Treatment for relapsed acute promyelocytic leukemia: what is the best post-remission treatment?

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Background
Arsenic trioxide (ATO) is the standard treatment for relapsed acute promyelocytic leukemia (APL). However, consensus on post-remission therapies is still lacking.

Methods
We evaluated 52 patients who experienced relapse following initial treatment of APL between 2000 and 2019 at Catholic Hematology Hospital. Among them, 41 patients received reinduction treatment, 30 with ATO-based regimen, whereas 11 with conventional intensive chemotherapy (IC).

Results
The ATO reinduction group showed a significantly higher second molecular complete remission (mCR2) rate, superior neutrophil and platelet recovery, and a lower infection rate than the IC reinduction group. No significant differences were observed in survival outcomes after post-remission treatment among the ATO-based (N=19), autologous (N=12), and allogeneic (N=6) hematopoietic stem cell transplantation (HSCT) groups. In the ATO-based and autologous HSCT groups, among patients with mCR2 after ATO reinduction, nine and five patients experienced a second relapse, respectively (50.7% vs. 41.7%, P=0.878). Among these patients, seven received salvage allogeneic HSCT; six remained alive. The other seven patients received ATO without HSCT. Five died from disease progression, and two survived and have been in mCR2 since.

Conclusion
Post-remission treatment outcomes of patients with relapsed APL were not significantly different, regardless of the treatment option, suggesting the feasibility of ATO-based treatment without HSCT in mCR2. Allogeneic HSCT may be an effective salvage treatment modality for patients with a second relapse. Owing to a few cases of relapsed APL, multicenter prospective studies may help elucidate the efficacy of each post-remission treatment.

Key Words
Acute promyelocytic leukemia, Relapse, Arsenic trioxide, Stem cell transplantation, Post-remission therapy

INTRODUCTION

Arsenic trioxide (ATO), monotherapy or combined with all-trans retinoic acid (ATRA), is an effective treatment for remission in patients with relapsed acute promyelocytic leukemia (APL) after frontline anthracycline-based therapy with limited toxicity, particularly concerning myelosuppression [1]. Despite the high complete remission (CR) rate observed with ATO, which is up to 80-85% in relapsed APL cases.

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following initial anthracycline-based treatment [2], the second relapse rate is also relatively high (approximately 41–48%) [3, 4]. In patients who show ATO-induced second complete remission (CR2), no consensus has been established concerning appropriate post-remission approaches owing to a lack of randomized studies. Autologous or allogeneic hematopoietic stem cell transplantation (HSCT) is the major post-remission treatment [5]. Autologous HSCT is suitable for patients who achieve a second molecular CR (mCR2) based on good performance status and age [6]. Allogeneic HSCT should be limited to patients who do not show mCR2 because of the relatively high treatment-related mortality [7, 8]. HSCT, a post-remission treatment administered after CR2, is covered by national health insurance in Korea. This may be challenged by the feasibility of prolonged ATO treatment without HSCT owing to the advantages of lower toxicity and applicability for patients who are not deemed suitable for HSCT [9, 10]. However, the efficacy of repeated ATO or ATO combined with novel agents warrants further evaluation. To evaluate optimal post-remission treatment options, we examined clinical outcomes of patients with relapsed APL.

**MATERIALS AND METHODS**

### Study population and diagnosis

All patients with relapsed APL diagnosed and treated at the Catholic Hematology Hospital from 2000 to 2019 were screened for this retrospective analysis. Patients diagnosed with APL were treated with anthracycline-based intensive chemotherapy (IC) combined with ATRA as a first-line induction regimen. After achieving CR, all patients underwent three cycles of consolidation therapy and two-year maintenance therapy involving the administration of 6-mercaptopurine plus ATRA as previously described [11]. Among 356 patients with APL treated at our institute, 52 patients had relapsed APL and 41 relapsed APL patients who received reinduction treatment were included in our study (Fig. 1, Table 1). All patients were diagnosed based on morphology, immunophenotype study, and conventional karyotype analysis with a demonstration of translocation t(15;17) of blast cells from bone marrow (BM) [12]. Reverse transcriptase-polymerase chain reaction (RT-PCR) and real-time quantitative polymerase chain reaction (RQ-PCR) assays for promyelocytic leukemia/retinoic acid receptor-α (PML-RARα) fusion gene were performed for genetic diagnosis and measurable residual disease (MRD) evaluation. We included hematologic, cytogenetic, or molecular relapses and identified additional chromosomal abnormalities. The Catholic Medical Center Institutional Review Board approved this single-center retrospective study (KC21RASI0641). All analyses were performed according to the institutional review board guidelines and the Declaration of Helsinki.

