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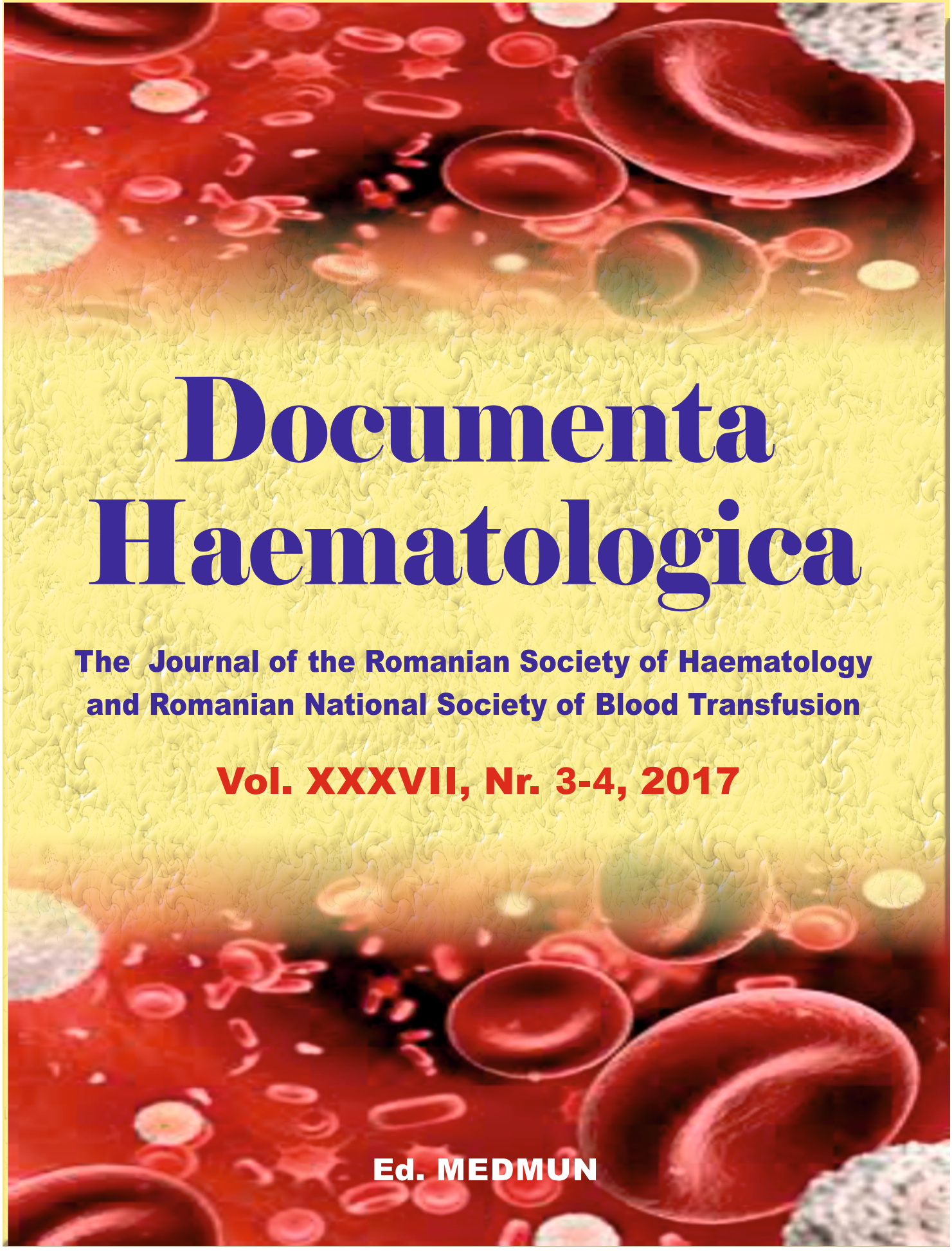

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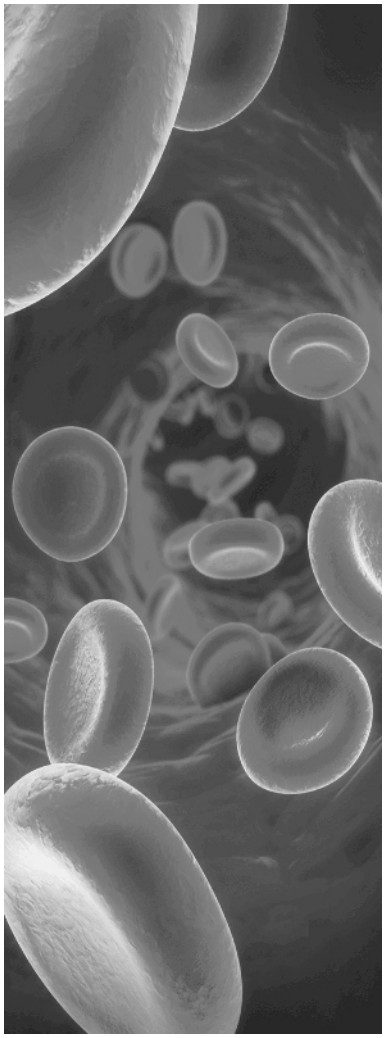

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NATIONAL SOCIETY OF BLOOD TRANSFUSION FROM ROMANIA

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A very unusual T lymphoproliferative disorder – ALK ALCL in leukemic phase – Case presentation

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Abstract

ALK- positive anaplastic large cell lymphoma (ALCL) is a subtype of T cell nonHodgkin's lymphoma. The leukemic form is rarely encountered and it was described especially in children, associatedwith anaplastic lymphoma kinase (ALK) positiveALCL. In rare instances, ALK- positive ALCL presents in leukemic phase, with small cell variant and it has a very poor prognosis. We present the case of a 18 years old female patient with large lymphocyte, null type ALK- positive ALCL in leukemic phase, whose evolution was rapidly unfavorable towards death.

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Introduction

According to 2016 revised WHO clasification[1], anaplastic large cell lymphoma comprises four definitive entities: analpastic large cell lymphoma ALK-positive, analpastic large cell lymphoma ALK-negative, primary cutaneous anaplastic large cell lymphoma, anaplastic B cell lymphoma and a provisional entity breast implant-associated ALCL.

ALCL represents 3% of all lymphoma cases in adult patients and 12% of peripheral T cell lymphomas[2].

ALK-positive ALCL has a male predominance; the median age at diagnosis is 27 years old, unlike the ALK-negative form that has a significantly higher age at presentation (54-61 y). Both ALK-positive and ALK-negative formsare typically in an advanced stage at patient's presentation, with B symptoms, high IPI score and lymph node involvement[3]. Extranodalinvolvement is encountered in 60% of ALK-positive ALCL including skin, bone, soft tissues, bone marrow and spleen. ALK-negative ALCL has a predilection for the liver, GI tract and the skin (26% of cases)[4]. Leukemic phase[5] and CNS involvment[6] are rare in ALCL and carry a worse prognosis.

The two systemic forms of ALCL cannot be differentiate on a morphologic basis, both express CD30 and the specific difference is the expression of ALK protein in the ALK-positive ALCL, due to a translocation t(2;5)(p23;q35), resulting in formation of Nucleophosmin-Anaplastic lymphoma kinase (NPM-ALK) protein[7].

ALK-negative ALCL represents 15-50% of the anaplastic lymphomas. It must be differentiated from primary cutaneous ALCL that is ALK-negative in the majority of cases, as well as from other B and T lymphomas with anaplastic morphology[7].

In general, ALCL express EMA and citotoxicity markers (TIA1, Granzime B, perforin)[8].Immunophenotypically, most ALK-positive anaplastic lymphomas express CD2 (67%), CD7 (60%), CD3 (45%), CD4 (33%), CD8 (14%). ALK-negative anaplastic lymphomas express CD2 (100%), CD3 (50%), CD4 (40%), CD7 (40%), CD5 (25%) and CD8 (20%)[9]. CD25 was identified in 88% of anaplastic lymphoma cases which suggests that it could be a useful marker for immunophenotypic diagnosis as well as a potential therapeutic target[10,11].

ALK-negative ALCL patients have a poor prognosis, with the 5-years overall survival rate of 30-49% versus 70-86% survival rate reported for ALK-positive patients[4,12]. Leukemic phase, CNS involvement and bone marrow infiltrate at diagnosis as well as the lymphohistiocytic and the small cell subtypes are associated with a shorter survival. CD56 expression (NK marker) also confers a poor prognosis, irrespective of the ALK expression.[13]. Large number of cytotoxic T lymphocytes, granzime B positivity and high BCL2 expression also correlate with an unfavorable prognosis.[4,14]

The optimal therapy for ALCL patient is not well defined. Standard chemotherapy is CHOP based regimens, as in other aggressive lymphomas. Dose intensified protocols failed to demonstrate superiority over the classic regimens[15], and the addition of Etoposide to CHOP was beneficial only in ALK-positive ALCL patients younger than 60 years[16]. Several clinical studies evaluated the role of high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HDC/HSCT) in first remission in patients with systemic ALCL. The disease status at transplantation is a major predictive factor for the outcome, as the results in chemorefractory cases were disappointing. NCCN guidelines (National Cancer Consortium Network) includeHDC/HSCT as consolidation therapy in first complete remission for all PTCL patients, except for ALK-positive ALCL[17]. In relapse/refractory settings, HDC/HSCT is an important strategy in both ALK-positive and ALK-negative patients. Allogeneic transplantation has also been tried in chemoresistant patients in small series[18]. CD30 specific antibody-drug conjugate, brentuximabvedotin is effective in relapse/refractory cases[19,20], as well as histone deacetilase inhibitors (romidepsin)[21]and antimetabolite Pralatrexate[22] .

Case presentation

We present the case of an 18 years old female who presented to our department with generalized lymphadenopathy, hepatosplenomegaly and persistent fever up to 39 degree Celsius, not responding to antibiotherapy. Screening tests for infectious diseases (CMV, EBV, HBV, HCV, HIV, HTLV, Toxopalsmosis) as well as for autoimmune diseases (anti-double stranded DNA, anti-nuclear antibody, lupus cells test) were negative. Her blood count showed marked and rapidlyprogressing leucocytosis and lymphocytosis (WBC= 174000/µL; lymphocytes= 60900/µL), and the peripheral blood smear showed a population of pleomorphic atypical cells, some of them with medium-sized, irregular, incised nuclei and other large blastoidcells with round nucleus, fine chromatine, proeminent nucleoli, and basophilic, vacuolated cytoplasm (figure 1).

