS, leukemia-free survival; OS, overall survival; allo-HSCT, allogeneic hematopoietic stem cell transplantation. Values in italics indicate p values <0.1.

The timing of allo-HSCT is a key issue particularly the remission status at allo-HSCT may have profound impact on transplantation outcome. Multiple reports suggest that leukemia burden remains as the most important factors for patients with AML receiving allo-HSCT either in both remission and refractory status [26, 27]. For example, in patients with AML in CR1, the pre-transplantation MRD was considered as key prognostic factor [26]. As to the patients with non-remission AML, the Japanese database analysis demonstrated that the percentage of bone marrow blasts (<20 vs. 20–60 vs. ≥60%) with or without circulating blasts was associated with treatment outcome after allo-HSCT [28]. These data indicate that attempts to achieve a CR or successful leukemia debulking may benefit for rAML and allo-HSCT is not regularly recommended for patients unless they obtained remission after salvage chemotherapy.

Unfortunately, the response to salvage chemotherapy for rAML is limited in the clinical settings. Clinical reports indicate that salvage chemotherapy may benefit only patients with long CR1 duration (>18 months) and/or with favorable cytogenetics while patients with short CR1, high-risk cytogenetics, or FLT3-ITD usually had a low response rate [29–31]. For patients not responding to salvage therapy, the accumulated toxicity and infections complications may have negative impact on the subsequent allo-HSCT.

In this multicenter analysis in relative young adult patients with a median age of 40 years, we aim to evaluate
the impact of salvage chemotherapy and allo-HSCT on the overall outcome of patients with rAML. Several groups of patients were identified according to the treatment received: patients undergoing direct allo-HSCT without salvage chemotherapy, patients obtaining CR to salvage chemotherapy with or without subsequent allo-HSCT, and patients not responding to salvage chemotherapy with or without subsequent allo-HSCT. Overall, our data demonstrated that direct allo-HSCT without salvage chemotherapy might be an option in rAML. The 4-year OS and LFS were superior than patients underwent salvage chemotherapy overall and were also comparable for those patients received subsequent allo-HSCT after CR/CRi with salvage chemotherapy. To rule out the possible impact of difference of patients’ characteristic, a propensity analysis was performed with 23 patients undergo direct allo-HSCT were paired with patients undergoing salvage chemotherapy with fuzzy match for age, sex, risk stratification, and bone marrow blast (as shown in online suppl. Table 2). The analysis confirmed that direct transplantation was superior to patients undergo salvage chemotherapy. Secondary, we also analyzed the impact of

Fig. 3. Kaplan-Meier curves of OS and LFS in patients underwent to allo-HSCT or not. LFS, leukemia-free survival; OS, overall survival; all-HSCT, allogeneic hematopoietic stem cell transplantation.

Allogeneic Stem Cell Transplantation for Patients with Refractory AML.
Table 3. Multivariable analysis of prognostic factors associated with OS and LFS for all patients (n = 220)

| Parameters       | OS   | LFS               |
|------------------|------|-------------------|
|                  | RR   | 95% CI            | p value | RR   | 95% CI            | p value |
| Age              | 0.91 | 0.64–1.29         | 0.59    | 0.86 | 0.61–1.19         | 0.35    |
| Salvage chemo    | 1.08 | 0.54–2.19         | 0.82    | 1.12 | 0.58–2.16         | 0.73    |
| Allo-HSCT        | 2.38 | 1.53–3.68         | <0.001  | 2.83 | 1.85–4.33         | <0.001  |

LFS, leukemia-free survival; OS, overall survival; CI, confidence interval; RR, risk ratio; all-HSCT, allogeneic hematopoietic stem cell transplantation. Values in italics indicate p values <0.1.

Fig. 4. Kaplan-Meier curves of OS and LFS in patients with age <40 versus ≥40 years. LFS, leukemia-free survival; OS, overall survival; all-HSCT, allogeneic hematopoietic stem cell transplantation.
intensity of chemotherapy on the overall outcome. In univariate analysis, there was no difference. Finally, in the multivariate analysis, only allo-HSCT remained as significant for improved OS and LFS, while salvage chemotherapy was not critical for the treatment outcome. Our data were in line with previous AMLSG study, which showed that only allo-HSCT was the key factor for the treatment of rAML [32].

Based on these data, we may speculate that allo-HSCT should be considered for patients with rAML if eligible and direct allo-HSCT without salvage chemotherapy can be treatment option especially for those patients with high-risk factors who are unlikely to respond to salvage chemotherapy. As in our previous study with sequential chemotherapy of FLAG-IDA followed by Flu-Bu conditioning regimen with an interval of 7 days in rAML, we demonstrated that almost all patients had an extreme hypocellular bone marrow after FLAG-IDA. Therefore, the conditioning regimen was given at time of bone marrow with extreme low leukemia burden, which may mimic a transplantation given at remission or low MRD level [33]. The other rationale for up-front transplantation is related to the development or accumulation of resistance or refractoriness to chemotherapy and toxicities with multiple cycles of salvage chemotherapy, which may have an negative impact on the overall outcome of subsequent allo-HSCT.

