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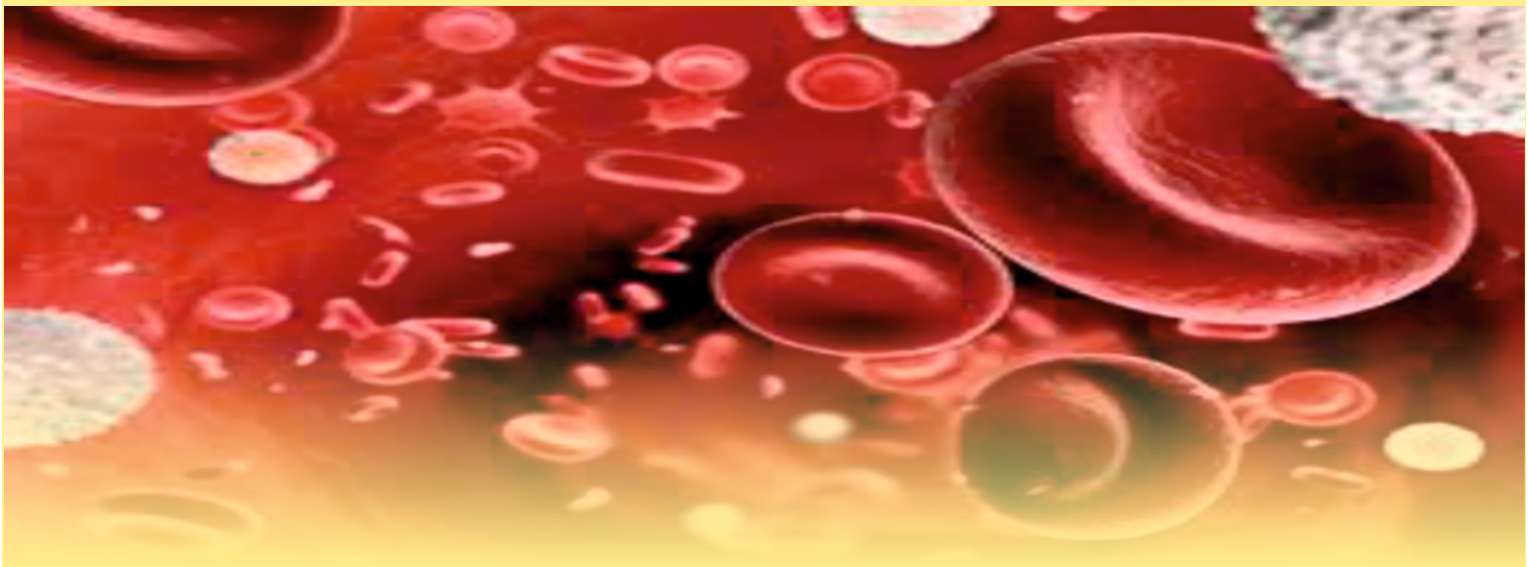