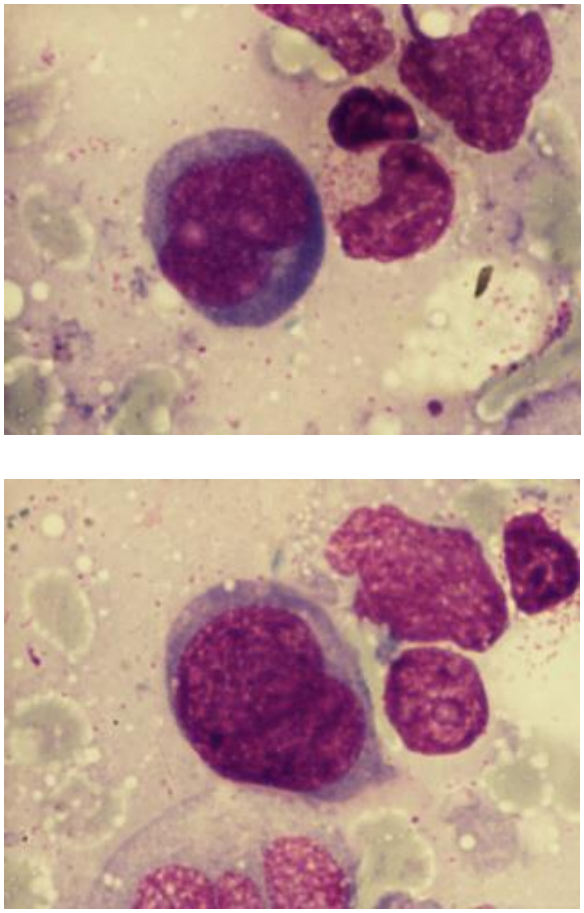

Figure 1: peripheral blood smear with pleomorphic atypical lymphocytes with irregular nuclei, fine chromatine, proeminent nucleoli, and basophilic, vacuolated cytoplasm (MGGx100)

Lymph node biopsy and IHC stains demonstrated paracortical malignant tumor cell proliferation positive for CD30, CD7, ALK, EMA and Granzime B and negative for CD3- CD4- CD8- CD56- CD33- CD19- CD10- CD34- CD38- CD28-/+. Bone marrow biopsy showed 45% atypical lymphocytes. The final diagnosis was stage IVB ALK-positive anaplastic large cell lymphoma. Initial treatment was CHOP-14 associated with intrathecal administration of Methotrexate for CNS prophylaxis. After 6 cycles of chemotherapy only a partial response was obtained (decreased lymphadenopathy and splenomegaly) and we decided to switch chemotherapy to DHAP. The patient's condition worsened, fever and peripheral blood lymphocytosis reappeared as well as lymphadenopathy and liver and spleen enlargement. A papular non-pruritic rash of the arms was noticed (figure 2) and skin biopsy was performed that confirmed perivascular and peri-annexiallymphomatous infiltratesthat expressed CD30 and ALK. Further intensification of therapy with ALL-type protocol was started but unfortunately the patient died due to disease progression 7 months after the initial diagnosis.

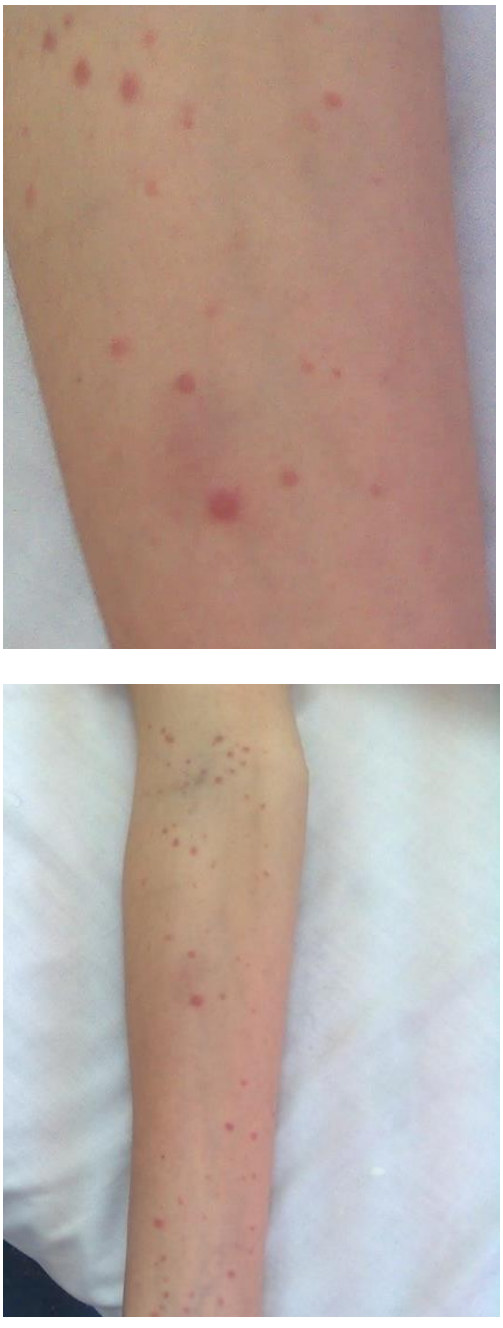

Figure 2: Papular non-pruritic rash of the arms

Discussion

The leukemic presentation ALCL is a rare condition described especially in children and young adults and associated with the small cell variant of ALK positive ALCL[23]. In adult patients, leukemic forms of ALCL are mainly ALK-negative[7]. Our case was a leukemic presentation of ALK positive ALCL, with medium and large blastoid cells that expressed a rarer null-type phenotype, CD30+ CD4- CD8- CD7- CD3 – CD56 -. Although some clinical studies showed that CD56 positive ALK positive ALCL carries a worse prognosis[13], the absence of CD56 positivity in our case was not associated with a favorable outcome. The leukemic presentation was the main feature that dictated the patient's evolution, despite the ALK positive expression.

Conclusion

The leukemic presentation of ALK positive ALCL is a rare and aggressive condition with various morphologic and immunophenotypingfeatures that carries a very unfavorable prognosis. Even though CHOP based regimen is effective in the usual presentation, the leukemic phase needs further studies for newer therapies.

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The subtlety of a rare disorder - acquired Hemophilia B

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Abstract

A 77-year-old female with no pathologic personal history or family history of hematologic disease and no history of bleeding disorder, suddenly develops a large abdominal hematoma and disseminated bruising on the limbs, in the absence of trauma or anticoagulant treatment. Global coagulation tests revealed prolonged APTT and a slightly increased INR which have led to testing of intrinsic pathway clotting factors; laboratory investigations was diagnostic for acquired hemophilia B - with the presence of inhibitor for factor IX. Subsequent investigations suggested the cause of acquired haemophilia was amyloidosis secondary to a lung infection process.

Keywords: Hemophilia B, acquired inhibitors,immunosuppression, bleeding, recombinant factor VII

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Introduction

Hemophilia B is a rare genetic disorder in which the affected person has an insufficient level of factor IX required for proper hemostasis. As a result, clinical bleeding will be present. The genetic defect is linked to the X chromosome, therefore malesdevelop the disease andfemales are carriers. Except when the woman comes from a mother carrying the affected X chromosome and a hemophilic father. Hemophilia B occurs in about 25,000 male newborns and has a much lower incidence than hemophilia A (factor VIII deficiency) found in 1 out of 5,000 male newborns.[1] The case presented here is an even more unusual situation in which the deficit is acquired by an autoimmune mechanism that leads to the formation of antibodies directed against factor IX and expression of a hemorrhagic pattern different from the congenital form (often in the form of muscule hematomas: psoas, retrofaringianetc).

In about half of the cases, the reason for immune hyperactivity is unknown.Sometimes it is associated with other conditions: pregnancy, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, dermatologic conditions such as psoriasis or pemphigus vulgaris, temporal arteritis, Sjogren syndrome, inflammatory bowel disease, Goodpasture syndrome, graft-versus-host disease, myasthenia gravis, Graves'disease, autoimmune hemolytic anemia, autoimmune hypothyroidism), underlying malignancy such as hematologic malignancies (chronic lymphocytic leukemia, non-Hodgkins lymphoma, multiple myeloma, Waldenstrommacroglobulinemia), solid organ tumors (lung, prostate, pancreas, breast) or it can be triggered by certain medications (antibiotics: penicillin, sulfonamides; chloramphenicol, phenytoin,

methyldopa, interferon alpha,fludarabine); acute hepatitis B or C; respiratory disease (asthma, chronic obstructive pulmonary disease).[2]

Immunosuppression to eradicate an acquired inhibitor should be started immediately upon diagnosis in all patients.[3] Even those who are not actively bleeding remain at risk for life-threatening hemorrhage until the autoantibody has been eliminated,[4]and overall survival is improved in patients who achieve a complete response with eradication of inhibitor.[5]Optimal therapy is controversial, and current data are derived from observational and retrospective studies including a limited number of patients with different primary clinical conditions.[6] Predictors for a positive response are low level of inhibitors and a short interval between the appearance of the inhibitor and the start of therapy.[7] Long-term laboratory follow-up is needed to demonstrate a stable CR and rule out relapse, which occurs in up to 20% of patients with acquired hemophilia.[3,8,9]

Case report

We present the case of a 77-year-old woman with no pathologic personal history or family history of hematologic disease or bleeding disorder who presented at the emergency department for spontaneous appearance of a tumefaction in the left forearm followed shortly by development of disseminated bruising in the lower limbs, prepubian region, inguinal region and left periorbital region. The swelling in the forearm was diagnosed by ultrasonography as a hematoma.

From the patient's anamnesis we note that, a few days before presenting to the hospital, she had fever, chills, headaches and cough for which she self-medicated with NSAIDs and antibiotic (cephalosporin).The biological investigations performed in the emergency room revealed a moderate normochromic normocytic anemia, (Hb-9g / dl), normal white blood cell and platelet counts. However, the significant change was observed at the coagulation tests, more precisely a markedly prolonged APTT = 134 sec (normal value 22-36 sec) and with a slight increase of INR = 1.46 (normal value 0.8-1.14). The fibrinogen level was normal. All of these results suggested a predominant impairment of the intrinsic pathway of the coagulation, causing an ineffective hemostasis, as such there was a suspicion of an alteration of the coagulation factors involved in this pathway: factor VIII, factor IX, factor XI, factor XII, prekallikrein and kininogen.Deficit of either of this factors result in a prolonged APTT, but factor XII, prekallikrein and kininogen usually do not associate clinical bleeding thus, in this case the most likely involved factors are factor VIII, factor IX, factor XI. With the help of colleagues from the Laboratory of Haemostasis ofFundeni Hospital, levels of factor VIII, factor IX, vWF were measured and the presence of these factor inhibitors was evaluated.

It should be mentioned that investigations were done under cortisone treatment and fresh frozen plasma administration which had been started since admission. Theresults were: Factor VIII -315% (normal value 50-150), factor IX - 48% (normal value 60-150), von Willebrand factor activity -215% (normal value 40-175), vonWillebrand factor Antigen - 214% (normal value 60-150). By mixing the patient’s plasma with normal plasma, it was found that APTT correction was not made, which sugesstedthe presence of coagulation factor inhibitors. Corroborated, all of these data outlined the diagnosis of acquiredhaemophilia B.Subsequent investigations were directed

to identify a possible etiological substrate. An autoimmune condition was excluded. Tumor markers have been found negative. A thoracic-abdomino-pelvic computer tomography exam was performed which revealed the following pathological elements: the presence of a bilateral pleural effusion with a maximum of 17 mm; condensation syndromes in the middle lobe and bilateral lingual segment bilateral; 42 mm ascites fluid; globally enlarged heart with the predominance of right cavities; infracentimetric lymph node images with a max of 10 mm (laterocervical, axillary, paratracheal, berety tars, infracarinar); hepatomegaly (right lobe diameter 20 cm), homogenous, without IHBD dilation. From the sputum examination, Pseudomonas aeruginosa was isolated.The echocardiography showed an atypical myocardial infiltrate which suggested amyloidosis. Given this aspect, a serum protein electrophoresis with immunofixation was done which excluded the presence of a monoclonal protein.At the same time, serum amyloid A level was assessed (the major bleeding risk limited the performance of a biopsy of the abdominal wall or rectal mucosa). The level was approximately 9 times the normal value and was considered to be secondary amyloidosis to an infectious / inflammatory process. Most likely, the pulmonary infectious context and possibly self-administered medication at home were involved in triggering the immune mechanism of coagulation factor deficiency.