This strategy is also feasible for patients with primary refractory diseases. The OS and LFS were similar to patients with relapsed disease after initial remission (as shown in Table 4). Further analysis also showed that the outcome of direct allo-HSCT was as good as allo-HSCT after salvage chemotherapy for patients with PIF (data not shown). These findings may be in line with the early study, which showed that allo-HSCT with sequential FLAMSA regimen lead to a promising outcome in patients with refractory AML received only 2 cycles of chemotherapy [18].

As to the transplantation conditioning for rAML, standard conditioning to more intensified or sequential conditioning regimens have been reported with variables outcome [18, 33, 34]. In our series, there was no difference in OS and LFS between conditioning regimens as shown in Table 4, which may due to lack of statistical power, imbalanced distribution of patients’ characteristics and preferred regimens used in different centers. For example, the sequential conditioning regimen for up-front allo-HSCT was exclusively used in Rui Jin Hospital and Paoli-Calmettes Cancer Center, while other participating centers relied on standard MAC conditioning with more aggressive posttransplantation procedures such as early tapering of immunosuppression and prophylactic donor lymphocyte infusion [34].

One possible bias of our study is lack of description or definition of aggressiveness of rAML. Though there was no difference in the WBC count in patients receiving direct allo-HSCT and salvage chemotherapy (Table 1), salvage chemotherapy usually should be given to patients with rapid increased of leukocytes or hyperleukocytosis in the clinical setting. Those patients with more “indolent” disease with stable WBC can undergo direct allo-HSCT after work-up for transplantation. Other limitations of this study were obviously the retrospective nature, limited number of patients particularly in the group of direct allo-HSCT and lack of MRD data for analysis. Thus, no firm conclusion can be made based on potential

### Table 4. Subgroup analysis of patients underwent allo-HSCT

| Parameters                  | 4-year OS, % | 4-year LFS, % | p value | p value |
|-----------------------------|--------------|--------------|---------|---------|
| **Timing of allo-HSCT**     |              |              |         |         |
| Up-front                    | 51.5±10.6    | 45.0±10.7    |         |         |
| CR after salvage chemo      | 46.2±9.0     | 46.0±8.8     | 0.87*   | 0.70*   |
| No CR after salvage chemo   | 36.9±10.8    | 32.9±10.0    | 0.33*   | 0.36*   |
| **Disease status**          |              |              |         |         |
| PIF (n = 35)                | 46.3±9.0     | 44.6±8.9     |         |         |
| All others (n = 54)         | 39.3±8.1     | 39.0±7.6     | 0.14    | 0.18    |
| **Conditioning regimens**   |              |              |         |         |
| Conventional regimen        | 42.0±8.4     | 41.7±8.0     |         |         |
| Sequential regimen          | 46.1±8.6     | 42.7±8.7     | 0.58    | 0.53    |

CR, complete remission; PIF, primary induction failure; LFS, leukemia-free survival; OS, overall survival; allo-HSCT, allogeneic hematopoietic stem cell transplantation. * Up-front versus CR after salvage chemo. ^ Up-front versus no CR after salvage chemo.
selection bias. Even though with the limitation, we
believed that prospective clinical study with minimal selec-
tion bias is warranted to evaluate the role of direct allo-
HSCT without salvage chemotherapy in young adult pa-
tients with rAML.

Acknowledgements

We acknowledge all the clinical staff of Rui Jin Hospital, Tong
Ren Hospital, Chang Hai Hospital, Institut Paoli-Calmettes, and
Institute of Hematology & Blood Diseases Hospital, who helped
with constant support and collaboration.

Statement of Ethics

The study was approved by the Ruijin Hospital Ethics Commit-
tee (2018-98), and the subjects gave written informed consent. The
study procedures, including the collection and analysis of patients’
data, were in accordance with the Helsinki Declaration.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by the National Key R&D Program
of China 2017YFA0104502 and National Natural Science Founda-
tion Program 81770187.

Author Contributions

Z.-Y.W.*, W.-H.G.*, and H.-J.Z.* collected and analyzed the
data and helped to write the manuscript; C.-R.Y., Z.-W.W., L.W.,
and L.-N.W. helped to treat and follow-up the patients; L.T. and
M.W. analyzed the data; R.D. helped to write the manuscript; and
J.-M.W.*, P.-P.H.*, D.B.*, and J.H.* designed the study, supervised
the study, and wrote the manuscript.

