Impact of trisomy 19 on outcome according to genetic makeup in patients with acute myeloid leukemia

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Abstract

We retrospectively studied 97 acute myeloid leukemia patients with trisomy 19 (median age at diagnosis 57 years; range, 17-83 years) treated between 2001 and 2019 within two multicenter study groups. Trisomy 19 occurred alone in ten (10.5%) patients, with additional abnormalities being present in non-complex karyotypes in eight (8%) patients and in complex karyotypes in 79 (82%) patients. Altogether, karyotypes characterized by trisomies only were present in 27 (28%) patients. Data on response and outcome of intensively treated patients were available for 92 cases. The median follow-up was 6.4 years (95% confidence interval [95% CI]: 2.9-9.0 years). The complete remission (CR) rate after induction therapy was 52% (48 patients); the early death rate was 10% (n=9). Notably, patients with trisomy 19 as the sole abnormality had a CR rate of 89%. Allogeneic hematopoietic stem cell transplantation (allo-HCT) was performed in 34 (35%) patients (CR, n=19; active disease, n=15). Five-year relapse-free and overall survival rates were 26% (95% CI: 16-43%) and 20% (95% CI: 13-31%), respectively. Overall survival rates were significantly higher in patients with trisomy 19 as the sole abnormality or within karyotypes characterized by trisomies only (P=0.05). An Andersen-Gill model including allo-HCT as a time-dependent covariable on overall survival revealed that trisomy 19 as the sole abnormality or within karyotypes characterized by trisomies only was a favorable factor (hazard ratio [HR]=0.47; P=0.021); higher age at diagnosis had an adverse impact (10 years difference; HR=1.29; P=0.002), whereas allo-HCT did not have a beneficial impact (odds ratio=1.45; P=0.21). In our cohort, patients with trisomy 19 as the sole abnormality or within karyotypes characterized by trisomies only had a high CR rate and better clinical outcome.

Introduction

Trisomy 19 is a recurrent but very rare cytogenetic abnormality reported in patients with acute myeloid leukemia (AML).[1] In a large analysis of 5,876 younger adult AML patients treated in United Kingdom Medical Research Council (MRC) trials, only 58 (1%) harbored a trisomy 19.[1] The prognostic significance of this abnormality in AML patients is not clear. Informed clinical decision-making in situations in which cytogenetic analysis shows rare cytogenetic abnormalities has been hampered by a lack of consensus regarding the likely outcome of such patients. According to National Comprehensive Cancer Network guidelines[2] as well as European LeukemiaNet recommendations[3] AML patients with trisomy 19 in the absence of other abnormalities would be assigned to the intermediate-risk group. However, this risk group comprises a rather large, heterogeneous set of abnormalities, leaving the impact of trisomy 19 on outcome unclear. Apart from the benefit of achieving greater consensus in cytogenetic classification, establishing the outcome associated with rare cytogenetic abnormalities is important, particularly given the results of a meta-analysis suggesting a relapse risk in excess of 35% can provide a useful working threshold to identify patients in whom allogeneic hematopoietic stem cell transplantation (allo-HCT) may confer a survival benefit.[4]

Outcome seems to be poor as compared to that of patients with normal cytogenetics with a 10-year overall survival (OS) rate of 12% *versus* 38% (P<0.001) and 10-year cumulative incidence of relapse rate of 74% *versus* 49% (P<0.001).[1] Allo-HCT may improve survival if performed early in first CR. However, neither prospective clinical nor larger retrospective cohort studies are available to support these results.