Regarding the treatment and the evolution of the patient, corticosteroids (Dexamethasone followed by pulse with Solumedrol) and frozen fresh plasma transfusion have been started. Subsequently, immunosuppressant treatment with Azathioprine was supplemented. Also, targeted antibiotic treatment for Pseudomonas pulmonary infection was associated. Under this therapy, within 48 hours, the APTT decreased to 87 seconds (from 134 seconds). But although the biological picture was improvimg, bleeding continued and 6 days later she developed a significant posterior left thoracic hematoma (confirmed on the computer tomography exam) and an aggravated anemia with a decrease of Hb to 5,9 g/dl.

Due to the persistence / appearance of new bleeding events under cortisone and immunosuppressant treatment, recombinant factor VII (Novoseven) was considered, which is why the best decision was to transfer the patient to the specialized center for haemophilia of Fundeni Hospital. When the patient was admitted in this clinic the biological panel was net improved: APTT-49 sec; factor IX - 70%; APTT P + N -32 sec (= APTT correction). Treatment with Novoseven*90*µg/kg at 8 hours was initiated and Dexamethasone and Azathioprine administration was continued. Also, red blood cell transfusion and painkillers were necessary. During this therapy, which lasted for about 10 days, the clinical evolution was slowly favorable with regression in size and consistency of the chest hematoma and the remission of the other hematomas and ecchymoses present at diagnosis. Also, the biological panel was significantly improved so that, upon discharge, the APTT value was normalized (28 sec), Hb increased to 10 g/dl. At home, the patient continued treatment with cortisone and Azathioprine, with subsequent medical follow-ups.

Conclusion

Acquired B Hemophilia is an extremely rare bleeding disorder and occurs especially in the elderly. The pathogenic mechanism is immune with thethe occurrence of anti-factor IX

antibodies (antihemophilic B).Published treatment guidelines recommend immunosupression as soon as the diagnosis is made, because the patients remain at risk of severe and fatal hemorrhage until the inhibitor has been eradicated.[10] Immunosuppressive drugs usually administered are steroids alone or steroids plus cytotoxic agents (cyclophosphamide), although there is increasing use of rituximab either alone or in combination with other agents. [11]

There is no difference in inhibitor eradication or mortality between patients treated with steroids alone and combined therapy. [4,12] In the absence of rapid and appropriate treatment in specialized centers the consequence will be the occurrence of major bleeding manifestations, predominantly under the form of deep tissue hematomas with a high risk of mortality (between 7.9% and 22%)[4]. To date, very rare cases of acquired hemophilia B have been reported.

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Myelodysplastic Syndrome–Diagnosis and Treatment Protocol

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Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal hematological diseases, characterised by a defect in the maturation of myeloid progenitor cells, genetic instability, ineffective hematopoiesis, persistent cytopenias and an elevated risk of progression to acute myeloid leukemia. The main mechanism of ineffective hematopoiesis is the increased apoptosis of bone marrow cells, leading to cytopenias. The evolution in either indolent, over several years, or rapidly progressive to acute myeloid leukemia (AML), depending on the subtype of MDS.

Quantitative and qualitative defects in hematopoiesis lead to anemia, life threatening bleeding and infections.

The incidence of MDS is approximately 4-5 cases per 100000 per year, and is increasing with age: 30/100000 at over 70 years old, 40/100000 at over 80 years old. 10% of MDS cases are secondary to chemotherapy and radiotherapy.

Cytogenetic abnormalities are present in 40-50% of cases, having diagnostic and prognostic value. Molecular abnormalities frequently found in MDS were recently identified, also of important prognostic value.

Etiology

Both primary and secondary forms of MDS have been described.

Secondary forms appear after exposure to various environmental factors, having a median survival of 12 months, a rapid progression to AML and a poor response to chemotherapy. This exposure has been associated with an increased risk of MDS occurrence:

- occupational exposure to benzene, organic solvents, petroleum products, pesticides, mineral oil, halogenated organic substances
- ionizing radiation (atomic bomb survivors, occupational exposure, radiotherapy)
- alcohol
- smoking
- hair dye
- cytostatic drugs (alkylating agents, topoisomerase II inhibitors, monoclonal antibodies -^{131}I-conjugated anti-CD20).

Patients with aplastic anemia and nocturnal paroxysmal hemoglobinuria can develop MDS during the course of these diseases. There is also a great risk of developing MDS for patients with inherited bone marrow failure syndromes:

- Fanconianemia
- Severe congenital neutropenia

- Shwachmann-Diamond syndrome
- Diamond-Blackfan anemia
- Dyskeratosiscongenita
- Familial platelet disorder with predisposition to acute myelogenous leukemia
- Type I neurofibromatosis
- Down syndrome

Clinical manifestations

Clinical manifestations related to cytopenias:

- anemia
- infections caused by neutropenia or by qualitative neutrophil disorders
- bleeding caused by thrombocytopenia or by qualitative platelet disorders.

Autoimmune manifestations associated with a paraneoplastic process: seronegative polyarthritis, cutaneous vasculitis, peripheral neuropathy, cutaneous or mucous ulcers, iritis, pericarditis, pleural effusion, inflammatory bowel disease, pure red cell aplasia, autoimmune hemolytic anemia, Raynaud phenomenon, pyoderma gangrenosum, Sjogren syndrome, and glomerulonephritis. These autoimmune manifestations are responsive to corticosteroids.

Chronic myelomonocytic leukemia (CMML) patients can present with lymphadenopathy, splenomegaly or hepatomegaly (monocyte infiltration), chloromas (granulocytic sarcomas).

Sweet syndrome (or **neutrophilic dermatosis**) is characterized by painful papular lesions over the face, neck and extremities, lymphadenopathy, splenomegaly or hepatomegaly. It precedes transformation to AML and is responsive to corticosteroid treatment.

Diagnosis

MDS should be considered when one ore more cytopenias are present in peripheral blood, and when signs of dysplasia or blast cells are seen on the peripheral blood smear.

The following are considered cytopenias:

- hemoglobin (Hb) lower than 10 g/dL
- absolute neutrophil count (ANC) lower than 1.8×10^9/L
- thrombocytes fewer than 100×10^9/L

A full blood count and a bone marrow examination are mandatory in order to confirm a diagnosis of MDS.

The **complete blood count** consists of: hemoglobin (Hb), hematocrit (Ht), white blood cells count, platelet count, reticulocyte count, red blood cell indices, leukocyte formula, and peripheral blood smear (at least 200 cells analysed)

A **bone marrow examination** is mandatory. The bone marrow aspirate smear and bone marrow biopsy are needed.

The **bone marrow smear**:

- it comprises the May-Grunwald-Giemsa staining or Perls Prussian Blue Staining
- it should be performed to confirm the diagnosis, and repeated whenever disease progression is suspected
- it assesses bone marrow cellularity and the percentage of blasts in a count of 500 cells; at least 25 megakaryocytes and 100 erythroblasts must be observed
- the myelodysplasia is significant when at least 10% of the cells pertaining to abone marrow lineage show dysplastic features; the number of dysplastic lineages and the presence of Auer rods are also evaluated

The **bone marrow biopsy**is essential at diagnosis:

- Hematoxylin and eosin (HE) stain, peroxidase stain (Auer rods, peroxidase deficiency), iron stain (Prussian Blue stain)
- bone marrow cellularity: hypercellular, normocellular or hypocellular bone marrow (differential diagnosis between hypoplastic MDS and aplastic anemia may be difficult in some cases), megakaryocyte morphology, assessment of the presence and grading of bone marrow fibrosis (negative prognostic factor)
- immunohistochemistry (IHC) for CD34, CD 117, blasts and immature erythropoiesis markers, is especially useful when the bone marrow aspirate is inconclusive because of bone marrow fibrosis; IHC for p53 has prognostic value
- abnormal localization of immature progenitors – ALIP (negative prognostic factor)

Dysplastic features:

Macrocytic anemia with a low reticulocyte count is present in the majority of patients.

Approximately 50% of patients are neutropenic at diagnosis or develop neutropenia in the course of the disease evolution. Quantitative and qualitative defects of the granulocyte lineage are present.

Determining blast percentage on the bone marrow smear is the most important aspect in a patient with MDS, because it assesses the impairment of the abnormal stem cell differentiation capacity, and it constitutes an important prognostic factor. An AML diagnosis is established by a blast percentage of at least 30% (FAB classification) or at least 20% (WHO classification). This assessment must be done on the bone marrow smear and not by flow cytometry, because in the latter the sample may be diluted with peripheral blood.

Thrombocytopenia is present in about half of MDS patients, and it may by the only cytopenia in 5% of cases. Thrombocytosis is rare and it is associated with chromosome 5q deletion syndrome (5q- syndrome) or with JAK2 mutation (RARS with thrombocytosis).

Peripheral blood	**Modifications:**
Erythrocytes	Anisocytosis, poikilocytosis, dimorphic red blood cells, megalocytes, hypochromia, basophilic stippling, erythroblasts, teardrop cells, ovalocytes, schistocytes
Granulocytes	Pseudo Pelger-Huet cells, hypo/agranular granulocytes, left shift
Platelets	Giant platelets, platelet anisocytosis
Bone marrow smear	**Modifications:**
Cellularity	hypercellularity, rarelyhypocellularity
Erythropoiesis	Megaloblastoid changes, multinucleated erythroblasts, nuclear bridging, vacuoles, nucleo-cytoplasmic maturation asynchrony, atypical mitoses, sideroblastosis, ringed sideroblasts, PAS-positive precursors
Granulopoiesis	Left shift, increased blast count, +/– Auer rods, hypo/agranular cells, pseudo Pelger-Huet cells, nuclear anomalies (multinucleated cells, abnormal chromatin clumping), myeloperoxidase deficiency, increased count orabnormal morphology ofmonocytes
Megakaryopoiesis	Micromegakaryocytes, mononuclear megakaryocytes, hypersegmentation, multiple isolated nuclei

Other necessary laboratory tests:

- Folic acid blood levelsand vitamin B12 (methylmalonic acid level)
- Serum iron,serum ferritin, total iron binding capacity
- Exclusion of thalassemia and other hemoglobinopathies
- LDH, bilirubin, transaminases, alkaline phosphatase, albumin, uric acid, creatinine, serum protein electrophoresis, serum immunoglobulin levels, β2 microglobulin
- Thyroid function tests (TSH), antinuclear antibodies
- Coombs test andhaptoglobin
- Serum erythropoietin level (before administering red blood cell transfusions)
- HLA (human leucocyte antigen) typing, HLA-DR15 forhypoplastic MDS
- Screening for paroxysmal nocturnal hemoglobinuria (PNH): Hamtestandsucroselysistest, flow cytometry (absent glycosylphosphatidyl inositol associated antigen, because of the absence of PIG-A gene, absence of CD55 and CD59on red blood cells and CD 11b on monocytes).
- Viral tests: anti HIV antibodies, Parvovirus B19 tests (hypoplastic MDS), CMV tests, HBV and HCV viruses
- JAK2 V617F mutation for RARS with thrombocytosis (it provides additional information, but it does not influence prognosis and treatment
- Copper deficiency test for patients with gastrointestinal malabsorption, severe malnutrition, gastric bypass surgery

Non-clonal dysplastic features occur in other diseases: hematologic and non-hematologic malignancies, benign disorders. Other **hematologic neoplasms** withdysplastic features besides MDS are myelodysplastic/myeloproliferative neoplasms, unclassifiabl e(MDS/MPN-UC), acute myeloid leukemia (AML with myelodysplasia-related changes and therapy-related AML), primary myelofibrosis, chronic myeloid leukemia (chronic phase or accelerated phase), other myeloproliferative neoplasms. **Benign disorders** withdysplastic features may be hereditary or acquired, presenting with unilineage or multilineage dysplasia.

