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Research paper

Red blood cell alloimmunization in 184 patients with myeloid neoplasms treated with azacitidine – A retrospective single center experience

M. Leisch[a,b], L. Weiss[a,b], N. Lindlbauer[c], C. Jungbauer[d], A. Egle[a,b], E. Rohde[c], R. Greil[a,b,e], C. Grabmer[c,1], L. Pleyer[a,b,e,1,*]

[a] 3rd Medical Department with Hematology and Medical Oncology, Hemostaseology, Rheumatology and Infectious Diseases, Laboratoy for Immunological and Molecular Cancer Research, Oncologic Center, Paracelsus Medical University, Salzburg, Austria
[b] Center for Clinical Cancer and Immunology Trials as Salzburg Cancer Research Institute, Salzburg, Austria
[c] Department of Blood Group Serology and Transfusion Medicine, SALK – Paracelsus Medical University, Salzburg Austria
[d] Austrian Red Cross, Blood Service for Vienna, Lower Austria and Burgenland, Vienna, Austria
[e] Cancer Cluster, Salzburg, Austria

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ABSTRACT

Alloimmunization to Red Blood Cell (RBC) antigens frequently occurs in patients with myeloid neoplasms (AML, MDS and CMML) and potentially poses the patient at risk for delayed hemolytic transfusion reactions and limited supply of compatible RBC-units. However, there is comparatively little data on transfusion associated characteristics in this patient cohort. We therefore retrospectively analyzed transfusion requirements and clinical outcomes of 184 patients with myloid neoplasms treated with azacitidine at the Paracelsus Medical University Salzburg, which were included in the Austrian Registry of Hypomethylating Agents.

The mean blood component requirements for AML, MDS and CMML were 39.8, 67.4 and 31.4 RBC units and 31.7, 27.6 and 19.1 platelet (PLT) units respectively. In spite of an extended and stringent RBC unit matching policy (ABO, RhD, RhCcEe and K antigens), 20 (11%) patients formed at least one alloantibody ("allo-group"), whereas 164 patients (89%) did not ("non-allo-group"). The most frequent antibody specificity was anti-E, followed by anti-Wra −Lua, −D, −C and −Jka. Alloimmunization was associated with higher numbers of transfused RBC units (68 vs. 38; p = 0.001), as well as with longer time under transfusion (16.7 vs. 9.4 months; p = 0.014). Median overall survival (OS) did not differ significantly between the "allo"- and "non-allo-group".

1. Introduction

Acute myeloid leukemia (AML), myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are clonal myeloid stem cell neoplasms with an incidence of 3–20 per 100.000 per year and are characterized by accumulation and proliferation of immature bone marrow blasts, as well as subsequent hematopoietic insufficiency resulting in peripheral blood cytopenias (i.e. anemia, thrombocytopenia, neutropenia) [1,2].

AML, MDS and CMML are particularly common in older individuals and are generally associated with shorter survival especially in patients older than 60–70 years of age, who are not candidate for intensive chemotherapy regimens or allogeneic bone marrow transplantation [3].

Despite different disease biology and prognosis of AML, MDS and CMML, treatment options for older individuals are limited and therefore patients are often treated in a similar way i.e. with hypomethylating agents (HMA; i.e. azacitidine, decitabine).

Azacitidine (AZA) was initially approved for the treatment of intermediate 2 and high risk MDS according to IPSS score as well as AML with 20–30% bone marrow blasts, based on the results of the AZA-MDS-001 trial [4,5]. Recently AZA has also been approved for AML with over 30% bone marrow blasts in patients who are no candidates for allogeneic bone marrow transplantation [6,7]. There are several phase II studies which demonstrated efficacy of AZA in the treatment of CMML, as reviewed recently [8], and AZA is approved for the treatment of patients with CMML with 10–29% bone marrow blasts.

Although significant improvements regarding treatment outcomes of elderly patients with AML, MDS and CMML in the era of HMAs [4,5,9–13] these diseases remain incurable.

Most patients require chronic transfusion of Red Blood Cell (RBC)-

* Corresponding author at: 3rd Medical Department with Hematology and Medical Oncology, Hemostaseology, Rheumatology and Infectious Diseases, Laboratoy for Immunological and Molecular Cancer Research, Oncologic Center, Paracelsus Medical University, Salzburg, Austria.
E-mail address: l.pleyer@salk.at (L. Pleyer).
[1] These authors contributed equally to this work.

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and/or platelet (PLT)-units during the course of their disease: transfusion dependence (a) is often present before treatment initiation, and sometimes used as an indication for therapy initiation with HMA, (b) may persist in patients not responding or refractory to HMA, and (c) can also re-occur in patients who eventually relapse after achieving a response.

Alloimmunization to RBC antigens in patients occurs with a frequency of 0.1–1.37% per RBC unit transfusion, depending on clinical condition and treatment [14–16].

Even higher rates with 1.7–3.3% were reported in patients with Sickle Cell Disease [17].

Due to chronic transfusion dependence, the prevalence of RBC "alloantibodies" or "irregular RBC-antibodies", in patients with myeloid malignancies is high [18]. When alloimmunization occurs, it can result in shortage or delayed supply of suitable RBC-units, hemolytic transfusion reactions and substantial increases of health care costs [19].

