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Long-term response in refractory AML following azacitidine-failed MDS by salvage decitabine-bridged allogenic transplantation

TO THE EDITOR: Myelodysplastic syndromes (MDS) are a group of heterogeneous hematological malignancies which demand personalized and risk-adapted clinical management [1]. Current therapeutic approaches are rather limited for patients unsuitable for allogeneic stem cell transplantation (SCT), the only realistic and potentially curative treatment measure that exists [1]. With regard to patients with high risk MDS, the standard of care is currently represented by treatment with hypomethylating agents (HMAs), such as decitabine and azacitidine. The latter is used as initial therapy in most cases, and induces responses in 40–50% of treated patients [2, 3]. Obstacles to azacitidine administration as well as recommendations for the optimization of treatment with this agent have been reported [2, 4]. However, despite optimal management of azacitidine treatment, the duration of its clinical benefit, although variable, is usually transient and almost all patients ultimately experience loss of response to the drug, disease progression, and therefore very poor outcomes [1, 2, 5, 6]. After this loss of response or disease progression despite treatment, there are no standard care regimens available [5]. Rescue strategies including intensive chemotherapy (ICT) only provide minor benefits, whereas allogeneic SCT is feasible only in a minority of cases. With these results in mind, especially the catastrophic outcome of azacitidine-failed patients, typical concerns about decision making and clinical management in these settings can be summarized by an unusual case we observed which is reported herein. A 59-year-old woman was admitted for profound malaise due to pancytopenia on March 2015. The bone marrow (BM) and trephine biopsy revealed refractory anemia with an excess of blasts-2 (RAEB-2), remarkable multilineage dysplasia, and 18% of BM infiltrating blasts; the karyotype analysis and molecular study for typical abnormalities found in MDS were negative. She was diagnosed as having an Inter-2 MDS, according to the International Prognostic Scoring System [7]. On the basis of the patient's overall fitness level, and given the lack of a suitable familiar donor to proceed to immediate allogeneic SCT, we recommended therapy with azacitidine (75 mg/m^2, schedule 5+2+2). Therapy was started on April 2015 without significant adverse effects. Meanwhile, a matched unrelated donor (MUD) was fruitlessly sought. After six cycles (September 2015), a partial remission (according to Cheson's criteria) was achieved [8]. Because of this, the same treatment was continued for another three cycles until December 2015, when a progressive pancytopenia unveiled progression to secondary acute myelogenous leukemia (AML). At the time of evolution, standard

cytogenetic tests, FISH analyses, and mutational studies which are usually performed in the AML diagnostic work-up (such as BCR/ABL P190, BCR/ABL P201, RUNX1/RUNXT1, CFBbeta/MYH11, DEK/CAN,FLT3-ITD and NPM1) were found to be negative; therefore, as the patient was considered eligible for an anthracycline-based induction ICT, she received one course of standard "3+7" consisting of daunorubicin 45 mg/m^2 daily (days 1–3) and cytarabine 100 mg/m^2 daily (continuous IV infusion days 1–7). Unfortunately, the patient was resistant to this induction ICT; her BM, which was revaluated 14 and 28 days after the induction treatment, remained severely dysplastic with —20% of leukemic infiltration (December 2015). In addition, the course of therapeutic aplasia was complicated by a severe pulmonary aspergillosis, which was successfully treated with voriconazole. The patient complained of painful dysesthesia of the lower limbs, and a magnetic resonance imaging (MRI) scan of the spine revealed a massive osteolytic lesion at the D11 vertebral body without neural compression. A percutaneous biopsy of D11 revealed the AML localization of the involved vertebral body, and a vertebloplasty was performed (April 2016). At that time, the patient was properly informed of the seriousness of her clinical situation, as well as the absence of effective standard therapeutic options, and that some available measures were only for palliative purposes. Despite this, she asked us to continue the anti-leukemic therapy, while evaluating any form of potentially applicable causal options. After the approval from the Institutional Board of our hospital, the patient consented to therapy with decitabine at the daily dosage of 20 mg/m^2 for five days every four weeks (July 2016); she received four courses without any side effects [9, 10]. Prior the start of decitabine treatment, a BM exam was performed revealing 20% of BM infiltrating blasts, whereas karyotype and molecular findings were normal. Meanwhile, the patient received stereotactic radiation therapy on the D11 vertebral body up to a total dose of 24 Gy, given in 3 fractions (8 Gy per day, September 2016) without any adverse reaction. Given the progressive improvement of blood counts and the significant reduction in transfusion requirements achieved after the fourth course of decitabine (November 2016), we performed a comprehensive BM reassessment; this showed a complete remission (CR) with incomplete hematological recovery [8]. In the light of her good clinical condition as well as the therapeutic response to decitabine (certainly better than we could have expected in an AML patient refractory to multiple treatment lines and complicated by extramedullary localizations), she was considered a fit candidate for haploidentical SCT. The patient underwent haploidentical SCT with her daughter as donor in January 2017 [11]. The conditioning regimen consisted of thiotepa 5 mg/kg on days −6 and −5, fludarabine 50 mg/m^2 on days −4−3−2, and intravenous busulfan 3.2 mg/kg on days −4−3. The stem cell source was unmanipulated bone marrow. Graft versus host (GvHD) prophylaxis consisted of Post-Transplant Cyclophosphamide (PTCy) 50 mg/kg given on days +3 and +5 and cyclosporine A 1.5 mg/kg given as a continuous i.v. infusion from days 0 to +20, adjusted for blood levels (200 to 400 ng/mL), and then orally until day +180. The patient achieved a neutrophil count of 0.5×10^9/L on day +17 and a platelet count of 30×10^9/L on day 28; chimerism was full donor, by microsatellites, from the first evaluation on day +30. In particular, no acute graft versus host disease (GvHD) or other clinically significant side effects occurred. During her follow-up, a second vertebroplasty was performed on August 2018, due to the osteopenic collapse of the D12 vertebral body in the absence of any histological finding of AML localization. To date (October 2019), 43 and 23 months from the MDS primary diagnosis and allogeneic SCT, respectively, the patient has maintained a stable and long lasting CR and is well and active. In conclusion, in this case, decitabine achieved the CR of a secondary, pretreated and refractory AML, allowing for a bridge to successful allogenic SCT. Although the favorable clinical course of our patient has to be considered as unusual in contrast to what we unfortunately observe in most of the patients with high-risk MDS after azacitine-failure (or its transformation into secondary AML), it offers some interesting insights to consider. The achievement of a CR using decitabine in a patient who had previously received azacitidine is quite rare; it is well known that decitabine therapy is typically of little benefit after azacitidine failure [12]. In our case, as a mere speculation, we believe that the long period of time (about one year) that elapsed between the administration of decitabine from the first hypomethylating treatment with azacitidine may have contributed to re-establishing a good enough sensitivity to epigenetic therapy. This reported experience demonstrates the efficacy and applicability of haploidentical SCT, bridged by decitabine in our case, even for cases of clinically complex and pretreated patients with a long disease history. Also, the availability of novel agents able to induce a significant clinical response in patients with refractory AML could increase the number of patients who could benefit from allogeneic SCT (in its various practices) as an effective consolidation strategy, even after a long history of disease.