Acquired conditions associated with non-clonal dysplastic features:

- Medication: mycophenolate mofetil, tacrolimus, ganciclovir, chlorambucil, cytostatic agents (cyclophosphamide, anthracyclines, cytarabine, hydroxycarbamide, azathioprine), zidovudine, isoniazid, chloramphenicol (it can cause the appearance of ringed sideroblastsand cytoplasmic vacuolation), granulocyte and granulo-monocytic growth factors(G-CSF, GM-CSF)
- Vitamin B12 and folic acid deficiency
- HIV infection, severe systemic infections (tuberculosis, malaria, leishmaniasis), Parvovirus B19 infection
- Alcohol consumption
- Systemic lupus erythematosus
- Protein malnutrition, copper deficiency, zinc excess

Inherited conditions associated with non-clonal dysplastic features:

The disease usually manifests itself during childhood:

- Hereditary sideroblastic anemia:an X-linked disorder with mutationsin ALAS2 gene, dimorphic red blood cells;the bone marrow shows

erythroblastic hyperplasia, defective hemoglobinization and cytoplasmic vacuolation
- Congenital dyserythropoietic anemia, thalassemia intermedia and minor, homozygous hemoglobin C disease, congenital erythropoietic porphyria
- Thiamine-responsive anemia; Wolfram syndrome associated with mutations in WFS1 gene, diabetes insipidus, diabetes mellitus, optic nerve atrophy, deafness, and trilineage dysplasia; Rogers syndrome associated with mutations in SLC19A2 gene, sensorineural deafness.
- Pelger-Huetanomaly: autosomal dominant disease characterized by bilobed neutrophils, difficult to distinguish from MDS, withthe parents showing similar traits.
- Neutrophil-specific granule deficiency: autosomal recessive conditioncharacterized by lactoferrin deficiency, hypogranular and bilobed granulocytes, recurrent fungal and bacterial infection.
- Mutations in GATA1 gene associated with β-thalassemia, thrombocytopenia, congenital erythropoietic porphyria, microcytosis, and multilineage dysplasia.
- Pearsonsyndrome, which is characterized by mutations in the mitochondrial genes, neutropenia, cytoplasmic vacuoles in hematopoietic cells, exocrine pancreatic dysfunction, lactic acidosis.

Cytogenetic examination

The cytogenetic examination is necessary for the diagnosis and prognosis of MDS, representing an important parameter for the prognostic scoring systems. It is performed on a bone marrow aspiration sample at diagnosis. At least 20 metaphases must be analysed, according to the ISCN (International System for Human Cytogenetic Nomenclature).

Cytogenetic abnormalities are present in 30-80% of cases, more frequently in MDS forms secondary to chemotherapy and radiation therapy.

The cytogenetic examination is useful for the assessment of the disease prognosis, being one of the main components of the prognostic scores: IPSS, R-IPSS, W-PSS.

Recurrent chromosomal abnormalities are considered presumptive for MDS diagnosis in patients with persistent cytopenias of undetermined significance:

Unbalanced cytogenetic abnormalities	Balanced cytogenetic abnormalities
-7 or del(7q) -5 or del(5q) i(17q) or t(17p) -13 or del(13q) del(11q) del(12p) or t(12p) del(9q) idic(X)(q13) complex karyotype	t(11;16)(q23;p13.3) t(3;21)(q26.2;q22.1) t(1;3)(p36.3;q21.1) t(2;11)(p21;q23) inv(3)(q21q26.2) t(6;9)(p23;q34)

Therapeutic implications of chromosomal disorders:
- **Chromosome 7 abnormalities** are associated with a negative prognosis,therefore patients should undergo hematopoietic stem cell transplantation; chances of obtaining a complete response after induction therapy are higher when using hypomethylating

agents, compared to conventional chemotherapy.

- In **complex or monosomal karyotype** the overall survival after hypomethylating agentsis low, with a short term cytogenetic response.
- **Del 13q and +8** are associated with bone marrow insufficiency and a positive response to immunosuppressive therapy in patients with aplastic anemia.
- **Del 5q** has a positive response to lenalidomide.

FISH Test

Fluorescence in situ hybridization (FISH) uses DNA-specific probes in order to identify each chromosome. This method analyses hundreds of cells and is not dependent onthe stage of cell division cycle. The sensitivity of the method is much higher, but its use is limited to the detection of standardcytogenetic abnormalities. Both peripheral blood and bone marrow aspiration samples can be analysed. It can detect structural and numerical alterations of chromosomes in MDS:**5q31, cen7, 7q31, cen8, TP53, 20q, cenY**.

A FISH test is indicated when when the cytogenetic examination (conventional metaphase karyotyping) does not reveal abnormalities or cannot be performed (myelofibrosis, hypoplasia, insufficient number of metaphase cells. It completes the conventional cytogenetic examination, but it does not substitute it.

Molecular abnormalities

Myelodysplastic syndromes in early stages and with a slow progression to AML can constitute prototypes for the“multistep” concept of leukemogenesis, with accumulating cellular and molecular defects during the initiation and progression of the disease. The detection of certain somatic mutations is necessary for prognostic assessment and treatment plan (hematopoietic stem cell transplantation, targeted therapy).

Somatic mutations are identified through DNA sequencing (Next Generation Sequencing). Over 40 mutated genes involved in the pathogenesis of MDS have been described, being present in more than 80% of patients. Many of these anomalies are associated with unfavorable prognosis:

- mutations in **TP53** are associated with a complex karyotype
- mutations in **RUNX1, NRAS, TP53** are associated with excess blasts types or severe thrombocytopenia

The prognostic impact of somerecurrent mutationshas been validated. Mutations in 5 genes are associated with a negativeprognostic,independent of IPSS or R-IPSS: ***TP53*, *EZH2*, *RUNX1*, *ASLX1, and ETV6***. Patients with int-1 IPSS score and one of these mutations present should be considered as IPSS int-2.

Genes involved in the pathogenesis of MDS:

Gene function	*Gene*	*Frequency*
Chromatin remodeling and epigenetic regulation factors	TET2 ASXL1 DNMT3a IDH1/2	15-25% 10-20% 10% 5-10%
Pre-ARNm splicing factors	SF3B1 SRSF2 U2AF1	15-30% 10-15% 5-10%
Transcription factors	RUNX1 TP53	10-15% 5-10%
Molecules implicated in splicing	N RAS/K RAS	10%

Therapeutic implications of somatic mutations:

- Targeted therapies: oral **IDH1/IDH2** inhibitors, luspatercept for mutations in **SFEB1**(clinical trials).
- Allogeneic stem cell transplant for somatic mutations in **TP53** and **complex karyotype**.
- Del5q associated with **TP53** mutations does not respond to lenalidomide.
- Assessment of stem cell transplant response: **TP53** mutation is associated with relapse and post-transplant exitus; they are more frequent in young patients under 40 years old and is not influenced by the conditioning regimen.
- Mutations in **RAS** and **JAK2** have unfavorable evolution and are in need of new targeted therapies.

Immunophenotyping

In MDS there is an impairment in the formation of progenitor cells, leading to abnormal antigen expression in mature myelomonocytic,erythroid and megakaryocytic cell lineages. Immunophenotyping by multiparameter flow cytometry is useful when the dysplastic features are limited, and a normal karyotype is present, making the MDS diagnosis difficult to establish. It can differentiate between MDS and non-clonal cytopenia. The International Flow Cytometry Working Group, pertaining to Leukemia Network, comprised of members from 18 European, Japanese and American institutions, have standardized the MDS flow cytometry principles in March 2008. This working group has proposed a combination of cell surface markers for erythroid, myeloid, and monocytic progenitor cells, and also for circulating neutrophils and monocytes, which are used in diagnosing MDS.

The presence of 3 or more abnormalities in the maturation pattern of erythroid and myeloid lineages is highly suggestive of MDS. Isolated anomalies do not establish a diagnosis. The method is analysing abnormal expression of lineage-specific antigens, any increase, decrease or loss of antigen expression, the expression of immature antigens of mature cells (and the reverse), and the expression of lymphoid antigens on myeloid cells. The level of antigen expression is defined as aberrant of it varies by +/– 0.5 log from normal hematopoietic cells. Some markers have prognostic value: CD7 is encountered in high risk MDS; theincrease in CD13 expression on mature neutrophils is associated with unfavorable prognosis, as is the presence ofcirculating myeloid progenitor cells in the peripheral blood.

Immunophenotyping has limited value in counting CD34+ cells in the bone marrow, due to the possibility of dilution with peripheral blood. The cut-off for bone marrow blast percentage by flow cytometry is 3% (compared to 5% on the bone marrow aspirate smear)

Markers proposed forimmunophenotyping in MDS:

Compartment	*Mandatory*	*Optional*
Erythroid compartment	CD 71/CD235a/ CD117	CD105, CD34/CD117, CD36
Myeloid progenitor cells compartment	CD34 combined with CD117/CD11B/HLA-DR/CD15 Markers of lineage infidelity: CD5, CD7/CD13, CD19, CD56	CD123,TdT
Mature myeloid cells compartment	CD11b/CD13/CD16, CD11b/CD117/HLA-DR/CD10 CD34 combined with CD5, CD7, CD15, CD19, CD56, CD33/CD14	CD65, CD123
Monocytic compartment	CD11 b/HLA-DR, CD34 combined with CD5,CD7, CD19, CD56, CD64/CD14, CD33/CD14, CD33/CD36	CD64/CD36

MDS Classification

FAB (French-American-British)Classification, 1982

FAB subtype	*Blast % in peripheral blood*	*Blast % in bone marrow*
Refractory anemia (RA)	<1%	<5%,
Refractory anemia with ringed sideroblasts(RARS)	<1%	<5%, >15% RS
Refractory anemia with excess blasts (RAEB)	<5%	5-20%
Refractory anemia with excess blasts in transformation (RAEB-t)	≥5%	21-30 % or Auer rods
Chronic myelomonocytic leukemia (CMML)	<5% >1x10^9/L monocytes	5-20% blasts and 5% immature monocytes or 20% immature monocytes and 5% blasts

WHO Classification of MDS,2016

WHO subtype	*Peripheral blood*	*Bone marrow*
MDS with unilineage dysplasia	1-2 cytopenia(s)	Unilineage dysplasia≥10% of a single cell lineage, <5% blasts
MDS with ringed sideroblasts(MDS-RS)	Anemia, no blasts	≥15% ringed sideroblasts, or ≥5% ringed sideroblasts if SF3B1 mutation is present
MDS with multilineage dysplasia	Cytopenia(s), <1x10^9/Lmonocytes	Dysplasiain ≥10% of cells in ≥ 2 lineages, <15% RS or <5% RS if SF3B1 mutation is present, <5% blasts
MDS with excess blasts-1 (MDS-EB-1)	Cytopenia(s), ≤2-4% blasts, <1x10^9/L monocytes	Dysplasia in one or morecell lineages, 5-9% blasts, no Auer rods
MDS with excess blasts-2 (MDS-EB-2)	Cytopenia(s), 5-19% blasts, <1x10^9/L monocytes	Dysplasia in one or more cell lineages, 10-19% blasts, +/– Auer rods
MDS unclassified	Cytopenias, ≤1% blasts in at least 2 tests	Unilineage dysplasia or no dysplasia with cytogenetic abnormalities typically found in MDS, <5% blasts
MDS with isolated del(5q)	Anemia, normal or increased platelet count	Unilineage erythroid dysplasia, isolated del(5q), <5% blasts, +/– other anomalies except for -7/del(7q)
Refractory cytopenia of childhood (provisional entity)	Cytopenias, <2% blasts	Dysplasiain 1-3 lineages, <5% blasts

