A single-center retrospective analysis of extramedullary relapse after allogeneic stem cell transplantation for myeloid neoplasms

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Extramedullary (EM) relapses after allogeneic hematopoietic stem cell transplantation (HSCT) are among the major causes of treatment failure. We retrospectively analyzed 174 patients with myeloid leukemia and myelodysplastic syndrome who underwent HSCT at the Hematology and Oncology Department of the Kyoto University Hospital between 1990 and 2009 to evaluate the incidence of EM relapses and determine its clinical features and appropriate treatment strategies. Of 53 patients who had a relapse after HSCT, 10 had an EM relapse, including 7 patients with a multiple-site EM relapse and 4 patients with an accompanied bone marrow (BM) relapse. Longer latency between HSCT and occurrence of relapse (486.5 versus 251 days) and a higher incidence of chronic graft-versus-host-disease (GVHD) before relapse (70% versus 26%) were observed for EM relapses than for BM relapses. Interestingly, EM relapses developed shortly after the intensification of the treatment for chronic GVHD (median 63 days, range: 28-339), indicating that immunosuppressive therapy triggers EM relapses. At 1 year, the survival rate after relapse was 46.7% for EM relapses. Therefore, effective management of EM relapses, frequently accompanied by chronic GVHD, is warranted.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative strategy for myeloid neoplasms; however, disease relapse after HSCT remains the most common cause of treatment failure. Although extramedullary (EM) relapses have been reported to be a rare manifestation of relapse in myeloid leukemia after allogeneic HSCT, recent studies have shown higher incidences of EM relapses than previously reported. Thus, the establishment of an adequate treatment strategy is essential. Several studies have evaluated the clinical features of EM relapses after allogeneic stem cell transplantation. EM relapses develop in various sites, including immunological sanctuary sites such as the central nervous system (CNS) and reproductive organs, and occur after a longer interval from the time of allogeneic HSCT than bone marrow (BM) relapses. Several risk factors, including younger age, EM involvement prior to allogeneic HSCT, the presence of advanced diseases at the time of allogeneic HSCT, unfavorable cytogenetics, and the involvement of M4/5 French American British subtypes, have been suggested. Higher incidences of acute and chronic graft-versus-host-disease (GVHD) before EM relapses have also been reported. However, for a better understanding of the clinical features and pathogenesis of EM relapses after allogeneic HSCT, further study is required. In the present study, we retrospectively analyzed 174 consecutive patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and chronic myeloid leukemia (CML), who underwent allogeneic HSCT in the Kyoto University Hospital’s Department of Hematology and Oncology between 1990 and 2009.
Patients and Methods

For this single-institution retrospective cohort study, we reviewed the medical records of patients with AML, MDS, and CML who underwent their first allogeneic HSCT at the Hematology and Oncology Department of the Kyoto University Hospital between 1990 and 2009. Patients with myeloproliferative disorders other than CML were excluded.

Complete remission (CR) was defined as the absence of disease after clinical, radiologic, and pathological evaluation. BM relapses were defined as relapses in only the BM and/or peripheral blood. EM relapses were defined as relapses in the extramedullary site, and multiple EM relapses were defined as the presence of two or more independent EM masses or the involvement of leukemia at first relapse. We divided patients with EM relapses into two subgroups: those with EM relapses without BM relapses and those with EM relapses concurrent with BM relapses. For the analysis of the pattern of the relapses, only the first relapse after CR was evaluated; cases of refractory disease after allogeneic HSCT and EM involvement after the experience of a BM relapse were not evaluated.

Statistical comparisons of characteristics, across the types of relapse, were conducted using Fisher’s exact test for categorical variables and the Wilcoxon test for continuous factors. The rates after HSCT or after a relapse were estimated using the Kaplan-Meier method, and they were compared using the log-rank test. Data were analyzed using the R software.

This study was approved by the Kyoto University Institutional Review Board and was conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all patients.

Results

Patient characteristics, overall survival rates, and relapse rates of all patients

Between 1990 and 2009, 174 adult patients with AML, MDS, and CML underwent HSCT at the Hematology and Oncology Department of Kyoto University Hospital. Of the 174 patients, 123 had AML, 21 had MDS, and 30 had CML. Patients’ characteristics, such as age, sex, conditioning regimen, donor, stem cell source, GVHD prophylaxis, disease status at the time of HSCT, and treatment outcomes, are shown in Table 1. The median observation time from the HSCT was 984 (range: 7-7,126) days. Hundred-and-four (59.8%) patients remained in CR, while 53 (30.5%) patients experienced a relapse after remission. The survival rate at 3 years after allogeneic HSCT was 60.1% (95% confidence interval (CI): 51.3-66.7%), and the cumulative incidence of a relapse at 3 years was 38.9% (95% CI: 30.6-46.3%).

