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Original Article

Secondary Acute Myeloid Leukemia and De Novo Acute Myeloid Leukemia with Myelodysplasia-Related Changes - Close or Complete Strangers?

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Abstract

Aim: To compare the main features of patients with secondary acute myeloid leukemias (AMLs) after post-myelodysplastic syndrome (AML-post-MDS) or post-myeloproliferative neoplasms (AML-post-MPN) and myeloid blast crisis of chronic myeloid leukemia (CML-BC) vs. *de novo* AMLs with myelodysplastic characteristics (*dn*-AML-MDS).

Materials and methods: Bone marrow/peripheral blood samples of 94 patients with secondary AMLs (30 with AML-post-MDS, 20 with AML-post-MPN, and 14 with CML-BC) and 30 with *dn*-AML-MDS were included. Demographic, morphological, phenotypic, cytogenetic, and survival data were analyzed.

Results: Comparative analysis showed no differences in sex and age, except for the younger age in CML-BC (p=0.005). Leukocytosis was a prevalent feature of CML-BC vs. AML-post-MPN, AML-post-MDS and *dn*-AML-MDS (p<0.001). At leukemia onset, thrombocytopenia was characteristic of AML-post-MDS and *dn*-AML-MDS whereas normal PLT counts were found in AML-post-MPN and CML-BC (p=0.001). Dysplasia in ≥2 lineages was observed in almost all *dn*-AML-MDS (96.8%) and AML-post-MDS (100%) compared to AML-post-MPN (33.3%) and none of the CML-BC (p=0.001). Aberrant co-expression of 1-4 lymphoid-associated markers was detected in 67.5% of all patients, including CD7, CD19, CD56, and CD22. We found chromosome aberrations in 57.8% of patients, more frequently in *dn*-AML-post-MDS than in AML-post-MPN, CML-BC, and AML-post-MDS. While *NPM1* mutations distribution was similar in the two MDS-related AML groups, FLT3-ITD was higher in AML-post-MDS (26.3%) than in *dn*-AML-MDS (4.5%) (p=0.049). Regarding *EVI1*, CML-BC (80%) and AML-post-MPN (37.5%) showed higher incidence of gene overexpression compared to AML-post-MDS (13.3%) and *dn*-AML-MDS (5.0%) (p=0.001). Median time to leukemia was significantly shorter in AML-post-MDS (4.80±1.04 months) than in AML-post-MPN (20.3±2.86 months) and CML-BC (34.7±16.3 months) (p=0.008), and median overall survival was poor in all groups.

Conclusions: Similarities and differences between patients with secondary AMLs may represent different biology which translates into different clinical course and may require different therapeutic approach in future.

Keywords

acute myeloid leukemia, blast crisis, myelodysplasia, myeloproliferative disorder

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Abbreviations used in the article

AMLs	acute myeloid leukemias	**BM**	bone marrow
AML-post-MDS	post-myelodysplastic syndrome	**sAML**	secondary acute myeloid leukemia
AML-post-MPN	post-myeloproliferative neoplasms	**LT**	leukemic transformation
CML-BC	myeloid blast crisis of chronic myeloid leukemia	**MPN**	myeloproliferative neoplasms
***dn*-AML-MDS**	*de novo* AMLs with myelodysplastic characteristics	**CML**	chronic myeloid leukemia
		TKI	tyrosine kinase inhibitors
PLT	platelet count	**TTL**	time to leukemia
MDS	myelodysplastic syndrome	**OS**	overall survival
PB	peripheral blood	**LAM**	lymphoid-associated markers

INTRODUCTION

Acute myeloid leukemia (AML) is a malignant hematologic disease resulting from clonal expansion of myeloid blasts ≥20% in peripheral blood (PB) and/or bone marrow (BM). It is a heterogeneous category in terms of morphology, genetic characteristics, and clinical presentation. Disease can occur *de novo* in cases in which it arises without an identified prior stem cell disorder or proven leukemogenic exposure; or as secondary (sAML) to a prior hematologic disorder with potential for leukemic transformation (LT), such as myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN).[1,2]