WHO Classification ofmyelodysplastic/myeloproliferative neoplasms (MDS/MPN), 2016

WHO subtype	*Peripheral blood*	*Bone marrow*	*Frequent mutations*
Chronic myelomonocytic leukemia (LMMC)-0	>1x10^9/L monocytes <2% blasts ≥10% monocytes	Dysplasia in ≥1 hematopoietic lineage, <5% blasts	TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL
LMMC-1	>1x10^9/L monocytes 2-4% blasts ≥10% monocytes	Dysplasiain ≥1 hematopoietic lineage, 5-9% blasts	TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL
LMMC-2	>1x10^9/L monocytes 5-19% blastsor Auer rods ≥10% monocytes	Dysplasiain ≥1 hematopoietic lineage, 10-19% blasts, or Auer rods	TET2, SRSF2, ASXL1, RUNX1, NRAS, CBL
Atypical chronic myeloid leukemia (aCML), BCR-ABL negative	L >13x10^9/L Neutrophil precursors ≥10% <20% blasts dysgranulopoiesis	Hypercellularity <20% blasts	SETBP1, ETNK1
Juvenile myelomonocytic leukemia (JMML)	>1x10^9/L monocytes <20% blasts ≥10% monocytes Increased HbF	>1x10^9/L monocytes <20% blasts Ph negative Hypersensitivity to GM-CSF	PTPN11, NF1, N/KRAS, CBL,SETBP1, JAK3
MDS/MPN unclassifiable	Dysplastic and myeloproliferativetraits No anteriorMDSor MPN	Dysplastic and myeloproliferative traits	TET2, NRAS, RUNX1, CBL, SETBP1, ASXL1
MDS/MPN with RS and thrombocytosis (MDS/MPN -RS-Tr)	Dysplastic and myeloproliferative traits Tr ≥450x10^9/L	Dysplastic and myeloproliferative traits ≥15% RS	SF3B1, JAK2, MPL, CALR
Chronic neutrophilic leukemia (CNL) (BCR-ABL negative)	L ≥25x10^9/L withneutrophils/ band neutrophils ≥80%, myeloid precursors ≤10%, no dysplasia	Myeloid hyperplasia with mature cells, <5% blasts, no dysplasia	CSF3R (G-CSFreceptor)

Prognostic Scoring Systems inMDS

Prognostic Scoring Systems for evaluating prognosis in MDS:

- IPSS 1997
- WPSS 2005, 2011
- R-IPSS 2012

The International Prognostic Scoring System (**IPSS**), 1997:

Blast% in BM	Karyotype	Cytopenias	Score
<5%	Favourable (normal, 5q-, 20q-,Y-)	0-1	0
5-10%	Intermediate (any other abnormality)	2-3	0,5
	Unfavourable (complex: ≥3 abnormalities, chromosome 7)		1
11-20%			1,5
21-30%			2

Risk category, survival andrisk of progression to AMLaccording to IPSS:

Risk category	Score	Median survival (years)	25% progression to AML(years)
Low	0	5,7	9,4
Intermediate-1	0,5-1	3,5	3,3
Intermediate-2	1,5-2	1,1	1,1
High	≥2,5	0,4	0,2

Cytopenias are defined as: hemoglobin (Hb)<10g/dL, ANC<1.8x10^9/L, platelet count <100x10^9/L.

Starting from IPSS, in 2005 Malcovati and collaborators have proposed a new prognostic scoring system based on the WHO classification (WHO Prognostic Scoring System– WPSS), the cytogenetic examinationand transfusion dependence. A revised scoring system (R-WPSS) was published in 2011, with a Hb cut-off of <9g/dLfor men and <8g/dL for women.

Risk category, survival and risk of progression to AML according to **R-WPSS** (2011):

	Score			
Score	0	1	2	3
WHO subtype	RA,RARS, 5q-	RCMD, RCMD-RS	RAEB1	RAEB2
Severe anemia Hb<9g/dLfor men and<8g/dL for women	no	yes		
Cytogenetic risk(IPSS)	good	intermediate	poor	

The Revised International Prognostic Scoring System (IPPS-R) was published in September 2012. Its parameters are the cytogenetic examination, bone marrow blast percentage, and the severity of each cytopenia.

IPSS-R: Cytogenetic abnormalities, prognostic subgroups, and median survival:

Prognostic subgroups	Cytogenetic abnormalities	Median survival (years)	25% progression to AML(years)
Very good	-Y, del(11q)	5,4	
Good	Normal, del(12p), del(20q), del(5q), double including del(5q)	4,8	9,4
Intermediate	Del(7q), +8, +19, i(17q), any other single or double independent clones	2,7	2,5
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del7(q), complex: 3 abnormalities	1,5	1,7
Very poor	Complex: >3 abnormalities	0,7	0,7

IPSS-R Prognostic Score Values:

Prognostic variable	0	0,5	1	1,5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very Poor
BM Blast %	≤2%	-	>2%-<5%	-	5%-10%	>10%	-
Hb (g/dL)	≥10	-	8-<10	<8	-	-	-
Platelets($x10^9$/L)	≥100	50-<100	<50	-	-	-	-
ANC ($x10^9$/L)	≥0,8	<0,8	-	-	-	-	

IPSS-R Prognostic Risk Categories:

Risk category	Risk score
Very low	≤1,5
Low	>1,5-3
Intermediate	>3-4,5
High	>4,5-6
Very high	>6

IPSS-R: Prognostic Risk Category Clinical Outcomes:

	Very low	Low	Intermediate	High	Very high
Patients %	19%	38%	20%	13%	10%
Median survival, years (CI 95%)	8,8 (7,8-9,9)	5,3 (5,1-5,7)	3,0 (2,7-3,3)	1,6 (1,5-1,7)	0,8 (0,7-0,8)
Hazard ratio (CI95%)	0,5(0,46-0,59)	1 (0,93-1,1)	2,0 (1,8-2,1)	3,2 (2,9-3,5)	8,0 (7,2-8,8)

IPSS-R: Prognostic Risk Category Clinical Outcomes:

	Very low	Low	Intermediate	High	Very high
Patients (6485),%	19%	37%	20%	13%	11%
AML25%*, (CI95%)	NR (14,5-NR)	10,8 (9,2-NR)	3,2 (2,8-4,4)	1,4 (1,1-1,7)	0,73 (0,7-0,9)
Hazard ratio (CI95%)	0,5 (0,46-0,6)	1 (0,9-1,2)	3,0 (2,7-3,5)	6,2 (5,4-7,2)	12,7 (10,6-15,2)

AML25%* (median time in which 25% of patientsprogress to AML)

IPSS-R:Age groups survival

Age, years	Very low	Low	Intermediate	High	Very high
All patients	8,8	5,3	3	1,6	0,8
≤60	NR (13,0-NR)	8,8 (8,1-12,1)	5,2 (4,0-7,7)	2,1 (1,7-2,8)	0,9 (0,8-1,0)
>60-70	10,2 (9,1-NR)	6,1 (5,3-7,4)	3,3 (2,5-4,0)	1,6 (1,5-2,0)	0,0 (0,7-1,0)
>70-80	7 (5,9-9,9)	4,7 (4,3-5,3)	2,7 (2,4-3,1)	1,5 (1,3-1,7)	0,7 (0,6-0,8)
>80	5,2 (4,2-5,9)	3,2 (2,8-3,8)	1,8 (1,6-2,6)	1,5 (1,2-1,7)	0,7 (0,5-0,8)
≤60 (median 52)	NR	8,8	5,2	2,1	0,9
>60 (median 74)	7,5	4,7	2,6	1,5	0,7
≤70 (median 62)	13,3	7,7	3,9	1,7	0,9
>70 (median 77)	5,9	4,2	2,5	1,4	0,7

Treatment

The choice of treatment in a patient with MDS is made by taking into account the prognostic category, the IPSS, IPSS-R and R-WPSS risk categories, patient age and performance status. Progression to AML is associated with chemotherapy resistance, as opposed to de novo AML. The only curative therapy is allogeneic stem cell transplant, which is limited to a small number of patients because of the age limit and lack ofstem cell donors.

Patients are closely monitored for a few months in order to assess the evolution of cytopenias and disease progression. A part of them present with slowly progressing asymptomatic cytopenias, which do not need prolonged treatment, while others rapidly progress to AML.

Treatment options in MDS are: supportive care, low dose chemotherapy, intensive chemotherapy (similar to AML), allogeneic stem cell transplant, taking part in clinical trials.

The patient must be included in a risk category as soon as a diagnosis is set:

- **Lower risk** (low or intermediate-1 IPSS;very low, lowor intermediate IPSS-R;very low, lowor intermediate WPSS)
- **Higher risk** (intermediate-2 of high IPSS;intermediate, highor very high IPSS-R;highor very high WPSS)

Patients with IPSS-R intermediate risk are categorized as lower risk patients, but they can also be considered higher risk if they do not respond to treatment or if they present other negative prognostic factors (increased age, performance status, high serum ferritin or LDH levels).

Patients with therapy-related MDS are considered high risk and they usually respond poorly tochemotherapy.

A treatment algorithm taking intoaccount the risk category, based on the **National Comprehensive Cancer Network Guidelines, version 1.2019** will be presented hereafter.

Lower risk patients (low or intermediate-1IPSS;very low, low or intermediateIPSS-R;very low, low or intermediateWPSS), according to NCCN guidelines, presenting with one or more symptomatic cytopenias, or with a high bone marrow blast count, should mainly

receive supportive treatment(red blood cell and platelet transfusion).

For patients with symptomatic anemia there are several treatment options:

Del (5q) with or without other cytogenetic abnormalities (except for chromosome 7 disorders), withlow or intermediate IPSS, should receive**lenalidomide**:

- It is not recommended for patients with low neutrophil or platelet count.
- The initial dose (ANC over $0.5x10^9$/L, platelet countover $50x10^9$/L) is 10 mg/day for 21 days, at the same hour, with a glass of water, before or after meals,every 28 days(monthly),2-4 months in totalfor response assessment.
- Treatment should not be initiated when ANC<$0.5x10^9$/L or platelets<$25x10^9$/L.
- Treatment will be continued if a positive response is obtained (Hb 10-12 g/dL, not over 12 g/dL), lowering the dose according to tolerance.

