Impact of IDH1 and IDH2 mutational subgroups in AML patients after allogeneic stem cell transplantation

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Abstract

Background: The role of allogeneic hematopoietic cell transplantation (alloHCT) in acute myeloid leukemia (AML) with mutated IDH1/2 has not been defined. Therefore, we analyzed a large cohort of 3234 AML patients in first complete remission (CR1) undergoing alloHCT or conventional chemo-consolidation and investigated outcome in respect to IDH1/2 mutational subgroups (IDH1 R132C, R132H and IDH2 R140Q, R172K).

Methods: Genomic DNA was extracted from bone marrow or peripheral blood samples at diagnosis and analyzed for IDH mutations with denaturing high-performance liquid chromatography, Sanger sequencing and targeted myeloid panel next-generation sequencing, respectively. Statistical as-treated analyses were performed using R and standard statistical methods (Kruskal–Wallis test for continuous variables, Chi-square test for categorical variables, Cox regression for univariate and multivariable models), incorporating alloHCT as a time-dependent covariate.

Results: Among 3234 patients achieving CR1, 7.8% harbored IDH1 mutations (36% R132C and 47% R132H) and 10.9% carried IDH2 mutations (77% R140Q and 19% R172K). 852 patients underwent alloHCT in CR1. Within the alloHCT group, 6.2% had an IDH1 mutation (43.4% R132C and 41.4% R132H) and 10% were characterized by an IDH2 mutation (71.8% R140Q and 24.7% R172K). Variants IDH1 R132C and IDH2 R172K showed a significant benefit from
Background
Isocitrate dehydrogenase (IDH) gene mutations are among the most common genetic alterations in acute myeloid leukemia (AML), detected in 15–20% of patients with AML [1, 2]. They represent mutational alterations in early leukemogenesis [3]. Still, their prognostic and predictive relevance is not fully resolved and standard AML risk stratification does not yet include IDH1 or IDH2 mutations [4]. However, there is growing evidence that IDH mutations contribute both prognostic and predictive value [2, 5, 6]. There have been inconsistent results regarding outcome, including complete remission (CR) rate, relapse-free survival (RFS) and overall survival (OS) depending on IDH1 and IDH2 mutational status, respectively [2, 7–12]. For example, some reports attribute a favorable prognosis to IDH mutations [8, 13], whereas other reports indicate an adverse prognosis for patients with IDH mutations [2, 10, 14–16]. Furthermore, some data suggest the existence of IDH mutations have no impact on survival [11, 12]. Supposedly, this is based on different biologic features of certain subtypes of mutations and co-mutational patterns.

To date, two isoforms of IDH are known to be potentially mutated in AML encoded on chromosome 2 band q33 (IDH1) and chromosome 15 band q26 (IDH2), respectively [15, 17, 18]. IDH1 is localized in the cytoplasm and IDH2 is found in mitochondria [19]. Their physiologic role is the enzymatic involvement in the citrate metabolism (Krebs cycle) catalyzing decarboxylation of isocitrate to α-ketoglutarate (α-KG) in an NADP+ associated manner. IDH mutations induce the loss of this catalytic activity, leading to reduction of α-KG and to the production of the oncometabolite 2-hydroxylglutarate (2-HG) accumulating in leukemic cells [20, 21]. 2-HG potentially alters gene expression via DNA and histone hypermethylation and hereby blocks differentiation of hematopoietic progenitor cells [7, 22].

During the last decade, certain mutational subtypes including hotspot mutations affecting codon 132 of IDH1, as well as codon R140 and R172 of IDH2 were identified and have been associated with differential enzymatic potential, consequently suggesting these variants to contribute to disease heterogeneity as well as to contradictions in prognostic predictions [19, 23, 24].

From a therapeutic point of view, they represent attractive drugable targets in clinical routine, as IDH inhibitors (e.g., ivosidenib for IDH1 mutations and enasidenib for IDH2 mutations) have been introduced for patients with relapsed or refractory AML (r/r AML) and/or elderly/frail AML patients as frontline therapy harboring IDH mutations with promising results regarding response and survival [25–27]. Recent reports also demonstrated promising results with the combination of IDH inhibitors and hypomethylating agents as frontline therapy [28, 29]. Further, IDH inhibitors are investigated in prospective clinical phase I and II trials as maintenance therapy after allogeneic hematopoietic cell transplantation (alloHCT) and/or salvage strategies in case of relapse in the posttransplant setting (e.g., NCT03564821 and NCT04522895).

So far, the role of alloHCT for IDH mutated (IDHmut) AML patients is based on reports from studies with rather small patient numbers or from monocentric analyses [30, 31]. The aim of this study was to evaluate the predictive impact of defined IDH mutational subgroups on outcome of alloHCT in first complete remission (CR1) after intensive induction therapy in a well-defined, large multi-center cohort of IDHmut AML patients.

Patients and methods
Patients
For analysis, we studied a cohort that comprised a total of 3234 intensively treated AML patients under 70 years who either underwent alloHCT (n = 852) or chemotherapy only (n = 2382) in CR1. Only patients with sufficient material of bone marrow (BM) and/or peripheral blood (PB) samples available were included in this study. Patients were enrolled within the prospective SAL AML registry (NCT03188874) or one of the following clinical trials: AML96 [32], AML2003 [33], AMLCG1999 [34], AML60+ [35], AMLCG2008 [36], and SORAML [37] (Additional file 1: Table S1). Briefly, intensive chemotherapy regimens consisted of anthracyclines combined with cytarabine in standard dosing. Patients were not treated with IDH1- or IDH2-inhibitors. Treatment response and outcome measures were classified according to standard criteria [4, 38, 39]. All patients gave their written informed consent on analyses of data. The study
was approved by the respective ethics committees and conducted in accordance to the Declaration of Helsinki.

