Leukemia Research Reports 17 (2022) 100326

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Microtransplantation for myeloid sarcoma: Two case reports

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A B S T R A C T

Myeloid sarcoma (MS), is a rare extramedullary tumor with a poor prognosis and high recurrence rate. Microtransplantation is one of the alternative methods of traditional transplantation, which does not rely on HLA complete matching, has low toxicity and may retain part of graft-versus-leukemia (GVL) effect. It has been reported that microtransplantation can significantly improve the survival rate of elderly AML patients. At present, there is no report on the application of micro transplantation in MS. We will report two cases of MS treated by micro transplantation. The disease-free survival was 66 months and 55 months respectively.

1. Introduction

Myeloid sarcoma (MS) is an extramedullary myeloid tumor composed of myeloid blasts, which can manifest as part of acute myeloid leukemia (AML) and in several cases present in solitude (1, 2). It often suggests a dismal prognosis for poorly-understand biology, lack of specific treatment strategies, and marrow relapse tendency (2, 3). About 75-90% of solitary extramedullary AML patients will develop metachronous intramedullary AML with a median period from 5 to 12 months, if delayed or inadequately systemically treated (4, 5). Radiotherapy, surgery, and local chemotherapy can quickly relieve symptoms, but cannot improve the overall prognosis (5-7). Systemic chemotherapy for AML is the recommended treatment for MS, which can significantly prolong the leukemia-progression and survival, but with low complete remission rate and high recurrence rate (7). Allogeneic or autologous HCT consolidation after chemotherapy demonstrates superior result, with infection-related mortality and graft-versus-host disease (GVHD) (8, 9). Unfortunately, a suitable donor is not always available.

Microtransplantation, HLA-mismatched granulocyte colony-stimulating factor-mobilized donor peripheral blood stem-cell infusion, had demonstrated improved survival and limited GVHD in both elderly and young AML patients following chemotherapy (10-13). It provides an alternative solution for patients without HLA-matched donors by overcoming the limitations of HLA restriction.

The efficiency and safety of microtransplantation in these people with MS is unknown. Herein, we report the first two cases of microtransplantation in MS patients. Both achieved durable disease control and had well-tolerated side effects.

2. Case report

Case 1

The first patient, a 38-year-old female, presented for fatigue and fever (maximum temperature, of 39°C) in May 2014, with hemoglobin 119 g/L, white blood cell count of 2.11 $\times 10^9$ /L (absolute neutrophil count 1.16$\times 10^9$ /L, lymphocyte count 0.53$\times 10^9$ /L, monocyte count 0.32$\times 10^9$ /L, basophil count 0.10$\times 10^9$ /L, eosinophil count 0$\times 10^9$ /L), red blood cell 3.73x10^9/L, platelet 125x10^9/L, alanine aminotransferase 111 IU/L, aspartate aminotransferase 94 IU/L, lactate dehydrogenase 503 IU/L, C-reactive protein 14.3 mg/L, EBV-DNA negative, β2-microglobulin 0.211 mg/L. Physical examination revealed only splenomegaly. Color Doppler ultrasound indicated enlarged lymph nodes in the bilateral axillary, the left clavicle, and the right subclavian area. Positron emission tomography/ computed tomography (PET/CT) showed increased Fluoro-2-deoxy-D-glucose (FDG) metabolism in the lymph nodes aforementioned. An excision biopsy of the right axillary lymph node showed structure abnormality and the interfollicular area hyperplasia. Some medium-sized cells were found in the interfollicular area and the lymphatic sinuses, with moderate amount of cytoplasm, round or oval red-stained nuclei, and unclear nucleoli. Immunohistochemical (IHC) staining showed as follows: MPO (+), CD68/PGM-1 (+), CD43 (+), CD56 (scattered+), CD20 (-), CD3ε (-), CD4 (-), CD8 (-), CD30 (-), CD99 (-), CD123 (-), EMA (-), ALK-1 (-), granzyme B (few+), TIA-1 (part+), EBER1/2 in situ hybridization (-) (Fig.1). Pathologists concluded myeloid sarcoma as the first diagnosis, considering the tumor cells expressed granulocyte and mononuclear system biomarkers.