Lenalidomide

Indications: MDS with del (5q)

Dose adjustmentbased onneutrophil count, platelet count andcreatinine clearance:

Dose reduction stages:

Starting dose	10 mg once daily, days 1-21, every 28 days
Dose level-1	5 mg once daily, days 1-28, every 28 days
Dose level-2	2,5 mg once daily, days 1-28, every 28 days
Dose level-3	2,5 every other day (every 48 hours), days 1-28, every 28 days

Thrombocytopenia	
Decrease to< 25 x 10^9/L	Discontinue treatment
Recovery to ≥ 25 x 10^9/L, but < 50 x 10^9/L, at least 2 testsover ≥ 7 days, or platelet count recovery to ≥ 50 x 10^9/L	Reinitiate treatment by lowering the dose to nextdose level (dose level -1, - 2 or -3)
Neutropenia	
Decrease to < 0,5 x 10^9/L	Discontinue treatment
Recovery to ≥ 0,5 x 10^9/L	Reinitiate treatment by lowering the dose to next dose level (dose level -1, - 2 or -3)

Renal function (Clcr)	**Dose adjustment**	
Moderate renal impairment (30 ≤ Clcr< 50 mL/min)	Starting dose	5 mg once daily (days 1-21,every 28 days)
	Dose level-1*	2,5 mg once daily (days 1-28, every 28 days)
	Dose level-2*	2,5 mg every other day (days 1-28, every 28 days)
Severe renal failure (Clcr< 30 mL/min, without dialysis)	Starting dose	2,5 mg once daily (days 1-21, every 28 days)
	Dose level-1*	2,5 mg every other day (days 1-28, every 28 days)
	Dose level-2*	2,5 mg twice a week (days 1-28, every 28 days)
End stage renal disease (ESRD) (Clcr< 30 mL/min, requiring dialysis) Lenalidomide must be administered after the procedure during days with hemodialysis sessions	Starting dose	2,5 mg once daily (days 1-21, every 28 days)
	Dose level-1*	2,5 mg every other day (days 1-28, every 28 days)
	Dose level-2*	2,5 mg twice a week (days 1-28, every 28 days)

Discontinue treatment when:

- Patients do not show at least a minor erythroid response after 4 months of treatment (defined by a ≥50% decrease in blood transfusions, or an increase of Hb levels by 1g/dL in transfusion independence cases);
- Occurrence of grade 3 or grade 4 toxicity, considered to be associated withlenalidomide (discontinue treatment andreinitiate bylowering the dose to next dose level when the toxicity is grade 2 or below).

Adverse reactions:

- Cutaneous eruptions(grade 2 or 3);
- Angioedema, grade 4 cutaneous eruptions, exfoliativeorbullous eruptionswhen suspectingStevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reactions with eosinophilia and systemic symptoms (DRESS) – treatment should not be reinitiated when discontinued because of these reactions;
- Pregnancy –teratogenic effects;
- Acute liver failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis,and mixed cytolytic/cholestatic hepatitis;
- Infections, varicella-zoster virus (VZV) or hepatitis B virus (HBV)reactivation;
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism);
- Diarrhea, constipation, nausea, cutaneous eruptions, fatigue, muscle cramps.

Lenalidomide is not reimbursed in RomaniaforMDS with del(5q).

In the absence of del (5q), with or without other cytogenetic abnormalities, and serum erythropoietin (Epo) levelsof <500mUI/mL:

- Erythropoiesis-stimulating agents (ESAs - epoetinalfa orDarbepoetin) +/– G-CSF
- Lenalidomide

MDS with < 15% RS:

- **Epoetinalfa 40000-60000 U 1-2x/weeksubcutaneously orDarbepoetinalfa 150-300 (500) µg every 2 weeks, subcutaneous injection**

- Positive response,Hb 10-12 g/dL, not over 12 g/dL:continue treatment and lower the dose according to tolerance;
- No response: Hb level does not increase by at least 1.5 g/dL (when iron deposits are adequate), or the blood transfusion necessity does not decrease after 6-8 weeks oftreatment;
- If no response in obtained,**G-CSF** can be added to Epo:1-2 µg/kg once or twice a week, subcutaneous injection

and/or

- **Lenalidomidă** (10 mg/day, 21 days/month, if ANC >0.5x10^9/L and platelet count>50x10^9/L).

MDS with > 15% RS:

Epoetinalfa 40000-60000 U 1-2x/weeksubcutaneously orDarbepoetinalfa 150-300 (500) µg every 2 weeks, subcutaneous injection and G-CSF 1-2 µg /kg once or twice a week, subcutaneous injection

- Positive response,Hb 10-12 g/dL, not over 12 g/dL:continue treatment and lower the dose according to tolerance;
- No response: Hb level does not increase by at least 1.5 g/dL (when iron deposits are adequate), or the blood transfusion requirement does not decrease after 6-8 weeks oftreatment.

G-CSF is not reimbursed in Romania for this indication (MDS +/– RSwithout neutropenia).

Tretment with Erythropoiesis-stimulating agents(ESAs)

ESAs increaseHb levels andşialleviateanemia-related symptoms in MDS patients.

The main predictive factors for response to ESAs are the following:

- Low or absent red blood cell transfusion requirement;
- Endogenous serum erythropoietin level of < 500mUI/ml at diagnosis;
- WHO subtype (RA and RARS);
- Patients with low or intermediate-1 IPSS score;
- Unilineagedysplasia;
- Short time between diagnosis and treatmentinitiation.

The Scandinavian-American Prognostic Scoring System allows assessment of ESA response, by taking into accountserum Epo levelsat diagnosisand blood transfusion requirement.

Scandinavian-American ScoreforESA response assessment:

Serum Epo(mUI/mL)	Score	Transfusion requirement	Score	Final score	Response
<100	+2	< 2 RBC units/month	+2	>+1	Favourable74%
100-500	+1	≥2 RBC units/month	–2	+1 - –1	Intermediate 23%
≥500	–3			<–1	Unfavourable7%

ESAs (epoetinalfa and beta, darbepoetin)treatment recommendations:

- Low risk and intermediate-1 MDS, Hb<10g/dL, serum Epo<500mUI/mL;
- recommended dose: 30000-60000U/week (once or twice/week);darbepoetin300 µg/week or 500 µg/ 2 weeks, for at least 8 weeks, followed by an increased dose if no response is obtained;
- if transferrin saturation levels decrease< 20%, iron supplements are necessary;
- if patients respond to ESAs, either the dosage or the frequency of administration should be reduced in order to maintain a Hb level of 10-12 g/dL;
- the addition of G-CSF (300 µg/week)is recommendedin order to maintain the ANC between 5-10x10^9/L, in patients with RARS or with serum Epo levels < 500mUI/mLand insufficient response toESAs (synergistic effect on cytochrome c).

Adverse reactions:

- localized rash, cutaneous reactions;
- flu-like symptoms;
- high blood pressure;
- theappearance of anti-erythropoietin neutralizing antibodies, leading to pure red cell aplasia.

An increase in adverse events, chronic heart failure, myocardial infarction, stroke, and exitus, are related to aHblevel of > 13.5 g/dL.

Eporesistance and loss of therapeutic effect are influenced by numerous factors:

- iron deficiency orfunctional iron deficiency in the presence of inflammatory diseases(oral or intravenous iron supplementation, even when serum ferritin level is not low);
- disease progression or transformation into AML;
- pure red cell aplasia;
- other types of anemia.

Patients with serum Epo levels of > 500 mUI/mL, or Epo levels of <500 mUI/mL and no response to ESAs:

Patients may be responsive to **immunosuppressive therapy** under the following conditions:

- < 60 years of age;
- bone marrow blasts ≤5%;
- hypocellular bone marrow;
- HLA-DR 15 positive;
- existing PNH clone;
- cytotoxic T cellcloneswith STAT-3mutation;
- normal karyotype or chromosome 8 trisomy.

Horse antithymocyte globulin (equine ATG) and/or cyclosporine (aplastic anemia protocol):

- **antithymocyte globulin(ATG) 40 mg/kg/day, intravenously over 4-6 hours, 4 days and/or cyclosporine 5-12 mg/kg/day starting with day 14, therapeutic level: 200-400 ng/mL.**

When immunosuppressive therapy is not indicated, **hypomethylating agents (DecitabineorAzacitidine), Lenalidomideor clinical trials** are recommended:

- **Azacitidine**: 75 mg/m^{2}s.c.ori.v., days 1-7, every 28 days (orthe alternative schedule:days 1-5 and 8-9, every 28 days)
  or
- **Decitabine**: 20 mg/m^{2}i.v. over 1 hour, days1-5, every 28 days
  or
- **Lenalidomide**: 10 mg/dayoral administration, days1-21, every 28 days

In the absence of clinical response after 6 cycles of Azacitidineor 4 cycles of Decitabine, either **stem cell transplantation** or **inclusion in clinical trials** should be considered.

Lenalidomide is not reimbursed in Romania.

Azacitidine and Decitabine are not reimbursed in Romania for low risk MDS.

Higher risk MDS patients (intermediate-2 of high IPSS; intermediate, high or very high IPSS-R;high or very high WPSS) :

- Patient evaluation for intensive chemotherapy;
- Patients eligible for intensive chemotherapy: young age, few or no comorbidities, good performance status, adequatepsychosocial and familial support.

An international group of experts from the European Society for Blood and Marrow Transplantation, European LeukemiaNet,Blood and Marrow Transplant Clinical Trials Network, and MDS International Foundation, have established the indications of bone marrow transplantation for patients with MDS and CMML:

- patients with higher risk MDS;
- lower risk R-IPSS and unfavorable-risk cytogenetics;
- severe cytopenia;
- high blood transfusion demand.

If HLA compatible siblings areavailable, **allogeneic stem cell transplantation** is recommended. When there is no compatible donor, hypomethylating agents or intensive chemotherapy should be administered.

Patients eligible for hematopoietic stem cell transplantation:

- allogeneic stem cell transplantation is the only curative treatment;
- a bone marrow transplantationspecialist should be consulted at diagnosis, before an extensive blood transfusion support, infectious complications or progression to AML;
- for patients with BM blasts <10% the transplant should be done promptly if a compatible donor is available;
- for patients with BM blasts >10% cytoreductive therapy is recommended;

- inclusion in clinical trials should be considered at any stage of treatment;
- allogeneic stem cell transplantation(from a compatible sibling, unrelated donor,orother alternatives – haploidentical donoror cord blood) witheither standard conditioning regimensorreduced intensity conditioning;
- Azacitidineor Decitabine (followed byallogeneic stem cell transplantation)are used as bridging to transplantuntil a donor is found, but they do not delaythetransplantation;
- Standard intensive chemotherapy or clinical trials for new therapies (preferable) followed by allogeneic stem cell transplantation;
- there is no standard regarding first-line treatment failure;
- stem cells may be procured from HLA compatiblesiblings orunrelated donors, umbilical cord blood cells, related HLA haploidentical donors;
- high-dose conditioning regimens are used for younger patients;
- older patients receivereduced intensity conditioning regimens;
- numerous studies have aurevealed that 60% of low riskpatients and 20-40% of high riskpatientshaveprolonged survival after allogeneic transplantationfrom a compatible donor.

The Italian Bone Marrow Transplant Group led by Alessandrino and Portahas confirmed the benefits of early stem cell transplantation for patients younger than 60, with int-2 or high risk IPSS, on whom the procedure should be performed as soon as possible. A delay may be accepted for patients with intermediate-1 risk, with survival gain. This decision should be made for each individual case, also taking into account other factors (neutrophil and platelet count).

Patients with CMML-2 should be treated with hypomethylating agents followed by allogeneic transplantationas soon as possible.

Therapy-related MDS (t-MDS) has a worse prognosis compared with de novo MDS.

Post-transplant negative prognostic factors:

- over 35 years of age;
- unfavourable-risk cytogenetics;
- advanced disease;
- high non-relapse mortality;
- 5-year relapse-free survival rate is 29%.

MDS with myelofibrosis:

- it is associated with se severe pancytopenia;
- stem cell transplant is recommended beforeprogression of fibrosis;
- 3-year survival rate, based onthe stage of fibrosis: absent or mild fibrosis 49%, moderate fibrosis 40%, severe fibrosis 21%.

Hypoplastic MDS:

- difficult to distinguish from aplastic anemia;
- the indication for stem cell transplantation isdependent upon theseverity of cytopenias, transfusion requirement, and probabilitateaprobability of response toimmunosuppressive therapy.

