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Allogeneic Hematopoietic Cell Transplant Outcomes in Patients Carrying Isocitrate Dehydrogenase (IDH) mutations

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Abstract

Background: Mutations in isocitrate dehydrogenase 1/2 (IDH1/2) genes result in NADPH-dependent reduction of α-ketoglutarate and formation of 2-hydroxyglutarate, which blocks normal cellular differentiation and promotes leukemogenesis. Nearly 20% of AML cases carry IDH1/2 mutations. While multiple investigators have described the prognostic implications of IDH mutations in AML patients receiving chemotherapy, the impact of these mutations on outcomes after allogeneic hematopoietic cell transplantation (alloHCT) is unknown.

Patients: We report on the clinical outcome of a cohort of AML patients, tested for IDH mutations and underwent alloHCT at City of Hope (2015–2017). Of a total of 317 screened patients, 99 underwent alloHCT, of which 23 carried and 76 did not carry IDH mutations (control).

Results: No statistical significance was detected in patient's overall survival (p=0.84). With a median follow up of 7.8 months, 1-year relapse rate of 29% and 13% was seen in IDH mutated and control group, respectively (p=0.033). IDH1/2 mutation status remained significantly

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CONFLICT OF INTEREST

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associated with relapse (HR=2.8, p=0.046) after inclusion of pre-HCT disease status in a multivariable model.

Conclusions: Our results, despite low patient numbers, indicates that IDH mutations are associated with higher relapse rate post-alloHCT. Further prospective studies investigating post-transplant IDH inhibition is required to improve outcomes in AML patients carrying IDH mutations.

MICRO ABSTRACT

The impact of IDH mutations on transplant outcomes is unknown. We retrospectively screened 99 AML patients who underwent alloHCT (2015–2017) of which 23 carried and 76 did not carry IDH mutations (control). Overall survival was not different among the two groups, but significantly higher rate of relapse was detected in IDH mutated group by univariate and multivariate analysis.

Keywords

retrospective study; allogeneic HCT; IDH1/2 mutations; Survival; Relapse rate

INTRODUCTION

Isocitrate dehydrogenase 1 (IDH1) and its mitochondrial homolog *IDH2*, are key component enzymes in the Krebs cycle, involved in conversion of isocitrate to α-ketoglutarate (α-KG). Somatic mutations in *IDH1* or *2* are seen in approximately 15–30% of patients diagnosed with acute myeloid leukemia (AML), with an incidence of 6–16% for the *IDH1* and 8–19% for the *IDH2* mutation.[1] While these mutations are less frequent in patients with MDS (5%)[2] and MPN, the mutation frequency goes up to 20% with leukemic transformation.[3] Mutant *IDH* enzymes catalyze NADPH-dependent reduction of α-KG to the oncometabolite R-2-hydroxygluterate (2HG).[4] Upon translocation to the nucleus, 2HG competitively inhibits α-KG-dependent enzymes, including members of the TET protein family (TET1–3), 5-methylcytosine hydroxylases, and jumonji-C domain-containing group of histone lysine demethylases. Inhibition of these epigenetic regulators by 2-HG produces a hypermethylation with altered gene expression, leading to differentiation arrest in hematopoietic precursors.[5,6] Therefore, somatic mutations in *IDH1/2* impair normal myeloid differentiation, increase stem/progenitor cells, and promote leukemogenesis.[2]

Multiple studies have investigated the prognostic implications of *IDH1/2* mutations in AML patients undergoing induction and consolidation chemotherapy with variable results, from a negative prognostic impact of *IDH* mutations with standard chemotherapy [7–9] to no adverse or even improved remission/survival after induction chemotherapy.[10,11] Some studies show that co-occurrence of *NPM1* alteration with either *IDH1* or *2* mutation, results in an improved overall survival (OS),[12–14] whereas other studies report lower OS in AML patients with *IDH* mutations who are otherwise cytogenetically normal (FLT3-ITD^{wt}).[9,15,16] In a report by Marcucci *et al,*[10] patients with *IDH1* mutation had shorter disease-free survival (DFS), whereas *IDH2* mutated patients had a lower complete remission (CR) rates. The variability in outcomes across these studies might be due to heterogeneity in the location

of hotspot mutations, other co-existing mutations, and serum levels of 2-HG, which also correlate with clinical outcome in AML patients carrying *IDH1/2* mutations.[17,18]

