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Unrelated HLA mismatched microtransplantation in a patient with refractory secondary acute myeloid leukemia

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ABSTRACT

Microtransplantation (MST), a type of HLA-mismatched allogeneic cellular therapy, is a promising, cellular therapy for acute myeloid leukemia (AML). MST transfuses granulocyte colony-stimulating factor (G-CSF)-mobilized, HLA-mismatched donor peripheral blood stem cells into patients undergoing conventional chemotherapy. MST, using haploidentical donors, has been shown to yield clinical benefit without any permanent marrow engraftment in AML. Consequently, graft-versus-host disease concerns are rendered irrelevant with no need for immunosuppression. We describe the first reported patient with refractory AML who underwent salvage MST from an unrelated, complete HLA-mismatched donor. The patient achieved remission without complication, warranting further study of unrelated HLA-mismatched donor MST in AML.

1. Introduction

Acute myeloid leukemia (AML) continues to be a daunting challenge with a majority of patients succumbing to the disease. Allogeneic stem cell transplantation (alloSCT) is proven effective in mitigating relapses among high-risk individuals. AlloSCT's therapeutic efficacy is partly mediated by a graft-versus-leukemia (GVL) effect, however, it is rife with infection-related mortality and graft-versus-host disease (GVHD). The extrication of deleterious GVHD ramifications from the GVL effect has been described as “the holy grail of” alloSCT [1].

One promising alternative to alloSCT is a form of HLA-mismatched allogeneic cellular therapy known as microtransplantation (MST) [2]. MST utilizes granulocyte colony-stimulating factor (G-CSF)–mobilized, HLA mismatched donor peripheral-blood stem cells (GPBSCs) that are transfused into patients after receiving conventional chemotherapy [3]. MST does not entail long-term engraftment of donor cells. Hence immunosuppression is not needed. MST is safe and efficacious, possibly engendering the GVL effect as well as functional immune reconstitution without the GVHD risks.

MST trials have primarily employed haploidentical donors [2]. Studies – as part of larger cohorts – have used some complete, unrelated HLA mismatched donors [4,5], but no separate outcome data for the patients who received 0/10, unrelated HLA mismatched products was published in those studies. These MST protocols were also incorporated into up-front treatments. To date, studies of unrelated, complete mismatched microtransplantation in refractory settings have not been published to our knowledge. In the case below, we describe the first reported patient with refractory AML who underwent salvage MST from an unrelated, complete HLA mismatched donor. The patient achieved remission, safely tolerating the regimen without evidence of infection, engraftment failure, or GVHD.

2. Case description

The patient was a 61-year-old female with myelodysplasia that evolved into AML. Cytogenetics were characterized by hyperdiploidy of chromosome 1 and a translocation between 1q and 15q. She promptly received “7 + 3” induction chemotherapy with cytarabine and an anthracycline agent, registering a complete remission (CR). The patient was not initially considered for alloSCT because no suitable donor was available at that time.

After one cycle of cytarabine consolidation, the patient was transitioned to 5-azacytidine due to inadequate hematologic recovery. After five monthly cycles the patient became increasingly neutropenic with an absolute neutrophil count (ANC) declining from 900 to 100 (Fig. 1). She eventually relapsed with circulating myeloid precursors and bone

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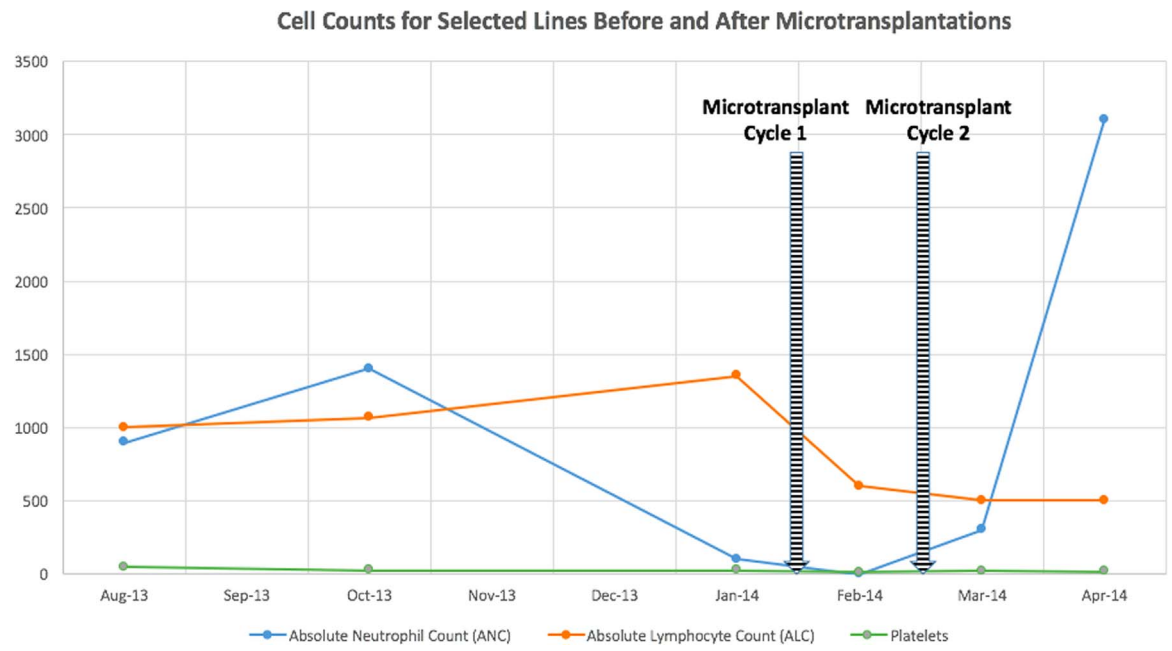

