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Letter to Editor

Acute Myeloblastic Leukemia with Multiple Extramedullary Relapses

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Dear Editor

Extramedullary relapse is a rare event in acute myeloblastic leukemia (AML) in contrast to acute lymphoblastic leukemia (ALL) which is associated with bone marrow relapses and extramedullary relapses (EMR) due to sanctuary sites such as testis and central nerve system (CNS).[1] Only 2% of patients with AML with medullary relapse were detected to have coexistent testicular relapse, although this ratio is much higher as 30-70 % in autopsy series.[1, 2] Testicular relapse harbours systemic relapse and aggressive systemic and adjunctive local treatments such as radiotherapy (RT) need to be started appropriately; although there is not any worldwide determined algorithm for isolated EMR, yet.

Here we present an AML case who developed multiple EMRs after allogeneic stem cell transplantation (Allo-SCT). He was successfully managed with gemtuzumab ozogamicin (GO) plus local RT.

A 39-year-old man diagnosed AML, monoblastic/monocytic subtype according to the World Health Organisation 2016 classification was considered as standard risk for AML due to the absence of any cytogenetic abnormality or aberrant mutations. Flow cytometry analysis of the bone marrow showed CD 33 positivity (58%) and CD 56 negativity (1%). After remission induction and consolidation chemotherapy, he underwent Allo-SCT from his matched sibling donor (sister) with the busulfan-cyclophosphamide conditioning regimen at 2017. During the follow-up, no graft versus host disease (GVHD) occurred and cyclosporine for GVHD prophylaxis was discontinued accordingly. Full donor chimerism (100%) was obtained at the end of the 3rd month after transplantation. After 27 months of Allo-SCT, he was admitted to hospital with new painless right testicular swelling. Scrotal ultrasound showed a 4 cm mass which required unilateral orchiectomy. Pathological examination and IHC study demonstrated 100 % CD34 positive blast involvement consistent with extramedullary relapse. Meanwhile, his blood counts were normal and bone marrow was free of relapse. Chimerism status of the bone marrow was re-evaluated which still showed 100% donor chimerism. CNS fluid examination showed no blast cells, supported by a negative flow cytometry result. In order to detect other potential extramedullary lesions, Position Emission Tomography (PET-CT) was performed and a 11x8x8 cm sized femoral mass was detected (figure 1a). The biopsy of the mass was in favour of involvement by myeloblasts. The patient performance status was very well and he had no sign of systemic involvement. The patient was planned to receive gemtuzumab ozogamicin (GO) and RT to the femoral mass. 28 Gy RT was given in 14 fractions in addition to 2 cycles of GO 3 mg/m^2 intravenously; monthly on days 1, 4 and 7. The femoral mass disappeared in MR imaging and control PET scans (figure 1b). GO treatment had to be interrupted due to overwhelming pneumonia and long-lasting neutropenia

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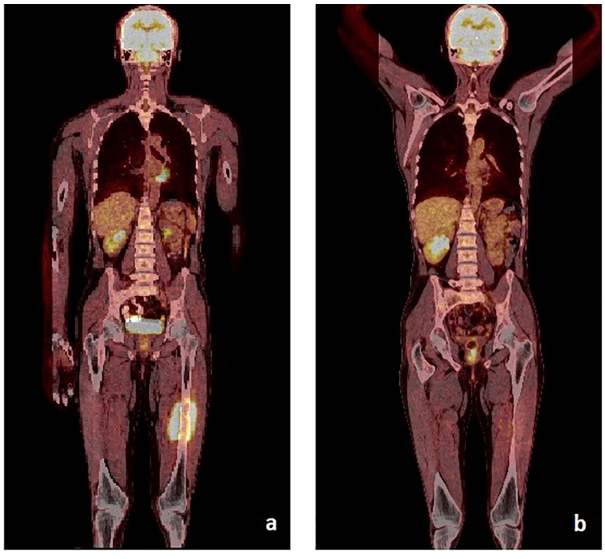


Figure 1: PET-CT images at initial EMR diagnosis (a) and after GO treatment (b).

for 2 months. However, 6 months later, a control PET scan showed a retroperitoneal 4 cm and left femoral 7 cm-sized new developing masses, again with no medullary involvement. fludarabine, high dose cytarabine (Ara-C), idarubicin and granulocyte-colony stimulating factor (FLAG-IDA) regimen was initiated at this time, so that complete resolution of the masses was achieved according to the control PET scan. Finally, he was planned to undergo the second SCT from his sister (the same donor) due to absence of any other suitable donor.

One of the suggested predictors for AML to present with extramedullary involvement is to have the features of monocytic/monoblastic or myelomonocytic subtype.[1] Also t (8; 21), inv (16) positivity, CD56 expression and relapsed/refractory disease at the time of the transplant are associated with increased risk of EMR. [3, 4] Chronic GVHD is considered to decrease relapse risk after SCT, but whether graft versus leukemia affect (GVL) also decreases the relapse rate is not well understood.[5] Some data support the use of total body irradiation instead of busulfan in the conditioning regimen to decrease the risk of EMR.[1, 6] EMR may develop especially in central nervous system and reproductive organs due to inherent barriers which facilitates escaping from systematic chemotherapy.[4] When EMR develops, the median time to marrow relapse is suggested to be around 7 months.[4]

The second SCT due to lack of effective therapeutic options can be considered for previously transplanted patients, but some studies report disappointing results and failure to eliminate EMR.[3, 7] There are also remarkable data supporting the benefit of single agent GO to treat EMR after Allo-SCT, since it doesn't suppress GVL effect.[8] There is no standardized algorithm for new developing EMRs without medullary involvement while on GO therapy. Also, there is no definitive value of CD33 level at the time of diagnosis or during the appearance of EMR to predict response to GO. Regarding our patient, there was no aforementioned risk factor to develop EMR except having monoblastic/monocytic subtype. Donor lymphocyte infusion could be considered for our patient, especially after detecting new extramedullary masses; but FLAG-IDA regimen was preferred, considering the resistant nature of the EMR and also to avoid GVHD with the fact that the patient had full donor chimerism. Informed consent was obtained from the patient for publication.

In this regard, GO-based approach with adjunctive RT is the reasonable option for isolated EMR after Allo-SCT, although it should be followed closely to detect progression or development of systemic relapse. Further studies are necessary to determine the most beneficial strategy for EMR.

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Conflict of Interest: None declared.

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