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https://doi.org/10.1016/j.lrr.2022.100326
Received 27 February 2021; Received in revised form 16 May 2022; Accepted 17 May 2022
Available online 21 May 2022

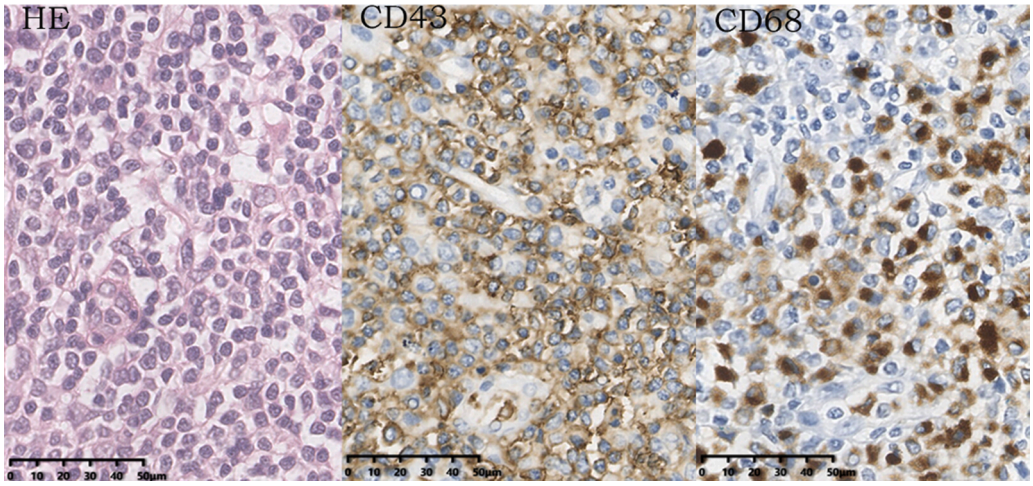

Fig. 1. The lymph node biopsy immunohistochemistry in Case 1 at diagnosis.
Immunohistochemistry of the lesion biopsy: MPO (+), CD68/PGM-1 (+), CD43 (+), CD56 (scattered+), CD20 (-), CD3ε (-), CD4 (-), CD8 (-), CD30 (-), CD99 (-), CD123 (-), EMA (-), ALK-1 (-), granzyme B (few+), TIA-1 (part+), EBER1/2 in situ hybridization (-).

Further bone marrow smear, fluorescence in situ hybridization (FISH), and gene expression panel studies were negative, with a normal diploid karyotype. The final diagnosis was primary MS.

The patient received standard induction chemotherapy with DA regimen (daunorubicin 45 mg/m^2, D 1-3; cytarabine 100 mg/m^2, D 1-7). She achieved complete remission after the induction and had another 6 courses of DA regimen during the donor matching. No severe adverse events but myelosuppression and infections were observed after the first chemotherapy. She and her father had a 7/12 match at HLA-A, B, C, DR, DP, and DQ. Without an HLA-matched related or unrelated donor, the patient initiated microtransplantation. During the period, G-CSF mobilized hematopoietic stem cells from her father peripheral blood were obtained. She received mircotransplantation 24 hours after the third DA regimen in July 2014, with 98ml infusion in which the CD34+ cell dose was 1.1x10^6/L. The recovery of WBC and platelet was 10 and 11 days, respectively. She got the second microtransplantation after the fifth chemotherapy in September 2014, with 180ml infusion containing 1.9x10^6/L CD34+ cells. Without any GVHD prevention, there's no acute or chronic GVHD detected after each microtransplantation. Regular blood and bone marrow minimal residual disease (MRD), ultrasound, CT, and PET/CT were performed to assess whether the patient achieved complete remission (CR). No abnormalities were found in these results until March 2020. She was admitted again for fever and fatigue. Physical examination revealed the enlarged bilateral cervical, axillary, and inguinal lymph nodes. Core needle biopsy showed the hematopoietic tissue proliferation, with the interfollicular area infiltrated by some medium-sized, medium-cytoplasm, and nucleus deformation cells. IHC staining showed the following results: D117(-), CD21 (-), TdT(-), CD34(-), CD99 (-), CD30 (-), CD5 (-), CD38 (+, part), CD123 (+, minority), S100 (-), ALK (-), CD56 (+, minority), CD4 (Weak +, partial), CD10 (-), Ki67 (+, about 20%–30%), and EBER1/2 in situ hybridization (-). MS relapsed and she is preparing for the allo-HSCT nwith an unrelated the HLA-identical donor. The disease-free survival (DFS) following micro-transplantation is 66 months.

