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Micro-transplantation in an elderly patient with very high risk MDS:A case report and literature review

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ABSTRACT

Introduction: The prognosis of patients with myelodysplastic syndromes (MDS) (very high risk) is poor.HLA-mismatched allogeneic T-cell infusion which is called micro-transplantation can not only shorten the time of bone marrow suppression, but also improve the treatment response of patients.
Case presentation: A 74-year-old woman presented with fatigue and showed pancytopenia on routine blood count. She was diagnosed with MDS (very high risk) after bone marrow examination,then she received 4 cycles of micro-transplantation. The progression-free survival was 22 months and overall survival was 33 months.
Discussion: The patient showed good tolerance to micro-transplantation with manageable toxicities and short myelosuppression time.

1. Introduction

Myelodysplastic syndromes (MDS) is a hematologic malignancy, which is mainly manifested as hematopoietic dysfunction, ineffective hematopoiesis, and progression to acute myeloid leukemia (AML) [1]. According to the *Re-* vised International Prognostic Scoring System (IPSS-R), patients in the intermediate-2 and high-risk groups need to receive chemotherapy. However, older patients with MDS who have poor performance status scores are often unable to tolerate standard doses of chemotherapy. Therefore, there is an urgent need for appropriate treatments to reduce the incidence and severity of adverse events after chemotherapy while ensuring the efficacy of chemotherapy.

Micro-transplantation (MST) is a novel type of cellular immunotherapy. After the end of chemotherapy, the donor's HLA-mismatched peripheral blood stem cells are transfused, and the MST recipient forms a transient or permanent donor micro-chimerism state, thus exerting the graft-versus-tumor effect (GVHD) [2]. Clinically, evidence shows that MST has good efficacy and shortens the duration and risks of myelosuppression after chemotherapy in the treatment of elderly patients with intermediate and high-risk MDS [3].

MDS patients in primary hospitals are characterized by advanced age, relatively poor performance status, and poor socioeconomic support. This study retrospectively analyzed the clinical data of an elderly patient with very high-risk MDS in Yiwu Central Hospital who received MST, and determined the clinical performance and safety of MST.

2. Case description

A 74-year-old female was presented with fatigue in august 2020 in local hospital. The blood routine showed a white blood cell (WBC) count of 2.4×10^9/L, platelet (PLT) count of 59×10^9/L, and hemoglobin (Hb) of 81 g/L. She then was admitted to our hospital for further treatment. The patient's past medical history was hypertension. Repeat blood count after admission showed a WBC count of 2.17×10^9/L, neutrophil count of 0.69×10^9/L, PLT count of 38×10^9/L, and Hb of 79 g/L. Bone marrow (BM) aspirates showed 13% blasts by histology, and pathological hematopoiesis can be seen in the three lineages. Bone marrow biopsy showed myeloblastic pleocytosis with abnormal localization of precursor cells (ALIP), while bone marrow hyperplasia was generally normal, and CD34+ cells accounted for about 10 % to 15 %. Flow cytometry showed 11.91 % blasts with positive for CD117, CD34, CD33, CD13, HLA-DR, CD38, CD123. Cytogenetics demonstrated normal female chromosomes. Next-Generation Sequencing (NGS) revealed mutations of ASXL1, SF3B1 and single CEBPA. Detection of bone marrow by Fluorescence in situ Hybridization (FISH) showed negative. A diagnosis of MDS-EB-2 with ASXL1, SF3B1, single CEBPA was established. The revised international prognostic scoring system (IPSS-R) score was 7 (very high). The patient received azacitidine (75 mg/m^2, day -11∼-5)