References

1 Mato AR, Morgans A, Lugcr SM. Novel strat-
egies for relapsed and refractory acute mye-
eloid leukemia. Curr Opin Hematol. 2008
Mar;15(2):108–14.
2 Thol F, Schlenk RF, Heuser M, Ganser A.
How I treat refractory and early relapsed
acute myeloid leukemia. Blood. 2015 Jul;
126(3):319–27.
3 Ferguson P, Hills RK, Grech A, Betteridge S,
Kjeldsen I, Dennis M, et al. An operational
definition of primary refractory acute mye-
eloid leukemia allowing early identification of
patients who may benefit from allogeneic stem cell transplantation. Haematologica.
2016;101(11):1351–8.
4 Ravandi F. Primary refractory acute myeloid
leukaemia: in search of better definitions and
therapies. Br J Haematol. 2011 Nov;155(4):
413–9.
5 Ravandi F, Cortes J, Faderl S, O’Brien S, Gar-
cia-Manero G, Verstovsek S, et al. Character-
istics and outcome of patients with acute mye-
eloid leukemia refractory to 1 cycle of high-
dose cytarabine-based induction chemotherapy. Blood. 2010 Dec;116(26):
5818–6153.
6 Löwenberg B, Ossenkoppele GJ, van Putten
W, Schouten HC, Graux C, Ferrant A, et al.
High-dose daunorubicin in older patients with
acute myeloid leukemia. N Engl J Med.
2009 Sep;361(13):1235–48.
7 Lee JH, Joo YD, Kim H, Bae SH, Kim MK,
Zang DY, et al. A randomized trial compar-
ing standard versus high-dose daunorubicin
induction in patients with acute myeloid
leukemia. Blood. 2011 Oct;118(14):3832–41.
8 Fernandez HF, Sun Z, Yao X, Lizow MR,
Luger SM, Piaetta EM, et al. Anthracycline
dose intensification in acute myeloid leukema-
ia. N Engl J Med. 2009 Sep;361(13):1249–
59.
9 Trifilio SM, Rademaker AW, Newman D,
Coye K, Carlson-Leuer K, Mehta J, et al. Mi-
toxantrone and etoposide with or without in-
termediate dose cytarabine for the treatment
of primary induction failure or relapsed acute
myeloid leukemia. Leuk Res. 2012 Apr;36(4):
394–6.
10 Schlenk RF, Döhner K, Mack S, Stoppel M,
Kiraly F, Götze K, et al. Prospective evaluation
of allogeneic hematopoietic stem-cell trans-
plantation from matched related and matched
unrelated donors in younger adults with
high-risk acute myeloid leukemia: German-
Austrian trial AMLD98A. J Clin Oncol.
2010 Oct;28(30):4642–8.
11 Willemez R, Suciu S, Meloni G, Labar B, M-
arie JP, Halkes CJ, et al. High-dose cytarabine
in induction treatment improves the outcome
of adult patients younger than age 46 years
with acute myeloid leukemia: results of the
EORTC-GIMEMA AML-12 trial. J Clin Onc-
ol. 2014 Jan;32(3):219–28.
12 Bergua JM, Montesinos P, Martinez-Cuadrón
D, Fernández-Abellán P, Serrano J, Sayas MJ,
et al. A prognostic model for survival after sal-
vage treatment with FLAG-Igα +/– gemtu-
zumab-ozogamicin in adult patients with ref-
fractory/refractory acute myeloid leukemia.
Br J Haematol. 2016 Sep;174(5):700–10.
13 Godwin CD, Gale RP, Walter RB. Gemptu-
zumab-ozogamicin in acute myeloid leukeme-
ia. Leukemia. 2017 Sep;31(9):1855–68.
14 Schlenk RF, Fröhling S, Hartmann F, Fischer
JT, Glasmaner A, del Valle F, et al. Phase III
study of all-trans retinoic acid in previously
untreated patients 61 years or older with acute
myeloid leukemia. Leukemia. 2004 Nov;
18(11):1798–803.
15 Schlenk RF, Lübbert M, Benner A, Lamparter
A, Krauter J, Herr W, et al. All-trans retinoic
acid as adjunct to intensive treatment in young-
er adult patients with acute myeloid leukemia:
results of the randomized AMLSG 07-04 study.
Ann Hematol. 2016 Dec;95(12):1931–42.
16 Stone RM, Mandrekar SJ, Sanford BL, Lau-
mann K, Geyer S, Bloomfield CD, et al. Mi-
dostaurin plus chemotherapy for acute mye-
eloid leukemia with a FLT3 mutation. N Engl
J Med. 2017 Aug;377(5):454–64.
17 Rashidi A, Weisdorf DJ, Bejanyan N. Treat-
ment of relapsed/refractory acute myeloid
leukemia in adults. Br J Haematol. 2018 Apr;
181(1):27–37.
18 Schmid C, Schleuning M, Schwerdtfeger R,
Hertenstein B, Mischak-Weissinger E, Bunjes
D, et al. Long-term survival in refractory acute
myeloid leukemia after sequential treatment
with chemotherapy and reduced-intensity
conditioning for allogeneic stem cell trans-
plantation. Blood. 2006 Aug;108(3):1092–9.
19 Decrooq J, Itzykson R, Viguouroux S, Michal-
let M, Yakoub-Agha I, Huynh A, et al. Similar
outcome of allogeneic stem cell transplanta-
tion after myeloablative and sequential condi-
tioning regimen in patients with refractory or
relapsed acute myeloid leukemia: a study from
the Societe Francophone de Greffe de Moelle et de Thérapie Cellulaire. Am J Hema-
tol. 2018 Mar;93(3):416–23.
Allogeneic Stem Cell Transplantation for Patients with Refractory AML.