Case 2

The second patient, a 26-year-old female was transferred to the Department of Hematology of our hospital on October 17, 2014, for discovering a mass behind her right earlobe 1 month. She denied comorbidities or past medical history. Her blood test results showed WBC 5.16×10^9/L(absolute neutrophil count 3.65× 10^9 /L, lymphocyte count 1.24× 10^9 /L, monocyte count 0.23× 10^9 /L, basophil count 0.02× 10^9 /L, eosinophil count 0.03× 10^9 /L), hemoglobin 122 g/L, and platelet 292×10^9/L at admission. Iliac bone marrow smear and biopsy showed no obvious abnormalities. A lumbar puncture was performed for the progressive headache after admission. The cerebrospinal fluid (CSF) pressure was over 200mmH_2O, with nuclear cell 90×10^6/L, monocyte

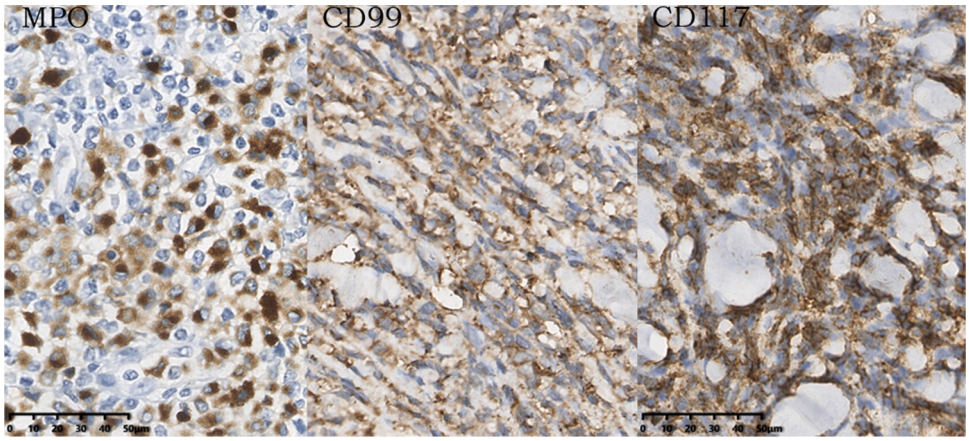

Fig. 2. The lesion biopsy immunohistochemistry in Case 2 at diagnosis.
Immunohistochemistry of the lesion biopsy: MPO, CD117, CD99, Ki-67 60% positive. Not expression CD3 ε, CD5, CD10, CD56, Bcl-2, Bcl-6, Mum-1.

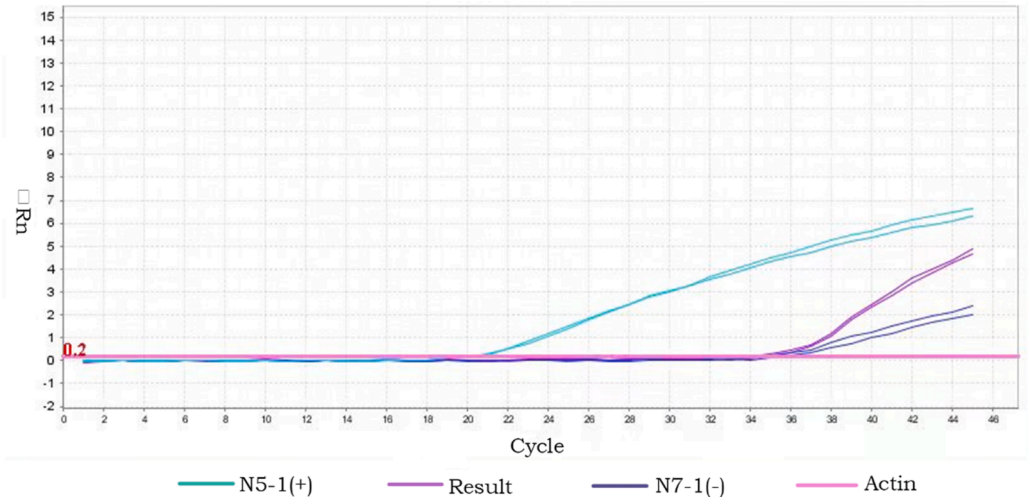

Fig. 3. The host microchimeric amplification in Case 2.
N5-1(+) means the rs610937 locus insertion of the donor, and N7-1(-) means the deletion of rs16458 locus.

56%, trace protein 0.3 g/L, glucose 4.6 mmol/L; and found 74% blasts by flow cytometry (FCM), mainly expression CD34, CD117, CD56, CD64, and HLA-DR but neither CD5 nor CD19. Imaging studies revealed space occupying lesions in the right cranial base and parapharyngeal space on MRI. PET/CT showed a mass with increased FDG metabolism in the right parapharyngeal space, invading the right nasopharyngeal wall and the right side of the occipitocciptal slop. Further biopsy of the mass proved to be a hematopoietic malignancy infiltration, mainly expression of MPO, CD117, CD99, Ki-67 60%, and not expression CD3 ε, CD5, CD10, CD56, Bcl-2, Bcl-6, Mum-1 (Fig2). Gene expression profile found RUNX1-RUNX1T1 fusion gene, with normal female karyotype. AML (RUNX1-RUNX1T1 fusion gene-positive) combined with myeloid sarcoma and central nervous system leukemia was diagnosed.