### Treatment for relapsed APL

Patients with relapsed APL received anthracycline plus ATRA, low-dose cytarabine with etoposide, or ATO with or without ATRA (Table 1). The reinduction regimen was decided based on age, performance, and the best treatment options for specific periods. Before 2009, IC was the backbone of reinduction therapy. Since 2009, we have utilized stand-

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**Fig. 1.** Flow chart of acute promyelocytic leukemia patients who relapsed after administration of first-line treatment.
Table 1. Baseline characteristics of patients with relapsed APL (N=52).

| Characteristics | N (%) |
|-----------------|-------|
| At diagnosis     |       |
| Age at diagnosis, median (range) | 39 yr (17–74) |
| Gender, male     | 32 (61.5%) |
| Sanz risk, at diagnosis |     |
| High             | 28 (53.8%) |
| Intermediate     | 13 (25.0%) |
| Low              | 11 (21.2%) |
| FLT3 mutation<sup>a</sup> |     |
| No FLT3 mutation | 23 (44.2%) |
| FLT3-ITD         | 8 (15.4%) |
| FLT3-TKD         | 3 (5.8%)  |
| PML-RAR<sup>α</sup> subtype<sup>b</sup> |     |
| BCR1             | 16 (30.8%) |
| BCR3             | 18 (34.6%) |
| Karyotype abnormality<sup>c</sup> |     |
| t(15;17) alone   | 28 (53.9%) |
| t(15;17) with 1 additional karyotype | 5 (9.6%) |
| t(15;17) with ≥2 additional karyotype | 14 (26.9%) |
| Bleeding tendency at diagnosis<sup>d</sup> | 41 (78.8%) |
| Coagulopathy at diagnosis<sup>e</sup> | 46 (88.5%) |
| Laboratory findings at diagnosis, median (range) |     |
| Leukocyte (10^9/L) | 11.44 (0.58–177.04) |
| Hemoglobin (g/dL) | 9.4 (4.0–14.0) |
| Platelet (10^9/L) | 29.0 (4.8–210.0) |
| PML-RAR<sup>α</sup> RQ-PCR (copies/10^4 ABL) | 457.0 (6.1–2520.0) |
| Differentiation syndrome | 10 (19.2%) |
| At first relapse  |       |
| Age at relapse (median) | 41 yr (19–75) |
| CR1 duration, median (range), mo<sup>f</sup> | 20.7 (5.1–84.3) |
| APL 1<sup>st</sup> relapse type |     |
| Hematologic relapse | 24 (46.2%) |
| Cytogenetic relapse | 6 (11.3%) |
| Molecular relapse | 22 (42.3%) |
| Laboratory findings, at relapse, median (range) |     |
| Leukocyte (10^9/L) | 3.47 (0.52–54.7) |
| Hemoglobin (g/dL) | 11.8 (4.0–15.6) |
| Platelet (10^9/L) | 96.0 (7.0–330.0) |
| PML-RAR<sup>α</sup> RQ-PCR (copies/10^4 ABL) | 329.5 (2.21–2400) |
| Sanz risk at relapse<sup>g</sup> |     |
| High             | 5 (20.8%) |
| Intermediate     | 5 (20.8%) |
| Low              | 14 (58.4%) |
| Patients who received reinduction therapy | 41 out of 52 patients |
| Arsenic-based regimen<sup>h</sup> |     |
| ATO only         | 27 (90.0%) |
| ATO+ATRA         | 3 (10.0%) |
| Conventional chemotherapy | 11 (21.2%) |
| IDA+ARA          | 7 (63.6%) |
| IDA+ATRA         | 2 (18.2%) |
| MTZ+ARA          | 1 (9.1%) |
| LDARA/etoposide  | 1 (9.1%) |

<sup>a</sup> FLT3 mutation was not evaluated in 18 (34.6%) patients. <sup>b</sup> PML-RAR<sup>α</sup> subtype was not evaluated in 18 (34.6%) patients. <sup>c</sup> The 5 (9.6%) patients’ karyotype was not available. <sup>d</sup> Bleeding tendency was defined as increased susceptibility to bleeding or bruising in patients diagnosed with APL. Any spontaneous bleeding or bruising in a patient was characterized a bleeding tendency. <sup>e</sup> Coagulopathy was defined as any derangement of hemostasis resulting in impaired clot formation in patients diagnosed with APL. Thrombocytopenia, PT/aPTT prolongation, decreased fibrinogen level, or prolonged bleeding time regardless of the bleeding event in a patient was characterized as coagulopathy. <sup>f</sup> The 12 (23.1%) patients experienced early relapse within a year. <sup>g</sup> Sanz risk classification at relapse was applied only to the hematological relapse group (N=24). <sup>h</sup> The median duration of the first ATO treatment was 37.0 days (range, 1.0–60.0). ATO reinduction was ceased for one patient one day after infusion because of septic shock. The patient died due to septic shock-induced multiorgan failure.

Abbreviations: APL, acute promyelocytic leukemia; ARA, cytarabine; ATRA, all-trans retinoic acid; BCR, breakpoint cluster region; CR, complete remission; ECOG, Eastern cooperative oncology group performance status; FLT3, FMS-related tyrosine kinase; IDA, idarubicin; ITD, internal tandem duplication; LDARA, low dose cytarabine; MTZ, mitoxantrone; PML-RAR<sup>α</sup>, promyelocytic leukemia-retinoic acid receptor alpha; RQ-PCR, real-time reverse transcriptase quantitative polymerase chain reaction; TKD, tyrosine kinase domain.
ardized ATO-based reinduction according to the European APL Group of Experts’ consensus [1]. For reinduction, ATO was administered at a dose of 0.15 mg/kg/day until CR2 was achieved. BM examination with MRD evaluation was performed on day 28 of the reinduction chemotherapy to determine the molecular (mCR), cytogenetic (cCR), or hematological (hCR) CR status. Patients were subjected to at least two consolidation cycles involving administration of ATO at a dosage of 0.15 mg/kg. Subsequently, the molecular response was assessed based on MRD to evaluate further treatment strategies.