Molecular and cytogenetic analyses
Pre-treatment BM or PB samples were used for genomic DNA isolation. After DNA extraction, samples were screened for \textit{IDH1} and \textit{IDH2} mutations. Samples collected until 2016 were analyzed in a batched fashion, from 2016 onwards, samples were analyzed in real time. AML patients treated within trials of the SAL registry were screened by denaturing high-performance liquid chromatography (DHPLC) as previously described [40]. In case of aberrant DHPLC-chromatograms, samples were analyzed either by Sanger sequencing or by sensitive ultradep next-generation sequencing (NGS) [41]. Another NGS-based myeloid panel approach (TruSight Myeloid Panel, Illumina, San Diego, CA, USA) focusing on genes frequently mutated in hematopoietic myeloid entities was used for a subset of SAL registry AML patients [42]. Concordant results were obtained in all SAL patient samples when samples were analyzed with both methods. Concordance was analyzed based on a set of 50 samples representing all mutational variants. A custom targeted NGS assay was deployed for patients enrolled in AML-CG trials [43]. Further mutational profiles (e.g., \textit{FLT3} and \textit{NPM1} mutations) were analyzed as described previously [44, 45]. The lower limit of detection was determined with 0.1% for ultradep NGS and 1–5% for DHPLC and panel NGS.

Statistical analyses
Statistical as-treated analyses on the impact of different \textit{IDH1} or \textit{IDH2} mutational subclasses were carried out using the free statistical computing environment R (Version 4.0.3). Continuous variables were compared using the Kruskal–Wallis test, while the Chi-square test was used to compare categorical variables between mutational groups. OS is reported for the whole cohort from study entry until date of death and was censored on date of last follow-up, if no death occurred; RFS is reported from date of CR1 until disease relapse or death and was censored on date of last follow-up. CR and survival rates were evaluated according to the current standard ELN criteria [4]. Effects of alloHCT were estimated using Cox regression models with alloHCT modeled as time-dependent covariate. Simon–Makuch plots were applied to visualize survival according to transplant status. To reduce bias toward benefit of alloHCT due to very early deaths of patients, landmarks of three months for OS (estimated time including two courses of induction therapy and scheduling alloHCT) and one month for RFS (anticipated time from CR1 after induction therapy until alloHCT) were implemented. Due to the time-dependent modeling of alloHCT, all patients start in the non-alloHCT group. Therefore, number at risk in the non-alloHCT groups at start of observational period includes also patients transplanted later. Number at risk of the alloHCT groups at time 0 reflects the number of patients at risk that changed from the non-alloHCT group to the alloHCT group until the first event or censoring was observed in that group, but not earlier than the landmark. Cox regression was also applied to identify independent prognostic variables for survival and to estimate univariate and adjusted hazard ratios (HR). Multivariable analysis included alloHCT in CR1, age at diagnosis, ELN risk group, secondary AML, therapy-related AML and ECOG performance status at diagnosis. The significance level was set at 0.05. For interaction analysis, we used multivariate Cox proportional hazard regression to analyze survival with respect to several variables simultaneously and to provide the hazard ratio for each factor. Furthermore, we performed multivariate Cox regression analysis to study the effect of the interaction of alloHCT and the respective \textit{IDH} submutational groups on outcome.