Methods

Patients and treatment

Information on 97 adult patients with trisomy 19 AML diagnosed between 2001 and 2019 (2001-2010, n=40; after 2010, n=57) was collected within a large, multicenter international cohort (Study Alliance Leukemia [SAL], n=53; Programa Español de Tratamientos en Hematología [PETHEMA], n=44). Detailed case report forms, including information on baseline characteristics, chemotherapy, allo-HCT, response, and survival, were collected from all participating centers. Inclusion criteria were adult AML patients with trisomy 19 and all patients who fulfilled these criteria were included by the participating groups/institutions. The diagnosis of AML was based on French-American-British Cooperative Group criteria,[5] and, after 2003, on revised International Working Group criteria.[6] Chromosome banding was performed using standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.[7] A complex karyotype was defined according to the 2017 European LeukemiaNet classification.[3] *FLT3* mutation screening for internal tandem duplications (ITD) and point mutations within the tyrosine kinase domain (TKD) was carried out at each institution as previously described.[8,9] Data collection and analysis were approved by the institutional review boards of the participating centers.

Treatment

Ninety-three (96%) of the 97 patients received intensive induction treatment either within clinical trials (n=22) or according to local institutional standards (n=71). Treatment protocols for patients treated within the SAL (n=53) included AML60+ (n=2),[10] AML96 (n=9)[11], and AML2003 (n=11).[12] Additionally, 31 patients were included within the prospective SAL registry (NCT03188874). All patients from PETHEMA (n=44) were included within the PETHEMA AML registry (NCT02607059).[13]

Induction therapy of the 71 patients treated according to local institutional standards consisted of the anthracycline/cytarabine based “7+3” regimen (n=50) or comparable intensive treatment (n=21).

Four (4%) of the 97 patients were treated non-intensively. Of those, one received low-dose cytarabine, one decitabine, one venetoclax in combination with azacitidine[14] and one patient volasertib or placebo in combination with low-dose cytarabine.[15] Response was assessed according to International Working Group recommendations.[6] All clinical studies were approved by the institutional review boards of the participating centers. All patients provided written informed consent to participation in one of the treatment trials or to therapy according to local standards.

Statistical analyses

Survival endpoints including OS and relapse-free survival were defined according to the revised recommendations of the International Working Group.[6] Comparisons of patients’ characteristics were performed with the Kruskal-Wallis rank sum test for continuous variables and Fisher exact test for categorical variables. To identify prognostic variables with respect to response to induction therapy a logistic regression model was used. Variables included white blood cell count, age, gender, complex karyotype, as well as trisomy 19 as the sole abnormality or trisomy 19 in combination with trisomies only (i.e., trisomy 19 and one additional trisomy as well as trisomy 19 and additional trisomies only within a complex karyotype). The median follow-up time was computed using the reverse Kaplan-Meier estimate.[16] The Kaplan-Meier method was

used to estimate the distributions of relapse-free survival and OS.[17] Confidence interval (CI) estimations for survival curves were based on the cumulative hazard function using the Greenwood formula for variance estimation. Log-rank tests were employed to compare survival curves between groups. The effect of allo-HCT (including all transplanted patients) on OS as a time-dependent intervening event was tested in a multivariable Andersen-Gill model.[18] Variables included in the model were trisomy 19 as the sole abnormality or trisomy 19 in combination with trisomies only, age with a difference of 10 years as well as allo-HCT. All statistical analyses were performed with the statistical software environment R, version 4.2.1, using the R packages rms, version 6.3-0, and survival, version 3.4-0.[19]

Results

Study cohort

Overall demographic and clinical data were collected from 97 patients diagnosed with AML and trisomy 19 between 2001 and 2019. The median age was 57 years (range, 17-83 years) and 35 patients (36%) were female. The patients' baseline characteristics are summarized in Table 1.

Cytogenetic and molecular analyses

Cytogenetic analysis revealed trisomy 19 as the sole abnormality in ten (10.5%) patients, with additional abnormalities in a non-complex karyotype in eight (8%) patients, and in a complex karyotype in 79 (82%) patients. In patients with trisomy 19, the most frequent additional abnormality was trisomy 8 (n=46, 47%). Of those, most had a complex karyotype (n=42, 91%). Trisomy 19 and one additional trisomy occurred in six (6%) patients (Table 2). In addition, trisomy 19 and additional trisomies only within a complex karyotype occurred in 11 (11.5%) patients. Altogether, karyotypes characterized by trisomy 19 as the sole abnormality or trisomy 19 and additional trisomies only were found in 27 (28%) patients (Figure 1).