Owing to the absence of randomized trials for optimal post-remission therapy, autologous or allogeneic HSCT, ATO-based regimens, or various modifications of maintenance therapies with or without ATO were considered based on the age, performance, type of frontline therapy, MRD status, previous CR1 duration, and donor availability. We recommended autologous or allogeneic HSCT for patients in a CR2 state capable of receiving high-dose chemotherapy as a consolidation regimen. Korean National Health Insurance Service covered autologous HSCT in patients with relapsed APL who have achieved mCR2, and allogeneic HSCT was selectively covered in patients with relapsed or refractory APL who had achieved hCR2, or cCR2 since October 2014. Although patients with CR2 status were recommended HSCT after consolidation, only a proportion of these patients consented. HSCT was primarily rejected owing to costs and the burden of intensive treatment-related complications. Therefore, a substantial proportion of patients decided to continue ATO-based post-remission treatment without HSCT but with conventional maintenance comprising mercaptopurine (50 mg/m²/day) plus ATRA.

Molecular studies

Molecular studies were performed using BM samples collected at diagnosis, after induction, reinduction, and each cycle of consolidation chemotherapy, and every three months after maintenance treatment. PML-RARα, the marker for MRD of APL, was detected by RT-PCR using the HemaVision Kit (DNA Technology, Aarhus, Denmark). The PML-RARα quantification was performed using RQ-PCR (Real-Q PML-RARα Quantification Kit, BioSewoom, Seoul, Korea) with a sensitivity of 5.0 log (10⁻⁵), and its level represented the ratio of PML-RARα expression normalized to the expression of the reference gene, ABL1 (1.0×10⁻⁴). The FLT3 mutation was also detected using multiplex allele-specific RT-PCR (ABSOLUTE FLT3 TKD/ITD RT-PCR, BioSewoom, Korea). As these molecular studies became available after 2006, molecular evaluation was not performed for patients treated before 2006.

Definitions

Hematological relapse was defined morphologically by the presence of ≥5% of blasts or abnormal promyelocytes in the BM, and cytogenetic relapse was defined as the presence of t(15;17) as a clonal abnormality without meeting the hematological relapse criteria. Molecular relapse was defined as PML-RARα RT- or RQ-PCR positivity in two consecutive tests and the absence of overt hematological or cytogenetic relapse. hCR was determined using conventional criteria including BM blasts and abnormal promyelocytes ≤5% with an absolute neutrophil count of ≥1.0×10⁹/L and a platelet count of ≥100.0×10⁹/L without transfusion dependency. cCR is defined as fulfilling the criteria of hCR with a positive PML-RARα RT- or RQ-PCR result. Molecular CR (mCR) was characterized as negative PML-RARα RT- and RQ-PCR results for BM cells. Sanz risk score predicted based on a combination of pretreatment leukocyte and platelet counts (low risk: platelet count >40.0×10⁹/L, intermediate-risk: platelet count ≤40.0×10⁹/L, and high risk: leukocyte count >10.0×10⁹/L) was a significant risk factor for relapse [13]. Adverse events during treatment were evaluated according to the common terminology criteria for adverse events (CTCAE) version 4.0.

Statistical analysis

All categorical variables were compared using the chi-square test or Fisher’s exact test, and continuous variables were assessed using the Student’s t-test or Mann-Whitney U test. Overall survival (OS) and disease-free survival (DFS) rates were estimated using the Kaplan-Meier method, and log-rank analysis was used to compare survival distributions. The cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) were calculated by cumulative incidence estimation, treating non-relapse death and relapse events as competing risks. All results were compared using the Gray test. Statistical significance was set at P<0.05, and two-sided values were reported. The statistical analyses were performed using the Statistical Package for Social Sciences, version 24.0 (IBM Inc., Chicago, IL), and cumulative incidence analyses were carried out with ‘R’ software version 3.4.1 (R Foundation for Statistical Computing, 2017).

RESULTS

Baseline characteristics

Out of 60 patients with relapsed APL, 52 and 8 showed first relapse and treatment-related MDS/AML, respectively (Fig. 1). All results were genetically confirmed. The baseline characteristics of 52 patients with relapsed APL are presented in Table 1. The median age was 41 years (range, 19-75 yr) with male predominance (N=32, 61.5%). The relapse was presented as hematological (N=24, 46.2%), cytogenetic (N=6, 11.5%), or molecular (N=22, 42.3%). Laboratory findings at relapse showed a wide variance in white blood cells, hemoglobin, platelet count, and PML-RARα RQ-PCR with median values of 3.47×10⁹/L (range, 0.52-54.7), 11.8 g/dL (range, 4.0-15.6), 96.0×10⁹/L (range, 7.0-330.0), and 329.5 copies/10⁴ ABL (range, 2.21-2400.0), respectively. At diagnosis, 21.2% of patients with relapse were characterized as low risk, 25.0% as intermediate risk, and 53.8% as high risk according to the Sanz criteria. The median CR1 duration before first relapse was 20.7 months (range, 5.1-84.3). Within one year
after achieving CR1, 12 (23.1%) patients relapsed. Among 52 patients with first relapse, 41 patients were treated with conventional cytotoxic (N=11) or arsenic-based regimens (N=30) for reinduction. The remaining 11 patients did not receive any reinduction treatment due to poor general conditions, such as combined bacterial and/or fungal infection or catastrophic cerebral hemorrhage with poor performance status.