Characteristics of patients with relapses

Of 53 patients who experienced a relapse, 43 (81%) developed a BM relapse and 10 (19%) developed an EM relapse. The comparison of the characteristics between patients who experienced BM and EM relapses are described in Table 2. There was no significant difference between the two groups in terms of age, sex, conditioning regimen, donor, stem cell source, disease status at the time of HSCT, and the number of
 adverse cytogenetic abnormalities (per The Southwestern Oncology Group/Eastern Cooperative Oncology Group classification). The median time to relapse from the time of HSCT was significantly longer in the EM relapse group (486.5 days, range: 147-1,810) than in the BM relapse group (251 days, range: 42-1,600) \(P<0.05\). In patients with an EM relapse, the incidence of chronic GVHD before the relapse was significantly higher than in those who had a BM relapse. Eleven of 43 (26%) patients experienced chronic GVHD in the EM relapse group, while 7 of 10 (70%) patients in the EM group experienced chronic GVHD \(P<0.05\). The incidence of acute GVHD did not differ between the two groups.

Characteristics of patients with EM relapse

EM relapses were confirmed histologically or cytologically in 7 patients. In the remaining 3 patients, granulosarcomas in the brain or skull were detected with a magnetic resonance imaging scan and diagnosed clinically. The 10 patients with an EM relapse included 6 cases of an EM relapse without a BM relapse and 4 cases of an EM relapse concurrent with a BM relapse. Three patients experienced EM involvement before the allogeneic HSCT. The sites involved in the EM relapse included the CNS \(n=6\), soft tissue \(n=4\), and bone \(n=3\). A brain mass was observed in 4 patients with a CNS relapse, and tumor cells were detected in the cerebrospinal fluid of 4 patients. The spinal bone was involved in 3 patients. Five of 6 patients with CNS involvement experienced specific symptoms, including headache, dizziness, nausea, neuropathy, and seizure, before diagnosis. Seven of the 10 patients in this group experienced multiple-site involvement at the first relapse. Of the patients who had an EM relapse without a BM relapse, 5 experienced chronic GVHD before the relapse and treatment intensification for chronic GVHD. Treatment intensification for chronic GVHD included the addition of immunosuppressive agents, such as prednisolone \(n=5\), tacrolimus \(n=3\), and mycophenolate mofetil \(n=1\). The median duration between the treatment intensification for chronic

### Table 2. Comparison of patients with BM relapses and EM relapses

| CHARACTERISTICS                              | BM relapse n (%) | EM relapse n (%) | \(P\) value |
|----------------------------------------------|------------------|------------------|-------------|
| Male/Female                                  | 19/24            | 6/4              | 0.488       |
| Age, years (range)                           | 49 (19-67)       | 39 (21-65)       | 0.460       |
| AML/MDS/CML                                  | 34/3/6           | 7/2/1            |             |
| Conditioning regimen                         |                  |                  | 0.124       |
| Myeloablative (TBI/Non-TBI)                  | 33 (29/4)        | 5 (5/0)          |             |
| Non-myeloablative (Flu Bu±TBI/Flu Mel±TBI)   | 10 (7/3)         | 5 (3/2)          |             |
| Donor                                        |                  |                  | 0.484       |
| MRD/URD or MMRD/MB                           | 20/20/3          | 3/5/2            | 0.376       |
| Stem cell source                             | BM/PBSC/CB       |                  |             |
| Disease status at HSCT                        |                  |                  |             |
| AML/MDS                                      |                  |                  |             |
| CR                                           | 14               | 5                | 0.465       |
| Not CR                                       | 21               | 3                | 0.318       |
| untreated                                    | 2                | 1                |             |
| CML                                          |                  |                  |             |
| CP                                           | 5                | 1                |             |
| AP/BC                                        | 1                | 0                |             |
| Adverse cytogenetic abnormality (AML)        | 9 (21%)          | 3 (30%)          | 0.397       |
| Time to relapse, days, median (range)        | 251 (42-1,600)   | 486.5 (147-1,810)| <0.05      |
| Acute GVHD                                   |                  |                  |             |
| II-IV                                       | 18 (42%)         | 5 (50%)          | 0.703       |
| III-IV                                      | 7 (16%)          | 2 (20%)          | 1           |
| Chronic GVHD before relapse                  | 11 (26%)         | 7 (70%)          | <0.05       |

TBI, total body irradiation; Flu, fludarabine; Bu, busulfan; Mel, melphalan.
GVHD and the EM relapse was 63 days (range: 28-339), as shown in Table 3.

