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Review

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Chronic myelomonocytic leukemia "myelodysplastic type" in transformation to acute myeloid leukemia - diagnostic and therapeutic options: case report and literature review

Leucemie mielomonocitară cronică forma mielodisplazică în transformare spre leucemie acută mieloidă - diagnostic și opțiuni terapeutice: prezentare de caz și revizuirea literaturii

Mihaela Cîrstea[1,*], Adriana Coliță[2], Bogdan Ionescu[1], Didona Vasilache[1], Camelia Dobrea[1,2], Cerasela Jardan[1], Mihaela Dragomir[1], Anca Gheorghe[1], Delia Codruța Popa[1,2], Zsofia Varady[1], Anca Roxana Lupu[2,3], Daniel Coriu[1,2]

[1]Centre of Hematology and Bone Marrow Transplant, "Fundeni" Clinical Institute, Bucharest, Romania,
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Hematology Department, Coltea Hospital, Bucharest, Romania

Abstract

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder that is characterized by the presence of an absolute monocytosis (1 x 10^ 9/l) in the peripheral blood, the overlap of myelodisplastic aspects and myeloproliferative aspects in the bone marrow and tendency to transform into acute myeloid leukemia. CMML is considered to be the most aggressive chronic myeloid leukemia. We present the case of a 48 years old woman who was hospitalized in March 2013 in the Center of Hematology and Bone Marrow Transplantation for anemia related symptoms. Initial investigations showed anemia, relative monocytosis (10% monocytes of the WBC differential) with an increasing absolute number of monocytes (> 1,000/µl) in the following months. Initial exploration of the bone marrow (aspirate and bone marrow biopsy and immunohistochemistry IHC tests) revealed elements of trilinear dysplasia and an increased percentage of myeloblasts (11-14%). In the next four months myeloblasts percentage remained below 20% (8-14%) and it has been observed a gradually increasing of monocytoid elements (> 20%). Immunophenotyping in the bone marrow aspirate identified a monocytic proliferation with high percentage (8%) of immature cells. The karyotype reported the presence of clones with t (1;3). Initially diagnosed as RAEB-2 (WHO) the case was recomitted in CMML-type 2 with a progression to acute myeloid leukemia (AML). Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been performed after getting the best possible therapeutic response with AML chemotherapy type (complete remission). Allo-HSCT was performed using myeloablative conditioning, 12 months after diagnosis. The patient is now in complete remission, 24 months after allo-HSCT.

Keywords: *chronic myelomonocytic leukemia, acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation.*

*** Corresponding author:** Mihaela Cirstea, Centre of Hematology and Bone Marrow Transplant, "Fundeni" Clinical Institute, Bucharest, Romania e-mail: mihaelamustata84@yahoo.com

Rezumat

Leucemia mielomonocitară cronică (LMMC) este o afecțiune clonală a celulei stem hematopoietice care se caracterizează prin prezența unei monocitoze absolute (1x 10^9/l) în sânge periferic, suprapunere de aspecte de mielodisplazie cu aspecte mieloproliferative în măduva osoasă și tendința de transformare în leucemia acută mieloidă (LAM). LMMC este etichetată ca cel mai agresiv neoplasm mieloid cronic. Prezentăm cazul unei paciente de 48 ani internată în martie 2013 în Centrul de Hematologie și Transplant Medular pentru suferințe legate de anemie. Investigațiile inițiale au arătat anemie, monocitoză relativă (10% monocite în formula leucocitară) cu creșterea numărului absolut de monocite (>1,000/µl) în următoarele luni. Explorarea inițială a măduvei osoase (aspirat, puncție biopsie măduva osoasă și teste de IHC) a evidențiat elemente de displazie trilineară și procent crescut de mieloblaști (11-14%). În următoarele 4 luni procentul de mieloblaști a rămas sub 20% (8-14%) și s-a notat creșterea treptată de elemente monocitoide (>20%). Imunofenotiparea pe aspirat de măduva osoasă a identificat o proliferare de celule monocitare cu procent crescut (8%) de celule imature. Cariotipul a semnalat prezența unei clone cu t (1;3). Diagnosticată inițial ca AREB-2 (WHO) cazul este reincadrat ca LMMC-tip 2 cu progresie spre leucemie acută mieloidă. Se decide allotransplantul cu celule stem hematopoietice după obținerea prin chimioterapie tip LAM a celui mai bun răspuns terapeutic posibil (remisiune completă). Allotransplantul cu celule stem hematopoietice s-a efectuat la 12 luni de la diagnostic cu condiționare mieloablativă. Pacienta se afla în remisiune completă la 24 luni de la allotransplantul cu celule stem hematopoietice.

Cuvinte cheie: *leucemia mielomonocitară cronică, leucemia acută mieloidă, allotransplantul cu celule stem hematopoietice.*

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Introduction

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder that is characterized by the presence of an absolute monocytosis (1 x 10 ^ 9/l) in the peripheral blood, the overlap of myelodisplastic aspects and myeloproliferative aspects in the bone marrow and tendency to transform into acute myeloid leukemia [1,2]. CMML was initially defined in 1982 as the 5th category of myelodysplastic syndrome (MDS) by the French American British (FAB) group and was divided according to the degree of leukocytosis in two subtypes: MDS-CMML (leukocytes <13 x 10 ^ 9 /l) and MPN-CMML (WBC> 13 x 10 ^ 9 / l) [3]. MDS-CMML is considered a stage in the evolution of CMML. In 2001, WHO reclassified CMML as a new entity and included it in ''MDS/ MPNs overlap diseases'' along with juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (aCML) and MDS /MPN unclassifiable (MDS /MPN-U). In 2008, the category of ''MDS / MPN overlap disease'' is named ''MDS/MPN neoplasms'' emphasizing the neoplastic nature of these diseases [2].