### Reinduction chemotherapy

The baseline characteristics and clinical responses of 41 patients treated for relapsed APL according to the reinduction groups are presented in Table 2. Thirty patients were treated with an ATO-based reinduction regimen (median duration 37 days, range 1–60 days), and 11 patients were treated with IC. No significant difference was observed with respect to median age (39.5±2.3 vs. 39.4±3.5 yr, \( P=0.969 \)), gender (male subpopulation 60.0% vs. 45.5%, \( P=0.489 \)), and time to CR2 (48.7±3.6 vs. 39.4±7.2 days, \( P=0.263 \)) between the two groups. However, the ATO-based reinduction group comprised a higher number of patients showing molecular relapse (60.0% vs. 0%, \( P=0.001 \)) than those with hematological relapse (33.3% vs. 81.8%, \( P=0.006 \)) compared to the IC group.

After ATO-based reinduction, 13.3%, 30.0%, and 56.7% of patients achieved hCR2, cCR2, and mCR2, respectively, with no deaths observed and no patients died due to BM aplasia. Furthermore, 9.1%, 54.5%, and 18.2% of patients in the IC reinduction group achieved hCR2, cCR2, or mCR2, respectively; 9.1% of patients showed reinduction failure, and 9.1% died due to BM aplasia. Furthermore, patients in the ATO-based reinduction group achieved significantly more mCR2 (56.7% vs. 18.2%, \( P=0.029 \)) after reinduction. Overall, the CR2 rate without death was 100% in the ATO-based group (100% vs. 81.8%, \( P=0.017 \)). Hence, the ATO-based regimen was effective and safe. No significant difference was observed in hepatopathy incidence (36.7% vs. 54.5%, \( P=0.476 \)) and neutropenia severity (Grade III & IV, 76.7% vs. 100%, \( P=0.160 \)). In contrast, a significant difference was observed in neutrophil (19.3±2.9 vs. 31.1±2.8 days, \( P<0.01 \)) and platelet recovery (7.1±2.3 vs. 25.3±2.8 days, \( P<0.01 \)) periods, thrombocytopenia severity (grade III and IV, 30.0% vs. 0%, \( P<0.01 \)), and infection rate (36.7% vs. 0%, \( P=0.001 \)) among the two groups.

### Table 2. Characteristics and response according to reinduction regimens (N=41).

| Characters                              | Arsenic-based regimen (N=30) | Conventional cytotoxic regimen (N=11) | \( P \) |
|----------------------------------------|-----------------------------|--------------------------------------|-------|
| Age (median)                           | 39.5±2.3                    | 39.4±3.5                             | 0.969 |
| Gender (male)                          | 18 (60.0%)                  | 5 (45.5%)                            | 0.489 |
| Sanz risk at diagnosis (high risk)     | 21 (70.0%)                  | 2 (18.2%)                            | 0.011 |
| Sanz risk at relapse (high risk)       | 3 (10.0%)                   | 2 (18.2%)                            | 0.127 |
| Relapse type                           |                             |                                      |       |
| Hematologic relapse                    | 10 (33.3%)                  | 9 (81.8%)                            | 0.006 |
| Cytogenetic relapse                    | 2 (6.7%)                    | 2 (18.2%)                            | 0.288 |
| Molecular relapse                      | 18 (60.0%)                  | 0 (0.0%)                             | 0.001 |
| Response                               |                             |                                      |       |
| Neutrophil recovery                    | 19.3±2.9                    | 31.1±3.5                             | 0.017 |
| Platelet recovery                      | 7.1±2.3                     | 25.3±2.8                             | <0.01 |
| Response type                          |                             |                                      |       |
| Overall CR                             | 30 (100%)                   | 9 (81.8%)                            | 0.067 |
| Hematologic CR2                        | 4 (13.3%)                   | 1 (9.1%)                             | 1.000 |
| Cytogenetic CR2                        | 9 (30.0%)                   | 6 (54.5%)                            | 0.272 |
| Molecular CR2                          | 17 (56.7%)                  | 2 (18.2%)                            | 0.029 |
| Death in aplasia                       | 0 (0.0%)                    | 1 (9.1%)                             | 0.268 |
| Reinduction failure                    | 0 (0.0%)                    | 1 (9.1%)                             | 0.268 |
| Time to CR2, days                      | 48.7±3.6                    | 39.4±7.2                             | 0.263 |
| CR2 without death                      | 30 (100%)                   | 9 (81.8%)                            | 0.017 |
| Adverse events                         |                             |                                      |       |
| Neutropenia, Gr. III-IV                | 23 (76.7%)                  | 11 (100.0%)                          | 0.160 |
| Thrombocytopenia, Gr. III-IV           | 9 (30.0%)                   | 11 (100.0%)                          | <0.01 |
| Infection & FUO                        | 11 (36.7%)                  | 11 (100.0%)                          | <0.01 |
| Leukocytosis                           | 3 (10.0%)                   | 0 (0.0%)                             | 0.551 |
| Hepatopathy                            | 11 (36.7%)                  | 6 (54.5%)                            | 0.476 |
| Differentiation syndrome               | 2 (6.7%)                    | 0 (0.0%)                             | 0.388 |