The natural history of myeloproliferative neoplasms, both Ph(+) chronic myeloid leukemia (CML) and Ph(−) MPNs, has been well documented, but the mechanism underlying progression from an initial, rather indolent chronic phase to an advanced phase remains obscure. The risk of transformation in CML to a blast crisis (CML-BC) in the tyrosine kinase inhibitors (TKI) era appears to be quite low (<2% per year). Approximately 4%-6% of patients diagnosed with MPN transform into AML (AML-post-MPN).[3] However, the LT pathogenesis in MPN remains not fully understood.[4]

About one-third of patients with MDS transform into AML.[5] Myelodysplastic syndrome develops when clonal mutations that suppress healthy stem cells predominate in bone marrow resulting in ineffective hematopoiesis. The exact mechanisms behind this progression are still poorly understood; however, accumulation of cytogenetic and molecular aberrations is assumed to play a certain role leading to imbalance between apoptosis and prevailing proliferation within hematopoiesis.[6] The increase of blasts ≥20% is classified as AML with MDS-related changes (AML-MRC), characterized with a low complete remission rate and short survival time.[7] According to 2016 WHO classification, AML-MRC is a heterogeneous group including not only AML after MDS (AML-post-MDS), but also *de novo* AMLs exhibiting morphologic or genetic dysplastic features without a clear history of prior MDS (*dn*-AML-MDS). Newer classification proposals challenge this approach.[8]

In general, AMLs evolving from an antecedent hematological disorder or bearing dysplastic morphological and/or genetic features without a clear history of prior disease tend to be difficult to manage and are associated with a poor prognosis. Although distinct categories are tied to different biologic processes, the malignant clones demonstrate similar phenotypes, common clinical presentation after LT and are frequently insensitive to traditional AML chemotherapeutic agents. Current classification introduces some overlapping and confusing criteria resulting in highly heterogeneous entities, which makes the understanding of the specific nature of this clinical convergence and the introduction of biologically relevant management approaches difficult.

AIM

Therefore, we aimed at a comparative study of patients with AMLs developed through different pathways – *de novo*, post-MDS, post-MPN, and CML, regarding their major clinical and laboratory characteristics, genetic aberrations, and outcomes.

MATERIALS AND METHODS

This study included 94 adult patients diagnosed and treated at Sofia's National Hematology Hospital over a 5-year period, including 55 male and 39 female patients with a median age of 61±44.7 years (range, 26-89 years). Informed consent according to the criteria of the local ethical commission was obtained. Diagnosis was based on an integrated assessment of clinical, morphological, immunophenotypic and genetic features according to WHO classification criteria for 2016[1] as follows: 30 patients with *dn*-AML-MDS, 30 with AML-post-MDS, 20 with AML-post-MPN, and 14 with myeloid CML-BC. Additional four lymphoblastic CML-BC were observed in this period, including 3 B-cell and 1 T-cell, which were excluded from the study.

Demographic data, main hematological parameters (Hgb, WBC, PLT), blasts % and dysplasia in hematopoietic populations in BM and/or PB samples at diagnosis were evaluated. Complete blood counts and microscopic differential counts of May-Grünwald-Giemsa-stained BM samples were performed.

Immunophenotyping of leukemic cells from BM and/

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or PB was performed using a panel of fluorochrome-labeled antibodies recommended by Euro Flow: CD1a, CD2, cyCD3, sCD3, CD4, CD5, CD7, CD8, CD9, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD20, CD21, CD22, CD24, CD25, CD33, CD34, CD35, CD36, CD38, CD44, CD45, CD45RA, CD56, CD58, CD64, CD66c, CD71, cyCD79a, CD81, CD99, CD105, CD117, CD123, CD203c, CD300e, HLADR, NG2, TCRαβ, cyTCRβ, TCRγδ, cyIgμ, sIgκ, sIgλ, sIgM, NuTdT, cyMPO.[9]

Chromosome G-banding was successful in 65 BM samples. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature criteria 2016.[10]

Additional molecular analysis of *FLT3-ITD, NPM1* mutations and *EVI1* gene overexpression were performed using polymerase chain reaction-based assays.

