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Prevalence of extramedullary relapses is higher after allogeneic stem cell transplantation than after chemotherapy in adult patients with acute myeloid leukemia

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ABSTRACT

Although studies have demonstrated a high prevalence of extramedullary (EM) relapse after allogeneic stem cell transplantation (allo-SCT) in patients with acute myeloid leukemia (AML), the prevalence of EM relapse has not been compared with that after chemotherapy. This study investigated the prevalence of EM relapse among 498 adult AML patients (median age, 57 years; range, 15–82 years) who underwent intensive chemotherapy. A total of 281 relapses occurred in 210 patients (36 after allo-SCT; 245 after chemotherapy), and 33 relapses (11.7%) were accompanied by EM disease. Among these relapses, EM disease was more frequently observed at relapse after allo-SCT than after chemotherapy (25% vs. 9%, respectively; $p = 0.008$). Eight of 33 relapses after the first allo-SCT had EM disease, and only presence of extensive chronic graft-versus-host disease (GVHD) was identified as a predisposing factor for EM relapse. Additionally, the 1-year overall survival rate after relapse was not significantly different when comparing those with EM relapse and those with BM relapse (38% vs. 16%, respectively; $p = 0.279$). These data suggest that AML patients undergoing allo-SCT should be closely followed for signs of EM relapse, especially those with extensive chronic GVHD.

1. Introduction

Although allogeneic stem cell transplantation (allo-SCT) can be curative for various advanced hematologic malignancies, relapse is the most serious cause of treatment failure after allo-SCT [1,2]. Among patients with acute myeloid leukemia (AML), the site of relapse is usually the bone marrow (BM), but several investigators have reported that extramedullary (EM) relapses can also occur after allo-SCT [3,4]. While a large scale study by the European Group for Blood and Marrow Transplantation reported that the prevalence of EM relapse after allo-SCT was 0.65% [5], this prevalence is likely underestimated. Indeed, other analyses in small cohorts suggested that the prevalence of EM relapse was 20–50% [6–11]. However, no study has investigated the comparative prevalence of EM relapse in patients undergoing allo-SCT versus those treated with chemotherapy.

When compared with BM relapse, EM relapse after allo-SCT possesses several unique characteristics, including onset at longer duration from transplant [9], close association with graft-versus-host disease (GVHD) [9,10], and survival benefit after relapse [10,11]. However, these findings were not consistently described among several different studies, and, in fact, some discrepancies in these parameters were noted.

Therefore, this large-scale retrospective analysis of 498 adult AML patients was performed to determine the prevalence of EM relapse after allo-SCT versus after chemotherapy and to identify factors associated with development of EM relapses as well as the impact of EM relapse on outcomes.

2. Patients and methods

2.1. Study population

Among 523 consecutive patients who had been diagnosed with AML between January 1990 and March 2010 at one of our three cooperative hospitals in Gunma, Japan, the medical records of 498 patients who received intensive chemotherapy were retrospectively analyzed. The remaining 25 patients underwent management

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with supportive care only and were excluded. All patients gave informed consent to participate in accordance with the Declaration of Helsinki before initiation of treatment, and this study was approved by the Institutional Review Board of Gunma University Hospital.

2.2. Definition

AML was diagnosed according to the French–American–British (FAB) classification [12] or the World Health Organization classification [13]. EM sites included the presence of EM tumors that were identified upon physical examination and/or by imaging studies (computed tomography scan or magnetic resonance imaging) and that responded to chemotherapy or local irradiation. Pathological confirmation was not necessarily required. Patients with hepatomegaly and/or splenomegaly were excluded from the definition of EM sites. EM relapse included both that with and without concurrent BM disease. Cytogenetic subgroups were classified as favorable, intermediate, and adverse risk according to a largely accepted classification system as follows [14]: (a) favorable risk included *t*(8;21), *t*(15;17), and inv(16); (b) intermediate risk included normal karyotypes, 11q23 aberrations, and others; (c) adverse risk included −5, −7, del(5), 3q abnormalities, and complex karyotype (5 or more abnormalities).

2.3. Chemotherapy regimens

All 498 patients were treated according to the Japan Adult Leukemia Study Group (JALSG) treatment protocols (JALSG AML92 [15], AML95 [16], AML97 [17], GML200 [18], or AML201 [19,20]). All protocols consisted of single induction therapy with anthracycline (daunorubicin or idarubicin) plus cytarabine or enocitabine and were followed by three or four courses of consolidation therapy.