Results
Patients' characteristics
The study cohort consisted of 3234 patients with AML, whereof a total of 852 patients received alloHCT in CR1 after intense induction therapy. Patients carrying an \textit{IDH}\textsuperscript{mut} were significantly older than patients carrying the wildtype allele (\textit{IDH}\textsuperscript{WT}) \((p < 0.001)\). Compared to \textit{IDH}\textsuperscript{WT} and \textit{IDH}\textsuperscript{mut}, patients with \textit{IDH2}\textsuperscript{mut} were characterized by a significantly lower serum LDH \((p = 0.012)\), whereas \textit{IDH}1\textsuperscript{mut} patients showed a median higher count of peripheral blasts compared to \textit{IDH}\textsuperscript{WT} and \textit{IDH2}\textsuperscript{mut} patients \((p < 0.001)\) and bone marrow blasts \((p < 0.001)\) at diagnosis, respectively. Regarding other laboratory findings, \textit{IDH1}\textsuperscript{mut} and \textit{IDH2}\textsuperscript{mut} patients had comparable platelet counts at diagnosis, which were significantly higher than those found in \textit{IDH}\textsuperscript{WT} patients \((p < 0.001)\). The \textit{IDH}\textsuperscript{mut} cohort harbored a significantly lower rate of complex karyotypes \((p < 0.001)\), with \textit{IDH1}\textsuperscript{mut} patients being associated with the lowest rate. Also, patients harboring \textit{IDH1} mutations were more likely to be associated with the ELN2017 favorable-risk and less likely associated with the ELN 2017 adverse-risk category \((p < 0.001)\), while patients without \textit{IDH} mutations and \textit{IDH2}\textsuperscript{mut} patients showed similar distributions. No differences in gender, AML subtype (de novo AML, secondary AML, therapy-related AML), white blood count or hemoglobin were detected between \textit{IDH}\textsuperscript{mut} and \textit{IDH}\textsuperscript{WT} patients. An overview of relevant results is depicted in Table 1.
| AML patients analyzed for IDH mutations | IDH$^{\text{WT}}$ | IDH1$^{\text{mut}}$ | IDH2$^{\text{mut}}$ |
|-----------------------------------------|-------------|----------------|----------------|
| n = 3234                                | n = 2638    | n = 253        | n = 353        |
| Age (years), median (IQR)               | 51 (40–59) | 54 (44–62)     | 55 (47–62)     | <.001          |
| Sex, n/N (%)                            |             |                |                | .845           |
| Female                                 | 1312/2638 (49.7) | 130/253 (51.4) | 179/353 (50.7) |
| Male                                   | 1326/2638 (50.3) | 123/253 (48.6) | 174/353 (49.3) |
| Disease status, n/N (%)                 |             |                |                | .082           |
| De novo                                | 2238/2622 (85.4) | 228/252 (90.5) | 304/353 (86.1) |
| sAML                                   | 255/2622 (9.7) | 21/252 (8.3)   | 34/353 (9.6)   |
| t-AML                                  | 129/2622 (4.9) | 3/252 (1.2)    | 15/353 (4.2)   |
| Hb (mmol/l), median (IQR)              | 5.71 (4.9–6.7) | 5.65 (5.1–6.6) | 5.84 (5–6.8)   | .215           |
| Platelets (Gpt/L), median (IQR)        | 51 (28–95)   | 71 (36–126)    | 72 (41–147)    | <.001          |
| WBC (Gpt/L), median (IQR)              | 14.98 (3.9–49.1) | 12.51 (2.6–44.2) | 12.6 (2.8–45.3) | .824 |
| Bone marrow blasts (%), median (IQR)   | 63 (40–80)   | 73 (54–88)     | 70 (44–83)     | <.001          |
| Peripheral blasts (%), median (IQR)    | 27 (7–63)    | 50 (15–81)     | 36 (9–70)      | <.001          |
| LDH (U/L), median (IQR)                | 430 (273–760.8) | 425.4 (261–762) | 368 (236–624)  | .012           |
| Complex karyotype, n/N (%)             | 258/2532 (10.2) | 4/235 (1.7)    | 14/336 (4.2)   | <.001          |
| ELN risk 2017, n/N (%)                  |             |                |                | <.001          |
| Favorable                               | 998/2462 (40.5) | 117/227 (51.5) | 132/332 (39.8) |
| Intermediate                            | 886/2462 (36) | 89/227 (39.2)  | 132/332 (39.8) |
| Adverse                                | 578/2462 (23.5) | 21/227 (9.3)   | 68/332 (20.5)  |
| NPM1 mut, n/N (%)                       | 840/2621 (32) | 149/252 (59.1) | 160 (45.3)     | <.001          |
| FLT3-ITD mut, n/N (%)                   | 629/2630 (23.9) | 55/252 (21.8)  | 82/353 (23.2)  | .741           |
| CEBPA mut, n/N (%)                      | 220/2595 (8.5) | 3/253 (1.2)    | 18/351 (5.2)   | <.001          |
| IDH1 mut, n/N (%)                       | 0/2638 (0)    | 253/253 (100)  | 10/353 (2.8)   |
| R132C                                  | –           | 92/253 (36.4)  | 1/10 (10)      |
| R132G                                  | –           | 17/253 (6.7)   | 1/10 (10)      |
| R132H                                  | –           | 118/253 (46.6) | 8/10 (80)      |
| R132L                                  | –           | 12/253 (4.7)   | –              |
| R132S                                  | –           | 14/253 (5.5)   | –              |
| IDH2 mut, n/N (%)                       | 0/2638 (0)   | 10/253 (4)     | 353/353 (100)  |
| R140G                                  | –           | –              | 1/351 (0.3)    |
| R140L                                  | –           | –              | 6/351 (1.7)    |
| R140Q                                  | –           | 10/10 (100)    | 269/351 (76.6) |
| R140W                                  | –           | –              | 4/351 (1.1)    |
| R172K                                  | –           | –              | 68/351 (19.4)  |
| R172S                                  | –           | –              | 1/351 (0.3)    |
| V161L                                  | –           | –              | 1/351 (0.3)    |
| WT                                     | –           | –              | 1/351 (0.3)    |
| IDH1 and IDH2 mut, n/N (%)              | 0/2638 (0)   | 10/253 (4)     | 10/353 (3)     |
| IDH1 VAF (%), median (IQR)              | –           | 39 (26.2–43.2) | 38.1 (31.7–43.6) | .252 |
| alloHCT in CR1, n/N (%)                 | 714/2638 (27.1) | 53/253 (20.9) | 85/353 (24.1)  | .066 |

p-Values indicating parameters that show significant differences are highlighted in bold.
IDH mutations and mutational subgroups

In our cohort of AML patients undergoing either alloHCT or chemo-consolidation in CR1, 18.4% ($n = 596$) had an IDH$^{\text{mut}}$ with a median variant allele frequency (VAF) of 39% (IQR 26.2–43.2) for IDH1 and 38.1% (IQR 31.7–43.6) for IDH2. A total of 7.8% ($n = 253$) had mutated IDH1, 10.9% ($n = 353$) had mutated IDH2, while 0.3% ($n = 10$) had mutations in both IDH1 and IDH2. The most common IDH1 mutational subgroups were R132C (36%) and R132H (47%), while R132G, R132L and R132S were present in only few patients (7%, 5% and 6%, respectively). The two most frequent IDH2 mutations were R140Q (77%) and R172K (19%) with only a minority of patients (4%) carrying R140G, R140L, R140W, R172S, V161L or WT subtypes.