The diagnostic criteria for CMML revised by WHO in 2016: 1) persistent peripheral blood (PB) monocytosis 10^9/L with monocytes accounting for 10% of white blood cell (WBC) count; 2) not meeting WHO criteria for BCR-ABL+ CML, PMF, PV, ET; 3) no evidence of PDGFRA or PDGFRB or FGFR1 rearrangement or PCM1-JAK2- should be excluded in cases with eosinophilia); 4) <20% blasts (myeloblasts, monoblasts, promonocytes) in the blood and bone marrow (BM); 5) dysplasia in one or more myeloid lineages.

If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if: a) an acquired clonal cytogenetics or molecular genetic abnormality is present in hematopoietic cells or b) the monocytosis has persisted for at least 3 months, and c) all other causes of monocytosis (infection, inflammation, malignancy) have

been excluded [4]. Rare cases of MPN can be associated with monocytosis and may simulate CMML. A previous documented history of MPN excludes CMML [4]. Based on the percentage of blasts and promonocytes in the blood and BM, WHO (2008) divided CMML into two categories: a) CMML-1: <5% blasts and promonocytes in peripheral blood and <10% blasts and promonocytes in BM; b) CMML-2: 5-19% blasts and promonocytes in peripheral blood and 10-19% blasts and promonocytes in BM [1,3]. Cytogenetic abnormalities were detected in approximately 30% of cases and included trisomy 8, monosomy 7, del (7q), 12 p rearrangements and were described in cases with an increased percentage of blasts in the blood and bone marrow and in those with dyseritro or dysgranulopoiesis. A CMML Specific Cytogenetic System stratifies patients into three risk groups: high risk (+8, -7, del (7q), complex karyotype), low risk (normal karyotype, -Y), intermediate risk (all other abnormalities) with overall survival 4%, 26%, 35% at 5 years [5]. The WHO 2016 revision of CMML was supported by recent advances in genetics and molecular pathogenesis. 90% of patients with CMML present molecular abnormalities, but none of them is specific. Recurrent mutant genes encode signaling molecules, epigenetic regulators, ‘’splicing factors’’, regulators of transcription, tumor suppressor genes (TP53). TET2 (50-60%), SRSF2 (40-50%), ASXL1 (30-40%), RUNX1 (15%) are the most frequently involved. ASXL1 mutation is associated with poor prognosis. Recurrent mutations in genes (TET2, ASXL1, SRSF2) are not specific to the disease, but their increased frequency in CMML has created a ‘’unique genomics identity’’. A ‘’clonal architecture’’ was admitted in CMML, in which an orderly accumulation of mutations of the progenitor cell exists: first mutations involve TET2 (or IDH1 or IDH2) or ASXL1 followed by mutations in spliceosome component (SRSF2). In about 30-40% of cases there is a mutation in the signal transduction including hypersensitivity to GM-CSF and that results in myeloproliferative phenotype [6]. RAS mutations contribute to evolution of CMML to the proliferative phenotype. The JAK2 V617F mutation appears in <10% of MPN-CMML [7].

CMML is considered to be the most aggressive myeloid chronic cancer with a survival rate of 20% in 3 years [8]. The incidence is 1 / 100,000, with an average age of 70 years and M: F ratio = 2/1 [7]. CMML is heterogeneous: some cases have a slow evolution, other cases progress rapidly into acute myeloid leukemia (AML). The disease presents with a variable clinical and biological phenotype: patients with MDS-phenotype present cytopenias, mild bleeding, transfusion dependence, and those with the MPN phenotype present leukocytosis, monocytosis, hepatosplenomegaly, pleural effusions, skin lesions, constitutional symptoms (night sweats, weight loss, cachexia) [9,10,11]. Rare cases of CMML have been reported following cytostatic chemotherapy or following MDS [7,12,13]. One of the most important prognostic indicators in CMML is the number of blasts. CMML-1 characterized by <5% blasts in the blood and <10% blasts in BM, had a risk of 18% of transformation into AML at 5 years. CMML-2 with 5-19% blasts in the blood and 10-19% blasts in BM is associated with 63% risk of transformation into AML at 5 years [14]. Recent reports have shown that a more precise prognostic can be obtained in CMML with 3 blast based grouping and the WHO 2016 revision incorporates the CMML-’’0’’ category into the classification. CMML-’’0’’ is a category for cases with < 2% blasts in PB and <5% blasts in BM [4,15]. Patients with CMML-’’0’’ have a better prognosis and a lower risk of progression to AML than CMML 1 and 2.