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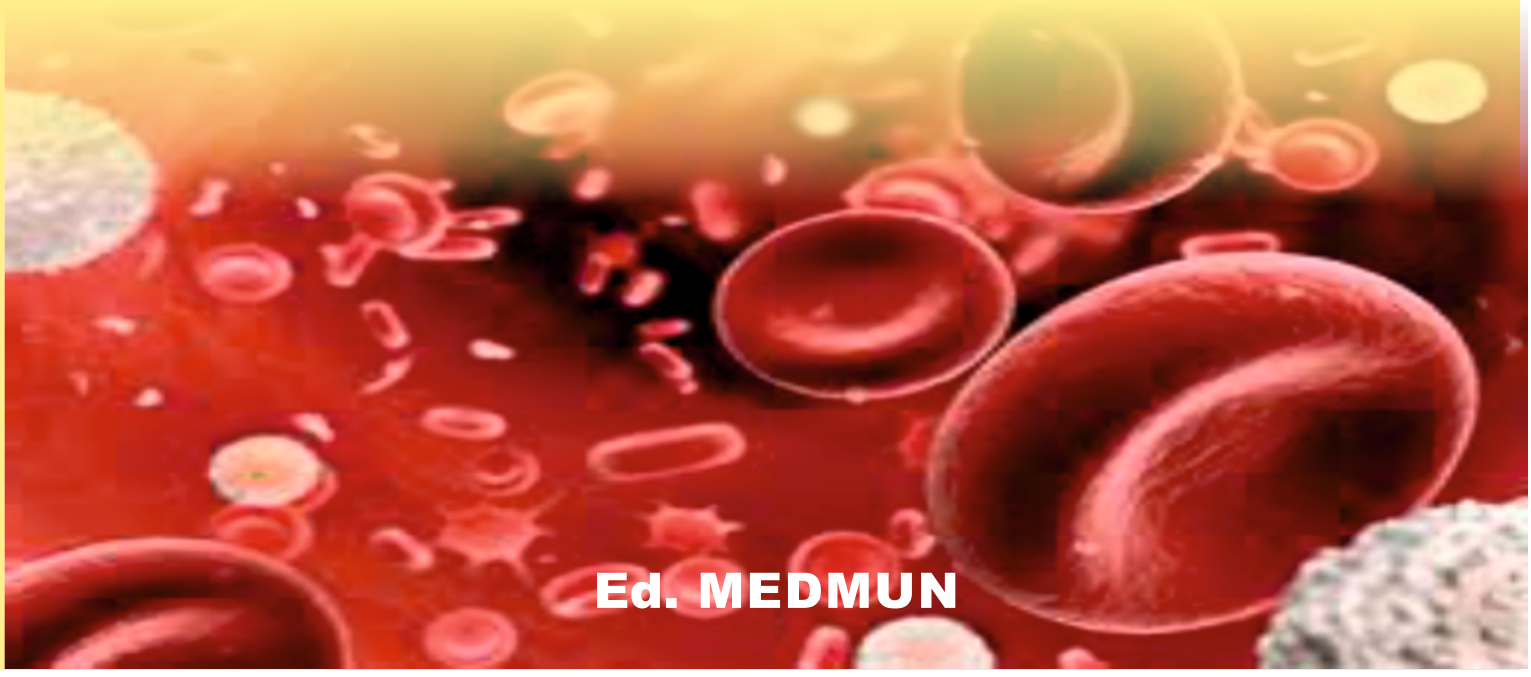

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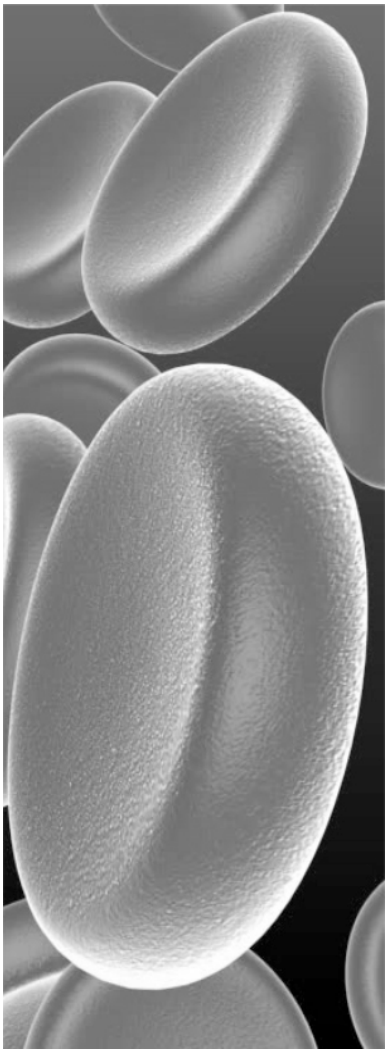

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The impact of CML phase at diagnosis, prognosis scores and response to tyrosine kinase inhibitors on overall survival: one centre experience

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Abstract:

This article represents the first published Romanian centre experience with first and second generation TKI in CML. The purpose of this paper is to analyze the impact of CML phase and prognosis scores at diagnosis on overall survival in the TKI era. The patients' distribution was in favor of the male gender with an average age at diagnosis of 50 years. At diagnosis, most patients were in CP. EUTOS score has statistical impact on achievement of CCyR at 12 months and MMR at 18 months but also on overall survival. The median survival time during TKI has been correlated with CML phase at diagnosis and during treatment. TKIs have improved overall survival but it does not cure CML.