The patients’ distributions were as follows (Fig. 1): Among the 852 patients undergoing alloHCT in CR1, 16.2% ($n = 138$) harbored an IDH$^{\text{mut}}$. Here, a similar distribution of IDH$^{\text{mut}}$ could be seen: 6.2% ($n = 53$) harbored an IDH1 mutation, and again the two major subgroups were R132C (43.4%) and R132H (41.5%) with small numbers of patients mutated in R132G, R132L and R132S (1.9%, 9.4% and 3.8%, respectively). IDH2 mutations were found in 10% ($n = 85$) of alloHCT patients, also with similar distributions of IDH2 subgroups R140Q (71.8%) and R172K (24.7%), with a minority of patients carrying R140L (2.4%) and R140W (1.2%). No patients of the alloHCT group had mutations in both IDH1 and IDH2.

The non-alloHCT consolidation group included 19.2% ($n = 458$) IDH$^{\text{mut}}$ patients. Among these patients, 8.4% ($n = 200$) and 11.3% ($n = 268$) carried IDH1 and IDH2 mutations, respectively. Only a minority were characterized by mutations in both IDH1 and IDH2 (0.4%). In line with the data of the alloHCT group, the two major IDH1 subgroups in the non-alloHCT cohort were R132C (34.5%) and R132H (48%) and few patients harbored R132G, R132L and R132S (8%, 3.5% and 6%, respectively). Comparing the alloHCT and the non-alloHCT group regarding IDH mutational distribution, the alloHCT cohort was characterized by a significant lower percentage of IDH1 mutations ($p = 0.042$), while there was no statistically differential distribution of IDH2 mutations between these two groups ($p = 0.306$).

Co-mutational characteristics

Regarding co-mutational aspects, the majority of the study cohort had at least two different mutations, with only 3.5% of the IDH$^{\text{WT}}$ patients, 0.9% of patients carrying an IDH$^{\text{mut}}$ and none of the patients with an IDH$^{\text{mut}}$ without any co-mutation at all ($p = 0.012$). On the other hand, significant results could be found in the following co-mutational pairs: a significantly higher rate of concomitant NPM1 mutations was seen in IDH$^{\text{mut}}$ patients, with IDH1$^{\text{mut}}$ patients being characterized by the highest rate of co-occurring NPM1 mutations (IDH1$^{\text{mut}}$ 59.1% vs. IDH2$^{\text{mut}}$ 45.3% vs. IDH$^{\text{WT}}$ 32%, $p < 0.001$). In contrast, the FLT3-ITD co-mutational frequency was not significantly different between IDH$^{\text{WT}}$ and IDH$^{\text{mut}}$ patients ($p = 0.741$). Despite small number of events, other mutations affecting signaling still showed significant lower rates in the presence of IDH$^{\text{mut}}$, including mutations in NRAS (IDH1$^{\text{mut}}$ 6.1% vs. IDH2$^{\text{mut}}$ 5.6% vs. IDH$^{\text{WT}}$ 12.3%, $p = 0.006$). Biallelic mutations in CEBPA were found with a significantly lower frequency in IDH$^{\text{mut}}$ patients (IDH$^{\text{mut}}$ 0.5% vs. IDH2$^{\text{mut}}$ 1.1% vs. IDH$^{\text{WT}}$ 6.4%, $p < 0.001$). Further, we detected possible co-mutational patterns with tumor suppressors like WT1 (IDH1$^{\text{mut}}$ 1.7% vs. IDH2$^{\text{mut}}$ 2.2% vs. IDH$^{\text{WT}}$ 7%, $p = 0.006$). Epigenetic modifiers

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**Fig. 1** Consort diagram of patients’ distributions. Consort diagram of the study cohorts’ distribution according to the type of consolidation strategy (alloHCT vs. chemo-consolidation), IDH mutational status and respective submutational groups.
like mutations in DNMT3A and TET2 were also significantly differentially mutated according to IDHmut status (IDH1mut 26.1% vs. IDH2mut 32.8% vs. IDHWT 17.4%, p < 0.001 and IDH1mut 3.5% vs. IDH2mut 7.2% vs. IDHWT 12.4%, p = 0.003, respectively). Also, mutations in transcription factor GATA2 and cohesion complex STAG2 significantly differed between the IDHmut and IDHWT population (IDH1mut 0.9% vs. IDH2mut 2.2% vs. IDHWT 6.5%, p = 0.005 and IDH1mut 4.3% vs. IDH2mut 6.7% vs. IDHWT 2.9%, p = 0.029, respectively). An overview of co-mutational distributions is given in Fig. 2 and Table 2.

**Impact of alloHCT on survival according to IDH mutational subgroups**

Regarding the whole cohort undergoing alloHCT or conventional chemo-consolidation in CR1, a significant survival benefit for alloHCT in both IDHWT and IDHmut group was revealed (Fig. 3). This positive effect for alloHCT is valid for OS (HR = 0.8, 95% CI 0.69–0.96, p = 0.012; Fig. 3a), as well as RFS (HR = 0.6, 95% CI 0.54–0.73, p < 0.001; Fig. 3b). Median OS was 49 months (IDHWT non-alloHCT) versus 46 months (IDHmut non-alloHCT) versus 110 months (IDHWT alloHCT), while the IDHmut cohort receiving alloHCT did not reach median OS. Median RFS was 17 months (IDHWT non-alloHCT) versus 17 months (IDHmut non-alloHCT) vs. 74 months (IDHWT alloHCT), while median RFS was also not reached in the IDHmut cohort receiving alloHCT. Interestingly, when undergoing alloHCT, a trend toward better OS and RFS could be detected in the IDHmut group compared with the IDHWT group. Vice versa, a negative trend for survival was revealed in IDHmut patients compared with IDHWT patients when receiving chemo-consolidation only (Fig. 3). Overall, there was no statistical difference in OS of either consolidation strategy for patients carrying an IDH1 mutation (5-year OS 40% [non-alloHCT] vs. 47% [alloHCT], p = 0.27; Fig. 4a), alloHCT led to a better RFS in univariate analysis (5-year RFS 30% [non-alloHCT] vs. 51%, p = 0.009; Fig. 4b). In contrast, IDH2mut patients gained an advantage in OS.