MDS originating in germline mutations:

- it occurs in young patients (40-50 years old);
- family history of dyskeratosis congenita, Fanconi anemia, Shwachmann-Diamond syndrome, Diamond-Blackfan anemia, GATA2 mutations;
- early allogeneic transplantation is recommended;
- specific conditioning regimens.

Unfavorable prognostic factors in patients with**int-1 and low risk**

MDS(allogeneic stem cell transplantation should be done as soon as possible):

- transfusion requirement≥2 units/month;
- life threatening cytopenias:anc<0.3x10^9/l, platelet count<30x10^9/l
- very unfavourable risk cytogenetics;
- progression of anemia with high transfusion requirements and lack of response to ESAs in lower risk mds patients;
- the presence and acquisition of mutations associated with unfavourable risk (e.g. Tp53)

Allogeneic transplantation offers normal stem cells and graft versus leukemia effect, as opposed to autologous stem cell transplant. The mortality rate remains high because of regimen-related toxicity and graft-versus-host disease, especially amongst older patients.

High dose chemotherapy followed by **autologous stem cell transplantation** does not completely eliminate the MDS clone. Some studies have reported disease-free survival after autologous transplantation as consolidation therapy of remission following chemotherapy. The relapse rate after this procedure is 75%, and 100% in patients with high risk cytogenetics. 4-year disease-free survival rate is 15%. There are no differences in survival rates between AML-type chemotherapy and autologous stem cell transplant.

Patients with high risk of progression to AML, advanced age, high comorbidity index, **very unfavorable cytogenetic risk and very unfavorable molecular abnormalities**, and high IPSS-R score have little chance of undergoing allogeneic transplantation, therefore inclusion in investigational clinical trials is recommended.

The use of **hypomethylating agents**in MDS with excess blasts has been reported in numerous studies. Azacitidine is less toxic than AML-type chemotherapy, being preferred in reduced intensity conditioning regimens.

The Seattle Working Group and a french study have shown a similar post-transplant evolution between patients who received intensive chemotherapy and patients treated with hypomethylating agents. A lower toxicity has been observed in the second group, but with less efficiency regarding long term survival and complete remission rate.

If stable disease is obtained after 6 cycles of hypomethylating agents, the patient is considered eligible for stem cell transplantation.

Cases with complex and/or monosomal karyotype are associated with post-transplant relapse and high mortality rate, therefore Azacitidine constitutes a treatment option.

Mutations in **DNMT3A, TET2, IDH1, IDH2** genesare associated with multilineage dysplasia and unfavourable risk. Mutations in **SRSF2, RUNX1, U2AF1, ASXL1, TP53** also have a negative prognosis. Patients with mutated **JAK2** and **RAS** genes have an unfavourable post-transplant evolution. Mutations inTP53 combined with a complex karyotype are associated with very unfavourable post-transplant evolution.

Clinical trials are recommended for patients with **ASXL1, RUNX1, RAS, JAK2, and TP53** mutations.

Patients who are not eligible for stem cell transplantation:

Hypomethylating agents: Azacitidine (preferable) or Decitabine

- **Azacitidine**: 75 mg/m^2s.c.or i.v., days 1-7, every 28 days (or the alternative schedule:days 1-5 and 8-9, every 28 days)

or

- **Decitabine** 20 mg/m^2, i.v. over 1 hour, days 1-5, every 28 days;
- **Clinical trials.**

Response rates to Azacitidine and Decitabine are similar. Survival benefit in a phase III clinical trial has been reported only for Azacitidine. Hypomethylating agents must be administered for at least 4-6 cycles for a correct response assessment. Patients who show clinical improvement continue treatment as maintenance therapy.

Supportive care or clinical trials are recommended in cases with no therapeutic response or with relapsed disease.

Decitabine is not reimbursed in Romania for MDS.

Vidaza (Azacitidine)

Indicated for treatment of adult patients, not eligible for hematopoietic stem cell transplantation, with:

• Intermediate-2 and high risk MDS;

•CMML with 10-29% bone marrow blasts, without myeloproliferative disease;

• AML with cu 20-30% blasts and multilineage dysplasia.

Administration:

- Initial dose: 75 mg/m^2,s.c., days 1-7, with a pause of 21 days (28 days cycle);
- 100 mg vial, dissolving in 4 mL of sterile water for injections, 25 mg/mL;
- The total dose is split in two 2 equal parts with different sites of injection;
- It is administered subcutaneously in the upper part of the arm, thigh or abdomen;
- The injection sites must be changed, with new injections at a distance of at least 2.5 cm, and never insensitive areas (with bruising, erythema or edema).

In case of adverse reactions at the sites of injection, it may be administered intravenously: a vial is dissolved in 10 mLof sterile water for injections, with administration in 50-100 mL of saline solution 0.9% or Ringer's lactate solution.

At least 6 cycles are needed for response assessment.

Premedication:

- Allopurinol 300 mg po/day, with dose adjustment in case of renal impairment;
- Hydrocortisone 1% cream for local application at injection sites in case of inflammation, rash, pruritus;
- proton pump inhibitors / H_2 receptor antagonists;
- antiemetic drugs.

Treatment should be continued as long as a clinical benefit is observed, or until disease progression. Patients must be monitored in order to assess response, hematologic toxicity and renal toxicity.

Necessary tests when starting treatment:

- complete blood count, uric acid, liver and renal function tests, bicarbonate level, LDH;
- serum ferritin, vitamin B12, folic acid, thyroid function tests;
- coagulation tests, blood type;
- viral markers for HBV, HCV, HIV;
- ECG;
- bone marrow aspiration, bone marrow biopsy, cytogenetic examination.

Necessary tests before every cycle:

- complete blood count, uricacid, liver and renal function tests, bicarbonate level;
- after treatment a full blood countmust be done weekly.

Dose adjustment in case of hematologic toxicity

Hematologic toxicity= the lowest leukocyte/neutrophil count during a cycle (nadir), if the platelet count falls below50x10^9/Land/orANC falls below 1x10^9/L.

Hematologic recovery = blood cell countduringrecovery≥ cell countat nadir + (0.5x[initial cell count– cell countat nadir]).

Patients without a low initial blood cell count (white blood cells (WBC) > 3.0 x 10^9/Landabsolute neutrophil count (ANC) > 1.5 x 10^9/L; platelet count > 75 x 10^9/L), before the first cycle:

If after treatment hematologic toxicity is observed, the next cycle must be postponed until the platelet count and ANC both recover.

If recovery is obtained in an interval of 14 days, dose adjustment is not necessary.

If hematologic recovery is not obtained in 14 days, the dose must be lowered according to the following table.

After dosage adjustment, the duration of a cyclemust return to 28 days.

Blood cell count at nadir		% of dose for next cycle, if recovery * is not obtained in an interval of 14 days
ANC (x 10^9/L)	Platelets (x 10^9/L)	
≤ 1	≤ 50	50%
> 1	> 50	100%

Patients with low initial blood cell count (WBC<3.0 x 10^9/Lor ANC<1.5 x 10^9/L; platelet count<75 x 10^9/L) before the first cycle:

If after treatment with Vidaza ANC or platelet counts get reduced by less than 50% of the initial values, or by more than 50%, but with an improvement in the differentiation of any cell lineage, the next cycle must not be postponed, and the dose should stay the same.

If the leukocyte, neutrophil or platelet counts are reduced by more than 50% compared to initial values, with no improvement in any cell lineage differentiation, the next treatment cycle should be postponed until hematologic recovery of platelets and neutrophils.

If hematologic recovery is obtained in an interval of 14 days, dose adjustment is not necessary.

If recovery is not obtained in 14 days, bone marrow cellularity should be evaluated.

If bone marrow cellularity is> 50%, dose adjustment is not needed.

If bone marrow cellularity is≤ 50%, treatment should be postponed and the dose should be lowered according to the following table:

Bone marrow cellularity	% of dose for next cycle, if recovery* is not obtained in an interval of 14 days	
Recovery* ≤ 21 days	Recovery* > 21 days	
15-50%	100%	50%
< 15%	100%	33%

*Recovery= cell count ≥ cell count at nadir + (0.5 x [initial count – cell count at nadir])

Contraindications:

- known hypersensitivity to the active substance or any of the excipients;
- advanced malignant hepatic tumor;
- breast feeding.

Warnings and precautions:

Hematologic toxicity: anemia, neutropenia and thrombocytopenia, especially during the first 2 cycles:

- the complete blood count must be repeated whenever necessary for response and toxicity monitoring, and at least once before each tratament cycle.

Hepatic impairment:

- no administrationif AST/ALT/ serum bilirubin levels are over 2 times the normal value;

- progressive liver encephalopathy and exitus in patients with metastatic disease causing extensive tumor burden, during treatment with Azacitidine.

Renal impairment:

- if serum creatinine doubles its value compared to levels before Azacitidine treatment, either the next cycle is postponed, or the dose is lowered by 50%;
- severe tubular damage: hypophosphatemia, hypokalemia, hyponatremia, with or without creatinine increase – bicarbonate, urea, creatinine monitoring;
- if serum bicarbonate falls below 19 mmol/L, bicarbonate should be administered orally, and the dose of Azacitidineis lowered by 50%.

Adverse reactions:

- hematologic reactions: thrombocytopenia, grade 3-4 neutropenia, especially during the first 2 cycles;
- infections;
- bleeding: gastrointestinal hemorrhage, intracranial hemorrhage;
- hypersensitivity, anaphylaxis;
- cutaneous reactions: transitory cutaneous eruptions, erythema and cutaneous lesions, which may require antihistamines, corticosteroids and nonsteroidal anti-inflammatory drugs;
- gastrointestinal adverse reactions: constipation, diarrhea, nausea and vomiting.

Supportive care

Supportive care is the standard treatment option for elderly patients not eligible for stem cell transplant.

In symptomatic cytopenias it constitutes an adjuvant therapy for the main treatment, and it comprises:

- leukoreducedred blood cell transfusion (leukoreduced packed red blood cells), according to clinical tolerance for preventing alloimmunization;
- iron chelation therapy;
- platelet transfusion, preferably apheresis, for symptomatic thrombocytopenia(not for prophylactic use when platelet count >10 x 10^9/l);
- patients eligible for stem cell transplant receive irradiated blood products and negative CMV blood products for negative CMVIgGpatients;
- antibiotics for bacterial infections (prophylactic use only for recurrent infections);
- Aminocaproic acidor other antifibrinolytic agents for platelet transfusion refractory bleeding or severe thrombocytopenia;
- hematopoietic growth factors.

Management oftransfusion dependence

Anemia is the main main clinical manifestation inMDS patients. It is present at diagnosis in 90% of cases. Other times it occurs in the course of the disease. Its management is very important because anemia affects quality of life.

It is administered to symptomatic patients, when Hb level falls between 8 and 9 g/dL orfor higher Hb values, but with limited cardiopulmonary capacity. It is not recommended for Hb<7g/dL. Anemia causes a rise in cardiac output, left ventricular hypertrophy and exacerbation of coronary artery disease manifestations in patients with cardiac comorbidities, representing the main non leukemic cause of death.

Management of iron overload

MDS patients who receive more than 20-30 units of packed RBC develop iron overload. This condition is associated with an increased risk of progression to leukemia, a high risk of infections and an increased post-transplant mortality rate.

Excess iron is stored in the liver, pancreas, heart, andcentral nervous system.