With advances in our understanding of the biology of AML, availability of DNA sequencing platforms and AML mutation testing, improved clinical outcomes and overall survival have been achieved for patients with relapsed AML. [19–21] Simultaneously, rates of non-relapse mortality (NRM) is decreased in patients with leukemia following alloHCT, mainly due to the modulation of conditioning regimen intensity, advancement in graft-versus-host disease (GVHD) prophylaxis and treatment, and improved donor selection and supportive care.[22] However, relapse of the primary malignancy has remained the major cause of treatment failure and mortality for these patients. Based on most recent data from the Center for International Blood and Marrow Transplant Research, relapse of primary disease is the major cause of death after HLA matched (57%) and unrelated donor (46%) HCT at or beyond 100 days post-transplant. The survival outcomes of patients who relapse after alloHCT are uniformly poor, especially if the relapse occurs relatively early after transplant.[23–25]

The most recent European LeukemiaNet (ELN) guidelines classify AML with *IDH* mutations as an intermediate risk disease.[26] Based on the current guidelines, allogeneic hematopoietic cell transplantation (alloHCT) is recommended for AML patients with intermediate risk disease in their first remission based on a post-induction chemotherapy relapse risk of 35–40%.[27] Herein, we investigated if *IDH* mutations impact transplant outcomes in AML patients by comparing outcomes of patients carrying *IDH* mutations to those not carrying these mutations. To our knowledge, there are no reports on the impact of *IDH1/2* mutations on the outcome of AML patients who underwent alloHCT.

METHODS

Study Population

We reviewed the medical records of AML patients who were screened for *IDH1/2* mutations, using Next Generation Sequencing (NGS), from 2015 to 2017 at City of Hope (COH), and retrospectively analyzed the relapse rates, OS and other HCT-related outcomes. The NGS panel comprised of a comprehensive panel of somatic mutations and gene fusions commonly seen in hematologic malignancies. This study was approved by the institutional review board (IRB) of COH.

NGS Library Preparation and Bioinformatics Analysis

NGS libraries were prepared from genomic DNA (40 ng) using the SureSelect target enrichment system (Agilent Technologies Inc.) after transposase-based fragmentation and adapter ligation. The adapter-ligated library was amplified by polymerase chain reaction and quality control was performed for sizing and concentration. Target regions were captured using a customized SureSelect library (Agilent Technologies) for all coding exons plus ten flanking bases of 72 genes. After hybridization of 750 ng of adapter-ligated library with biotin-labeled probes that are specific to target regions, the dual-index tag were added during post-capture polymerase chain reaction amplification. The amplified captured libraries were

quality-controlled using a high sensitivity DNA Bioanalyzer kit (Agilent Technologies Inc.) then pooled and sequenced using Miseq V2 Reagent Kit/300 cycles with 150 bp paired-end sequencing. Alignment of sequence reads to the human genome (GRCh37/hg19), variant calling and annotation was performed independently using two software applications – CLCBiomedical Workbench (CLC Bio, Aarhus, Denmark) and NextGENE (Softgenetics, State Collage, PA, USA). Annotated variants were processed using previously published criteria.[28,29] Synonymous variants, variants located >2 bp outside protein-coding regions, polymorphisms present in >1% in population databases including ExaC, Exome Variant Server and the 1000 Genomes Project, and variants with <30X coverage were filtered. The remaining variants were evaluated using tumor-specific databases (COSMIC, cBioportal), information retrieved from literature, sequence conservation, and *in silico* prediction algorithms, including SIFT, Polyphen-2, and FATHMM, for clinical significance.

Flow Cytometry MRD Assay

The MRD flow cytometry assay was sent out to an outside laboratory, using an assay with detection sensitivity of more than 0.01% of white cells. This was achieved by validating the ability to add twice as many cells in order to more consistently collect one million white cell events. The 18 fluorchromes used in this assay were CD4, CD5, CD7, CD13, CD14, CD15, CD16, CD19, CD33, CD34, CD38, CD45, CD56, CD64, CD71, CD117, CD123, and HLA-DR. For a detailed description of this assay please refer to Wood et al[30].

Statistical Analysis

Wilcoxon and chi-square or Fisher's exact tests were used to compare the baseline characteristics between groups by *IDH1/2* mutation status whenever appropriate. Kaplan-Meier curves and the log-rank test were used to evaluate OS and progression-free survival (PFS) from the date of HCT. Cumulative incidence curves and the Gray test were used to examine the differences in relapse rates and NRM.