\( ^{a} \)Among 30 patients, 27 patients (90.0%) received ATO only, and three (10.0%) received ATO+ATRA. \( ^{b} \)Among 11 patients, 7 (63.6%) received IDA+ARA, and 2 (18.2%) received the IDA+ATRA regimen. The other two received MTA+ARA and LDARA/Etoposide. \( ^{c} \)This patient experienced reinduction failure and died later because of disease progression.

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; CNS, central nerve system; CR, complete remission; FUO, fever of unknown origin; IC, intensive chemotherapy.
Post-remission therapy

Out of 41 patients who achieved CR2, 39 (95.1%) underwent post-remission treatment as follows: ATO-based post-remission treatment without HSCT (N=19) or anthracycline-based IC (N=2) treatment with or without conventional maintenance comprising mercaptopurine (50 mg/m²/day) plus ATRA, or various consolidation regimens, either ATO or anthracycline-based IC followed by autologous (N=12) or allogeneic HSCT (N=6). Out of the two patients subjected to two cycles of anthracycline-based IC post-remission therapy, one patient died after achieving mCR2 due to septic shock. The other patient received ATO-based reinduction and consolidation therapy after a second relapse and survived.

Subsequently, we focused on comparing clinical outcomes of ATO-based post-remission treatment without HSCT versus HSCT post-remission treatment. Overall, 37 patients were analyzed. The clinical characteristics and survival outcomes in each post-remission treatment group are presented in Table 3. Nineteen patients in the ATO-based post-remission group without HSCT were treated with various doses of ATO (0.15 mg/kg/day, median 50 days, range 20-96 days). One patient died during the second cycle of ATO administration due to sudden cardiac arrest. Nine patients survived without relapse, and nine experienced a second relapse. A detailed treatment course and clinical outcomes of these patients are presented in Supplementary Table 1. Twelve patients with mCR2 underwent autologous HSCT. Nine patients received two cycles of ATO (25 days), and three patients received two cycles of IC before transplantation. After the last consolidation schedule, all patients in the autologous HSCT group were subjected to peripheral blood stem cell collection after anthracycline-based or intermediate-dose cytarabine-induced chemo-mobilization with granulocyte colony-stimulating factor administered at a dose of 5 μg/kg/day. Out of these 12 patients, one patient died because of septic shock during transplantation, six patients survived without relapse, and the remaining five who received an ATO-based consolidation regimen experienced a second relapse. Patients

| Table 3. Characteristics and outcomes according to post-remission treatment (N=37)†. |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|----------|
|                                              | ATO-based post-remission (N=19)              | Autologous HSCT (N=12)                      | Allogeneic HSCT (N=6) |
| Age, years (mean±SD)                        | 40.9±14.8                                   | 34.8±11.0                                   | 41.2±10.4 |
| Gender, male                                | 10 (52.6%)                                  | 8 (66.7%)                                   | 4 (66.7%) |
| Sanz risk at diagnosis (High risk)          | 13 (68.4%)                                  | 5 (41.7%)                                   | 3 (50.0%) |
| Sanz risk at relapse (High risk)            | 3 (15.8%)                                   | 0 (0%)                                      | 1 (16.7%) |
| CR1 duration, months (mean±SD)              | 23.1±11.4                                   | 19.4±11.5                                   | 21.8±12.3 |
| Early relapse ≤1 year                       | 2 (10.5%)                                   | 5 (41.7%)                                   | 3 (50.0%) |
| Type of relapse                             |                                            |                                            |           |
| Hematologic relapse                         | 6 (31.6%)                                   | 6 (50.0%)                                   | 5 (83.3%) |
| Cytogenetic relapse                         | 3 (15.8%)                                   | 0 (0%)                                      | 0 (0%)    |
| Molecular relapse                           | 10 (52.6%)                                  | 6 (50.0%)                                   | 1 (16.7%) |
| Leptomeningeal relapse                      | 10 (52.6%)                                  | 7 (58.3%)                                   | 4 (66.7%) |
| Consolidation regimens                      |                                            |                                            | 0.009     |
| Arsenic-based consolidation                 | 19 (100%)                                   | 9 (75.0%)                                   | 3 (50.0%) |
| Anthracycline-based consolidation           | 0 (0%)                                      | 3 (25.0%)                                   | 3 (50.0%) |
| Best response                               |                                            |                                            |           |
| Hematologic CR2                              | 0 (0%)                                      | 0 (0%)                                      | 1 (16.7%) |
| Cytogenetic CR2                              | 0 (0%)                                      | 0 (0%)                                      | 5 (83.3%) |
| Molecular CR2                               | 19 (100%)                                   | 12 (100%)                                   | 0 (0%)    |
| Follow-up period from relapse, months (mean±SD) | 67.9±56.3                                     | 53.9±50.5                                   | 62.6±57.2 |
| Survival outcomes                           |                                            |                                            | 0.791     |
| Overall survival                            | 64.9% (37.6-82.6)                           | 75.0% (40.8-91.2)                           | 66.7% (19.5-90.4) |
| Disease-free survival                       | 44.1% (20.9-65.2)                           | 50.0% (20.8-73.6)                           | 66.7% (19.5-90.4) |
| Cumulative incidence of 2nd relapse         | 50.7% (24.8-71.8)                           | 41.7% (13.9-67.9)                           | 0%        |
| Non-relapsed mortality                      | 5.3% (0.3-22.0)                             | 10.0% (0.5-37.4)                            | 33.3% (3.2-70.4) |
| Treatment after 2nd relapse                 | N=9                                        | N=5                                        | N=0       |
| Arsenic-based treatment only                | 4 (44.4%)                                   | 3 (60.0%)                                   | 0 (0%)    |
| Salvage allogeneic HSCT                     | 5 (55.6%)                                   | 2 (40.0%)                                   | 0 (0%)    |