20 Craddock C, Labopin M, Pillai S, Finke J, Bunjes D, Greinix H, et al. Factors predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukaemia. *Leukemia*. 2011 May; 25(5):808–13.

21 Michallet M, Thomas X, Vernant JP, Juentz M, Socie G, Esperou-Bourdeau H, et al. Long-term outcome after allogeneic hematopoietic stem cell transplantation for advanced stage acute myeloblastic leukemia: a retrospective study of 379 patients reported to the Societe Francaise de Greffe de Moelle (SFGM). *Bone Marrow Transplant*. 2000 Dec;269(11):1157–63.

22 Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017 Jan;129(4):424–47.

23 Creutzig U, Kaspers GJ. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2004 Aug; 22(16):3432–3.

24 Fung HC, Stein A, Slovak M, O’donnell MR, Snyder DS, Cohen S, et al. A long-term follow-up report on allogeneic stem cell transplantation for patients with primary refractory acute myelogenous leukemia: impact of cytogenetic characteristics on transplantation outcome. *Biol Blood Marrow Transplant*. 2003 Dec;9(12):766–71.

25 Duval M, Klein JP, He W, Cahn JY, Cairo M, Cannita BM, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *J Clin Oncol*. 2010 Aug;28(23):3730–8.

26 Anthias C, Dignan FL, Morilla R, Morilla A, Ethell ME, Potter MN, et al. Pre-transplant MRD predicts outcome following reduced-intensity and myeloablative allogeneic hematopoietic SCT in AML. *Bone Marrow Transplant*. 2014 May;49(5):679–83.

27 Walter RB, Buckley SA, Pagel JM, Wood BL, Storer BE, Sandmaier BM, et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. *Blood*. 2013 Sep;122(10):1813–21.

28 Ogawa H, Ikegame K, Daimon T, Uchida N, Fukuda T, Kakihana K, et al. Impact of pre-transplant leukemic blast% in bone marrow and peripheral blood on transplantation outcomes of patients with acute myeloid leukemia undergoing allogeneic stem cell transplantation for AML in non-CR. *Bone Marrow Transplant*. 2018 Apr;53(4):478–82.

29 Schlenk RF, Frec H, Weber D, Brossart P, Horst HA, Kraemer D, et al. Impact of pre-treatment characteristics and salvage strategy on outcome in patients with relapsed acute myeloid leukemia. *Leukemia*. 2017 May; 31(5):1217–20.

30 Breems DA, Van Putten WL, Huijgens PC, Ossenkoppele GJ, Verhoef GE, Verdonck LF, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005 Mar;23(9):1969–78.

31 Burnett AK, Goldstone A, Hills RK, Milligan D, Prentice A, Yin J, et al. Curability of patients with acute myeloid leukemia who did not undergo transplantation in first remission. *J Clin Oncol*. 2013 Apr;31(10):309–301.

32 Wattad M, Weber D, Döhner K, Krauter J, Gaidzik VI, Paschka P, et al. Impact of salvage regimens on response and overall survival in acute myeloid leukemia with induction failure. *Leukemia*. 2017 Jun;31(6):1306–13.

33 Wang L, Devillier R, Wan M, Decrooq J, Tian L, Fürst S, et al. Clinical outcome of FLAG-IDA chemotherapy sequential with Flu-Bu3 conditioning regimen in patients with refractory AML: a parallel study from Shanghai Institute of Hematology and Institut Paoli-Calmettes. *Bone Marrow Transplantation*. 2019 Mar;54(3):458–64.

34 Zhang WP, Yang D, Song XM, Ni X, Chen J, Chen L, et al. Allogeneic peripheral blood stem cell transplantation is a promising and safe choice for the treatment of refractory/relapsed acute myelogenous leukemia, even with a higher leukemia burden. *Biol Blood Marrow Transplant*. 2013 Apr;19(4):653–60.