The prognosis in CMML was the objective of numerous studies. There are 7 clinical prog-

nostic score models and 2 with incorporation of molecular markers (ASXL1 mutations) [6]. The commonly used system for CMML-MDS is IPSS-R (the International Prognostic Scoring System -Revised). Some of the most used prognostic scoring systems are: MDAPS (the MD Anderson Prognostic Scoring System), Mayo score, CPSS score (The CMML Specific Prognostic Scoring System) [13,16,17]. Score CPSS was created in 2013 using four prognostic variables for overall survival and risk of transformation into AML (FAB subtype, WHO subtype, CMML specific cytogenetic risk groups and transfusion dependence of packed red blood cells [17]. This score confirmed the prognostic impact of FAB and WHO subtypes, cytogenetics and admitted the importance of transfusion dependence. A recent review found that CPSS is the best score system in terms of predicting overall survival in CMML and it could be more robust if the number of platelets would be added [18].

Treatment in CMML is not standardized. The most common options are represented by hydroxycarbamide used for cytoreduction in patients with MPN phenotype and hypomethylating agents used for the MDS phenotype and cytopenias. Taking into account the current treatments, CMML remains an incurable disease. Nowadays, allogeneic hematopoietic stem cell transplantation (allo HSCT) is the only modality of treatment associated with long-term remission and curative potential [7].

Case presentation:

We present the case of a 48 year old woman who was admitted in March 2013 in the Center of Hematology and Bone Marrow Transplantation Fundeni Clinical Institute for the investigation of an anemic syndrome. Physical examination revealed: sclero-tegumentar pallor, no fever, no bleeding syndrome, lymphadenopathy or organomegaly.

Laboratory examinations revealed: Hb=7.0 g/dl, Ht=23%, MCV=100 fl, Platelets= 241,000/µl, WBC=7,790/µl nonsegmented 1% segmented 35% eosinophils 1% lymphocytes 52% monocytes 10% (770 /µl). Bone marrow aspirate showed the presence of 10-11% myeloblasts and elements of dysplasia: hypogranular granulocytes, megaloblastoid forms to the erythroid series, hypolobulated megakaryocytes **(Figure 1).** The peroxidase stain on bone marrow aspirate was positive in 14% blasts (myeloblasts). Bone marrow biopsy (BMB) showed: normal cellularity, moderate hyperplasia of granulocytic series, rare erythroblast groups, small megakaryocytes (MK) with hypolobulated nucleus. Immunohistochemistry (IHC) stain for CD34 revealed 12-14% positive cells **(Figure 2)**.

On the cytogenetic examination, 6 metaphases were obtained and t (1;3) was found in 3 metaphases. Between March and June 2013 patient required repeated hospitalizations for anemia related symptoms and required repeated transfusions of packed red blood cells. Growth factors (erythropoietin, granulocyte colony stimulating factor G-CSF) were not administered. The complete blood counts performed during these months have changed: the presence of blasts (1%) in PB, neutropenia and gradual increase of absolute value of monocytes > 1000/µl (values 1400-1700/µl). The bone marrow aspirate (at 3 months from the presentation) showed: 5-6% myeloblasts and 6-7% promonocytes. On BMB, CD34+ cells were 12-14%. At five months from diagnosis, the percentage of myeloblasts in bone marrow (aspirate, BMB and IHC for CD34) remained below 20% (8-14%) and an increase in the population of polymorphic monocytoid elements (34%) was noted, which was characterized by immunophenotyping as monocytic component with high percentage of young cells (8%) **(Figure 3)**.

The cytogenetic study was repeated in July 2013. Bone marrow samples were cultured us-

ing overnight and synchronized culture and processed by conventional cytogenetic procedures with GTG banding**.** Twenty metaphases were analyzed and the karyotypes were described according to International System for Human Cytogenetic Nomenclature (ISCN) 2013 [19].