Clinical course and treatment outcomes of patients with EM relapses

The clinical course, treatment, and outcomes of patients with EM relapses are described in Table 4. All the patients who had an EM relapse without a BM relapse received radiation therapy. One patient who had isolated bone involvement received no other treatment, but the other 5 patients received radiation therapy combined with systemic chemotherapy and/or intrathecal injections. The treatment modality for patients who had an EM relapse concurrent with a BM relapse varied between patients. Except 1, all the patients who had an EM relapse without a BM relapse achieved CR, but 3 patients experienced additional EM involvement after the treatment.

BM involvement was observed in 2 patients after the experience of the re-relapse of EM involvement. One patient with EM and BM relapses survived after the second allogeneic HSCT, but the other 3 patients died.

The probability of survival after a relapse was not different between those in the BM relapse and EM relapse groups, and the survival rates at 1 year were 53.4% (95% CI: 40-71.2) and 46.7% (95% CI: 23.3-93.6), respectively (Figure 1).

Discussion

In this study, we described the frequency, clinical features, risk factors, and survival probability associated with cases of myeloid leukemia EM relapses after allogeneic HSCT. The overall relapse rate was 30.5% and the EM relapse rate was 5.7%, with a median follow-up duration of 984 days. EM relapses accounted for 19% of the total initial relapses. This relapse rate is consistent with that of recent reports that suggested an EM relapse rate of 5-12% after allogeneic HSCT. In our study, 6 of the 10 patients with an EM relapse did not have a BM relapse. Other reports stated that approximately half of the patients with EM relapses were not associated with BM relapses. We also observed a longer duration between the time of allogeneic HSCT and EM relapses than between allogeneic HSCT and BM relapses, which is consistent with the data of previous reports.

In our study, a high frequency of multiple-site involvement in cases of EM relapse was observed. Seven of the 10 patients in the EM relapse group experienced multiple-site EM involvement. In addition, 4 of 10 patients experienced an additional EM relapse after treatment. One patient in particular experienced an additional EM relapse more than 1 year after treatment. Our data, in addition to published reports, suggest that EM relapses frequently occur in multiple sites.
Table 4. Clinical course and treatment outcomes of EM relapse patients

| Age at relapse | Sex | Disease | Status at HSCT | EM involvement before HSCT | Conditioning regimen | Donor | Stem Cell Source | Acute GVHD grade | Chronic GVHD | Treatment for chronic GVHD | Multiple EM relapse | Involved site | Concurrent BM relapse | Survival (post relapse) | treatment | Response | Additional EM relapse (interval, days) | Additional BM relapse (interval days) | status |
|---------------|-----|---------|----------------|-----------------------------|----------------------|-------|-----------------|------------------|--------------|---------------------------|-------------------|-------------|-----------------------|------------------------|----------|----------|----------------------------|----------------------|--------|
| 30            | M   | AML    | CR             | No                          | Myeloablative (TBI)  | URD   | BM              | No               | No           | -                         | Yes               | muscle     | No                    | 988+                   | CR       | Yes (506) | No                     | Alive                |        |
| 44            | F   | AML    | Not CR         | No                          | Non-myeloablative    | URD   | BM              | No               | Extensive    | PSL                      | No                | CNS, bone, paraspinal region | 1,084     | IT, RT     | Not CR               | Yes (95) | Yes (905) | Dead                   |                      |        |
| 35            | M   | APL    | Not CR         | CNS                         | Myeloablative (TBI)  | CB    | CB              | 2                | Extensive    | Taxotere + PSL           | Yes               | CNS        | No                    | 1,506+                 | CTx, RT  | CR                   | No | No | Alive                   |                      |        |
| 51            | F   | MDS    | CR             | No                          | Myeloablative (TBI)  | URD   | BM              | 3                | Extensive    | Tacrolimus + CyA + PSL + MMF | Yes               | CNS        | No                    | 216                    | IT, RT   | CR                   | No | No | Dead                   |                      |        |
| 65            | M   | MDS    | untreated      | No                          | Non-myeloablative    | MRD   | PBSC            | No               | Extensive    | Taxotere + PSL           | No                | bone       | No                    | 225                    | RT       | CR                   | Yes (97) | No | Dead                   |                      |        |
| 58            | F   | CML    | CP             | No                          | Non-myeloablative    | URD   | BM              | 2                | Extensive    | unknown                  | No                | CNS        | No                    | 171+                   | CTx, IT, RT | CR                   | No | No | Alive                   |                      |        |
| 29            | M   | AML    | CR             | No                          | Non-myeloablative    | CB    | CB              | 1                | No           | -                         | Yes               | bone       | Yes                   | 276+                   | CTx, 2nd HSCT | CR                   | No | - | Alive                   |                      |        |
| 61            | M   | AML    | CR             | No                          | Non-myeloablative    | URD   | BM              | 2                | No           | No                        | CNS               | Yes        | 116                   | RT                     | Not CR   | No                   | - | Dead |                      |                      |        |
| 21            | F   | AML    | CR             | soft tissue                 | Myeloablative (TBI)  | MRD   | BM              | No               | Local        | -                         | Yes               | head and neck | Yes                   | 111                    | CTx, RT, DU | Not CR               | Yes | - | Dead                   |                      |        |
| 25            | M   | AML    | CR             | No                          | Myeloablative (TBI)  | MRD   | BM              | 4                | Extensive    | Taxotere + PSL           | Yes               | Subcutaneous, CNS       | Yes (46)   | IT         | NE                   | No | - | Dead                   |                      |        |