There was only one case of gene fusion (inversion 16) being present besides trisomy 19. A total of 65 patients (67%) underwent mutation testing for *NPM1* and *FLT3*-ITD. Of those, three (5%) and one (1.5%) harbored *NPM1* and *FLT3*-ITD mutations, respectively. None of 12 patients with available data had a *FLT3*-TKD mutation. Four (8%) of 51 analyzed patients were *CEBPA* double-mutated (Table 1).

Response to induction therapy

Four patients were treated with non-intensive therapies because of higher age (median, 66.9 years; range, 55-70.6 years) or comorbidities. Of those, only one achieved a CR after one cycle of venetoclax/azacitidine treatment. The patient received a second cycle of venetoclax/azacitidine and went on to allo-HCT. Unfortunately, he relapsed 77 days later and succumbed to his disease 73 days later. Cytogenetically, the patient showed a trisomy 19 and additional trisomies only within a complex karyotype. Molecularly, *NPM1* and *FLT3*-ITD were unmutated. All three other patients treated with non-intensive therapy did not respond and died within 1.5 years (median, 11.6 months; range, 2.8-18 months). Two of them had trisomy 19 within a complex karyotype (consisting of other abnormalities than trisomies only) and one patient had trisomy 19 as the sole abnormality.

Data on response to intensive induction therapy were available for 92 patients (data were missing for 1 patient). CR after induction therapy was achieved by 48 (52%). Early death occurred in nine (10%) patients.

Notably, patients with trisomy 19 as the sole abnormality had a CR rate of 89% (n=8/9); the patients with trisomy 19 and one additional trisomy as well as trisomy 19 and additional trisomies only had a CR rate of 73% (n=11/15) as compared to 43% (n=29/67) in patients with trisomy 19 within a

Table 1. Baseline characteristics of patients with acute myeloid leukemia and trisomy 19.

Characteristic	Total N=97
Female gender, N (%)	35 (36)
Age in years, median (range)	57 (17-83)
Type of AML, N (%)	
De novo	66 (68)
s-AML	16 (16)
t-AML	9 (9)
Missing	6 (6)
Cytogenetics	
Only trisomy 19, N (%)	10 (10)
Additional abnormalities, N (%)	87 (90)
≥3 abnormalities, N	79
Trisomy 19 & trisomy 8, N	46
Trisomies only, N	17
t(8;21) or inversion (16), N	1
Molecular genetics, N (%)	
NPM1 mutated*	3 (5)
FLT3-ITD positive*	1 (2)
CEBPA double mutated**	4 (8)
ELN risk group, N (%)	
Favorable	4 (4)
Intermediate	14 (14.5)
Unfavorable	79 (81.5)
WBC count x10^9/L, median (range)	6.7 (0.1-151)
Platelet count x10^9/L, median (range)	48.5 (4-307)
Hemoglobin in g/dL, median (range)	9.2 (4.5-16.5)
% BM blasts, median (range)	66 (1-99)

Results may not add up to 100 due to rounding. *Available for 65 (67%) patients; **available for 51 (53%) patients. AML: acute myeloid leukemia; s-AML: AML after previous myelodysplastic syndrome/myeloproliferative neoplasm; t-AML: therapy-related AML; *NPM1: nucleophosmin 1*; *FLT3*: *fms-related tyrosine kinase 3*; ITD: internal tandem duplication; *CEBPA: CCAAT enhancer binding protein A*; ELN: European LeukemiaNet; WBC: white blood cell; BM: bone marrow.