Key words: *CML= Chronic Myeloid Leukemia,BCR-ABL1=Break Cluster Region – Abelson, TKI=Tyrosine Kinase Inhibitor*

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Introduction:

Chronic myeloid leukemia (CML) is a clonal neoplasia of hematopoietic pluripotent stem cells according to the 2008 World HealthOrganization (WHO) classification of chronic myelo-proliferative neoplasms (MPN). In most cases, CML is characterized by balanced translocation between 9 and 22 chromosomes also known as Philadelphia chromosome. The molecular equivalent of this translocation is BCR-ABL1 oncogene which translates into erythroid, myeloid and megakaryocytic progenitor expansion and reduced sensibility of progenitors to the normal hematopoietic process. CML can be diagnosed in one of threestages: chronic phase (CP), accelerated phase (AP) and blast phase or crisis (BP).The introduction of Imatinib, first generation TKI (tyrosine kinase inhibitor) which targets BCR-ABL1 oncogene, had improvedprognosis and overall survivalin CML population and reducedrisk of progression to the advancedphase (AP and/or BP). The 15 years experience with Imatinib treatment demonstrated that although the drug improves progression free and overall survival, it does not offer the cure and second generation of tyrosine kinase inhibitors (TKI) were developed for primary and/or secondary Imatinib resistant CML cases.

Aim:

This article representsthe first Romanian observational retrospective study which collected data from 189 CML patients diagnosed and monitored within the Hematology and Bone Marrow Transplant Department of Fundeni Clinical Institute from January 2004 until January 2013.The purpose of this paper is to analyze the impact of the CML phase and prognosis scores at diagnosis on the overall survival in the TKI era.

Material and methods:

The study was conducted in accordance with local and ethical regulatory requirements. All patients signed informed consents before being included in the study. The European LeukemiaNet recommendations (ELN) for AP and BP were used

in this study. CP was defined as not meeting criteria for AP and BP.

The data analysis used the Microsoft Office 2007- EXCEL 2007 program and specialized products in biostatistics (MedCalc) and statistics (SPSS 15.0). For graphic and descriptive statistic representation, the following parameters were used: frequency, median, medium, standard deviation, etc.

Table 1. ELN recommendations for AP and BP

Phase	Definition
Accelerated phase	-Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow > 30%, with blasts <30% -Basophils in blood ≥20% -Persistent thrombocytopenia (<100 x 10^9/L) unrelated to therapy -Clonal chromosome abnormalities in Ph + cells(CCA/Ph+), major route, on treatment
Blast phase	-Blasts in blood or marrow ≥30% -Extramedullary blast proliferation, apart fromspleen

For CP patients, Sokal, Hasford (Euro) and EUTOS scores were calculated according to the equations (Table 2).

Table2. Calculation of risk scores

Score	Calculation	Risk definition by calculation
Sokal	Exp 0.0116 x(age-43.4)+0.0345 x (spleen-7.51) + 0,188 x [(platelets count-700)^2-0.563] + 0,0887 x (blast cells-2.10)	Low risk< 0,8 Intermediate risk = 0,8- 1,2 High risk> 1,2
Hasford	0.666 when age ≥ 50 y + (0.042 x spleen) + 1.0956 when platelet count >1500 x10^9L + (0.0584 x blast cells) + 0.20399 when basophils >3% + (0.0413 x eosinophils) x 100	Low risk ≤ 780 Intermediate risk = 780-1480 High risk > 1480
EUTOS	Spleen x 4 + basophils x 7	Low risk < 87 High risk > 87

Those parameters were calculated using SPSS and EXCEL programs. For qualitative and quantitative data analysis, MedCalc was used. For ROC and SPSS analysis, the following tests were used: Fischer test, Chi square test, t test (student) and variant analysis (ANOVA).The survival analysis

used Kaplan-Meier test from SPSS analysis. For comparisons between different categories the log rank test was used, the result being statistically significant if the P value (sig ib SPSS analysis) < 0.05 for a confidence interval of 95% (95% CI).

Results:

The patients' distribution according to the age group and gender are presented in (Table 3).

Table 3.CML patients' distribution according to the age group and gender

Age (years)	Females		Males		Total	
	Nr.	**(%)**	**Nr.**	**(%)**	**Nr.**	**(%)**
< 30	15	16,67	11	11,11	26	13,8
[30-39]	13	14,44	18	18,18	31	16,4
[40-49]	19	21,11	20	20,20	39	20,6
[50-59]	24	26,67	28	28,28	52	27,5
[60-69]	9	10,00	12	12,12	21	11,1
>= 70	10	11,11	10	10,10	20	10,6
Total	90	100,00	99	100,00	189	100,0

Our study enrolled 99 (52.38%) men and 90 (47.61%) women. The average age at diagnosis for women was 48 (18-81) and for men 50 years (17-79).

At diagnosis, 166 (87.8%) patients were in CP, 14 (7.4%) patients in AP and 9 (4.8%) patients in BP [myeloid transformation for 6 (3.2%) patients and lymphoid transformation for 3 (1.6%) patients].