RESULTS

A total 317 AML patients were screened for *IDH1/2* mutations form 2009 to 2017. Of these, 99 patients underwent alloHCT with 23 patients carried either *IDH1* or *IDH2* mutation (IDH ^{Mut}). The remainder of patients (n=76) who underwent alloHCT but were negative for *IDH* mutations were used as the control group for this study. Patient demographics and alloHCT characteristics are summarized in Table 1. Briefly, the median ages at transplant for patients with *IDH* mutation and those without *IDH* mutations were 64 years (range: 36–73) and 54 years (range: 18–71), respectively (p=0.007). Thus, the majority of the IDH mutated patients (74%) received reduced-intensity conditioning regimens (vs. 59% in the control group). Disease status prior to HCT, donor type, graft source, donor/recipient CMV serostatus, and GvHD prophylaxis regimens were similar across both groups. No patient in IDH mutated group received maintenance therapy post alloHCT.

Of the 23 patients carrying *IDH* mutations, 30% carried *IDH1* (R132C and R132H were the most prevalent) and 70% carried *IDH2* mutation (R140Q was the most prevalent). The mutation allele burden (mean) was 31.7% (range: 2–48) for IDH1 and 34.1% (range: 3–44)

for IDH2 mutated patients. No patients in the IDH mutated or control group had antecedent hematologic disorder preceding AML diagnosis. Co-mutation was detected in 3 patients with *FLT3-ITD* or *TKD*, and *NPM1* and *DNMT3A* mutations were noted in 4 and 1 patient, respectively. None of the patients carrying *FLT3-ITD* mutation were relapsed at their last follow-up. Cytogenetic analysis at diagnosis of AML revealed adverse risk in 21.7% of patients in the IDH^{mu} group and 31.6% in the control group (p=0.46). Multicolor flow cytometry based-minimal residual disease (MRD) analysis was done pre-HCT in 14 patients in the *IDH* mutation group and 30 patients in the control groups. The MRD positivity rates were 14.3% and 16.7% in the *IDH* mutated and control group, respectively (p=1.0). Of the 23 patients who were positive for *IDH* mutations, 6 (26%) received *IDH* mutation-directed therapy on a clinical trial pre alloHCT. Of these, 3 patients entered MRD negative status pre-HCT, but the other 3 did not have MRD testing done on the pre-HCT marrow. Four patients remain leukemia-free post alloHCT and 2 have relapsed.

There were no significant differences in 12-month OS (71% vs. 68%; P=0.84) between patients carrying or not carrying *IDH* mutations (Figure 1a). With a median follow-up of 7.8 months (range: 1.0–52.2), 6 patients in the *IDH* mutated and 11 patients in the control group relapsed (1-year relapse rate of 29% [95% CI: 9.6–51.6%] and13% [95% CI: 5.5–24.2%], respectively), (p=0.033) (Figure 1b and Table 2). When disease status prior the alloHCT was included in a multivariable model (Table 2), the presence of IDH1/2 mutations was significantly associated with relapse (HR=2.78, 95% CI: 1.0–7.6, adjusted p value=0.046). None of the patients carrying *IDH* mutation with *NPM1* or *FLT3-ITD/TKD* mutations relapsed post alloHCT, but one relapse was seen in an *IDH2* mutated patient with *DNMT3A* mutation. No long-term survivors were noted in IDH mutated patients after relapse post HCT. NRM was similar in the control group and IDH mutated group (p=0.17). The incidence of acute (grades II-IV) and chronic GvHD were similar between the two groups (p=0.73 and p=0.63, respectively).

Among the 218 AML patients who did not proceed to alloHCT, mainly due to advanced age or refractory leukemia, *IDH1* or *2* mutations were detected in 30 patients. Of these patients, 15 were enrolled on IDH-targeted therapies and 5 patients (16.6%) were alive at the last follow-up. The remaining 15 patients received best available therapy with 3 (10%) being alive at the last follow-up.