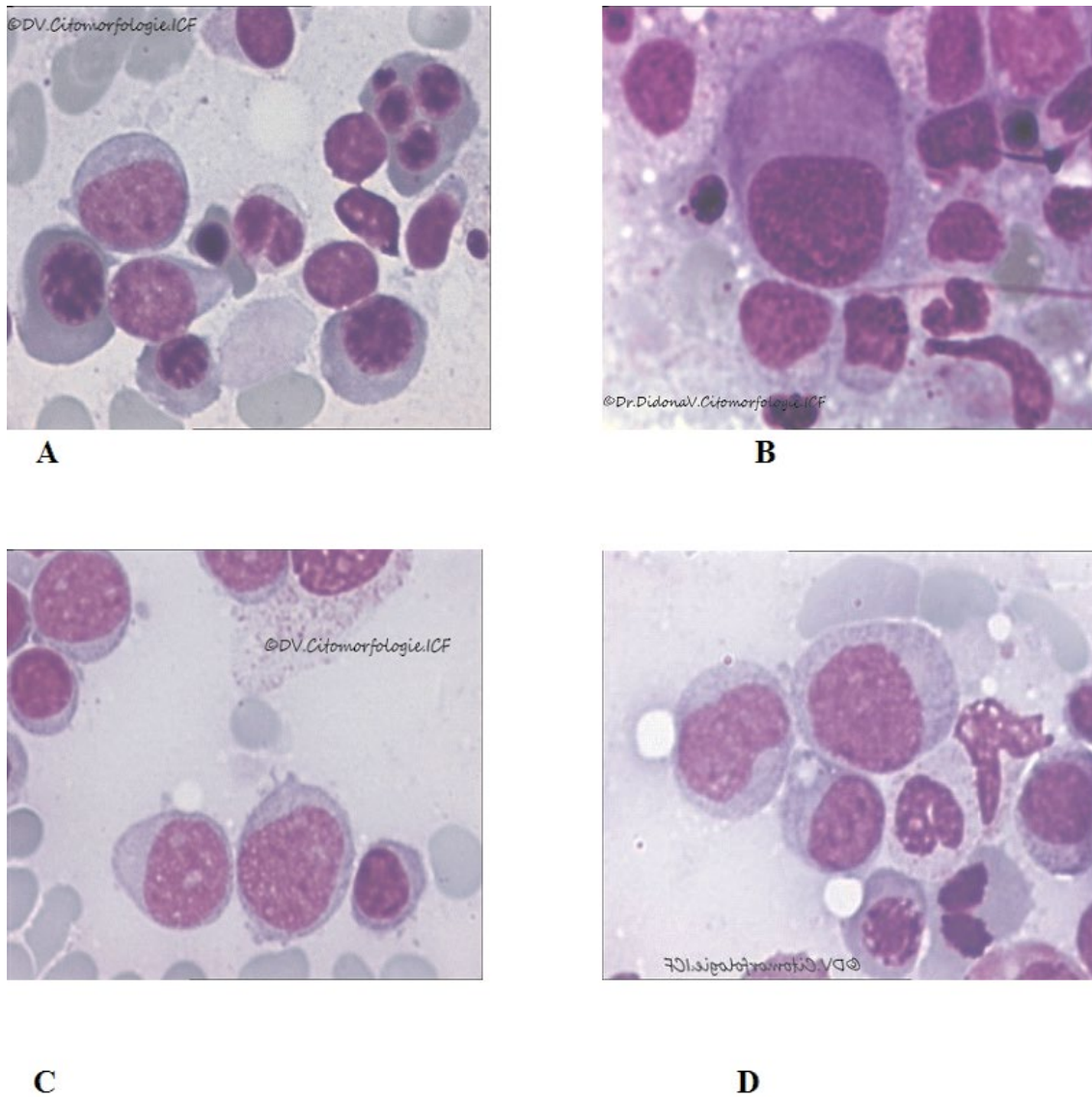
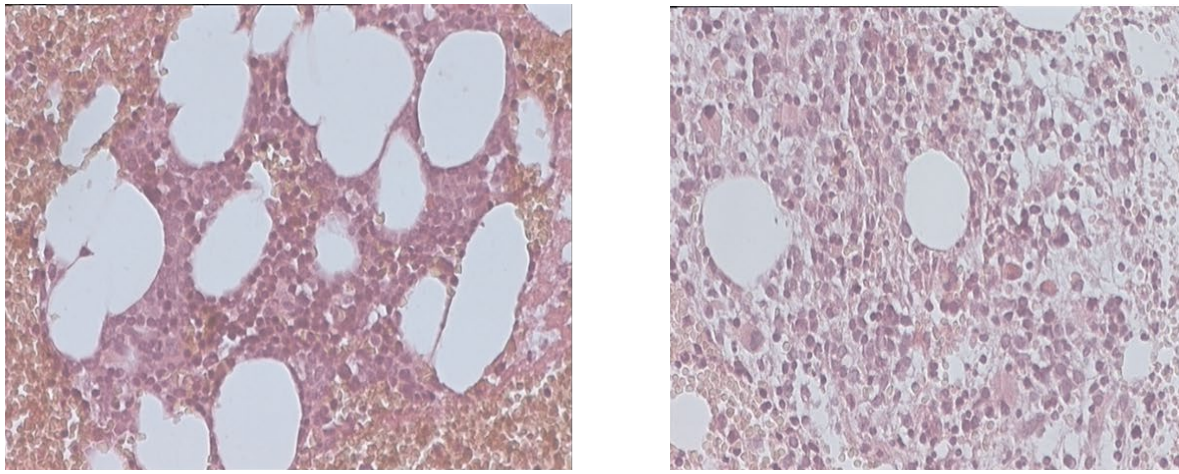


Figure 1. Bone marrow smear (MGG stain, ob 100x, oil immersion):
A - dysplastic bi- and multinucleated erythroblast;
B - atypical micromegakaryocyte;
C - myeloblasts;
D - monocytoid elements.



A B

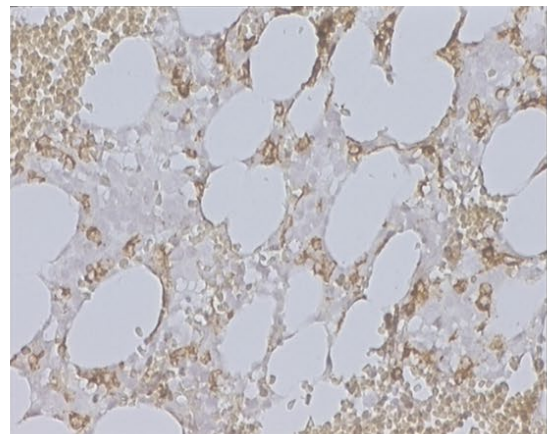


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Figure 2. A - Bone marrow trephine biopsy: preserved marrow cellularity, left shift deviation; megacaryocytes hypoplasia with nuclear hypolobulation. (H&E stain, ob 20x); B - Bone marrow trephine biopsy: left shift deviation; dysplastic megacaryocytes; C - Bone marrow trephine biopsy - high percentage (˜12-14%) of CD34 positive blasts (IHC stain for CD34, ob 20x).