CML phase	Freq.	Proc. (%)
CP	166	87.8
AP	14	7.4
BP from which:	9	4.8
-lymphoid BP	3	1.6
- myeloid BP	6	3.2
Total	189	100.0

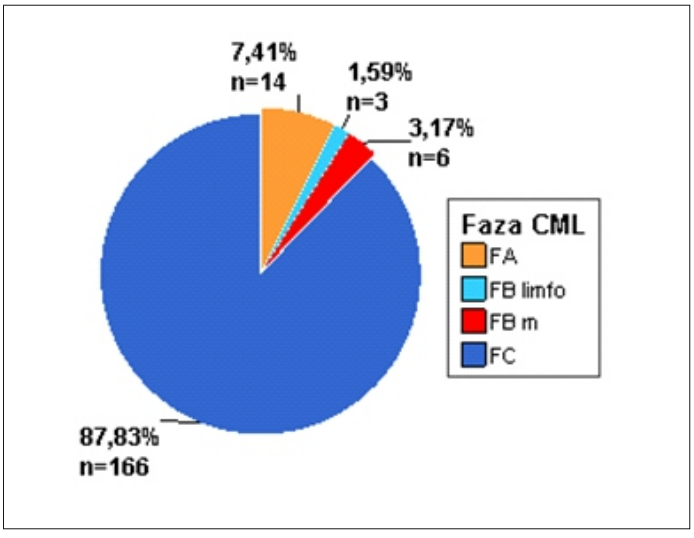


Figure 1. CML phase at diagnosis

During the analysis of 2015, 151 (79.9%) patients were in CP, 4 (2.1%) patients in AP and 34 (17.9%) patients died in BP [myeloid BP for 29 (15.3%) patients and lymphoid BP for 5 (2.6%) patients].

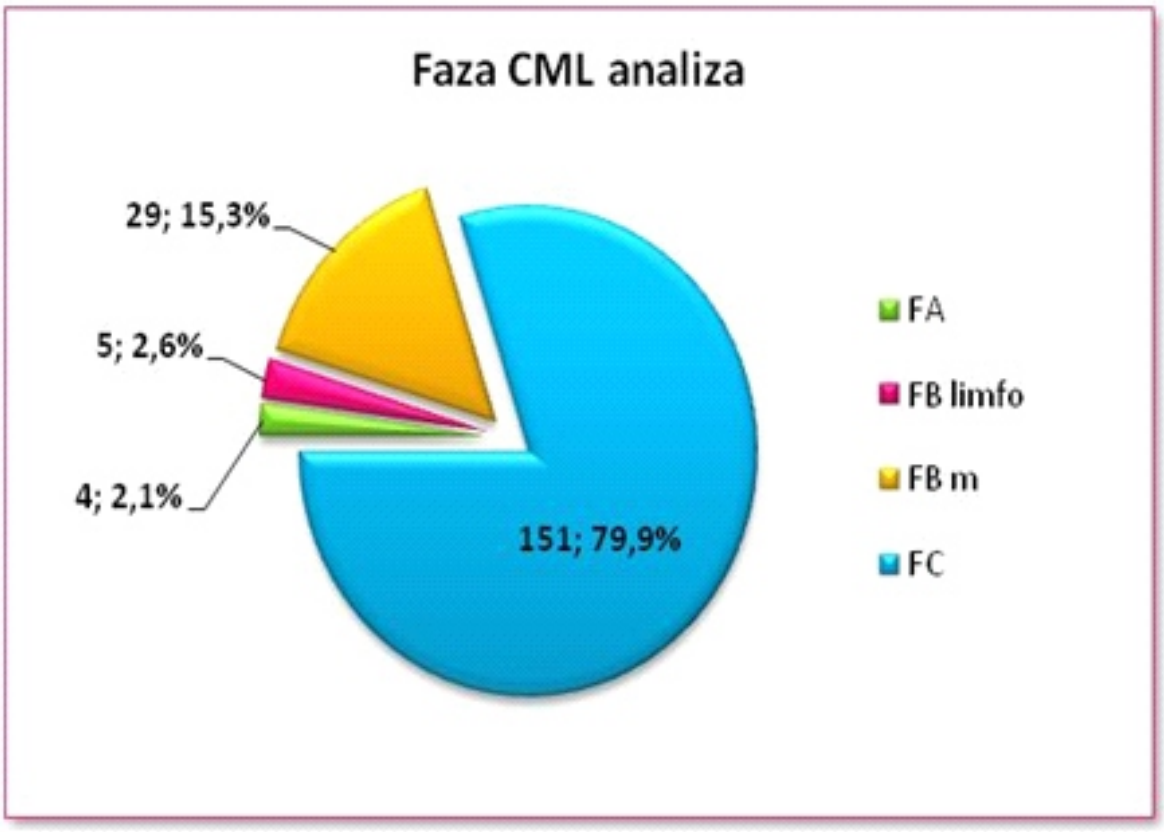
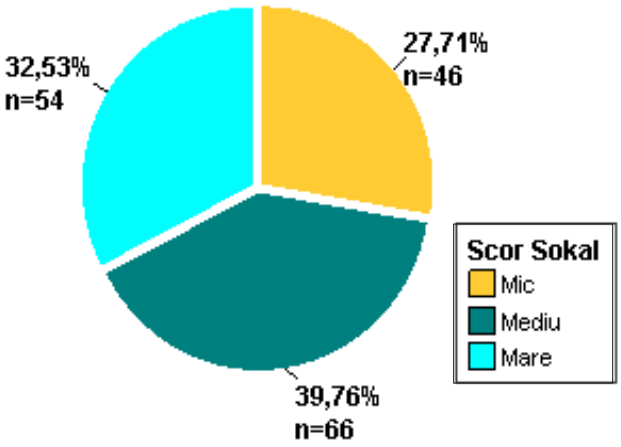


