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 metastatic intramedullary AML with a median period from 5 to 12 months, if delayed or inadequately systemically treated (2, 3). About 2-5% of elderly AML patients following chemotherapy (10-13). It provided an alternative solution for patients without HLA-matched donors by overcoming the limitations of HLA restriction.

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 × 10^9 /L (absolute neutrophil count 1.16 × 10^9 /L, lymphocyte count 0.53 × 10^9 /L, monocyte count 0.32 × 10^9 /L, basophil count 0.10 × 10^9 /L, eosinophil count 0 × 10^9 /L), red blood cell 3.79 × 10^12 /L, platelet 125 × 10^9/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 (-), CD3e (-), 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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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/m² D 1-3; cytarabine 100 mg/m², 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 microtransplantation 24 hours after the third DA regimen in July 2014, with 98ml infusion in which the CD34+ cell dose was 1.1×10⁶/L. The recovery of WBC and platelet was 10 and 11 days, respectively. She got the second microtransplantation in September 2014, with 180ml infusion containing 1.9x10⁶/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 with 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 5.16×10⁹/L (absolute neutrophil count 3.65×10⁹/L, lymphocyte count 1.24×10⁹/L, monocyte count 0.23×10⁹/L, basophil count 0.02×10⁹/L, eosinophil count 0.03×10⁹/L), hemoglobin 122 g/L, and platelet 292×10⁹/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 200mmH₂O, with nuclear cell 90×10⁹/L, monocyte...
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 CD34, CD117, CD56, MPO, CD117, CD99, Ki-67 60%, and not expression CD3 + N5-1(−).

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 CD34, CD117, CD56, MPO, CD117, CD99, Ki-67 60%, and not expression CD3 + N5-1(−).

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/m², D 1-4) consolidation therapy, combined with several intrathoracic chemotherapy (methotrexate, cytarabine, and dexamethasone). Severe myelosuppression 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 between the microchimerism rate and the incidence of GVHD, needs further study.

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.

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 microtransplantation 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 microtransplantation 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.

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**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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