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**Fig. 2** Heatmap of frequent co-mutations according to IDH mutation status. Heatmap grouped for epigenetic, signaling, transcription, cohesion and splicing pathways of AML patients achieving CR1 with IDH wildtype (IDH-wt) or mutated IDH (IDH-mut). Only patients from the SAL registry with a full dataset of myeloid panel sequencing were included.
Table 2  Overview of the co-mutational distributions

| Mutations | IDH1mut | IDH2mut | p-Value |
|-----------|---------|---------|---------|
| ASXL1 n/N (%) | 46/1187 (3.9) | 5/115 (4.3) | 14/180 (7.8) | 0.059 |
| BCOR n/N (%) | 30/1187 (2.5) | 3/115 (2.6) | 8/180 (4.4) | 0.342 |
| BCR/ABL1 n/N (%) | 26/1187 (2.2) | 3/115 (2.6) | 7/180 (3.9) | 0.383 |
| CBL n/N (%) | 14/1187 (1.2) | 2/115 (1.7) | 3/180 (1.7) | 0.779 |
| CEBPA biallelic (%) | 136/2129 (6.4) | 1/195 (0.5) | 3/274 (1.1) | <.001 |
| CSF3R n/N (%) | 13/1187 (1.1) | 2/115 (1.7) | 2/180 (1.1) | 0.825 |
| CLX1 n/N (%) | 22/1187 (1.9) | 2/115 (1.7) | 2/180 (1.1) | 0.779 |
| DNMT3A n/N (%) | 207/1187 (17.4) | 30/115 (26.1) | 59/180 (32.8) | <.001 |
| EZH2 n/N (%) | 29/1187 (2.4) | 5/115 (4.3) | 5/180 (2.8) | 0.472 |
| GATA2 n/N (%) | 77/1187 (6.5) | 1/115 (0.9) | 4/180 (2.2) | 0.005 |
| IKZF1 n/N (%) | 19/1187 (1.6) | 2/115 (1.7) | 1/180 (0.6) | 0.543 |
| JAK2 n/N (%) | 10/1187 (0.8) | 0/115 (0) | 2/180 (1.1) | 0.56 |
| KDM6A n/N (%) | 5/1187 (0.4) | 2/115 (1.7) | 0/180 (0) | 0.089 |
| KIT n/N (%) | 54/1187 (4.5) | 3/115 (2.6) | 2/180 (1.1) | 0.66 |
| KRS n/N (%) | 48/1187 (4) | 1/115 (0.9) | 3/180 (1.7) | 0.075 |
| NRAS n/N (%) | 146/1187 (12.3) | 7/115 (6.1) | 10/180 (5.6) | 0.006 |
| PHF6 n/N (%) | 23/1187 (1.9) | 1/115 (0.9) | 2/180 (1.1) | 0.553 |
| PTEN n/N (%) | 53/1187 (4.5) | 6/115 (5.2) | 6/180 (3.3) | 0.711 |
| RAD21 n/N (%) | 37/1187 (3.1) | 0/115 (0) | 4/180 (2.2) | 0.134 |
| RUNX1 n/N (%) | 61/1187 (5.1) | 4/115 (3.5) | 10/180 (5.6) | 0.702 |
| SMC1A n/N (%) | 14/1187 (1.2) | 1/115 (0.9) | 2/180 (0) | 0.955 |
| SMC3 n/N (%) | 8/1187 (0.7) | 2/115 (1.7) | 1/180 (0.6) | 0.425 |
| STAG2 n/N (%) | 34/1187 (2.9) | 5/115 (4.3) | 12/180 (6.7) | 0.029 |
| TET2 n/N (%) | 147/1187 (12.4) | 4/115 (3.5) | 13/180 (7.2) | 0.003 |
| TSPAN11 n/N (%) | 36/1187 (3) | 1/115 (0.9) | 1/180 (0.6) | 0.072 |
| WT1 n/N (%) | 83/1187 (7) | 2/115 (1.7) | 4/180 (2.2) | 0.006 |
| ZRSR2 n/N (%) | 13/1187 (1.1) | 0/115 (0) | 3/180 (1.7) | 0.399 |
| No co-mutation n/N (%) | 42/1187 (3.5) | 1/115 (0.9) | 0/180 (0) | 0.012 |

p-Values indicating parameters that show significant differences are highlighted in bold.

when undergoing alloHCT in univariate analysis (5-year OS 46% [non-alloHCT] vs. 61% [alloHCT], p = 0.026; Fig. 4a) and RFS was significantly better for alloHCT in multivariable analysis (5-year RFS 30% [non-alloHCT] vs. 60% [alloHCT]; HR = 0.49, 95% CI 0.3–0.8, p = 0.004; Fig. 4b).

More importantly, the relevance of mutational subtypes in IDH1 and IDH2 on survival could be delineated in our analysis (Fig. 5). Patients with IDH1 R132C had a higher OS when undergoing alloHCT in univariate analysis (5-year OS 40% [non-alloHCT] vs. 73% [alloHCT], p = 0.017; Fig. 5a), which was even more pronounced for RFS in multivariable analysis (5-year RFS 27% [non-alloHCT] vs. 55% [alloHCT]; HR = 0.42, 95% CI 0.17–1, p = 0.048; Fig. 5b). However, IDH1 R132H was not associated with superior survival (Fig. 5a,b). AlloHCT patients carrying IDH2 variant R140 mutations showed no significant difference in OS regarding the respective consolidation strategy (Fig. 5c), but significantly higher RFS compared with the chemo-consolidation group in multivariable analysis (5-year RFS 31% [non-alloHCT] vs. 58% [alloHCT]; HR = 0.4, 95% CI 0.23–0.7; p = 0.002; Fig. 5d). IDH2 variant R172 was associated with increased OS and RFS when undergoing alloHCT in univariate analysis (5-year OS 43% [non-alloHCT] vs. 68% [alloHCT], p = 0.049; Fig. 5c and 5-year RFS 25% [non-alloHCT] vs. 64% [alloHCT]; p = 0.009, respectively; Fig. 5d).