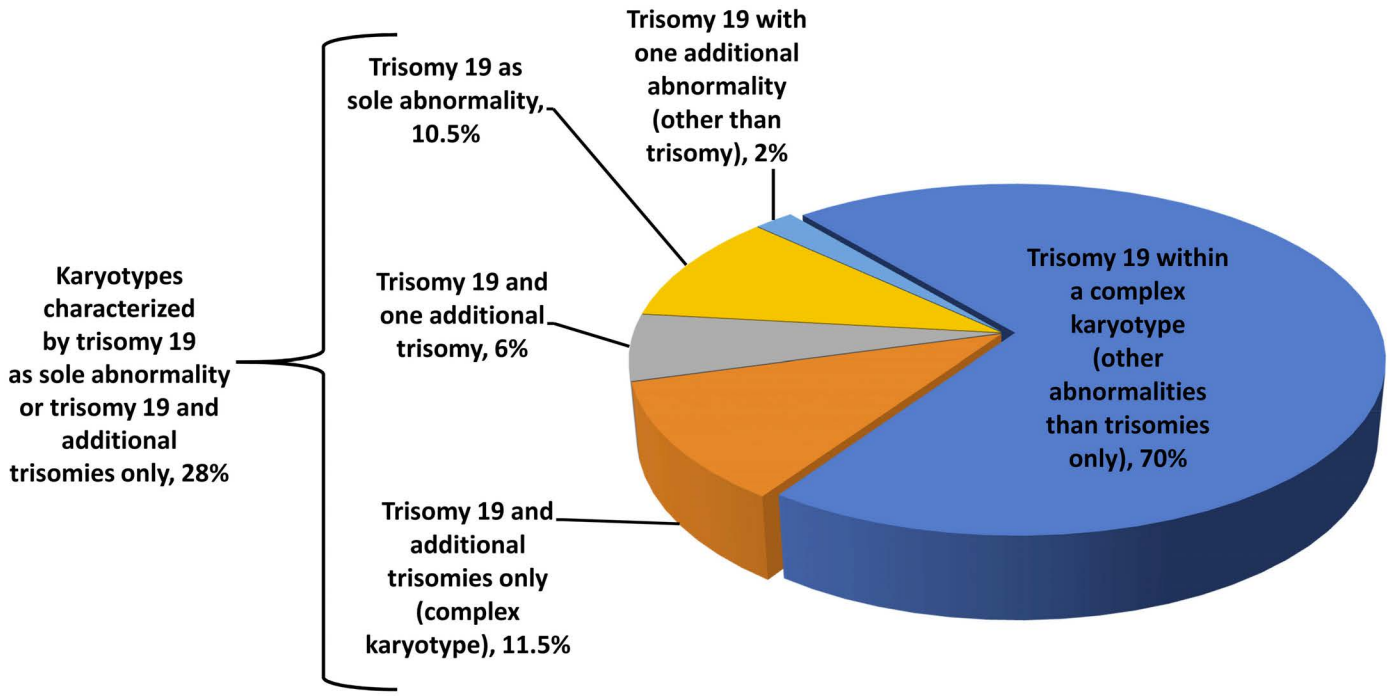

Figure 1. Cytogenetic abnormalities of 97 patients with trisomy 19 showing the categorization of cytogenetic abnormalities used for further analysis.

complex karyotype (consisting of other abnormalities than trisomies only). A logistic regression model with limited backward selection on response to induction therapy revealed trisomy 19 as the sole abnormality or within a karyotype characterized by trisomies only as favorable factors (odds ratio [OR]=5.55; *P*=0.005), whereas higher age at diagnosis had an adverse impact (10 years difference; OR=0.58; *P*=0.002).

Further therapy including intensive consolidation and allogeneic hematopoietic stem cell transplantation

Twenty-nine (60%) of 48 intensively treated patients in first CR received intensive chemotherapy consolidation consisting of high-dose cytarabine as a single agent or combined with additional cytostatic agents. Nineteen (40%) patients proceeded to allo-HCT in first CR with ten of the transplanted patients receiving consolidation chemotherapy prior to transplantation. Patients proceeding to allo-HCT were significantly younger (*P*=0.001) than patients receiving intensive consolidation with chemotherapy, whereas there was no difference in median white blood cell count (*P*=0.89) and European LeukemiaNet risk classification (*P*=0.37) between the two groups.

Among patients consolidated with chemotherapy, relapses occurred in 15 and three experienced treatment-related mortality after consolidation. In patients consolidated with allo-HCT in first CR, five patients relapsed and most of them died shortly thereafter (median, 1.5 months; range, 0.3-14.9 months); additionally, five patients died of transplant-related causes.