DISCUSSION AND CONCLUSION

This retrospective review shows for the first time to our knowledge that patients carrying the IDH^{mu} remain at a high risk of post allogeneic HCT relapse compared to IDH^{wt} patients. This opens the possibility of using IDH inhibitors as post HCT maintenance therapy. This strategy of post alloHCT maintenance therapy to reduce the incidence of relapse are well-established in treatment of acute leukemia. Addition of Tyrosine Kinase Inhibitors with induction chemotherapy and post-transplant maintenance in patients with Philadelphia chromosome positive ALL has shown improvement in overall, relapse free and event free survival.[31 32] Similarly, in patients with AML with FLT3-ITD mutations, sorafenib maintenance has resulted in better overall and event-free survival.[33,34] Results from the randomized, SORMIN study has shown improvement in RFS in patients who

received post-HCT sorafenib maintenance for 24 months.[35] Hypomethylating agents have been used to decrease relapse rates post alloHCT. Addition of azacitidine after alloHCT in high risk populations improved EFS and OS, indicating the efficacy of this strategy.[36] Similarly, decitabine at low dosage has been used as post HCT maintenance strategy and showed effective in reducing relapse rates.[37] Multiple clinical trials are ongoing to reduce relapse rate in AML patients after standard frontline chemotherapy using novel strategies such as checkpoint inhibitors such as Nivolumab (NCT02275533), SL-401 (NCT02270463), and lenalidomide and azacitidine (NCT01743859). Results of these trials will help with prolonging remission in older, unfit patients who are unable to go through alloHCT.

Although our study is limited by the relatively small number of patients, short follow-up duration, and heterogeneity of the cohorts, it is the first to describe the outcome of AML patients with *IDH* mutations who underwent alloHCT. In multivariate analysis, *IDH* mutation was the only predictor of relapse post-HCT. Multivariate analysis in our cohort of patients using conventional risk factors such as age, cytogenetics and pre-HCT MRD status did not predict for higher relapse rates post HCT. The lack of OS benefit in our study may be related to the short follow-up duration and small patient numbers. However, despite the small sample size, this study gives estimates of relapse rates in patients with *IDH* mutations undergoing alloHCT which can be informative in planning a larger observational studies or designing interventional studies post HCT. Additional multicenter studies are warranted in patients carrying *IDH* mutations to better understand the role of IDH mutations in patients with AML/MDS and improve leukemia free survival.

In our cohort of patients carrying IDH mutations, pre-alloHCT treatment with *IDH* mutation-directed therapy (n=6, 26%), resulted in MRD negative status in 50% of patients whereas the rest did not have MRD testing done on the pre-HCT marrow, thus their MRD status was unknown. More than half of patients who received *IDH* mutation-directed therapy (n=4, 66.7%) remained leukemia-free post alloHCT. However, given the small number of patients, it is hard to conclude if prior exposure to IDH inhibitors will influence relapse rates post alloHCT.

Lastly, in a phase I/II trial, patients with mutant-*IDH2* and advanced myeloid malignancies were treated with oral IDH2 inhibitor therapy (Enasidenib), and an overall response rate of 40.3% (20% CR) with median duration of response of 5.8 months was achieved.[38] Dinardo et al,[39] also published the results of a phase I dose escalation/expansion study, using IDH1 inhibitor, Ivosidenib, in patients with relapsed/refractory AML with IDH1 mutation. In this study, the overall response rate was 41.6% (95% CI: 32.9–50.8%) with CR rate of 21.6 %(95% CI: 14–7-29.8). Based on these data and our results, a prospective trial to evaluate Enasidenib for IDH2 mutated AML patients and Ivosidenib for IDH1 mutated patients as post-alloHCT maintenance is warranted.

CLINICAL PRACTICE POINTS

Based on published literature, the role of IDH mutations in patients with newly diagnosed AML is not clear. These patients are currently classified into the intermediate risk group, and allogeneic HCT is recommended for their treatment. However, data on the outcomes of

AML patients carrying IDH mutations, who subsequently undergo allogeneic HCT is scares. Our retrospective study for the first time has shown an increased risk of post allogeneic HCT relapse in AML patients carrying IDH mutations, indicating that these patients need to be followed closely post-transplant. This increased relapse rates was independent of the traditional risk factors for relapse such as intensity of conditioning regimen, poor risk cytogenetic markers, co-mutations and pre-HCT MRD status. FDA approval of IDH inhibitors in relapsed and refractory AML patients with IDH 1/2 mutations provides the possibility of using these agents for AML maintenance therapy and improving leukemia free survival.