The following therapy was administered: 79 (84.1%) received chemotherapy, including idarubicin/cytarabine-based ‘7+3’ regimen (n=27), ‘cytarabine + mitoxantrone + etoposide’ (n=8), cytarabine monotherapy (n=21), ‘idarubicin + cytarabine + imatinib’ (n=11), and ‘cytarabine + imatinib’ (n=3). Nine patients were treated with hypomethylating agents. The remaining 15.9% were treated with supportive care alone, including the use of hydroxyurea to control leukocytosis. Five of the patients received allogeneic stem cell transplantation.

Statistical analysis

Standard statistical methods were used to determine significance of differences among groups in distribution of continuous or nominal variables. Time to leukemia (TTL) was evaluated from diagnosis to LT. Overall survival (OS) was calculated from time of AML diagnosis until death. Estimation of the OS was done using Kaplan-Meier method and compared by the log-rank test. Reported differences at $p<0.05$ were accepted as statistically significant (SPSS v. 23, Stat soft Inc., Los Angeles, CA, USA).

RESULTS

Demographic data analysis revealed that mean age of patients with AML-post-MPN, AML-post-MDS and *dn*-AML-MDS was in the sixth decade (64.8±10.5 years, 61.2±16.9 years, and 62.8±13.9 years, respectively) and was higher compared to that of CML-BC patients (49.2±14.1 years, $p=0.005$), with a male predominance in all disease entities. Major clinical and laboratory characteristics of patients are shown in **Table 1**.

As to hematological parameters, all patients in our study were anemic, and no differences in their Hgb levels were observed. Leukocytosis was more common in CML-BC ($133.2\pm154.5\times10^9$/L) compared to AML-post-MPN ($73.1\pm81.4\times10^9$/L), AML-post-MDS ($26.3\pm43.3\times10^9$/L), and *dn*-AML-MDS ($15.6\pm32.8\times10^9$/L) patients ($p<0.001$). Patients with AML-post-MDS and *dn*-AML-MDS were characterized with thrombocytopenia at leukemia onset whereas mean PLT counts were within reference ranges in AML-post-MPN and CML-BC patients ($75.3\pm102.3\times10^9$/L; $91.0\pm103.7\times10^9$/L vs. $156.4\pm188.4\times10^9$/L; $278.1\pm241.8\times10^9$/L, respectively, $p=0.001$).

In terms of tumor burden, no significant differences were found in BM blasts % between groups with an average of 45% leukemic infiltration. However, estimation of morphology showed various patterns of dysplasia. Dysplastic changes in ≥2 lineages occurred in none of the CML-BC patients and only in 33.3% of the AML-post-MPN patients, as opposed to the *dn*-AML-MDS patients (96.8%) and AML-post-MDS patients (100%) ($p=0.001$). Granulocytic and megakaryocytic cells were mostly affected while no significant differences were found in erythroid series **(Table 1)**.

Immune phenotype of blast cells was immature myeloid defined by ≥2 myeloid-associated markers, e.g., CD33 (92.8%), CD13 (86.7%), myeloperoxidase (42.2%), CD64 (34.9%), CD14 (12.0%), as well as by immature markers CD34 (80.7%) and CD117 (95.2%) **(Table 1)**. In total, 67.5% of all patients had aberrant co-expression of 1-4 lymphoid-associated markers (LAM), most commonly CD7 (24%), CD19 (17%), CD56 (14%), and CD22 (14%), but without statistical differences among subgroups. Detection of ≥2 LAM in our hands was evenly distributed across leukemia subgroups and, in general, was related to lower overall survival - 4.9±2.1 vs. 6.1±1.8 months in patients with ≤1 lymphoid marker ($p=0.049$).

Chromosomal aberrations were found in 57.8% of patients. The most frequently involved chromosomes were 5 (29.2%); 1 (21.5%); 12 and 17 (18.5% each), and 7 and 11 (16.9% each). The overall incidence of cytogenetic abnormalities and of unbalanced abnormalities, in particular, did not differ between groups, while complex karyotypes were not detected in CML-BC, and balanced abnormalities were seen in only one CML patient and one patient with *dn*-AML-MDS. In addition, *dn*-AML-MDS showed the highest frequency of complex karyotypes (45.8%) and aberrations of chromosome 7 (36%) defining a distinctive genetic profile from AML-post-MDS and other sAMLs **(Fig. 1A)**.