†Among 41 patients who received reinduction treatment, one patient died during reinduction due to infectious complications, the other patient died due to refractory disease, and another two patients underwent IC consolidation only (one died after achieving CR due to septic shock, and the other patient received ATO-based reinduction and consolidation therapy after experiencing the 2nd relapse and was alive). Therefore, 37 patients were included in the analysis.

*Patients who achieved mCR2 with negative PML-RARα RQ-PCR received autologous HSCT, and positive PML-RARα RQ-PCR received allogeneic HSCT.

Abbreviations: ATO, arsenic trioxide; CR, complete remission; HSCT, hematopoietic stem cell transplantation.
in the allogeneic HSCT group (N=6) did not achieve mCR2. However, these patients achieved cCR2 or hCR2 before HSCT. Two patients who experienced early relapse underwent two cycles of IC consolidation and reached cCR2 before HSCT. Two patients underwent two cycles of ATO treatment (25 days each), and the other patient was administered six cycles of ATO treatment (10 days each) as consolidation therapy and achieved cCR2. One patient underwent allogeneic HSCT during hCR2 after two cycles of IC consolidation. Four patients achieved mCR2 after HSCT in the allogeneic HSCT group, and two died during transplantation because of septic shock. None of the patients that received allogeneic HSCT experienced a relapse.

**Survival outcomes**

After various consolidation and/or maintenance treatments for relapsed APL, four patients died during treatment, 20 patients achieved long-term mCR2, and 15 patients experienced a second relapse. The median follow-up was 34.3 months (range, 0.4–183.9 mo). The OS and DFS rates of all 41 patients with relapsed APL were 63.3% [95% confidence interval (CI), 45.7–76.6], and 43.7% (95% CI, 27.6–58.7), respectively. The CIR and NRM were 41.7% (95% CI, 25.5–57.1) and 14.9% (95% CI, 6.0–27.8), respectively. Survival outcomes in terms of OS, DFS, CIR, and NRM were not significantly different among ATO-based post-remission treatment without HSCT, autologous, and allogeneic HSCT groups (Fig. 2).

**Treatment after second relapse**

The same ATO-based reinduction protocol was used for all patients experiencing a second relapse (N=15). The responses were as follows: nine and four patients showed mCR3 and cCR3, respectively, and two showed disease progression without achieving CR3. Selected patients with available donors considered receiving allogeneic HSCT regardless of the CR status. Seven patients underwent salvage allogeneic HSCT, and eight received salvage reinduction and consolidation therapy, with or without maintenance regimen. Among the nine patients in the ATO-based post-remission treatment without HSCT group and one in the IC-based post-remission treatment group at the first relapse, five underwent allogeneic HSCT at the second relapse, and four of the five patients survived without relapse. One patient died because of CMV pneumonia after allogeneic HSCT. Four out of five patients who did not undergo HSCT died...
due to infectious complications during consolidation or disease progression despite treatment, while only a patient survived after achieving mCR3. In the autologous-HSCT treated group, five patients experienced a second relapse after transplantation. Two patients received salvage allogeneic HSCT, and were alive without relapse. The other three patients received only ATO-based treatment; one died from infection, and two survived without relapse. Therefore, six out of seven salvage HSCT-treated patients after the second relapse of APL and only three out of eight patients in the ATO-based post-remission group survived, suggesting that allogeneic HSCT can be considered as an alternative salvage treatment after the second relapse.

**DISCUSSION**

APL has a favorable prognosis. Typically, the complete remission rate is over 90%. However, 5% to 10% of patients with APL show relapse [14]. Most relapses are diagnosed within the first three years. Delayed relapses beyond three years are extremely rare [14]. For patients with relapsed APL, treatment options include anthracyclines, ATO with or without ATRA, cytarabine, and/or gemtuzumab ozogamicin (GO) regimens. The treatment choice depends on the first-line regimen used for induction and whether the relapse occurred during therapy [5, 15]. Currently, the standard regimen for managing relapsed APL after IC is ATO with or without ATRA, which has demonstrated high CR2 rates in several studies [16, 17]. With remarkable therapeutic results, ATO has been approved for the treatment of relapsed APL without a phase three study [18]. Here, the long follow-up period of APL enabled comparisons of the efficacy of ATO-based and conventional IC reinduction treatments and adverse events in patients with relapsed APL. ATO-based reinduction was significantly superior with respect to mCR2 with fewer adverse events compared to IC reinduction, showing its safety and efficacy and supporting its priority as reinduction treatment of relapsed APL.