The cytogenetic study showed 11 cells with t (1;3) and the other cells with normal karyotype (46, XX) **(Fig.4)**.

The molecular biology tests were negative for: BCR-ABL1, FLT3-ITD, NPM1, E2A-PBX1, MLL-AF4, CBFb- MYH11, SIS-TAL MLL- AF9.

This case was initially classified as myelodysplastic syndrome: refractory anemia with excess blasts (RAEB-2) (WHO). Initially, relative monocytosis (>10% monocytes) of differential white blood count at the moment of diagnosis and then absolute (> 1000 /µl) and persistent

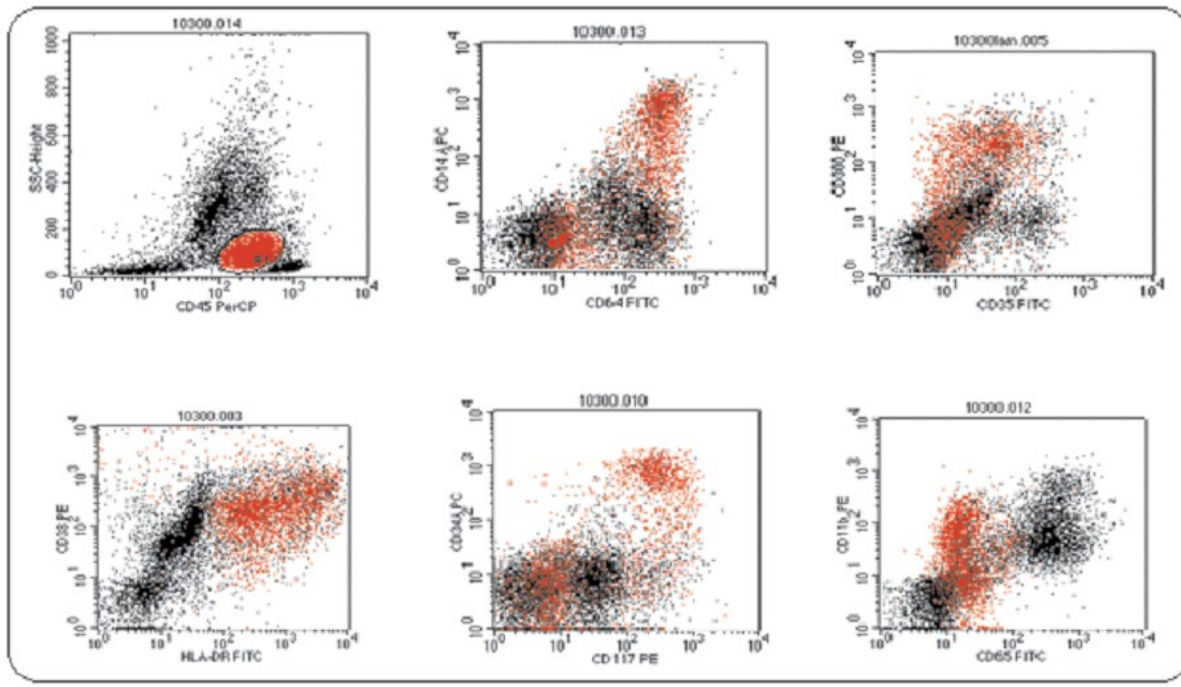

Figure 3. Bone marrow immunophenotyping (July 2013): identified a population of CD45 positive cells, internal complexity average (40%) expressing monocyte pathological cell markers (CD56 expressing) in various stage of maturation:

- Myeloid hematopoietic progenitors icMPO -/+ weak, CD117+, HLA-DR+, CD34+, CD13+, CD33+ weak, CD38+, CD 123 + weak (14%),
- Monoblasts CD64 + and CD14- (8%)
- Mature monocytes CD64 + and CD14 + (18%) they co-expressed Cd36, CD11b, CD300e +, CD4 + weak CD33 ++ intense, CD13 + heterogeneous, CD38 +, CD123 +weak, icMPO + weak, CD35 + partially.

monocytosis (> 3 months) and the progressive increase in percentage of polymorphic monocytoid cells in the bone marrow led to a change of the diagnosis to CMML-2 (WHO) with progression to AML. The criteria to support the diagnosis of CMML-2 in this case were: 1) initially relative monocytosis (10% of differential white blood count) and then absolute monocytosis (>1000 /µl) that persisted more than 3 months; 2) percentage of blasts in BM <20% composed of myeloblasts + monoblasts + promonocytes; 3) the presence of clonal cytogenetic abnormalities t (1;3); 4) absence BCR-ABL1; 5) dysplasia in bone marrow on erythroid, megakaryocytic and granulocytic series. This case was included in the following risk-groups: a) according to IPSS-R: very high risk with a survival rate of 0.8 years and 28% risk to evolution into AML at 0.73 years; b) according to CPSS: intermediate-2 risk groups; OS 15 months and risk of 49% of transformation to AML at 2 years. Patient data (48 years, young woman, without comorbidities, with a good Karnofsky performance status) and disease-related data (CMML- type 2 with a very