Fig. 1. From October 2013, the patient became progressively neutropenic during monthly cycles of 5-azacytidne. By January 2014, the AML had relapsed. After 2 cycles of microtransplantation, the patient demonstrated resolution of chronic, severe neutropenia. However, there were no major changes in platelet and lymphocyte counts after relapse despite microtransplantations.

marrow showing further clonal evolution in cytogenetics. The patient had no suitable donors for alloSCT. Consequently, she was enrolled onto a single patient, Institutional Review Board-sanctioned MST protocol.

Stem cells were derived from the patient's godson, who happened to be 29-year-old, unrelated donor with complete HLA mismatch. Filgrastim was administered to the donor at 10 mcg/kg daily for four days prior to apharesis to mobilize CD34+ stem cells. The patient received cytarabine conditioning at 1 g/m^2 twice daily for 3 days (Day −6 to −3). Donor stem cells were transfused into the patient at 1.14×10^6 CD34+ cells/kg (Day 0). Within 24 h after infusion, the patient exhibited a fever of 38.8 °C and diarrhea, which persisted for 68 h. She was treated for neutropenic fever, but her fever and rash were attributed to a cytokine release syndrome or "haplostorm" effect. This phenomenon is commonly encountered in haploidentical stem cell transplantation in which the mismatch of HLA-antigens induces cytokine release and fever [6]. On day 21, a repeat bone marrow biopsy showed a subsiding blast count from 50% to 30%. For additional leukemic de-bulking, a second cycle of microtransplantation was planned using cryopreserved cells from the same donor. The patient received MEC conditioning containing mitoxantrone 6 mg/m^2 (day 24–29), etoposide 80 mg/m^2 (day 23–28) and cytarabine 1 g/m^2 (day 25–28) followed by a second dose of stem cells at 1.44×10^6 CD34+ cells/kg on day 33 (from first cycle of chemotherapy). MEC was opted for because cytarabine alone was considered to be insufficient for more pronounced tumor dissolution. She had a similar "haplostorm" after her second MST, which spontaneously resolved after 34 h.

A bone marrow biopsy on day 33 demonstrated a blast count less than 5 percent; the patient had achieved a second complete remission with incomplete count recovery. Without any G-CSF, her ANC breached 500 on day 60. She was then discharged from the hospital. The ANC continued to accelerate to 1500 by day 70 (Fig. 2). A surveillance bone marrow biopsy on day 95 confirmed the persistency of remission. Despite leukemia eradication and immune reconstitution, the patient remained transfusion-dependent for both red cells and platelets, though less frequently than before her MST. The patient did not display any clinical signs, symptoms, or biochemical evidence of acute GVHD.

The patient's ANC ebbed upon discharge over the next 2 months. On day 150, her ANC decreased to less than 500. A bone marrow biopsy indicated 70 percent cellularity, myeloid hyperplasia, and no significant blast populations. Cytogenetics exposed three heterogeneous stem cell populations with one sub-clone containing a new trisomy 8, and another cell line exhibiting an additional X chromosome. The histologic and karyotypic pattern correlated with a protracted, continuously evolving myelodysplasia.

By day 164, the patient relapsed again with peripheral blood counts enumerating 26 percent blasts. She was then transitioned to FCE (fludarabine, cytarabine, etoposide) chemotherapy. In July 2014, the patient underwent alloSCT from a 9/10 HLA matched sibling donor with busulfan/cyclophosphamide myeloablative conditioning. Her post-transplant course was complicated by refractory grade 4 GVHD, and she expired approximately 6 months following alloSCT.

3. Discussion

MST's safety and efficacy using haploidentical donors has been corroborated by multiple clinical trials, including our own study [2]. The patient described here is the first reported case of unrelated MST in a patient with refractory AML demonstrating a clinical response, albeit short-lived. Despite stark HLA differences, patient never demonstrated any significant morbidity such as infection, engraftment failure, or GVHD that would be typical for mismatched stem cell grafts. The only complication that she experienced was a self-limited, "haplostorm." This requires further investigation in a large-scale study.