Despite a high CR2 rate observed with the ATO-based regimen among APL relapse cases, the second relapse rate remained high. Optimal post-remission treatment is essential for prolonging remission [5, 15]. No consensus has been established on post-remission treatment strategies after CR2. The superiority of HSCT over other treatment alternatives without transplantation has recently been questioned. Two small case series showed that prolonged ATO-based therapy alone or combined with other novel agents, such as gemtuzumab and ozogamicin without HSCT, can be effective as a post-remission treatment in relapsed APL cases [9, 10]. In contrast, a few small retrospective or transplantation registry-based studies compared the efficacy of consolidation with or without autologous HSCT in relapsed APL, with most supporting the superiority of autologous HSCT for survival outcomes compared to ATO-based post-remission treatment without HSCT [4, 19-21]. These small retrospective studies may be influenced by selection bias since a considerable number of patients ineligible for autologous HSCT were included in the ATO-based post-remission treatment without HSCT group. Additionally, except for one study [19], not all patients achieved mCR2 (7.8% to 11.0%) before receiving either autologous HSCT or ATO-based post-remission therapy without HSCT [4, 21]. A study based on two large transplant registries did not present the degree of CR in enrolled patients with relapsed APL [20]. Here, no significant difference was observed in survival outcomes, remission, and second relapse rates between the ATO-based post-remission treatment without HSCT and autologous HSCT post-remission treatment groups. Interestingly, most patients in the ATO-based treatment group without HSCT who received short-term ATO cycles (median 2 cycles, range of 1–6) as post-remission therapy with or without conventional maintenance therapy, primarily owing to costs, showed long-term event-free survival even without transplantation. No significant differences were observed in demographic characteristics, Sanz risk score at diagnosis and relapse, CR1 duration, early relapse rate, or the type of relapse between the two groups. Given that the previous studies presented contradictory results, our data suggest that well-designed prospective studies with large sample sizes are warranted to compare the efficacy of autologous HSCT versus ATO-based treatment without HSCT in patients who achieved mCR after reinduction therapy.

Since molecular persistence after consolidation became uncommon after the introduction of ATO-based approaches, autologous HSCT has a limited role as salvage therapy for patients with APL who experience early relapse within 12 months after CR1, first relapse with MRD positivity after consolidation, or second relapse after achieving CR2, thereby expecting dismal clinical outcomes [7, 8, 22, 23]. Several small and uncontrolled retrospective studies were performed to compare the efficacy of autologous and allogeneic HSCT as a post-remission treatment for patients with relapsed APL. Autologous HSCT was superior to allogeneic HSCT with respect to OS and DFS. No significant difference was observed in relapse rate, and worse NRM was detected in patients who underwent allogeneic HSCT [7, 8, 23]. Here, allogeneic HSCT was used as a salvage treatment for six of the first patients with a first relapse, including three patients with early relapse and three patients who did not achieve mCR2 after post-remission treatment. No patients relapsed after autologous HSCT but two died due to NRM (septic shock during mCR2). Allogeneic HSCT was also used as a salvage treatment for seven patients with a second relapse. Among them, six survived without relapse, and one patient died due to NRM (CMV pneumonia during mCR3). Our findings support the promising graft-versus-leukemia effect of allogeneic HSCT, even in patients who experienced a second relapse, in contrast to the poor survival of ATO-based consolidation without HSCT after secondary relapse. Similar outcomes of allogeneic HSCT in patients with a second relapse have been observed in the remission after ATO-based post-remission or autologous HSCT provide a rationale for studies comparing the two treatment modalities in patients with a first relapse.
This study may be biased because of its retrospective nature and a relatively small number of patients evaluated at a single institute. Moreover, significant prognostic factors for relapsed APL were not identified. However, a large-scale phase III trial for addressing these questions would be unlikely because relapsed APL would gradually decrease because of the low incidence of APL and remarkable advances in treatment outcomes. Thus, our data comparing various post-remission strategies for relapsed APL is significant. In contrast to previous studies, we compared ATO-based post-remission treatment with autologous HSCT only in patients who achieved mCR2. The follow-up period was sufficiently long to provide real-world data for various treatments of relapsed APL, a rare event.

ATO was an effective reinduction therapy for patients with relapsed APL and had a favorable toxicity profile compared to IC. Post-remission treatment outcomes of ATO alone and/or combined with autologous HSCT were not significantly different. Allogeneic HSCT was an effective salvage treatment modality for patients with a second relapse. Owing to a small number of relapsed APL, multicenter prospective studies may help elucidate the efficacy of each post-remission treatment.