CTx, chemotherapy; RT, radiation therapy; IT, intrathecal injection; DLI, donor lymphocyte infusion; GO, gemtuzumab ozogamicin; PSL, prednisolone.
both at the time of the initial relapse and after long intervals from the cessation of treatment. Because local therapy, including surgical resection and local radiation, is selected according to the type of case, an accurate evaluation of the EM involvement sites is required to determine an adequate treatment strategy.

Various factors, including unfavorable cytogenetics, M4/M5 FAB classifications, and EM involvement prior to allogeneic HSCT, have been suggested to be associated with an increased risk of EM relapses after allogeneic HSCT.

In our study, the incidence of chronic GVHD before a relapse was significantly higher in the EM relapse group than in the BM relapse group. Interestingly, the duration between the date of treatment intensification for chronic GVHD and the date of relapse was relatively short (median, 63 days), despite the fact that EM relapses occurred after a long interval from the time of allogeneic HSCT. These results suggest that the intensification of immunosuppressive therapy triggers the occurrence of EM relapses. The development of an EM relapse is considered to be the result of immune escape from the graft-versus-leukemia (GVL) effect. This is partly because EM relapses frequently involve immunological sanctuary sites including the CNS and reproductive organs, and the occurrence of acute GVHD is less effective in preventing EM relapse than BM relapse. However, the fact that the intensification of immunosuppressive therapy triggers the occurrence of EM relapses implies that the GVL effect still contributes to the prevention of EM relapses.

An appropriate treatment strategy for EM relapses has not yet been established. Solh et al. reported that the 6-month survival was better in patients who received a systemic or combined modality therapy than in patients treated only with local therapy. Yoshihara et al. reported the survival rate associated with EM relapses after the second haploidentical SCT to be 40% at 1 year. However, they also reported a higher frequency of repeat EM relapses. Our findings, which state that the intensification of immunotherapy triggers the occurrence of EM relapses, imply that treatments that do not affect effector cells but reduce the tumor burden are ideal in such cases. Donor lymphocyte infusion (DLI) may not be appropriate because most patients with EM relapses develop chronic GVHD. Several reports have investigated the effect of gemtuzumab ozogamicin, which does not affect the effector cells. In our study, one patient received gemtuzumab ozogamicin combined with radiation therapy and DLI, which resulted in long-term CR (506 days). The administration of gemtuzumab ozogamicin may be an effective treatment modality; however, further clinical studies are required.

In conclusion, EM relapses have a longer latency after HSCT and are associated with a higher incidence of chronic GVHD than BM relapses as well as with a high incidence of multiple EM relapses at the time of relapse and re-relapse. In addition, our observations suggest that the intensification of immunotherapy for chronic GVHD triggers the occurrence of EM relapses. The establishment of an adequate treatment strategy is warranted.

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Author’s Contributions

TI and TK designed the study. TI collected and analyzed the data and wrote the paper. TK, KY and AT-K supervised the project.

Conflict of interest disclosure

The authors declare that they have no conflicts of interest.
A summary of relevant information will be published with the manuscript.

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