Characteristics of patients undergoing allogeneic hematopoietic stem cell transplantation

Allo-HCT was performed overall in 34 (35%) patients, of

Table 2. Karyotypes characterized by trisomy 19 and additional trisomies only.

N	Karyotype
1	48,XY,+8,+19[19]/46,XY[1]
2	47,XX,+8[1]/48,XX,+8,+19[1]/46,XX[5] (+8 and +19 confirmed by FISH)
3	48,XY,+8,+19[3]/46,XY[22]
4	48,XX,+19,+21[2]/46,XX[23]
5	48,XY,+8,+19
6	48,XY,+19,+21
7	52,XY,+4,+4,+9,+10,+19,+22[6]/46,XY[18]
8	47,XY,+6[1]/48,XY,+4,+6[15]/48,XY,+6,+19[3]/46,XY[6]
9	47,XY,+19[1]/48,sl,+16[6]/49,sdl,+8[17]/46,XY[1] (+19 confirmed by FISH)
10	47,XY,+8[16]/58,XY,+Y,+2,+8,+8,+8,+8,+13,+15,+15,+19, +20,+22[4]/46,XY[2]
11	48,XY,+14,+19[3]/48;inc[1]/69,XXY[1]/46,XY[3]
12	54,XXY,+8,+10,+11,+12,+19,+21,+22[3]/46,XY[17]
13	49,XY,+8,+19,+20[4]/46,XY[16]
14	56-59,XY,+X,+1,+1,+6,+11,+12,+13,+14, +15,+19,+21,+21,+22[20]
15	49,XX,+15,+19,+21
16	98,XY,+X,+Y,+Y,+1,+1,+3,+3,+4,+4,+5,+5,+6,+6,+7,+7,+8,+8,+9, +10,+10,+11,+12,+12,+13,+14,+14,+15,+15,+15,+16,+17,+17, +18,+18,+18,+19,+19,+20,+20,+21,+21,+22,+22, +22[40]/46,XY[21]
17	52,XY,+X,+8,+13,+14,+17,+19[17]/46,XY[3]

Numbers 1-6: trisomy 19 and one additional trisomy. Numbers 7-17: trisomy 19 and additional trisomies only within a complex karyotype. FISH: fluorescence *in-situ* hybridization.

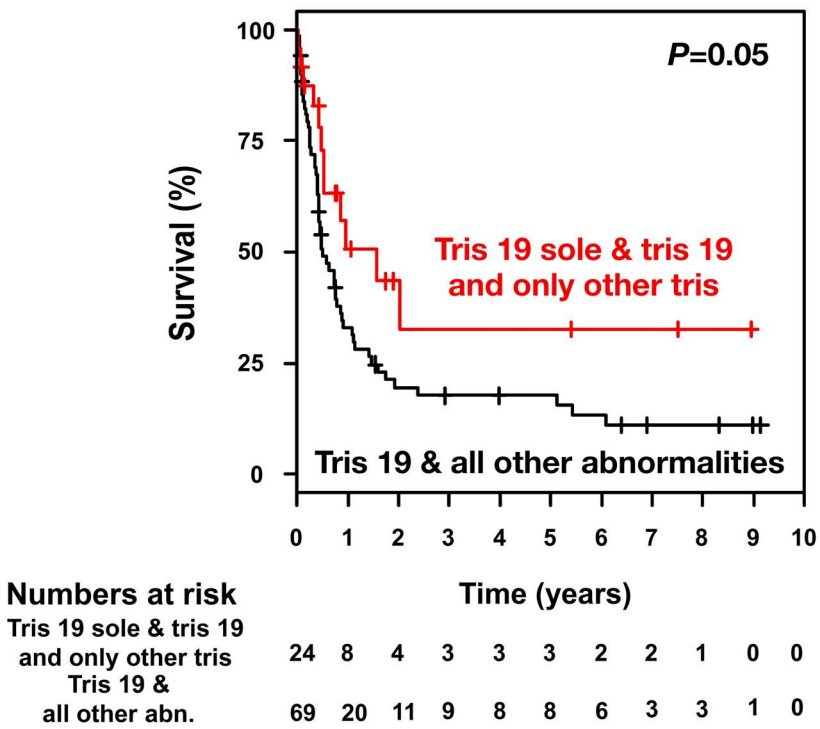

Figure 2. Kaplan-Meier plot of overall survival in intensively treated patients according to cytogenetic abnormality. Tris: trisomy; abn: abnormalities.