The reported general incidence of RBC alloimmunization in patients with MDS and other hematologic malignancies (mainly Non-Hodgkin lymphoma) ranges from 9 to 15% [20–23]. The incidence of alloimmunization was reported to be lower in AZA treated patients (2.3%) compared to non AZA treated patients (13.9%) in a recent study [29]. Whereas the development of RBC-alloantibodies was associated with decreased OS in patients with sickle cell disease [24], the impact of RBC alloimmunization on survival in patients with myeloid neoplasms has not yet been reported. Likewise, a more extensive characterization of transfused patients and investigation of associations broken down by disease would be desirable.

The purpose of this study was to (a) establish blood component requirements and the incidence of RBC alloimmunization grouped by diagnosis in a large retrospective series of patients with myeloid neoplasms uniformly treated with AZA using an extended antigen-matched RBC transfusion policy (beside ABO and RhD ("Rhesus")) for RhCcEe and K (Kell) antigens, (b) identify factors associated with RBC alloimmunization and (c) determine the impact of RBC alloimmunization on patient survival.

2. Materials and methods

We retrospectively analyzed the transfusion history according to our hospital blood bank data as well as clinical parameters of patients treated with AZA and included in the Austrian Registry of Hypomethylating Agents (NCT01595295; Ethics Committee approval 06.02.2009) treated at the 3rd medical department of the Paracelsus Medical University Salzburg, Austria between February 2009 and June 2015. All patients alive at the time of data acquisition provided written informed consent. The study was approved by local ethics committee. The only inclusion criteria were diagnosis of AML, MDS or CMML, treatment with at least one dose of AZA and at least one RBC transfusion event during the course of the disease. No formal exclusion criteria existed. Further details about this registry have been previously published [10–13].

This analysis only assessed transfusion events after the diagnosis of AML, MDS or CMML. Ten out of 184 patients required RBC transfusions prior to diagnosis for the following reasons: surgery (n = 4), trauma (n = 1) and prior chemotherapy for other diseases (n = 5). These transfusion events were not included into the analysis of total RBC transfusions and time under transfusion, but these patients were not excluded from this study. None of these patients developed an alloantibody.

Routine serologic phenotype matching consists of testing for ABO and RhD antigens. However, it is our practice to perform extended serologic phenotype matching (D, C, c, E, e and K) prior to each transfusion in patients with hematologic- or oncologic diseases. Also, all RBC-units were leukoreduced and irradiated prior to transfusion.

Diagnosis of AML, MDS and CMML was made according to WHO classification of tumors of hematopoietic and lymphoid tissue 2008 [2]. Response to treatment was assessed using the International Working Group criteria for MDS, CMML or AML, respectively [25,26]. Cytogenetic risk profile for MDS and CMML was assessed according to the IPSS Scoring System [27] and according to Medical Research Council (MRC) risk profile for AML [28]. OS was either calculated from date of diagnosis to death (termed "OS from diagnosis") or from initiation of AZA treatment to death (termed "OS from AZA start").

Statistical analysis was performed with SPSS software (version 21; IBM). Baseline characteristics were compared between groups using Chi square test for categorical variables and Mann Whitney tests for continuous variables. We used Mann Whitney tests to compare medians between groups, and Wilcoxon tests for non-parametric dependent variables. Survival was calculated using Kaplan Meier estimates and statistical testing for significance was done using the log-rank test. Results were termed statistically significant with p-values < 0.05 unless stated otherwise.

3. Results

3.1. Baseline characteristics

A total of 184 patients of 196 patients within the Austrian Registry of Hypomethylating Agents met the eligibility criteria. Twelve patients did not receive any RBC-units and were therefore excluded from this analysis. Baseline characteristics are outlined in Table 1. In total there were 97 patients with AML, 70 with MDS and 17 with CMML

Patients were grouped into two groups: RBC transfusion dependent with an alloantibody (i.e. patients that required at least one RBC-unit and developed at least one irregular RBC-alloantibody; termed "allo-group") and RBC transfusion dependent without alloantibody (i.e. patients that required at least one RBC-unit and developed no irregular RBC-antibodies; termed "non-allo-group").

In total, 20 patients (11%) developed at least one irregular RBC-alloantibody.

No significant differences regarding baseline characteristics, such as ECOG performance status, median age at diagnosis or cytogenetic risk profile was noted between the allo- and the non-allo-group. This remained true when analyzing patients according to WHO-diagnosis separately. Frequency of AML and MDS diagnosis was well balanced between the allo- and non-allo-group, however, there were no patients with CMML in the allo-group.

3.2. Treatment history and response

All patients were treated with AZA during their course of disease. Other prior treatments and concomitant therapies are listed in Table 1. Patients in the allo-group received significantly more Cyclosporin A and displayed a trend for higher usage of immunemodulating substances (i.e. lenalidomide, thalidomide). Otherwise, there were no significant differences regarding the frequency of other prior- or concomitant therapies.

Median time to AZA start from diagnosis was 3.7 and 4.0 months in the allo- and non-allo-group. Seventy five percent in the allo-group and 82% in the non-allo-group received AZA as first line therapy. However, only 30% of patients with MDS in the allo-group compared to 84% of patients with MDS in the non-allo-group received AZA as first line therapy ($p = 0.014$).

Patients with AML in the allo-group received a median of 7 cycles of AZA. This was significantly more than the median of 2 cycles of AZA for patients with AML in the non-allo-group ($p = 0.007$). No such difference was observed for MDS patients.

The overall response rate according to IWG criteria in patients receiving at least 3 cycles of AZA treatment was better in the non-allo-group (43.3%) than in the allo-group (22.2%). This difference was of borderline significance ($p = 0.06$). Of note, patients in the non-allo-group displayed better responses (i.e. more complete remissions (CRs)