In November 2014, the patient started IDA regimen (idarubicin 10 mg, D1-3, cytarabine 150 mg, D1-7) induction chemotherapy followed by 5 courses of intermediate-dose cytarabine (1000 mg/m^2, D 1-4) consolidation therapy, combined with several intrathecal chemotherapy (methotrexate, cytarabine, and dexamethasone). Severe myelosupression and infection occurred after each chemotherapy. Dynamic review of bone marrow smear and MRD, CSF routine test and MRD, and PET-CT indicated that the patient was in sustained remission until July 2016. Regular bone marrow smear evaluation found 1.5% blast cells in July 2016, alarming the tendency to relapse. Nonetheless, further homochronous bone marrow and CSF test didn't find the blast cells, and cranial PET/CT was negative at that time. An FLAG regimen intensified with idarubicin (fludarabine 40 mg, D1; idarubicin, 10 mg, D1–2; cytarabine 1000 mg, D 1, 3, and 5) was started on September 3, 2016. No suitable donor was found. The patient and her mother had a 4/8 match at HLA-A, B, C, and DR. She received 213 mL of peripheral blood stem cells mobilized by G-CSF and praxafor infusion from her mother on September 7, 2016. The total number of nucleated cells was 70.9×10^9, and that of CD34+ cells was 2.5×10^6/kg. Before and after the infusion of donor cells, no measures were adopted to prevent GVHD. The neutrophils and platelets recovery was 11 days and 13 days, respectively. No serious infection or other serious complications occurred, neither GVHD were observed. Sustained CR was observed after the microtransplantation during follow-up. The patient received another 3 courses intrathecal chemotherapy as the prophylaxis against central nervous relapse. The host microchimerism quantitative test showed that the donor cells in the patient were below the minimum detection (0.001%) by real-time fluorescence quantitative polymerase chain reaction on October 23, 2017. In August 2020, the donor cells in patients microchimerism accounted for 0.005% (Fig.3). The total DFS has thus far reached 76 months, and the DFS after microtransplantation was 55 months.

3. Discussion

Allo-HSCT after induction chemotherapy is the main treatment strategy for MS. Although allo-HSCT can significantly improve the survival rate of MS, its application is usually limited by HLA- mismatch, severe GVHD and high cost. Microtransplantation is an HLA-mismatched granulocyte colony-stimulating factor-mobilized donor peripheral blood stem-cell infusion, without HLA-restriction. At present, it has been reported that microtransplantation can improve the overall survival of elderly AML patients who cannot undergo HSCT, and shows high tolerance and low severe toxicity (10, 12-15). A multicenter clinical study found a high CR rate (74.6%) in AML patients aged 60 to 85 years after microtransplantation, with 1.1% underwent GVHD (10). And 7 patients of the mean age 31.3 years old got microtransplantaion without significant GVHD (11). However, safety and effectiveness of microtransplantation are still under dispute and need to be evaluated in large randomized clinical trials (16).

In case 1, we reported the practice of microtransplantation in a relatively young with primary MS. Without an HLA-matched donor, this patient received microtransplantation and got 66 months DFS after that, without severe GVHD, medullary relapse or AML transformation. This suggests that as an alternative treatment after remission, the microptransplantation has earned her enough time to find the HLA-matched donor or to wait for cord transplantation. In case 2, the patient underwent microtransplantation for bone marrow blast cells recurrence after chemotherapy. She had a durable CR after microtransplantation up to now. Previous studies reported that the maximum duration of microchimerism in AML and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) was 34 months and 50 months respectively (12, 15). In this case, microchimerism can still be detected 47 months after microtransplantation. It indicates that the donor component in the receptor may exist for a long time even without strong immunosuppressive condition. However, the relationship between the duration of microchimerism and survival time, and the relationship between the microchimerism rate and the incidence of GVHD, needs further studied. During the treatment, both of the patient's hematopoietic function recovered quickly, and no serious adverse events occurred.

4. Conclusion

In summary, we reported two cases of MS successfully treated with

chemotherapy combined with microtransplantation, indicating the possibility of microtransplantation as alternative maintenance treatment in MS patients who are not suitable for traditional myeloablative transplantation, or those do not have an available donor.

Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Acknowledgement

To Medical records and pathology departments for their collaboration

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2022.100326.

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