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plus a 4-day induction chemotherapy regimen consisting of cytarabine (10 mg/m^2, day -4∼-1), aclarubicin (10 mg/day, day -4∼-1), and G-CSF (150 mg every 12 h, day -5∼-1). G-CSF was discontinued when the neutrophil count reached 2 × 10^9/L. HLA-mismatched allogeneic CD3+ *T*-cell infusion was administered per cycle without GvHD prophylaxis 24 h (day 0) after the end of each chemotherapy. The hematopoietic stem cells from the same donor with 65 ml per cycle included mononuclear cell count 2.58 × 10^8/kg, CD34+ stem cell count 2.0 × 10^6/kg, CD3+ *T* cell count 0.68 × 10^8/kg. After infusion, the patient developed fever, with a maximum body temperature of 40 °C on day 2. The time for hematopoietic reconstruction was 7 days. After 1 cycle of treatment, the evaluation of efficacy was hematologic improvement, while bone marrow aspirates showed 6.5 % blasts and flow cytometry showed 4.879 % blasts with WBC count of 2.22 × 10^9/L, PLT count of 165 × 10^9/L, and Hb of 84 g/L. Then the patient continued the same regimen of chemotherapy and achieve a complete response (CR) with minimal residual disease (MRD) negativity. The highest body temperature was 38.2 °C and the time for hematopoietic reconstruction was 6 days. During the third cycle of chemotherapy, her PLT count had been maintained above 20 × 10^9/L without platelet transfusion and the time of fever was only 1 day. During the final course of MST, she did not developed fever and blood transfusion was also not needed. She then started on maintenance with azacitidine (75 mg/m^2, day 1∼7) every 2 months while bone marrow remission lasted 22 months without progression of disease. On October 24, 2022, she developed disease recurrence with 7 % blast cells by bone marrow aspiration and 3.843 % blast cells by flow cytometry. She received decitabine (15 mg/m^2, day 1∼5) plus Venetoclax chemotherapy regimen. Due to severe bone marrow suppression, she had to rely on blood transfusions for supportive treatment. She died on May 14, 2023 with an OS of 33 months.

3. Discussion

In recent years, MST can play a role in novel immunotherapeutic approaches. It can not only avoid the risk of GVHD but also achieve graft-versus-tumor (GVT) effect by infusion of HLA-incompatible donor cells to form a donor micro-chimerism state.[4] Recent studies prove, The main purpose of MST is to eliminate tumor cells, not immunosuppression. Therefore, the use of specific immunosuppressants such as fludarabine and anti-thymocyte globulin should be avoided as much as possible in the chemotherapy regimen to preserve the recipient's ability of restoring immune function.[5] Animal experiments have shown that the host exhibits long-term anti-tumor effects after the rejection of donor cells, suggesting that host-derived cells may dominate allogeneic anti-tumor effects.[6,7]

In this case, the patient was reported to be an elderly and very high-risk MDS, and the treatment regimen of azacitidine combined with CAG regimen was well tolerated, with PFS for 22 months and OS for 33 months. With the increase of the course of MST, the degree of bone marrow suppression after chemotherapy gradually decreases, and blood transfusion support are even not necessary. These characteristics are consistent with other studies [3]. The patient did not have GVHD and functional impairment of important organs in the 4 courses of MST treatment, and the cytokine release syndrome (CRS) was mainly manifested by high fever, which was obvious with the initial MST treatment, and the fever duration and maximum body temperature of the patient decreased compared with the previous courses.

We have summarized the following considerations during the treatment of this patient. (1) Although the MST regimen has the characteristics of good therapeutic efficacy, tolerable adverse reactions and short recovery time of bone marrow hematopoiesis for elderly patients, the indications and ethical screening of donors should still be strictly grasped. (2) The patient's first course of CRS response may be characterized by high fever. Because the anti-tumor effect of the graft is mainly exerted by donor T cells, it is necessary to avoid the use of hormones to reduce fever as much as possible, and can be used with non-steroidal anti-inflammatory drugs and physical cooling to relapse fever. (3) With the increase of the course of treatment, the myelosuppression period of the patient gradually shortened, the degree of myelosuppression gradually decreased, and the tolerance degree of the patient increased. (4) After the end of the 4 courses of MST, maintenance therapy with demethylating drugs was planned every 2 months, while the patient did not strictly follow the maintenance therapy, which may be related to the recurrence of her disease.

With the development of MST technology, collaboration is becoming more common. An international multicenter retrospective study showed that patients who received ≥2 courses of MST therapy had a higher 2-year OS rate and a lower recurrence rate than those who did not, and that only 2 of the 185 patients enrolled (1.1%) developed severe GVHD [8]. In addition to AML and MDS, a small sample (10 cases) study has also used MST for the treatment of relapsed and refractory lymphoma, showing a good response rate (CR rate of 60 %), with patients achieving CR without recurrence for 29.5 months of follow-up [9]. Therefore, MST has gradually attracted more and more attention due to its characteristics of not being limited by HLA matching, good efficacy, and tolerable adverse reactions, and we look forward to adding more sample size and research data to confirm the value of MST.

4. Consent statement

Written informed consent was obtained from the patient's next of kin to publish this report in accordance with the journal's patient consent policy.

CRediT authorship contribution statement

Kangli Wu: Writing – original draft. **Mingsuo Liu:** Formal analysis. **Yajun Wu:** Data curation. **Qiulian Luo:** Methodology. **Jin Chen:** Data curation. **Wanling Xu:** Data curation. **Xixi Yang:** Data curation. **Piaoru Hong:** Data curation. **Zhigang Qu:** Project administration.

Declaration of competing interest

The authors have no competing interests.

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