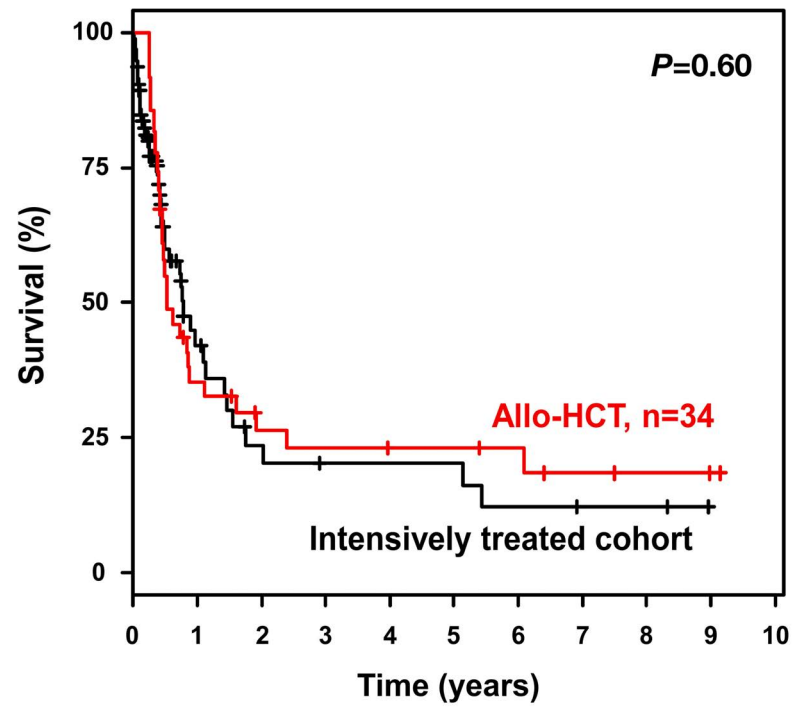

Figure 3. Simon Makuch plot of overall survival illustrating the impact of allogeneic hematopoietic stem cell transplantation evaluated as a time-dependent event. Allo-HCT: allogeneic hematopoietic stem cell transplantation.