Multivariable analysis

Further multivariable modeling of established factors affecting survival of AML patients (Additional file 1: Fig. S1) revealed significant results regarding age (HR = 1.03, p < 0.001), favorable (HR = 0.6, p < 0.001) and adverse (HR = 1.7, p < 0.001) risk category according to ELN risk stratification and ECOG performance status 0–1 (HR = 0.7, p < 0.001) on OS when analyzing the whole cohort. RFS was also significantly influenced by age (HR = 1.02, p < 0.001), ELN favorable (HR = 0.6,
p < 0.001) and adverse (HR = 1.5, p < 0.001) and ECOG performance status 0–1 (HR = 0.8, p = 0.001). Including IDH submutational groups into multivariable analysis, IDH2 R172 was an independent predictor for better OS (HR = 0.5, p = 0.02), which was even more pronounced for RFS (HR = 0.4, p < 0.001). IDH1 mutational subclasses were associated with a trend toward better OS (R132C, HR = 0.52, p = 0.15; R132H, HR = 0.64, p = 0.28) and IDH2 R172 (OS, HR = 0.98, p = 0.71). RFS, HR = 1.68, p = 0.008), and IDH2 R140Q (OS, HR = 1.12, p = 0.23; RFS, HR = 1.02, p < 0.001) and other IDH mutational subgroups (RFS, HR = 1.74, p = 0.043). However, the interaction term of chemo-consolidation and IDH2 R140Q demonstrated a trend toward improved outcome (OS, HR = 0.65, p = 0.139; RFS, HR = 0.74, p = 0.245).

Interaction analysis
For studying the effect of the interaction of alloHCT and the respective IDH submutational groups on outcome, we performed interaction analysis with the interaction of alloHCT and IDH WT AML patients as the reference term (Fig. 6a for OS, Fig. 6b for RFS). Interaction analysis demonstrated a trend toward improved outcomes for the interaction of alloHCT and IDH1 R132C (OS, HR = 0.52, p = 0.15; RFS, HR = 0.64, p = 0.28) and IDH2 R172 (OS, HR = 0.98, p = 0.71) predicted similar outcomes like the IDH WT cohort that was allografted. Other mutational IDH subgroups in the alloHCT cohort were almost at double risk for decreased outcome (OS, HR = 1.99, p = 0.18; RFS, HR = 2.11, p = 0.14). In contrast, the effect of the interaction of IDH WT and IDH mutational subgroups and chemo-consolidation only predicted worse outcome, which was mostly pronounced in the terms of IDH WT (OS, HR = 1.25, p = 0.006; RFS, HR = 1.61, p < 0.001), IDH1 R132H (RFS, HR = 1.68, p = 0.008), IDH2 R140Q (OS, HR = 1.43, p = 0.23; RFS, HR = 2.02, p < 0.001) and other IDH mutational subgroups (RFS, HR = 1.74, p = 0.043). However, the interaction term of chemo-consolidation and IDH2 R140Q demonstrated a trend toward improved outcome (OS, HR = 0.65, p = 0.139; RFS, HR = 0.74, p = 0.245).

Discussion
Here, we report that the unfavorable prognostic impact of specific IDH mutational subgroups on survival can be mitigated by alloHCT as frontline consolidation strategy in a well-defined AML study cohort. To the best of our knowledge, this is the largest multicenter analysis to determine the prognostic effect of IDH mutations in the course of alloHCT, comprising a cohort of 852 AML patients transplanted in CR1.
Considering the significant biological and molecular heterogeneity of AML, the ideal consolidation therapy is one of the main foci of scientific and clinical interest. Previous studies generated partly controversial results, either associating IDH<sup>mut</sup> with better outcome [8, 13] and studies reporting a negative impact on outcome [2, 14, 16]. More recently, it was shown that IDH mutational subgroups associated with different biological features have different prognostic impact, suggesting to provide an explanation for inconsistent results concerning prognosis and survival so far [6, 23, 46]. To add a next level of complexity, different mutational IDH variants are associated with differential co-mutational patterns or karyotypes, incorporating prognostic value and even potentially defining distinct genomic categories in AML [10, 15, 23, 46–49]. As recently shown, considering differential co-mutational rates of epigenetic modifiers like DNMT3A and TET2 in combination with the hypermethylating ability of IDH<sup>mut</sup>, some suppose IDH<sup>mut</sup> to be predictive of susceptibility to hypomethylating agents [50, 51]. These results indicate the need for more clarification in the clonal composition, hierarchy and development in the concept of disease biology of IDH<sup>mut</sup> AML, as latest data suggest [52].