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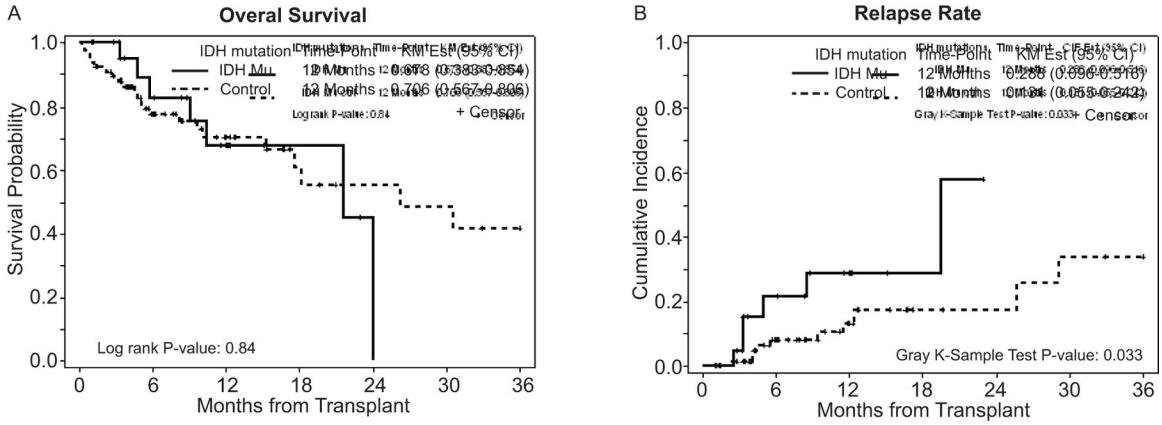

Figure 1.

a) Overall survival in patients carrying and not carrying IDH mutations and b) Relapse rate in patients carrying and not carrying IDH mutations.

Table 1.

Patient and transplant characteristics.

Variable	mIDH 1/2 (n=23)	Wt IDH (n=76)	Total (n=99)
Age at HCT			
Median Range	64.0 (36–73)	54.0 (18–71)	57.0 (18–73)
Sex			
Male	10(43.5%)	36(47.4%)	46(46.5%)
Female	13(56.5%)	40(52.6%)	53(53.5%)
Disease status at HCT			
CR-1	13(56.5%	34(44.7%)	47(47.5%)
1’st Relapse	2(8.7%)	6(7.9%)	8(8.1%)
CR-2	6(26.1%)	11(14.5%)	17(17.2%)
2”nd Relapse	-	1(1.3%)	1(1%)
≥3’rd CR	-	3(3.9%)	3(3%)
Induction Failure	2(8.7%)	21(27.6%)	23(23.3%)
HLA Match Degree			
HLA identical, Sibling	7(30.4%)	20(26.3%)	27(27.3%
HLA matched, Unrelated	4(17.4%)	5(6.6%)	9(9.1%)
HLA mismatched, Sibling	0	1(1.3%)	1(1%)
HLA mismatched, Unrelated	9(39.1%)	41(53.9%)	50(50.5%)
Haploidentical	3(13%)	9(11.8%)	12(12.1%)
Graft source			
Bone marrow	0(0%)	1(1.3%)	1(1%)
Cord blood	0(0%)	3(3.9%)	3(3%)
Peripheral blood stem cells	23(100%)	72((94.7%	95(96%)
CMV status			
Negative	1(4.3%)	4(5.3%)	5(5.1)
Positive	22(95.7%)	72((94.7%)	94(94.9)
Regimen			
RIC	18(78.2%)	50(65.7%)	68(68.6%)
MAC	5(21.7%)	26(34.2%)	31(31.3%)
GVHD prophylaxis			
Tacrolimus/sirolimus	18(78.2%)	53(69.7%)	71(71.7%)
Tacrolimus/Cytoxan	-	10(13.1%)	10 (10.1)
Tacrolimus/Cellcept	-	4(5.2%)	4 (4%)
Tacrolimus/MTX	1(4.3%)	5 (6.5%)	6(6%)
Other	4(17.3%	4 (5.2%)	8 (8%)

Table 2.

Multivariate Analysis

	Event/Total	1-Year Relapse (95% CI)	HR (95% CI)*	P-value*	HR (95% CI)†	P-value†
IDH1/2				0.033		0.046
Control	11/76	0.131 (0.055–0.242)	Reference		Reference	
Mutation	6/23	0.288 (0.096–0.516)	2.77 (1.04–7.32)		2.78 (1.02–7.60)	

*Based on Gray test in univariate analysis

†Based on Fine and Gray model adjusted for disease status in multivariable analysis

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