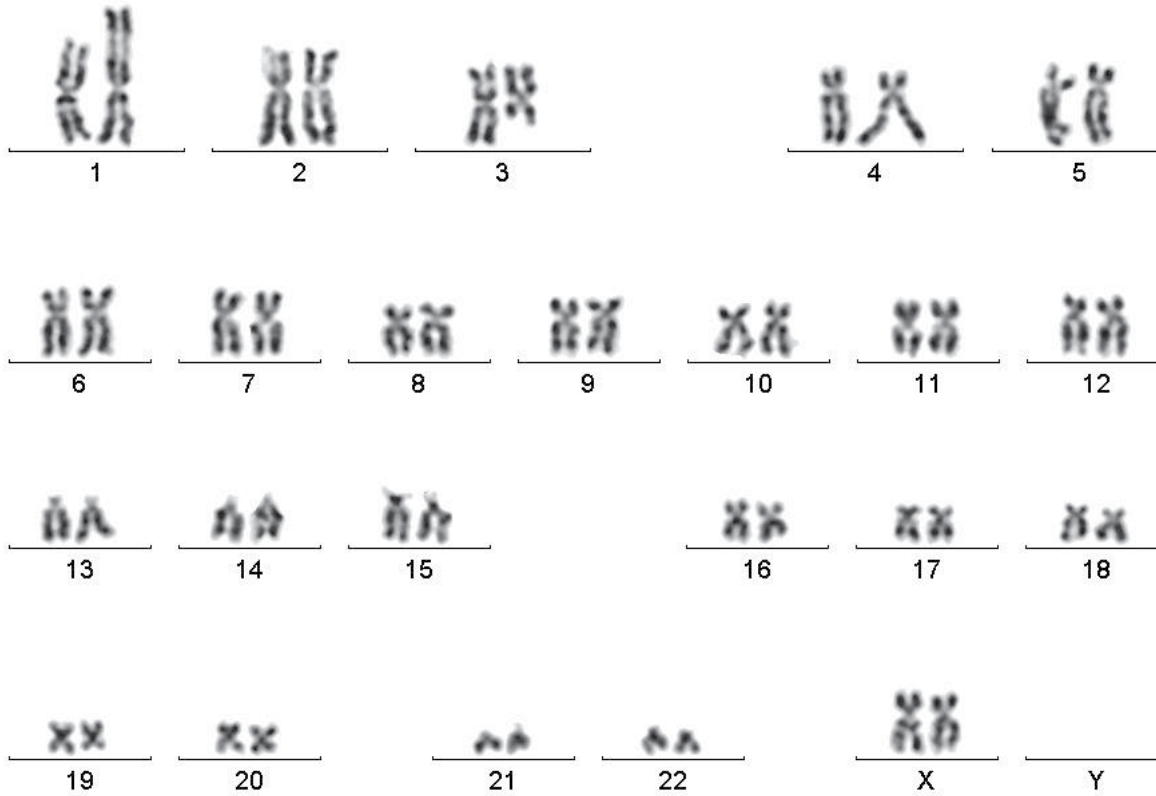

Figure 4. Cytogenetic analysis: 46, XX, t(1;3) (p36.2;q22).

high risk score concerning the survival and progression to AML) led to the decision to choose the allo-HSCT, once complete remission (CR) using AML type chemotherapy was obtained. The treatment consisted in AML type chemotherapy: 2 cycles ''3 + 7'' of daunorubicin and cytarabine (DNR + ARA-C) in June and September 2013 and 2 EMA cycles (Etoposide + Mitoxantrone + ARA-C) in November 2013 and January 2014. Each treatment was followed by long periods (~ 30 days) of severe febrile cytopenia. Recovery from cytopenia occurred after each treatment with an unusual increase in absolute number of monocytes and restoration of neutrophils number. Hematologic control in February 2014 revealed on bone marrow aspirate: 4% myeloblasts, 9% monocytoid elements. On April the 9th 2014, at 12 months after diagnosis, the patient underwent allo- HSCT with peripheral stem cell from matched unrelated donor. **Table 1** shows the patient's data when she was admitted for the transplant and the information related to transplantation and posttranplantation evolution.

Discussion:

Allo-HSCT is the only treatment option associated with long term remission and the only potential curative one in CMML. Data for Allo-HSCT results in CMML can be found in the reports on allo-HSCT in MDS and MPN or in retrospective studies on small number of CMML transplanted patients. There are no randomized prospective