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Differential impact of anti-thymocyte globulin dosing by disease risk index in alternative donor peripheral blood stem cell transplantation in patients with acute leukemia or myelodysplastic syndrome after reduced intensity conditioning

TO THE EDITOR: Chronic graft-versus-host disease (GVHD), one of the major hurdles in the way of successful hematopoietic cell transplantation (HCT), has increased in incidence with the widespread use of peripheral blood (PB) grafts and alternative donors, along with an increased number of older transplant recipients [1]. Although anti-thymocyte globulin (ATG) plays a protective role against GVHD across various transplant settings, including alternative donor PB HCT with reduced intensity conditioning (RIC), its optimal dosing in a specific transplant platform remains largely unknown [2, 3].

We hypothesized that the impact of different ATG doses can depend on the disease risk index (DRI). The present study aimed to explore this hypothesis by comparing transplant outcomes between total ATG doses of 6 mg/kg and 9 mg/kg in a homogenous population stratified by DRI. These patients received PB grafts from alternative donors after a specified RIC regimen for acute leukemia or myelodysplastic syndrome (MDS).

We retrospectively identified 130 eligible patients who had undergone their first HCT between February 2008 and March 2017 at Seoul National University Hospital (SNUH) and Seoul National University Bundang Hospital (SNUBH). The donors included 10/10 human leukocyte antigen (HLA) allele-matched unrelated donors (MUDs), 7/10 or 8–9/10 partially matched unrelated donors (PUDs), and 3–4/6 or 3–7/8 or 6/10 haploidentical familial donors (HIDs), while the graft source consisted of PB stem cells only. Conditioning included the administration of intravenous busulfan at a dose of 3.2 mg/kg on day D-7 and D-6, fludarabine at 30 mg/m^2 from D-7 to D-2, and rabbit ATG (Thymoglobulin) at 2.0 or 3.0 mg/kg from D-3 to D-1. Cyclosporine A or tacrolimus were additionally used with or without methotrexate. The study protocol was reviewed and approved by the Institutional Review Boards of SNUH and SNUBH.

Baseline characteristics of included patients are summarized in Supplementary Table 1. The median follow-up period for the total population was 35.00 months [95% confidence interval (CI), 30.34–39.66]. In the total population, the GVHD-free, relapse-free survival (GRFS), disease-free survival (DFS), and overall survival (OS) tended to be longer when using the 6 mg/kg dose than when 9 mg/kg was used, but without statistical significance (Fig. 1A-C). In 99 patients with low/intermediate DRI, those in the 6 mg/kg