While it is difficult to dissect out which component of MST was responsible for the clinical improvement seen in this patient, we hypothesize the diminution in the blast percentage to be secondary to the conditioning chemotherapy and the increase in the neutrophil counts to attributable to the cellular component of MST. Indeed, the remission marrow was documented just prior to the second MST cellular infusion, suggesting the vital role of the conditioning chemotherapy in leukemic de-bulking. But despite her prior induction chemotherapies and hypomethylating treatment, the patient never showed any amelioration in neutrophil count. An ANC of > 1500 was only achieved following MST, which utilized a combination of cellular therapy and chemotherapy. Alternatively, it is also plausible that the microtransplant enhanced the

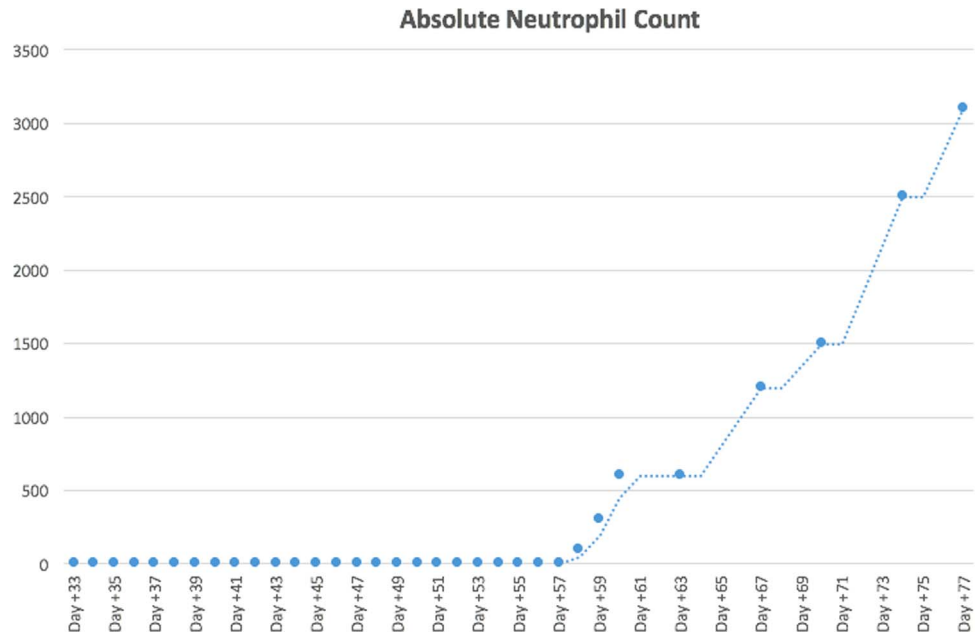

Fig. 2. The x-axis represents the number of days that elapsed from the first microtransplant infusion. The second infusion of stem cells occurred on Day + 33.

chemosensitivity of this patient's myeloid malignancy [7]. Unfortunately, no chimerism studies were performed to correlate the percentage of donor-derived blood cells with the blast and neutrophil count. This underscores a limitation with the case report and warrants the routine use of chimerism studies in subsequent protocols evaluating complete, unrelated microtransplantation.

The case report stresses a key drawback with HMMACT. The patient above had myelodysplasia-related AML and was unable to weaned from blood product transfusions. This experience is validated by studies in which patients with previous myelodysplasia or myeloproliferative disorder have longer time to neutrophil and platelet recovery, tending to follow the trajectory of the underlying pre-leukemic process [8–10]. In fact, Fig. 1 demonstrates no significant shifts in the levels of absolute lymphocytes or platelets after relapse despite two rounds of cell therapy. MST in myelodysplasia or secondary AML is also less likely to induce complete responses and has significantly decreased progression-free survival compared to other cohorts [4]. Therefore, the advantageous effects of MST could be negatively attenuated by underlying myelodysplasia or myeloproliferative neoplasm. Such patients may have to proceed to alloSCT soon after achieving remission with MST.

In summary, this case report illustrates the safety and efficacy of unrelated, complete mismatched MST in refractory AML, carving out a novel direction for MST as a salvage regimen for refractory/relapsed patients. By fomenting a GVL effect, unrelated MST could serve as a bridge to alloSCT by abetting a complete remission. Moreover, the stem cell source and degree of donor HLA mismatch is less relevant in MST than in alloSCT. Interestingly, haploidentical stem cell transplantation with higher degrees of HLA disparity confer better the outcomes than lower disparity [10]. Hence exploring unrelated MST may yield a more robust anti-leukemic therapeutic strategy.

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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