The molecular pattern also differed within the groups. *EVI1* overexpression was found during LT in a considerable proportion of CML-BC (80%) and AML-post-MPN (37.5%) patients, while it was less frequent in AML-post-MDS (13.3%) and *dn*-AML-MDS (5%) patients ($p=0.001$). *NPM1* mutations distribution was similar in the two MDS-related AML groups, while *FLT3-ITD* was higher in AML-post-MDS (26.3%) compared to *dn*-AML-MDS (4.5%) ($p=0.049$) **(Fig. 1B)**.

The median TTL was significantly shorter in AML-post-MDS (4.80±1.04 months) than in AML-post-MPN (20.3±2.86 months) and CML-BC (34.7±16.3 months) ($p=0.008$) **(Fig. 2A)**. The median OS after LT was dismal in all studied groups; however, the analysis had significant major limitations due to different treatment approaches **(Fig. 2B)**.

Table 1. Major clinical and laboratory characteristics of the patients

	dn-AML-MDS n=30)	AML-post-MDS (n=30)	AML-post-MPN (n=20)	CML-BC (n=14)	*p* value
Demographic parameters					
Male:female	1.14:1	1.64:1	1.44:1	1.6:1	NS
Age, (years) (mean±SD)	64.4±11.9	62±16.6	63.4±11.5	46.9±13.8	0.005
Hematological indexes					
Hgb, (g/L) (mean±SD)	81.3±18.2	82.2±15.6	84.4±20.5	78.9±20.3	NS
WBC, ($\times 10^9$/L) (mean±SD)	15.5±33.8	26.3±43.3	73.1±81.4	133.2±154.5	<0.001
PLT, ($\times 10^9$/L) (mean±SD)	92.5±107.8	75.3±102.3	156.4±188.4	278.1±241.8	0.001
Bone marrow morphology					
% blasts (mean±SD)	42.4±17.4	45.8±21.5	55.1±25.6	29.8±17.4	NS
Dysgranulocytopoiesis, (%)	96.55%	61.54%	44.44%	20.00%	<0.001
Dyserythropoiesis, (%)	48.28%	57.69%	22.20%	0.00%	NS
Dysmegakaryocytopoiesis, (%)	72.41%	61.54%	55.55%	20.00%	NS
Dysplasia in >2 cell lineages, (%)	96.55%	100.00%	33.33%	0%	<0.001
Phenotype					
CD13, (% pos. pts)	93.33%	88.46%	75.00%	81.82%	NS
CD33, (% pos. pts)	93.33%	88.46%	93.75%	100.00%	NS
CD64, (% pos. pts)	50.00%	34.62%	25.00%	9.09%	NS
CD117, (% pos. pts)	100.00%	88.46%	93.75%	100.00%	NS
MPO, (% pos. pts)	53.33%	42.31%	25.00%	36.36%	NS
Lymphoid-associated markers, (% pos. pts)	70.00%	65.39%	50.00%	90.91%	NS
>2 lymphoid-associated markers, (% pos. pts)	36.67%	26.93%	37.50%	45.46%	NS
Cytogenetic and molecular aberrations					
Normal karyotype, (% pts)	25% (6/24)	58.3% (14/24)	33.3% (2/6)	42.2% (5/11)	NS
Aberrant karyotype, (% pts)	75%	41.7%	66.7%	57.8%	NS
Complex karyotype, (% pts)	45.8% (11/24)	20.8% (5/24)	50% (3/6)	0%	0.05
Unbalanced abnormalities	16.7% (4/24)	20.8%	16.7% (1/6)	40.0% (4/10)	0.05
Balanced abnormalities	12.5% (3/24)	0%	0%	10.0% (1/10)	0.05
Chromosome 5, (% pts)	40.0%	29.2%	33.3%	0.00%	0.053
Chromosome 7, (% pts)	36.0%	8.3%	0.00%	0.00%	0.012
FLT3-ITD, (% pts)	4.5%	26.3%	25.0%	NA	0.049*
EVI1 overexpression, (% pts)	5.0%	13.3%	37.5%	80.0%	0.001
NPM1 mutation, (% pts)	9.5%	20.0%	50.0%	NA	NS
Clinical course					
TTL months, (median±SD)	NA	4.80±1.0	20.3±2.9	34.7±16.3	0.008
OS months (median±SD)	6.17±2.77	4.17±0.77	5.17±2.79	13.67±4.58	NS