Table 1. Clinical and laboratory data of the patient

Patient characteristics, A.N, at allo TCSH's time (IPV 2014)	Age: 49 years
	HCT-CI Score: 0
	Karnofsky Performance Status: 100%
	CPSS: intermediate 2
	IPSS-R: high risk
	Disease Status: PR
	Cellularity BM: 80%
	Blasts in BM:4-5%
	Karyotype: (1;3)
	Time from diagnosis in transplation: 12 months
	CMV: positive
Data related to the transplant	Sex donor: man
	Donor age: 30 years
	Donor type: unrelated
	No mismatch HLA:1 (DQB)
	ABO group: Pacient: grup 0 + Donor: grup 0+
	GVHD prophylaxis: CSA + MTX
	Conditioning regimen: myeloablative (Bu/ Cy/ ATG-F20)
	No stem cellsCD 34: 5x 10^6/kg
	RecipientCMV: positive Donor: negative
Data related to A.N. pacient's post alloTCSH evolution	Grafting time (days after transplantation) - Neutrophils > 500/µl Day20 - Platelets > 20,000/ µl Day24 -Ret > 1% Day33
	Complet chimerism: Day 100
	Acute GVHD: No Chronic GVHD: No
	CMV reactivation → without CMV reactivation infection
	Folow 24 months; (Alive in april 2016)
	Current status: CRt MO:1-2% Mbl + 1-2% monocytoid elements Bone marrow immunophenotyping: 1-2% monocytoid elements

Table 2. The main studies on Allo-HCST in CMML in 2012-2015 [20].

Reference	Year	N	Age	RIC	URD	OS	Relaps	NRM	Factors associated with shorter OS
Symeonidis [21]	2015	513	53	44%	44%	4Y-33	4Y-32%	4Y-41%	Not in CR at HSCT
Duon [22]	2015	209	57	46%	60%	5Y-44/18%	5Y-52%	5Y-22/26%	High CPSS, low KPS, bone marrow graft
Kongtim [23]	2015	83	57	23%	64%	3Y-55%	3Y-33%	1Y-31%	NR
Sharma [24]	2015	36	53	39%	NR	1Y-56%	NR	36%	GF, high HCT-Cl
Park [25]	2013	73	53	59%	43%	3Y-32%	3Y-35%	3Y-36%	Year of HSCT< 2004 and palpable spleno-megaly
Eissa [26]	2011	85	52	32%	55%	10Y-40%	2Y-24%	2Y-33%	Older age, low hemat-ocrit, HCT-Cl > 2, high CPSS
Krishnamuthy [27]	2010	18	54	28%	20%	3Y-31%	3Y-47%	3Y-31%	NR
Ocheni [28]	2009	12	56	42%	100%	2Y-75%	2Y-17%	2Y-25%	NR
Elliott [29]	2006	17	50	6%	18%	3Y-18%	41%	3Y-25%	No factors identified
Kerbauy [30]	2005	43	48	0	51%	4Y-41%	4Y-23%	34%	HCT-Cl > 2
Kroger [31]	2002	50	44	0	12%	2Y-21%	2Y-42%	1Y-55%	No factors identified

trials comparing allo-HSCT with non-transplant therapeutical options or comparing different conditioning regimens **(Table 2)** [20-31].

In 2015 two reports ‘’specifically’’ focused on the evolution of allo-HCST in CMML appeared. These reports were based on the evaluation of large series of patients. Duong et al. identified in the CIBMTR registry (Center for International Blood and Marrow Transplant Research) 209 adult patients who underwent allo-HSCT for CMML during 2001-2012 [22]. Duong and all have proposed to validate CPSS score on transplanted patients (this score has proven prognosis value on non-transplant patients). The main purpose of the study was to test the CPSS as a useful method to determine survival after allo-HSCT. The patients' average age at the moment of transplantation was 57 years (23-74 years), 70% were men, 60% had a Karnofsky performance score situated between 90-100%. Following CPSS: 88 patients (42%) were included in the low/ intermediate-1group, 79 patients (38%) in the intermediate-2 / high group and 42 patients (20%) did not have the necessary data to calculate their score. Based on cytogenetic score specific CPSS, the distribution was as follows: low risk-50%, intermediate risk-19%, poor risk- 17% and no cytogenetic data-14%. The median time from diagnosis to transplant averaged 8 months (2-170). Donors for the allogeneic HSCT were: HLA identical siblings (32%), matched unrelated donors (45%), partially matched unrelated donors (15%), mismatched unrelated donors (4%). The source of stem cells was: 16% bone marrow cells and 84% peripheral blood cells. 51% of patients received myeloablative conditioning regimens, 41% low intensity regimens and <9% other regimes. The graft versus host disease (GVHD) prophylaxis was based on cyclosporine (37%), FK 506 (61%), MTX (<1%). The median follow-up was 51 (3-122) months. The multivariate analysis of results showed that CPSS score, Karnofsky performance status and the graft's source (PB vs BM) are predictive of overall survival (OS) at 5 years and there was a significant difference between low-risk group/ intermediate-1 and intermediate-2/ high in terms of disease free survival (DFS) (26% vs 14%) and OS (44% vs 18%). There were no differences between low/ intermediate-1 and intermediate-2/ high in terms of relapse, GVHD, non-relapse mortality. A high CPSS score, a low performance score, the bone marrow as a source of cells for the graft were associated with an unfavorable outcome. The therapy before transplant (chemotherapy, hypomethylanting agents) did not influence the OS.