In accordance with previous reports, nearly 20% of the patients analyzed were characterized by IDH<sup>mut</sup>. Similar

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**Fig. 4** Overall survival according to IDH, IDH1 and IDH2 mutational status and allogeneic hematopoietic cell transplantation in CR1. Simon–Makuch plots for a overall survival and b relapse-free survival of AML patients with mutated (mut) IDH, IDH1 and IDH2 treated with allogeneic hematopoietic cell transplantation (blue) or conventional consolidation (red), respectively; p-values were determined with Cox model with time-dependent modeling of alloHCT; time in months; ns = not significant

**Fig. 5** Overall survival and relapse-free survival according to IDH1 and IDH2 mutational subgroups and allogeneic hematopoietic cell transplantation in CR1. Simon–Makuch plots for a and c overall survival and b and d relapse-free survival of AML patients with mutated IDH1 R132C, IDH1 R132H, IDH2 R140 and IDH2 R172 mutational subgroups treated with allogeneic hematopoietic cell transplantation (blue) or conventional consolidation (red), respectively; p-values were determined with Cox model with time-dependent modeling of alloHCT; time in months; ns = not significant
Fig. 5 (See legend on previous page.)
to our recent analysis \[6\], a significantly higher rate of NPM1/IDH co-mutations was seen. In the presence of IDH\textsuperscript{mut}, our present analysis also revealed significant differential co-mutational distributions compared with IDH\textsuperscript{WT} patients. These patterns, as well as their prognostic impact, have to be considered when analyzing outcomes in AML patients, as our study did not include these co-mutational aspects. Also in line with previous data, our IDH\textsuperscript{mut} cohort was characterized by significantly older age, as well as lower LDH concentration (especially for IDH\textsubscript{2} mut patients) and a higher count of peripheral blasts (pronounced in IDH\textsubscript{1} mut patients) and bone marrow blasts \[48\].

Most importantly, our present data is demonstrating a beneficial effect of alloHCT for IDH\textsuperscript{mut} AML patients, which is in line with recently published data of Duchmann et al. who demonstrated superior OS for IDH\textsuperscript{mut} AML patients treated with alloHCT in CR1 \[46\], but also contrary to previous studies associating IDH mutations with higher rates of relapse after alloHCT \[30\]. IDH\textsuperscript{mut} patients showed a trend toward prolonged OS and improved RFS compared with their wildtype counterparts when undergoing alloHCT and shorter OS and RFS compared with IDH\textsuperscript{WT} patients when receiving chemo-consolidation after CR1. Focusing on IDH\textsubscript{1} mutations, R132C was characterized by an improved OS and RFS if transplanted in CR1, an effect which could not be shown for R132H. This improvement in survival was shown previously only regarding OS and without discriminating between R132 variants \[46\]. Whether the difference in prognosis implicated by R132H is due to increased 2-HG levels causing blockage of differentiation in hematopoiesis needs further investigation \[53\]. Interestingly, R132C patients had the worst 5-year OS compared with the other three analyzed subtypes when consolidated with chemotherapy after CR1 in our study, but the highest 5-year OS of all IDH subgroups when treated with alloHCT in CR1, begging the question of differential susceptibility to allografting among IDH mutational subgroups. Furthermore, when incorporating our recently published data including co-mutational patterns of IDH\textsuperscript{mut} patients into our current analysis, we did not see a clear correlation between improved OS and a high frequency of NPM1 co-mutations, as IDH\textsubscript{1} R132C was the subgroup characterized by the lowest rate of co-occurring NPM1 mutations among all IDH\textsuperscript{mut} patients (IDH\textsubscript{1} R132C 24.2% vs. IDH\textsubscript{1} R132H 71% vs. IDH\textsubscript{1} other 64.2%) and was also less likely to harbor NPM1 mutations compared to IDH\textsuperscript{WT} patients (28.4%) \[6\]. The same trend is seen for FLT3-ITD, another mutation known to benefit from alloHCT, with IDH\textsubscript{1} R132C characterized by the lowest rate of co-occuring FLT3-ITD mutations \[6\]. On the other hand, IDH\textsubscript{1} R132H, which is associated with the highest rate of co-occuring NPM1 mutations (71% of patients) according to our recently published data, demonstrates the worst 5-year OS when undergoing transplantation. These retrospective data suggest that IDH\textsubscript{1} R132C could be a clear profiteer from alloHCT, as our recent analysis also revealed a trend toward reduced OS in patients carrying IDH\textsubscript{1} variant R132C after intensive

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**Fig. 6** Multivariable Cox model with single interaction terms. Single interaction terms for a overall survival and b relapse-free survival for IDH submutational groups IDH\textsubscript{1} R132C, IDH\textsubscript{1} R132H, IDH\textsubscript{2} R140Q and IDH\textsubscript{2} R172K, other IDH mutational subgroups (other) or IDH wildtype (wt) with either allogeneic hematopoietic cell transplantation (alloHCT) or chemo-consolidation (noHCT); p-values and hazard ratios were determined with Cox model.
induction chemotherapy, and that there could be a beneficial aspect of alloHCT alone independent of NPM1 or FLT3-ITD mutation status, providing a chance to overcome the worse prognosis for patients lacking “favorable” mutations like NPM1. However, low patient numbers in these subgroups of our analysis need to be taken into account and further validation is needed.