2.4. Transplantation procedures

Patients with high-risk disease, including those without favorable cytogenetic abnormalities and with relapsed disease, were considered as candidates for allo-SCT. Of the 498 patients analyzed in this study, 120 underwent allo-SCT. Since six patients underwent allo-SCTT twice or three times due to relapse or graft failure, a total 127 transplants were performed. Of these 127 transplants, 41 were from a related human leukocyte antigen (HLA)-matched donor, 62 were from an unrelated HLA-matched donor, and 24 were from cord blood. About 90% of transplants were conditioned with total body irradiation (TBI)-containing myeloablative regimens, and calcineurin inhibitors and short-term methotrexate were given as prophylaxis for GVHD in almost all cases. The incidences of acute and chronic GVHD were graded according to published criteria [21,22] in patients who were alive without relapse until day 30 and 100 after transplantation, respectively.

2.5. Statistical analysis

Overall survival (OS) was defined as the interval from the date of relapse after allo-SCT to the date of death. The χ^2-test was used for comparison of binary variables, and the Mann–Whitney *U* test was used for comparison of continuous variables. OS was estimated by the Kaplan–Meier method, and results were compared using the log-rank test. All calculations were performed using the SAS software package (SAS Institute, Inc., Cary, NC), and $p < 0.05$ was considered an indicator of statistical significance.

3. Results

3.1. Baseline characteristics

Of the 498 AML patients, 301 patients were men and 197 were women, and the median age was 57 years (range, 15–82 years). At the time of diagnosis of AML, 59 patients (11.7%) had developed EM disease. As we recently reported [23], patients with EM disease at diagnosis possess unique clinical features when compared with those with BM disease alone; these features include younger age (EM: median 46 years vs. BM: median 58 years; $p < 0.001$), higher white blood cell counts (EM: median, $27.1 \times 10^9\ L^{-1}$ vs. BM: $10.2 \times 10^9\ L^{-1}$; $p = 0.032$), and predominance of FAB M4 and M5 morphology (M4; EM: 30.4% vs. BM: 11.6%; $p = 0.001$, M5; EM: 18.1% vs. BM: 9.2%; $p = 0.042$).

3.2. Factors associated with EM relapse in the entire cohort

At the time of analysis, 281 relapses occurred in 210 patients, and among these relapses, 33 (11.8%) were EM relapses. Relapses were stratified according to the presence of EM disease, and their clinical characteristics are shown in Table 1. EM relapses were associated with younger age (EM: median 49 years vs. BM: median 57 years; $p = 0.046$) and FAB M4 morphology at diagnosis (EM: 25.0% vs. BM: 11.9%; $p = 0.042$), similar to the trend seen at the time of diagnosis. Additionally, patients with EM disease at diagnosis were more likely to develop EM disease at relapse again than those without EM disease (29.7% vs. 9.0%, respectively; $p < 0.001$). Further, EM disease was more frequently observed at relapse after allo-SCT than after chemotherapy (25.0% vs. 9.8%, respectively; $p = 0.008$) (Table 2).

3.3. Factors associated with EM relapse after allo-SCT

To clarify predisposing factors for EM relapse after allo-SCT, various parameters were examined among 33 patients who experienced relapses after the first transplant (EM relapse, 8 patients; BM relapse, 25), including disease status at transplant, conditioning regimens, stem cell sources, complete remission (CR) duration after

Table 1
Clinical characteristics of 281 consecutive AML relapses.

Relapses, *n* (%)	EM relapse33 (11.7)	BM relapse248 (88.3)	*p*-value
Median age at relapse, years (range)	49 (15–81)	57 (17–82)	0.046
No. men/no. women	16/17	147/101	0.238
FAB classifications at diagnosis, *n* (%)			
M0	1 (3.1)	11 (4.8)	0.664
M1	5 (15.6)	35 (15.4)	0.976
M2	12 (37.5)	106 (46.7)	0.328
M3	1 (3.1)	13 (5.7)	0.542
M4	8 (25.0)	27 (11.9)	0.042
M5	6 (18.8)	25 (11.0)	0.207
M6	0 (0.0)	8 (3.5)	0.28
M7	0 (0.0)	2 (0.9)	0.594
NA	1	21	
Cytogenetic abnormalities at diagnosis, *n* (%)			
Favorable	7 (21.2)	37 (15.4)	0.350
t(8;21)	3 (9.4)	22 (9.2)	0.969
inv(16)	3 (9.4)	8 (3.3)	0.103
t(15;17)	1 (3.1)	7 (2.9)	0.948
Intermediate	19 (59.4)	176 (71.0)	0.100
Normal	12 (37.5)	129 (53.8)	0.083
11q23	2 (6.3)	5 (2.1)	0.162
Adverse	3 (9.1)	26 (10.8)	0.802

EM, extramedullary; BM, bone marrow; Allo-SCT, allogeneic stem cell transplantation; FAB, French–American–British; NA, not available.

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