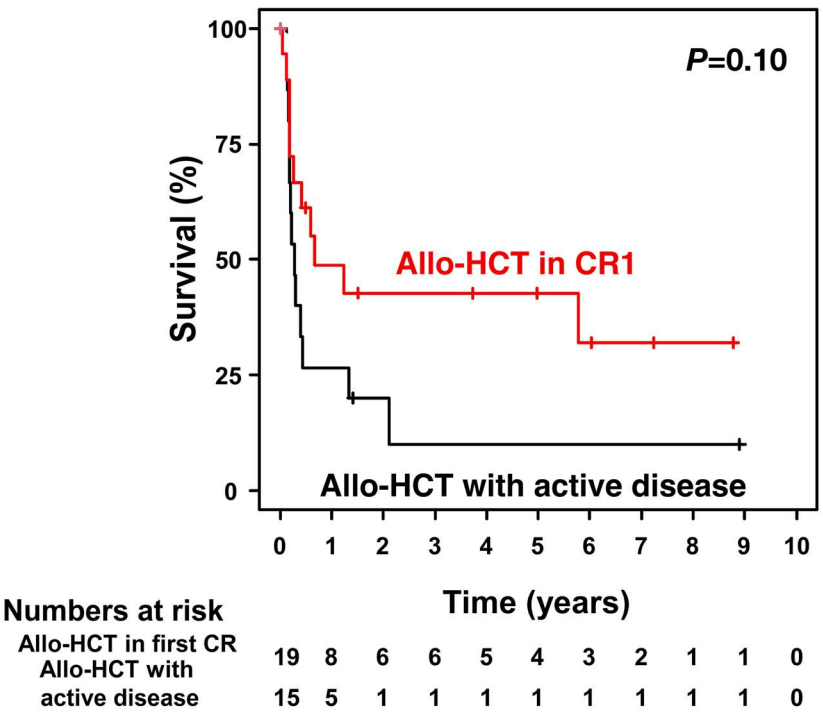

Figure 4. Overall survival after allogeneic hematopoietic stem cell transplantation according to remission status. Allo-HCT: allogeneic hematopoietic stem cell transplantation. CR1: first complete remission.

whom 19 patients were transplanted in first CR. Fifteen patients underwent allo-HCT with active disease. Fourteen patients received myeloablative conditioning and 18 patients reduced-intensity conditioning (missing data, n=2). The type of donor was matched related in 12 cases and matched unrelated in 22 patients.

Relapse-free and overall survival

The median follow-up of the cohort was 6.4 years (95% CI: 2.9-9.0 years). The median survival of non-intensively treated patients (n=4) was 0.8 years and none of these patients survived beyond 1.5 years. In intensively treated patients the 5-year relapse-free survival and OS rates were 26% (95% CI: 16-43%) and 20% (95% CI: 13-31%), respectively.

OS rates were significantly higher in patients with trisomy 19 as the sole abnormality or within a karyotype characterized by trisomies only as compared to all other abnormalities) (P=0.05) (Figure 2). An Andersen-Gill model including allo-HCT whenever performed as a time-dependent covariable revealed that trisomy 19 as the sole abnormality or within a karyotype characterized by trisomies only (hazard ratio [HR]=0.47; P=0.021) was a favorable factor, whereas age with a difference of 10 years (HR=1.29; P=0.002) had a negative impact. Allo-HCT (OR=1.45; P=0.21) did not have a significant impact.

The influence of allo-HCT, assessed in univariable analysis as a time-dependent co-variable, as post remission therapy on OS is also illustrated by a Simon Makuch plot (P=0.60) (Figure 3). There was a trend towards better OS measured from the date of allo-HCT if patients proceeded to allo-HCT in first CR (n=19) rather than being transplanted with active disease (n=15; P=0.10) (Figure 4). In patients achieving first CR, 5-year relapse-free survival was 35% (95% CI: 18-70%) for those patients proceeding to allo-HCT (n=19) as compared to 15% (95% CI: 3-80%) in those who received consolidation chemotherapy.

Discussion

The focus of our study was to characterize adult AML patients with trisomy 19 in an international, multicenter cohort study and compare outcomes according to treatment

strategies, with a specific focus on the impact of allo-HCT as compared to conventional chemotherapy on survival. Trisomy 19 seems to be a very rare abnormality,[1] and further large cohort studies on this abnormality are not available. Thus, its influence on outcome remains unclear. We here present the largest cohort of 97 patients with trisomy 19 to date, of whom 93 were treated intensively.

Trisomy 19 is frequently associated with complex karyotypes and, interestingly, with karyotypes characterized by trisomies only, but seems to be very infrequent in patients with gene fusions or disease-defining mutations.

Contrary to published data by the MRC reporting a high CR rate of 81% after intensive induction therapy,[1] we observed a high CR rate only in patients with trisomy 19 as the sole abnormality or within a karyotype characterized by trisomies only (that is, trisomy 19 and one additional trisomy as well as trisomy 19 and additional trisomies only within a complex karyotype). Currently, the prognostic impact of a complex karyotype, defined by trisomies only, also called a hyperdiploid karyotype, has not been addressed conclusively.[20-22] The prognosis of AML patients with trisomies only, particularly of those with a hyperdiploid karyotype, seems to be poor as compared to that of patients with intermediate-risk cytogenetics.[22] However, in our analysis patients with trisomy 19 as their sole abnormality or within a karyotype characterized by trisomies only, including a hyperdiploid karyotype, had a high CR rate and better clinical outcome.