*Comparing *dn*-AML-MDS with AML-post-MDS

DISCUSSION

To our knowledge, no study has been published to date directly comparing hematological parameters at diagnosis of sAMLs developing on the basis of Ph(+)/Ph(-)MPN and MDS with *dn*-AML-MDS. As expected, our data clearly demonstrated significantly higher platelet counts and leukocytosis in sAML-post-MPN/CML-BC, in comparison with AML-MDS either *de novo* or secondary to MDS. Thus, the upregulated proliferation, which is a hallmark of MPNs, appears to be an essential mechanism also in LT after MPN/CML, which is in line with other authors.[11] We found that WBC were higher in secondary MDS-associated cases than in *de novo* MDS-associated cases, which may support the

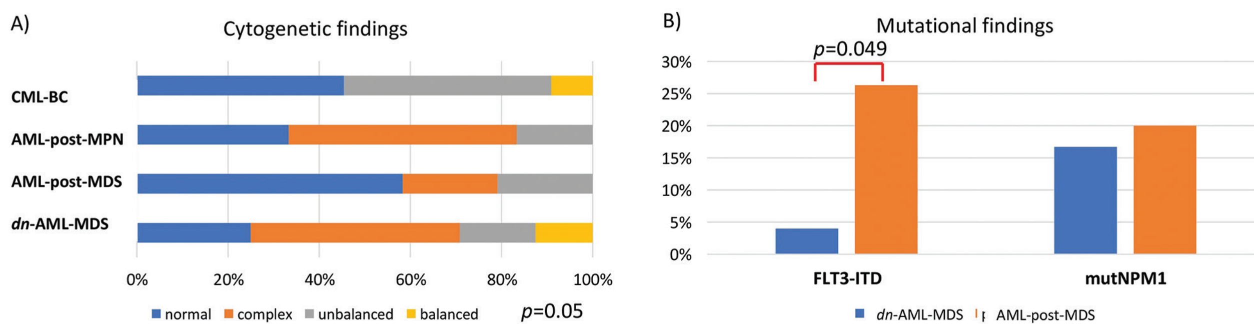

Figure 1. **A**) Cytogenetic incidence: aberrant karyotypes including normal did not differ between groups. **B**) Mutational findings in patient cohort comparing AML-post-MDS vs. *dn*-AML-MDS with significant difference regarding *FLT3-ITD* mutation.

