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Editorial
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Outcome of Allogeneic Bone Marrow Transplantation for Acute Myeloid Leukemia Following Single Agent Induction with Hypomethylation

*Higgins H, Hennig T, Chao N, Horwitz M, Sung A, Long G, Lopez R, Sarantopoulos S, Sullivan K, Choi T, Gasparetto C and Rizzieri D**

Division of Hematologic Malignancies and Cellular Therapy, Duke Cancer Institute, USA

Editorial

Acute myeloid leukemia can be difficult to treat as it is often a disease of the elderly and is associated with poor outcomes [1,2]. Allogeneic stem cell transplantation may be curative, though only a fraction of patients undergo this therapy, in part due to co-morbidities, not responding to aggressive induction therapy, or patient preference [3,4]. Azacitidine and decitabine have shown activity in AML and MDS and are commonly used in more infirmed patients because of their overall favorable tolerability with encouraging response rates [5,6]. It has been published that following their use for MDS or secondary AML, allogeneic transplant can be successful. It remains unclear, however, if this less aggressive induction is sufficient preparation for patients with de novo AML prior to allogeneic transplantation. Recent reports of success in using HMA as a 'bridge' have been reported for MDS, though data specific for AML remains sparse [7,8]. The impact of HMA on the immune system, as opposed to its reversal of methylation and gene silencing, has been the subject of growing interest as well. We report the outcomes of a small series of sequential patients treated at our center for AML with HMA as a single agent for induction prior to an allogeneic stem cell transplant.

Electronic patient records were searched using Deduce and our internal stem cell transplant database for all transplanted subjects to provide for accurate subject identification. Initial review indicated 457 patients with AML who underwent allogeneic transplant at our center over the past 15 years. Cross-filing with those who also received HMA as the sole therapy leading immediately to transplant lead to identifying 8 subjects who had MDS and 3 with AML. The 3 with AML (one secondary) are the focus of this retrospective analysis. Electronic medical records were manually reviewed for data abstraction (HH, TH and DR). This retrospective review was approved by the Duke University IRB.

Patients were aged 44, 61, and 67 years with a Charlson Comorbidity Index of 2, 4 and 4 respectively. Both patients with de novo AML had multiple chromosome abnormalities including alterations in chromosome 3 while the patient with a prior myeloproliferative disorder had normal chromosomes and one had known FLT3-TKD molecular mutation at diagnosis. Each had standard '7+3' failure prior to hypomethylators and patients received 3 or 4 cycles of HMA therapy before transplant conditioning, and all had <4% blasts prior to allogeneic transplant and fulfilled standard criterion for CR or CRi. One had ablative busulfan 16 mg/kg (4 days) with Fludarabine 30 mg/kg for 4 days and the other two received fludarabine with melphalan 200m g/m2. Graft Versus Host Disease (GVHD) prophylaxis included a calcineurin inhibitor and methotrexate (1), or mycophenylate (2). Two had a matched unrelated and one a haploidentical sibling donor. Two did not have any graft versus host disease, while one experienced grade 2 GVHD of the skin and gut.

One died of infection at day 41, a second relapsed at 7.5 months and died 18 months post-transplant while a third remains in long term remission 3 years post therapy.

Although advances have been made in recent years in the treatment of AML, allogeneic stem cell transplantation remains the only treatment with significant curative potential [4]. As many patients who may benefit from allogeneic immunotherapy are older or more infirmed, the use of less toxic induction therapies often followed by reduced intensity allogeneic therapies is emerging [4]. Use of HMA for treatment of leukemia but not as a 'bridge' is of course well published. Recently, Fili et al. [9] reported on 104 AML patients who were 'unfit' for aggressive chemotherapy with encouraging

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Correspondence:
David Rizzieri, Division of Hematologic Malignancies and Cellular Therapy, Duke Cancer Institute, Duke Health System, Durham, NC 27705, USA, Tel: 919 668 1040; Fax: 919 668 1091;
E-mail: david.rizzieri@dm.duke.edu

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remission rates, though in the relapsed setting such as our situation there were no complete remissions obtained in 66 such treated patients and this was not used as a bridge to transplant in any such cases. Data for HMA as sole induction prior to allogeneic transplant has focused almost exclusively on high risk MDS. Nishimori and colleagues reported a prospective pilot study 21 patients with MDS having 1year survival of 62% [7]. Vaso et al. [8] recently reported a large study in patients with MDS or low blast count AML who underwent this approach as well. They showed the majority of patients could be 'bridged' to transplant with a median survival of 20.9 months in those who were transplanted, however once again the number of patients who had AML in the transplanted sub-group was not specified [8]. A recent large multicenter retrospective review by Stahl et al. [10] found only 37 of 655 leukemia patients who received an HMA preceded to an allogeneic transplant, and only 16 of those had a response and proceeded immediately to the transplant as in our case series. They also indicate a portion of the patients are able to attain a long-term remission [10]. Our case series is specific to patients with leukemia and suggests potential success in allowing patients with AML to respond to HMA, engraft, and potentially enjoy a durable remission. It is interesting that remissions from HMA in these 3 cases were noted as they were refractory to standard induction. Reasons for this better than anticipated outcome may relate to differing impact on the host immune system by the HMA, not just its targeting of methylation status. Data has been published of the beneficial effect of HMA on CD8+ T cell expression as well as altering the expression of antigens that may be immune stimulatory [11,12]. In addition, beneficial effects of HMA on alterations in checkpoint inhibitor expression has been reported as well [7,8,13]. These potential benefits of HMA prior to allogeneic transplant deserve further investigation.

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