Nevertheless, most patients relapsed, which seems not to be largely improved by allo-HCT, suggesting that other treatment approaches are needed to prolong survival. The only factor associated with prolonged survival was trisomy 19 as the sole abnormality or within a karyotype characterized by trisomies only.

Treatment with venetoclax in combination with hypomethylating agents seems to be promising, particularly in patients with *NPM1*- or *IDH*-mutated AML.[23,24] Responses do also occur in patients with adverse genetic features, such as high-risk cytogenetic abnormalities as well as *TP53* mutations.[23,24] However, responses in such patients have been mostly short-lived and not durable. Whether other combinations, such as venetoclax/azacitidine and magrolimab, will lead to higher rates of remission and prolong survival is currently being evaluated within a phase III randomized trial (NCT05079230). In addition, venetoclax in combination with standard intensive chemotherapy is now being studied as frontline therapy in younger and older patients with AML (e.g., trials NCT03709758 and NCT04628026). Preliminary data suggest a very high overall response rate of 100% (n=10), with 75% (n=6/8) of the patients achieving minimal residual disease-negative remissions assessed using multiparameter flow cytometry.[25]

An isolated trisomy 19 can be detected in myeloid disorders,[26] and there seems to be an association with megakaryoblastic leukemia (M7).[27,28] In our cohort, we detected secondary chromosomal abnormalities in 90%, most frequently trisomy 19 within a complex karyotype or trisomy 19 in combination with trisomy 8. Regarding the molecular makeup, the frequencies of mutations in *NPM1*, *FLT3*-ITD or *CEBPA* as well as disease-defining fusion genes were very low, suggesting that other cooperating mutations may play a role in the pathogenesis. To date, however, the pathogenic role of trisomy 19 *per se* in leukemogenesis is still unclear.

Of note, allo-HCT, performed in first CR or with active disease did not result in improved outcome. This is in line with our recent findings in a cohort of AML patients characterized by trisomy 4.[29] Nonetheless, this is in contrast to previous reports[30-32] focusing on other trisomies such as +8, +11, +13 and +21 and may indicate that the outcome of patients with trisomies needs to be evaluated individually. However, we would like to emphasize that retrospectively collected data have serious limitations since the factors for allocating patients to allo-HCT, such as comorbidities, individual assessment of the treating physician, choice of conditioning, and availability of a donor, remain unknown and these need to be taken into account when evaluating the value of allo-HCT in our series. Furthermore, the presence of minimal residual disease, as detected by polymerase chain reaction, flow cytometry, or next-generation sequencing, was shown to be a predictive factor for outcome.[33-36] Thus, minimal residual disease status is being increasingly used to allocate patients for transplantation.[35] However, in our cohort of patients data on minimal residual disease status were not available. Thus, we could not separate those patients who went on to allo-HCT in first CR according to their minimal residual disease status.

In conclusion, patients with trisomy 19 are very heterogeneous, in particular with respect to genetic abnormalities. In our cohort, patients with trisomy 19 as their sole abnormality or within a karyotype characterized by trisomies only had a high CR rate and better clinical outcome. In the total cohort, it seems that allo-HCT may not improve OS; nevertheless, shortcomings of retrospective cohort studies need to be taken into account.

Disclosures

No conflicts of interest to disclose.

Contributions

SK and RFS were responsible for the concept of this paper, contributed to the literature search and data collection, analyzed and interpreted data, and wrote the manuscript. DM-C, RR-V, MH, MT, KS-E, CB, FS, TBdC, UK, CR-M, GH, M-LA, CS, MC, MK, MBG, SWK, MG, EJ, BS, SZ, UP, ADH, CDB, HS, CM-T, MB, PM, and CR contributed patients and critically revised the manuscript. CTh performed research and

critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Data-sharing statement

Questions regarding data sharing should be addressed to the corresponding author.

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