Iron chelation therapy: Deferoxamine, Deferasirox. These drugs cause a negative iron balance, they decrease or normalize labile plasma iron, reduce serum ferritin şia hepatic iron deposition. Desferoxamine is administered by continuous subcutaneous infusion and Deferasirox is administered orally.

Indications: patients who have received more than 20-30 unitsof packed RBC, serum ferritin level over 1000ng/mL, patients who are eligible for stem cell transplantation, patients with life expectancy of more than 3 years.

Objectives: lowering of serum ferritin level under 1000 ng/mLin patients with low risk or eligible for stem cell transplantation, quantification of hepatic iron deposition through T2*MRI.

Ferritin is an acute phase protein and in increases inliver diseases.

Exjade (Deferasirox):

- initial dose of 20 mg/kg, once daily (maximum dose:30 mg/kg);
- dosage is adjusted by 5-10 mg/kg, based on serum ferritin level evaluation after 3-6 months;
- Creatinine should be measured weekly in the first month;
- Adverse reactions: acute renal failure, increased transaminase levels, cutaneous eruptions, severe hypersensitivity reactions, visual and hearing impairment;
- ophthalmology and ENT consults are recommended before starting treatment.

Desferal (Deferoxamine): 20-40 mg/day, using a pump, i.m. or continuous infusion, 5-7 days/week.Vitamin C may be used as adjuvant to chelation therapy.A dose of 150-200 mg/dayincreases renal excretion.Very high doses can cause cardiac complications.

Adversereactions:

- infections (including septicemia), especially with Yersinia enterocolitica and Yersinia pseudo-tuberculosis. If patients being treated with Desferal present with fever and acute enteritis/enterocolitis, diffuse abdominal pain orpharyngitis, temporary treatment interruption is recommended, along with bacteriological testing and immediate start of antibiotics;
- severe fungal infections;
- visual and hearing impairment:o phthalmology and ENT consults before starting treatment;
- cutaneous allergy, anaphylaxis, local rash near injection site;
- eye lens opacity, gastrointestinal disorders;
- renal and hepatic impairment;
- thrombocytopenia;
- cardiovascular disease (arterial hypertension, cardiac arrhythmia);
- neurological disorders(convulsions, confusion);
- calf muscle cramps.

For iron chelation therapy serum ferritin monitoring, spot urine test,renal and hepatic function tests, ENT andophthalmological examinations are mandatory at the beginning of treatment and they must be repeated periodically once every 3 months.

Management of thrombocytopenia

Severe thrombocytopeniais present in 8-16% of MDS patients. It has a negative impact on survival and is associated with a high risk of hemorrhage-related mortality. Platelet transfusion is recommendedonly for platelet counts of$<10x10^9$/Lor$<20x10^9$/L with increased bleeding risk, in order to prevent alloimmunization.Single donor platelet apheresis is preferred.

Corticosteroids or IV immunoglobulins may be used when an

immune component of thrombocytopenia is suspected, with doses similar to immune thrombocytopenic purpura cases.

Antifibrinolytic agents (tranexamic acid) may be administered in order to ensure hemostasis when platelet counts are under<$20x10^9$/L, when active bleeding is present or if there is a high risk of bleeding.

Romiplostim and Eltrombopag, 2 thrombopoietin receptor agonists that stimulate thrombocyte production in ITP, are under evaluation for use in MDS. They are not reimbursed for treating thrombocytopeniain MDS and are not recommended for this use outside of clinical trials.

Patients should be advised to avoid high blood pressure and constipation (increased risk oflife-threatening bleeding).

Management ofneutropenia

There is no data which suggests a benefit in routine use of G-CSFand of antimicrobial or antifungal prophylaxis in neutropenic patients.

Antimicrobial or antifungal prophylaxis is recommended for neutropenic and non-neutropenic (neutrophil dysfunction) patients with recurrent infections, based on local flora.

Prophylactic use of G-CSF in patients with severe neutropenia has not shown an increase in survival rate.

Sepsis and febrile neutropenia must be treated according to local protocols.

Use of mouth wash, riguros hygiene measures, and high temperature cooking are also recommended.

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IN MEMORIAM

Societatea Română de Hematologie anunță cu profund regret dispariția prematură și fulgerătoare dintre noi a Profesorului Universitar Dr. Oltean Galafteon în data de 25 august 2019, la vârsta de 67 de ani.

Prof Dr Oltean Galafteon s-a născut la data de 2 decembrie 1951, în localitatea Idicel, județul Mureș, într-o familie de oameni simpli, cu un profund cult al muncii, cinstei, corectitudinii, onoarei și credinței. A studiat la Şcoala Generală Idicel Pădure (1962-65), Şcoala Generală. nr 5, Reghin (1965-66), Liceul „Petru Maior" Reghin (1966-70) remarcandu-se mereu pentru rezultatele școlare deosebite și conștiinciozitatea exemplară. Între 1970-1976 a urmat cursurile Institutului de Medicină și Farmacie Tg Mureș, pe care l-a onorat cu rezultate deosebite, obtinute prin inteligență, muncă și strădanie susținută.

După terminarea facultății a fost inițial medic stagiar (grupa specialităţi medicale) și pentru o scurtă perioadă (1978-79), medic de medicină generală la Dispensarul Medical comuna Corbu, județul Harghita. Începând cu anul 1979 si până la retragerea din activitate (2018) activitatea profesională și-a desfășurat-o in cadrul Clinicii Medicale I, Spitalul Clinic Județean de Urgență SCJU Tg Mureș: medic secundar (1979-82), medic specialist medicină internă (din 1982), medic specialist hematologie (din 1988), medic primar medicină internă (din 1991). Din 1997 până în octombrie 2018 a preluat șefia Clinicii Medicale nr. 1 Tg. Mureș şi al Compartimentului de Hematologie.

La nivelul SCJU Tg Mureș între 1997-2005 a fost membru în Consiliul de Administraţie, între 2006-2018 membru în Consiliul Medical, între 2004-2009 membru în Comisia de Etică iar între 2004-2018 coordonator al Programului de profilaxie şi tratament al bolnavilor hemofilici de la nivelul judeţului Mureş. În perioada 2001-2018 medicii rezidenți au avut în Domnul Profesor Oltean Galafteon un atent, responsabil și dedicat coordonator de rezidențiat în specialitatea medicină internă. An după an a fost președinte sau membru în numeroase comisii de examinare pentru obținerea titlului de medic specialist sau primar, atât în Tg Mureș cât și în alte centre din țară. De menționat de asemenea activitatea susținută de la nivelul Colegiului Judeţean al Medicilor Mureş, unde printre altele a fost președintele Comisiei de Avizări și Acreditări în perioada 1999-2007. La nivel național a activat ca și membru în comisii ale Ministerului Sănătații (între 2005-2014- Comisia de Hematologie Sanătății, între 2009-2014 -Subcomisia de Oncohematologie) sau ale Colegiului Medicilor din Romania (2009-2010 Comisia de Hematologie a CNAS, 2006-2016 președinte a Comsiei de Hematologie și Transfuzie Sanguina a CMR).

Activitatea didactică universitară, în cadrul Universității de Medicină și Farmacie din Tg Mureș, a reprezentat întotdeauna o mare pasiune. In 1992 a susținut, sub îndrumarea prof dr Dudea Corneliu, teza de doctorat cu titlul "Modificări ale hemostazei şi fibrinolizei în hepatite cronice şi ciroze hepatice (1992)". Pas cu pas a parcurs toate treptele ierarhice: asistent universitar (1979-91), şef de lucrări (1991-98), conferențiar universitar (1998-2001), profesor universitar (din 2001). Generații succesive de studenți, rezidenți, specialiști au avut privilegiul de a asista la cursurile universitare și postuniversitare pregătite întotdeauna cu

mare atenție, cuprinzând constant noutăți și multiple aspecte practice, prezentate cu un deosebit talent pedagogic.

De-a lungul prestigioasei cariere universitare a elaborat cursuri pentru studenți, capitole in cărti de specialitate. O mențiune specială merită cele trei cărti de specialitate publicate: "Aspecte diagnostice şi terapeutice în bolile hematologice" (1996), "Limfoame maligne" (in colaborare cu prof dr G Simu, 1997), "Limfoame maligne cu debut extraganglionar" (2001), apreciate nu doar de comunitatea medicală locală ci și la nivel național.

Activitatea științifică a reprezentat o preocupare constantă, domeniile de cercetare preferate fiind hematologia clinică, gastroenterologia, medicina internă. A fost autor sau coautor a 470 lucrări științifice (dintre care 110 in extenso) publicate în reviste din țară sau din străinantate. În peste 20 de studii clinice internaționale (pe probleme de hematologie) desfășurate la nivelul SCJU Tg Mureș a deținut calitatea de investigator principal. Circa 20 de lucrări de doctorat au fost coordonate și finalizare sub directa și exigența sa îndrumare; an după an a participat ca și președinte de comisie sau membru la susținerea a numeroase teze de doctorat atât în centrul universitar Tg Mureș cât și în alte centre universitare (Cluj Napoca, Iași, București). Domnul Profesor a fost președinte sau membru în comitetele de organizare a multor manifestări științifice locale sau la nivel național de asemenea director și/sau lector a numeroase cursuri postuniversitare.

Încă din 1988 Prof Dr Oltean Galafteon a fost un "soldat" activ și dedicat al Societii Române de Hematologie, din 1997 membru în Comitetul Național și vicepreședinte din octombrie 2011. Participarea în comitetele de organizare a numeroase si variate evenimente, susținerea de lucrări și prelegeri a fost întotdeauna o prioritate, o plăcere și o deosebită onoare. De menționat de asemenea calitatea de membru activ în o serie de alte societăți științifice naționale (Asociatia Română de Hemofilie, Societatea Română de Medicină Internă, Societatea Română de Medicină de Laborator, Societatea Română de Radioterapie și Oncologie Medicală, Societatea Română de Gastroenterologie și Hepatologie, Uniunea Societăților de Științe Medicale USSM, membru corespondent al Academiei Oamenilor de Știință din Romania, Grupul de Lucru pentru leucemia mieloidă cronică în România) și internaționale (Grupul Internațional pentru Studiul Limfoamelor Extranodale IELSG, Societatea Central-Europenană pentru Bolile Mieloproliferative CEMPO, Societatea Europeană de Hematologie EHA, Societatea Americană de Hematologie ASH, Societatea Europeană de Oncologie Medicală ESMO, Federația Mondială de Hemofilie, Societatea Europeană de Medicină Internă). An după an s-a implicat in calitate de membru în colectivele de redacție sau ca și referent științific în activitatea a numeroase reviste printre care Documenta Haematologica, Maedica-A Journal of Clinical Medicine, Revista Română de Medicină de Laborator, Acta Medica Marisiensis-UMF Tg Mures, Oncolog-Hematolog, InfoMedica.

Un intelectual desăvârșit, un medic de excepție, un bun didact, de o modestie și un bun simț rar întâlnit. A format generații întregi de studenți, mentor pentru mulți medici rezidenți și specialiști, coordonator a multor teze de doctorat și lucrări științifice. O viață dedicată specialităților Medicină Internă și Hematologie, trăită cu demnitate și necondiționată generozitate, oferite pacienților, colegilor și studenților săi. Hematologia românească a pierdut o mare personalitate iar noi un eminent coleg. Colaboratorilor apropiati le lipsesc și le vor lipsi sfaturile, îndrumările, încurajările sau "dojenile" părintești!.

Drum lin spre Lumină Domnule Profesor!. Dumnezeu să Vă ofere pacea și odihna pe care le meritați cu prisosință!