The second analysis of a large register of CMML transplanted adult patients with CMML was published by Symeonidis in the EBMT Register (European Blood and Marrow Transplantation) in 2015 [21]. The register includes 513 patients with an average age of 53 years. The conditioning regimens were: myeloablative conditioning (MAC) 249 patients; reduced-intensity conditioning (RIC): 226 patients. The donors were HLA-related (285 patients) and HLA-unrelated (208 patients). Regarding the status of the disease at the moment of transplantation, 122 patients were in complete remission (CR); 344 patients had no CR and 47 patients had unknown status. The engraftment occurred successfully in 95% of cases. Acute II-IV grade GVHD appeared in 33% of cases and chronic GVHD has been reported in 24% of cases. At 4 years, cumulative incidence for relapse mortality was 32% and for relapse-free mortality 41%. Overall survival at 4-years was 33% and relapse-free disease 27%. The transplanted patients in CR had a high probability of survival, relapse-free survival and OS. Based on multivariate analysis, the only significant factor for survival was the presence of CR at the time of the transplantation [21].

Allo-HSCT remains the curative treatment option for patients with CMML and is preferably performed after obtaining the best possible remission status: CR, as soon as possible after diagnosis [21]. The decision to choose allo HSCT in CMML, the moment of the transplant during the disease evolution and the choice of conditioning regimens are problems under continuous debates [32]. The decision of transplantation must keep in mind parameters of disease (markers of aggressiveness) and the patient parameters: age, performance status, comorbidity index. The decision to choose MAC vs RIC should be based on factors related to the patient. RIC has expanded the number of patients that can perform allo-HSCT. The introduction of RIC, a better supportive therapy and the HLA techniques for choosing the donor, all together led in the last years to a decrease in the non-relapse mortality.

At present, the proposals of international experts regarding the treatment of CMML takes into account disease phenotype (MDS- LMMC or MPN- CMML) and the percentage of blasts [16, 33]. For the patients with MDS-phenotype and blasts <10% the recommendations are supportive therapy (stimulating agents of erythropoiesis, iron chelation for patients with post-transfusion hemochromatosis) or allogeneic HSCT for young patients with sibling donors. In patients with MDS- CMML and blasts >10% in BM the supportive therapy can be completed with hypomethylating agents. An option for young patients can be the allo-HSCT. For patients with MPN phenotype and blasts <10% in bone marrow, hydroxycarbamidum and clinical trials can be an option. For patients with MPN phenotype and blasts > 10% in the bone marrow, allo-HSCT is the therapeutic indication for eligible patients. For noneligible patients, the hypomethylating agents or clinical trials may be a therapeutic option.

Conclusions

Allo HSCT is currently the only modality of treatment associated with long term remission and curative potential. For young patients with aggressive disease, severe prognosis score, ''high risk'' karyotype, an increased percentage of blasts in the bone marrow, allo-HSCT must be chosen in early stages of the disease, as soon as possible after obtaining complete remission or the best possible response after chemotherapy or hypomethylation agents. The achievement of CR before the transplantation procedure has been reported as an important favorable factor of prognosis for long-term evolution (the increasing OS, DFS). The availability of unrelated donors and alternative sources of stem cells (umbilical cord blood, haploidentical donors) makes the allotransplant available for more patients. Our case illustrates the fact that allo-HSCT is the only therapeutic option for therapy for a young patient with CMML-2 (WHO) with unfavorable prognosis score and imminent risk of transformation into AML.

Conflicts of interest

The authors declare that they have no conflict of interest.

List of abbrevations

aCML = Atypical chronic myeloid leukemia
Allo-HCST = allogeneic hematopoietic stem cell transplantation
AML = acute myeloid leukemia
ARA-C = cytarabine
BM = bone marrow
BMB = bone marrow biopsy
BU/CY/ATG-F20 = busulfan/ cyclophospha mide/anti-thymocyte globulin
CIBMTR = Center for International Blood and Marrow Transplant Research
CMML = chronic myelomonocytic leukemia
CMV = cytomegalovirus

CR = complete remission
CSA = cyclosporine
CPSS = CMML Specific Prognostic Scoring System
DFS = disease-free survival
DNR = daunorubicin
EBMT = European Blood and Marrow Transplantation
EMA = etoposide, mitoxantrone and cytarabine
ET = essential thrombocythaemia
FAB = French-American-British
FK506 = tacrolimus
G-CSF = granulocyte colony stimulating factor
GvHD = graft versus host disease
GF = graft failure
Hb = haemoglobin
HE = hematoxylin and eosin
Ht = haematocrit
HLA = human leucocyte antigen
HCT-CI = transplant comorbidity index
ISCN = International System for Human Cytogenetic Nomenclature
IHC = immunohistochemistry
IPSS = International Prognostic Scoring System
JMML = Juvenile myelomonocytic leukemia
KPS = Karnofsky performance status
MAC = myeloablative conditioning
MDAPS = MD Anderson Prognostic Scoring System
MDS = myelodysplastic syndrome
MDS- CMML = myelodysplastic type CMML
MDS/MPN-U = Myelodysplastic/myeloprolife rative neoplasms unclassifiable
MPN- CMML = myeloprolypherative type CMML
MPO = myeloperoxidase
MTX = methothrexate
OS = overall survival
PB = peripheral blood
PMF = Primary myelofibrosis
PV = Polycythemia Vera
RAEB-2 = refractory anemia with excess blasts
RIC = reduced-intensity conditioning
WBC = white blood cell
WHO = World Health Organization

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