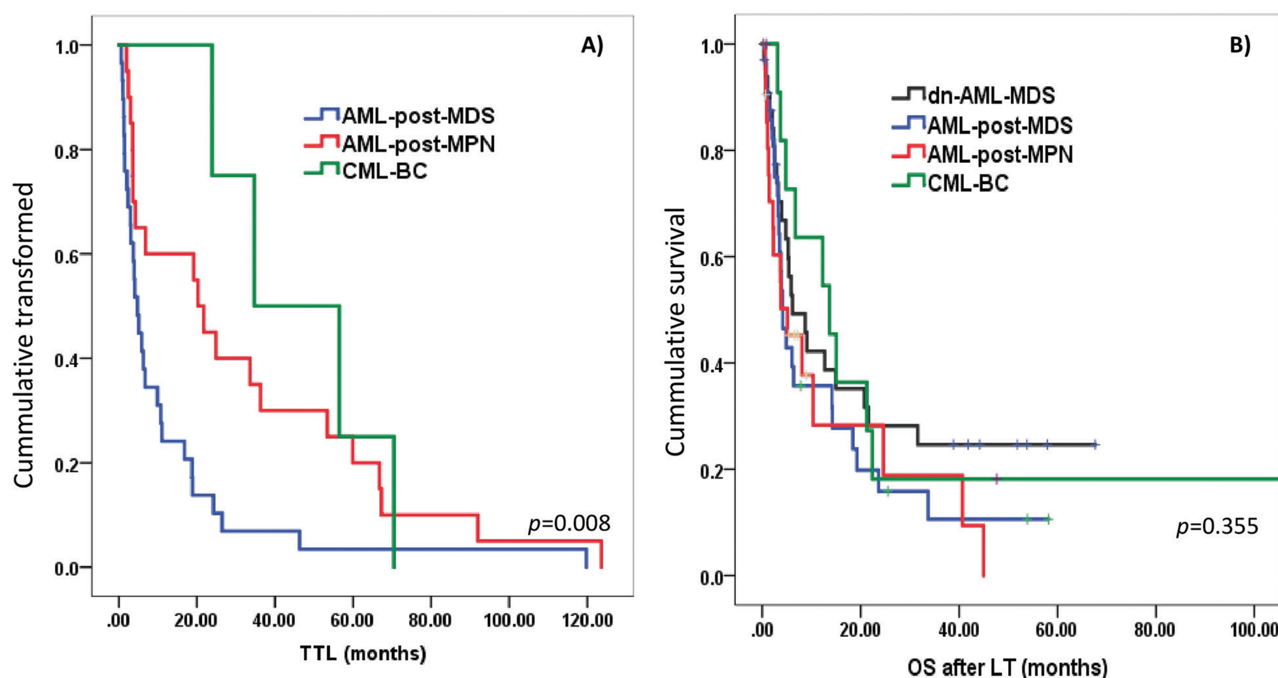

Figure 2. Comparison of the TTL in patients with sAML and CML-BC and the OS in the entire cohort. **A**) The median TTL is significantly shorter in AML-post-MDS (4.80±1.0 months) than in AML-post-MPN (20.3±2.9 months) and the longest in CML-BC (34.7±16.3 months) (Kaplan Meyer log rank test, p=0.008); **B**) No difference in the OS (Kaplan Meyer log rank test, p=0.355) despite the fact that CML-BC patients (median OS 13.67±4.58 months) tended to have the longest OS compared with the *dn*-AML-MDS (median OS 6.17±2.77 months) and sAMLs groups (median OS in AML-post-MDS, 4.17±0.7 months; median OS in AML-post-MPN 7 5.17±2.79 months).

hypothesis that these conditions follow to some extent a different pathogenesis pathway. Altered apoptosis-proliferation balance plays a key role in MDS progression to AML, demonstrated by increased anti-apoptotic and pro-proliferative signals as well as increased expression of Bcl-2 in our previous studies as well as by other authors.[12,13] Regardless of the different WBC counts, blasts % showed similar values. The distribution of immature cells in PB/BM in AML relates to tumor burden, but also to homing, mediated by the expression of cell surface molecules such as SCF-receptor, CD117, CXCR4 (CD184), LFA (CD11a/CD18), VLA-4, CD34, CD38, HLA-DR, etc. on leukemic blasts both in AML and CML.[14,15]

Morphological dysplasia is currently an important aspect of the discussion. It is a key characteristic of AML cases currently classified as AML-MDS, which is a heterogeneous group comprising *de novo* and secondary cases. As expected, we also found a significantly higher incidence of dysplastic changes in ≥2 lineages in both categories. However, evidence has recently showed that AML-MDS defined only by morphological findings may not represent a poor prognosis AML.[16-18] According to Haferlach et al., if cytogenetic alterations are considered, dysplastic morphology has no additional impact on prognosis.[19] However, Weinberg et al. found an association between frequent micro-megakaryocytes and shorter event-free survival.[18] A study of Miesner et al. showed no significant differences in prognosis between AML arising from MDS and *dn*-AML-MDS.[20]

However, our results did not prove any direct association between the presence of specific dysplastic morphology and the disease prognosis, myelodysplasia-related cytogenetics, and history of previous MDS or MPN (data not shown). Further detailed subgroup studies are warranted.