Authors’ Disclosures of Potential Conflicts of Interest

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

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## Supplementary Table 1. A summary of the clinical course of patients with relapsed APL in arsenic-based consolidation without HSCT group (N= 19).

| Patient No. | Sex  | Age (yr) | Sanz risk (initial) | CR1 duration (mo) | Reinduction treatment | Treatment response | Consolidation treatment | Maintenance treatmenta) | CR2 duration (mo) | 2nd relapse | 3rd relapse | Clinical outcome |
|-------------|------|----------|---------------------|------------------|----------------------|---------------------|-----------------------|------------------------|----------------|------------|------------|------------------|
| 1           | F    | 45       | Low                 | 30.2             | ATO                  | CHR2                | ATO 10 days 2 cycles | None                   | 3.4           | No         | No         | Expired due to V. fibr cardiac arrest during 2nd consolidation |
| 2           | F    | 36       | Intermediate        | 24.5             | ATO                 | ATO+ATRA           | CMR2                  | ATO 28 days 1 cycle  | 8 cycles      | 18.1       | No         | Alive without 2nd relapse |
| 3           | F    | 53       | High                | 33.2             | ATO                 | CMR2                | CCR2                  | ATO 28 days 2 cycles | 4 cycles      | 13.9       | Yes        | Yes               |
| 4           | M    | 18       | High                | 14.3             | ATO                 | CMR2                | CCR2                  | ATO 28 days 2 cycles | 8 cycles      | 153.3      | No         | No                 |
| 5           | F    | 41       | High                | 23.8             | ATO                 | CMR2                | ATO 28 days 1 cycle  | ATO 14 days 2 cycles | 8 cycles      | 145.7      | No         | No                 |
| 6           | M    | 26       | Intermediate        | 17.6             | ATO+ATRA            | CMR2                | ATO 28 days 1 cycle  | ATO 10 days 5 cycles | 8 cycles      | 87.6       | No         | No                 |
| 7           | F    | 31       | Intermediate        | 16.7             | ATO                 | CMR2                | ATO 28 days 1 cycle  | ATO 10 days 5 cycles | 8 cycles      | 141.5      | No         | No                 |
| 8           | F    | 51       | High                | 25.8             | ATO                 | CMR2                | ATO 10 days 6 cycles | 4 cycles               | 19.2          | Yesb)      | No         | Expired after salvage allo-HSCT due to CMV pneumonia |
| 9           | F    | 48       | High                | 36.7             | ATO                 | CMR2                | ATO 25 days 2 cycles | 8 cycles               | 24.9          | No         | No         | Alive without 2nd relapse |
| 10          | M    | 44       | High                | 18.0             | ATO                 | CMR2                | ATO 25 days 2 cycles | 8 cycles               | 72.3          | No         | No         | Alive without 2nd relapse |
| 11          | F    | 42       | High                | 33.4             | ATO                 | CMR2                | ATO 25 days 2 cycles | 8 cycles               | 48.2          | Yesc)      | No         | Alive without 3rd relapse after salvage allo-HSCT |
| 12          | M    | 35       | Low                 | 14.9             | ATO                 | CH2R                | ATO 25 days 3 cycles | 6 cycles               | 20.2          | Yesc)      | No         | Alive without 3rd relapse after salvage allo-HSCT |
| 13          | M    | 37       | High                | 49.6             | ATO                 | CH2R                | ATO 25 days 2 cycles | 8 cycles               | 55.7          | No         | No         | Alive without 2nd relapse |
| 14          | M    | 46       | High                | 14.1             | ATO                 | CMR2                | ATO 25 days 2 cycles | None                   | 8.3           | Yesd)      | Yes        | Alive with 3rd relapse after salvage allo-HSCT |
| 15          | M    | 22       | High                | 6.5              | ATO                 | CH2R                | ATO 25 days 2 cycles | None                   | 6.3           | No         | No         | Expired due to infectious complications after 2nd relapse |
| 16          | M    | 46       | High                | 12.5             | ATO                 | CMR2                | ATO 25 days 2 cycles | 8 cycles               | 8.3           | Yesc)      | No         | Alive without 3rd relapse after salvage allo-HSCT |
| 17          | F    | 29       | High                | 34.3             | ATO+ATRA            | CCR                 | ATO 10 days 5 cycles | LDARA 2 cycles        | None          | 110.3      | No         | No                 |
| 18          | F    | 62       | High                | 9.4              | ATO                 | CCR                 | ATO 25 days 2 cycles | None                   | 11.9          | Yes        | No         | Expired due to infectious complications after 3rd relapse |
| 19          | M    | 72       | High                | 17.0             | ATO                 | CCR                 | ATO 25 days 2 cycles | 8 cycles               | 28.4          | Yes        | Yes        | Expired due to disease progression after 3rd relapse |

*a)Maintenance consists of eight cycles of 6-mercaptopurine (50 mg/m²/day) plus ATRA per our hospital protocol.
*b)Five patients received allogeneic HSCT as salvage therapy after 2nd relapse of APL. The other two patients who received allogeneic HSCT relapsed after autologous HSCT.

Abbreviations: ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; CHR, complete hematologic response; CMR, complete molecular response; HSCT, hematopoietic stem cell transplantation; IDV, idarubicin; LDARA, low-dose cytarabine; MTZ, mitoxantrone.