Patients with IDH2 subtype R140 had no differential OS probability, but significantly prolonged RFS after alloHCT in CR1. In contrast, IDH2 R172 was characterized by significant higher OS, as well as higher RFS in the alloHCT cohort. These data suggest that allografting AML patients with an IDH2 R172 mutation as a consolidation strategy is a considerable option for these patients. Recently, Linch et al. also reported improved survival of AML patients carrying IDH2 R172 variant compared with a historical IDH2 R172 cohort presenting with poor prognosis, relating increased use of alloHCT as consolidation after CR1 with longer OS in the later cohort, as induction strategy was almost unchanged and patients of the later cohort were even significantly older [54]. Additionally, high levels of 2-HG as an oncometabolite and prognostic indicator are paralleled by unfavorable outcome and R172 has been shown to induce higher levels of 2-HG than R140 [24, 55–57]. However, our present data reveal an independent beneficial prognostic impact on survival of IDH2 R172. Again, although our IDH2 cohort was bigger and provided more statistical power, small patient numbers and underlying co-mutational patterns have to be considered when interpreting these data, although IDH2 R172 seems to define a distinct genetic AML subgroup, being mutually exclusive from class-defining genetic aberrations like NPM1 mutations as reported previously [6, 23, 49]. Duchmann and colleagues recently attributed co-occurring NPM1 mutations in IDH1 and IDH2 R140-mutated patients as the main prognostic component for improved survival [46]. However, these results were not analyzed in patients undergoing alloHCT or only in a small transplant cohort, respectively. In our non-alloHCT cohort, we could evaluate corresponding results when incorporating our recent results on IDH mutations and co-mutations [6]. Briefly, IDH subtypes with the highest 5-year OS in our present analysis (e.g., IDH1 R132H with 51% and IDH2 R140 with 46%) were also the subgroups with the highest frequencies of co-occurring NPM1 mutations (IDH1 R132H with 71% and IDH2 R140 with 49% of patients carrying additional NPM1 mutations). Along with these results, the IDH subgroup with a lower rate NPM1 mutation (IDH1 R132C with 24%) had the worst 5-year OS in our non-alloHCT cohort (40%). Again, IDH2 R172 was characterized by improved prognosis (5-year OS of 68%) independent of NPM1 mutations (with 2% of patients carrying NPM1) [6]. Hence, our results are in line with the data Duchmann et al. with an implied association that seems to arise between improved survival and NPM1 mutation status.

In summary, a better survival for AML patients with mutated IDH undergoing alloHCT in CR1 could be illustrated, with modest to statistically significant differences depending on the underlying IDH1/2 mutational variant. The improved prognostic effect of alloHCT was mostly pronounced in the mutational subgroups IDH1 R132C and IDH2 R172. However, limitations of this retrospective analysis include the lack of information about donor availability, patients’ performance status after induction therapy and small patient numbers for subgroup analysis. Still, the compiled results highlight the urgent need for increased knowledge about disease biology and the relevance of prognostic and predictive markers in order to apply individually adjusted treatment decisions and optimized consolidation strategies in AML. Ongoing studies are currently investigating the implementation of IDH inhibitors in the frontline setting of induction therapy (NCT03839771 and NCT04493164), which will add valuable data for the re-evaluation of the role of alloHCT in IDHmut patients when pre-treated with IDH inhibitors during induction, consolidation or as a maintenance therapy after alloHCT.

**Conclusion**

On the basis of our results, it is arguable that defined IDH mutational subgroups introduce predictive and prognostic potential in different therapeutic settings. Furthermore, the differential responsiveness and “alloreactivity” of single IDH subclones to alloHCT in CR1 should initiate further prospective investigations to validate these findings, especially in respect of co-mutational patterns influencing the predictive value of IDH mutations, offering the chance to add information for refined AML risk classifications to improve survival for AML patients.

**Abbreviations**

2-HG: 2-Hydroxyglutarate; α-KG: α-Ketoglutarate; alloHCT: Allogeneic hematopoietic cell transplantation; AML: Acute myeloid leukemia; AML-CG: AML-Cooperative Group; BM: Bone marrow; CEBPA: CCAAT/enhancer-binding protein alpha; CI: Confidence interval; CR1: First complete remission; DHPLC: Denaturing high-performance liquid chromatography; DNMT3A: DNA (cytosine-5)-methyltransferase 3A; ECOG: Eastern Cooperative Oncology Group; ELN: European Leukemia Net; Fig.: Figure; FLT3: Fms-like tyrosine kinase 3; GATA2: GATA-binding factor 2; HR: Hazard ratio; IDH: Isocitrateglutarate dehydrogenase; IDHmut: IDH Mutated; IDHWT: IDH Wildtype; LDH: Lactate dehydrogenase; NCT: National clinical trial; NGS: Next-generation sequencing; NPM1: Nucleophosmin 1; NRAS: Neuroblastoma RAS; OS: Overall survival; PB: Peripheral blood; RFS: Relapse-free survival; r/r: Relapsed/refractory; SAL: Study Alliance Leukemia; STAG2: Stromal Antigen 2; TET2: Tet methylcytosine dioxygenase 2; VAF: Variant allele frequency; vs.: Versus; WT1: Wilms Tumor 1.
Supplementary Information

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Additional file 1: Table S1 Overview of the clinical trials the study patients were selected from. Figure S1 Forrest Plot of variables evaluated in univariate analysis. Multivariate Cox proportional hazard regression for (A) overall survival and (B) relapse-free survival.

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Author contributions

DK, JMM and FS designed the study. GE and MB provided administrative support. All authors collected clinical and/or genetic data and provided patient samples. CT and SS performed molecular diagnostics. DK, MK, JS, JMM and FS analyzed and interpreted the data; all authors had access to primary clinical trial data. DK drafted the manuscript, JMM and FS provided critical revision. All authors read the manuscript and gave their final approval for publication.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study included samples from patients enrolled in NCT03188874, NCT00180115, NCT00180102, NCT00266136, NCT00180176, NCT01382147 and NCT00893373. The trials were approved by the respective ethics committees and conducted in accordance with the Declaration of Helsinki. All patients gave their written informed consent including analysis of data. The studies were monitored continuously by clinical and medical monitors. Safety reports were generated and submitted to an independent Data and Safety Monitoring Board (DSMB). Data quality controls were performed regularly and the medical monitors verified that the clinical trials, as well as data acquisition, were conducted in compliance with the International Conference on Harmonization Good Clinical Practice (ICH GCP), the study protocol and all applicable regulatory requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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