Immunophenotypic aberrancies such as the co-expression of LAM are still doubtable and most of the studies lack detailed subgroup analysis reflecting the secondary nature of AML.[21] The most frequently expressed aberrant markers detected in our cohort were CD7, CD19, CD56, and CD22. Our results regarding CD7 are consistent with reported general incidence of 20%-44% in AML[22], which in *de novo* AML is associated with *FLT3-ITD*[23]. Similar to our findings, Saito et al. found CD22 in 17.2% of sAML. [24] There is evidence that CD22 as well as CD56 expression in AML correlates with poor prognosis.[25,26] Various studies showed that CD19 is not restricted to cytogenetic or FAB categories and there may be certain geographical variations.[27,28] Detection of ≥2 LAM in our hands was evenly distributed across the leukemia subgroups and was related to lower OS; however, this should be confirmed in larger scale prospective controlled studies. AML development is the result of the stepwise acquisition of chromosomal and/or molecular abnormalities, whether the disease arises *de novo* in the absence of an identified exposure or prodromal stem cell disorder or if it evolves from antecedent hematological disorders such as MPN or MDS.[29,30] In total, we found chromosomal aberrations in 57.8% of all patients, which corresponds to commonly reported rates in AMLs in general (59.0%)[31-33], as well as to population-based cytogenetic studies of adult sAML and age/sex-matched *dn*-AML that showed comparable distributions of chromosome abnormalities[34]. The low number of cases in the separate subgroups did not allow us to establish statistically significant tendencies; however, *dn*-AML-MDS clearly demonstrated a distinct cytogenetic pattern – the highest incidence of abnormal karyotypes with the highest number of complex karyotypes, aberrations of chromosome 7 and a certain proportion of balanced abnormalities. Our findings contradict previous studies of more frequent aberrations in sAML (73.2%) compared to *dn*-AML-MDS (40%)[35,36]; however, both studies were limited in terms of insufficient number of patients. Similarly, the biology and genetic landscape of LT of Ph(+)/Ph(-)MPNs is much less understood compared to their chronic phases and further studies are needed.[37]

Apart from the impact of chromosomal abnormalities, the development of AML is driven by somatic mutations resulting in the clonal expansion of stem cells. In this connection, we investigated the distribution of some of the most relevant gene mutations in AML diagnosis. *FLT3* are one of the commonest, and clinically challenging, class of AML mutations. In general, they are detected in about twenty-five of *dn*-AML and are associated with increased relapse and inferior OS.[35,38,39] Pasca et al. found differences in the mutational landscape of AML-post-MPN and *dn*-AML in several key aspects, including lower frequencies of *FLT3*-mutations after MPNs.[40] Similarly, in the present study, we found *FLT3-ITD* in only 14% of AML-post-MPN compared to 23.3% in all AMLs according to our previously published data.[41] About all MDS-related AMLs, the incidence of *FLT3-ITD* in our study was comparable to literature data (14-16%).[42] Interestingly, the prevalence in AML-post-MDS was significantly higher compared to *dn*-AML-MDS, consistent with studies showing that *FLT3-ITD* mutation in MDS patients is associated with early transformation to AML.[43] However, no data could be found to explain the low numbers in the *de novo* group. In contrast to these differences, distribution of *NPM1* mutations was comparable between *dn*-AML-MDS and sAML-post-MDS/MPN. Approximately one-third of *dn*-AMLs are *NPM1*-mutated which correlates with unique molecular, pathological, and clinical features, but impact in sAML following MDS/MPN remains unclear.[44] Some studies showed that *NPM1* mutations in AML-post-MDS/MPN comprise 12%-14% and may be involved in the LT as they are characterized with higher frequency of secondary-type mutations and inferior prognosis.[45,46] Another relevant biomarker known to contribute to disease progression in myeloid malignancies is overexpression of *EVI1*. Deregulated *EVI1* gene expression is a molecular hallmark of inv(3)/t(3;3) but can also be detected in about 8%–10% of MDS, 6%–11% of *dn*-AML, and 30% of advanced CML that do not carry any 3q aberrations.[47] We detected *EVI1* overexpression with the highest incidence of patients with CML-BC and AML-post-MPN, and in a lower proportion of *de novo* and secondary MDS-related AMLs, none of which were associated with chromosome 3 aberrations. This is in line with the available observations suggesting that *EVI1* overexpression collaborates with *BCR-ABL1* in the evolution of TKI-resistant myeloid CML-BC. The transcriptional factor plays a role in leukemogenesis, affecting the survival, growth, and repopulation of hematopoietic stem cells. Therefore, it may be one of the genetic lesions in the progression of *JAK2*(+)-MPN to AML.[43,48]

Our data outline the presence of common characteristics, e.g., cytogenetic abnormalities, complex karyotypes, and chromosome 5 aberrations. However, differences could also be observed, e.g., prevalence of proliferation patterns, *EVI1*-overexpression, and lack of chromosome 7 aberrations in post-Ph(+)/Ph(-)MPN leukemias, *FLT3-ITD* patterns in *dn*-AML and sAMLs, etc.

Differences may underlie variations in the observed time to overt leukemia presentation which in our study is consistent with published data.[49,50] Survival analysis based on the mutational status - *NPM*, *FLT3* and *EVI1*, did not demonstrate significant impact on TTL and OS analyzed either in the entire cohort or in the subgroups (data not shown). The major limitation was the small size of the subgroups defined by the mutational status and the specific disease category. Therefore, the intention is to do this analysis after recruiting more patients in a prospective manner. However, the subsequent clinical behavior is ultimately decisive for the dismal outcomes and poor overall survival.[36,51]

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CONCLUSIONS

Our study has certain limitations, such as the retrospective design and the low number of patients in the separate categories compared. However, it clearly demonstrates similarities and differences among these four entities, which reflect the biological heterogeneity of diseases. Understanding the pathogenetic mechanisms may allow us to apply different preventive and/or therapeutic approaches in the future, and it is worth conducting further studies to investigate.

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Competing Interests

The authors have declared that no competing interests exist.

Author contribution

All authors have contributed equally to this work

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Вторичный острый миелолейкоз и острый миелоидный лейкоз De Novo с изменениями, связанными с миелодисплазией – подобные или совершенно различные?

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Резюме

Цель: Сравнить основные особенности больных вторичными острыми миелолейкозами (AML) после постмиелодиспластического синдрома (AML-post-MDS) или постмиелопролиферативных новообразований (AML-post-MPN) и миелоидного бластного криза хронического миелолейкоза (CML-BC) по сравнению с AML *De Novo* с миелодиспластическими характеристиками (*dn*-AML-MDS).

Материалы и методы: В анализ включены образцы костного мозга/периферической крови 94 пациентов с вторичными AML (30 с AML-post-MDS, 20 с AML-post-MPN и 14 с CML-BC) и 30 с *dn*-AML-MDS. Были проанализированы демографические, морфологические, фенотипические, цитогенетические данные и данные о выживаемости.

Результаты: Сравнительный анализ не выявил различий по полу и возрасту, за исключением более молодого возраста при CML-BC (p=0.005). Лейкоцитоз был преобладающим признаком CML-BC по сравнению с AML-post-MPN, AML-post-MDS и *dn*-AML-MDS (p<0.001). В начале лейкоза тромбоцитопения была характерна для AML-post-MDS и *dn*-AML-MDS, тогда как нормальные показатели PLT были обнаружены при AML-post-MPN и CML-BC (p=0.001). Дисплазия в ≥2 линиях наблюдалась почти во всех случаях *dn*-AML-MDS (96.8 %) и AML-post-MDS (100 %) по сравнению с AML-post-MPN (33.3 %) и ни в одном из случаев CML-BC (p=0.001). Аберрантная коэкспрессия 1-4 лимфоид-ассоциированных маркеров была обнаружена у 67.5% всех пациентов, включая CD7, CD19, CD56 и CD22. Мы обнаружили хромосомные аберрации у 57.8 % пациентов, чаще при AML-post-MDS, чем при AML-post-MPN, CML-BC и AML-post-MDS. Хотя распределение мутаций NPM1 было сходным в двух группах AML, связанных с МДС, FLT3-ITD был выше при AML-post-MDS (26.3 %), чем при dn-AML-MDS (4.5%) (p=0.049). Что касается EVI1, CML-BC (80 %) и AML-post-MPN (37.5 %) показали более высокую частоту гиперэкспрессии генов по сравнению с AML-post-MDS (13.3 %) и *dn*-AML-MDS (5.0 %) (p=0.001). Медианное время до лейкоза было значительно короче при AML-post-MDS (4.80 ± 1.04 месяца), чем при AML-post-MPN (20.3 ± 2.86 месяца) и CML-BC (34.7 ± 16.3 месяца) (p=0.008), а общая выживаемость была плохой во всех группах.

Заключение: Сходства и различия между пациентами с вторичными AML могут отражать различную биологию, что приводит к различному клиническому течению и может потребовать различного терапевтического подхода в будущем.

Ключевые слова

острый миелолейкоз, бластный криз, миелодисплазия, миелопролиферативное заболевание