Figure 2. CML phase at analysis

In our study, Sokal score was low in 46 (27.71%) patients, intermediate in 66 (30.76%) patients and high in 54 (32.53%) patients.

Sokal score	N	%
Low	46	27.71
Intermediate	66	30.76
High	54	32.53
Total	166	100.00

Figure 3. CP-CML patients distribution according to Sokal score



In our study, Hasford score was low in 54 (32.53%) patients, intermediate in 72 (43.37%) patients and high in40 (24.10%) patients.

Hasford score	N	%
Low	54	32.53
Intermediate	72	43.37
High	40	24.10
Total	166	100.00

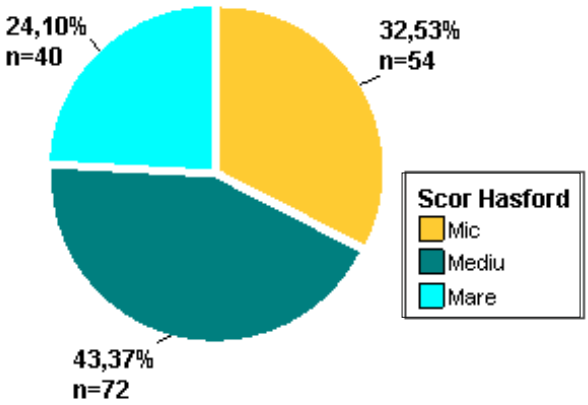


Figure 4. CP-CML patients distribution according to the Hasford score

In our study, EUTOS score in CP population was low in 141 (84.94%) patients and high in 25 (15.6%) patients.

EUTOS score	N	%
Low	141	84.94
High	25	15.6
Total	166	100.00

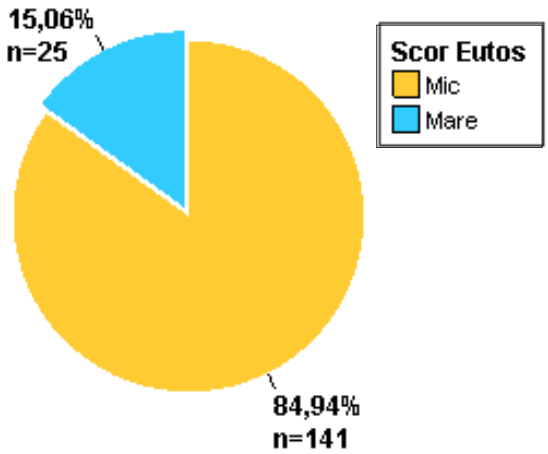


Figure 5.CP-CML patients distribution according to the EUTOS score

The impact of Sokal, Hasford and EUTOS scores at diagnosis on achievement of CCyR at 12 months, MMR at 18 months and on survival at 24, 36, 48, 60, 72, 84 and 96 months during TKI treatment using the Chi square test have been analyzed. Interpretation: if the correlation between analysed parameters would have statistical importance Sig> 0.05, if not Sig < 0.05.The table below summarizes the statistical impact (Table 4).

Table 4. The impact of Sokal, Hasford and EUTOS scoreson the achievement ofa complete cytogenetic response at 12 months, major molecular response at 18 months and on survival at 24, 36, 48, 60, 72, 84 and 96 months during TKI treatment according to Chi square testresults

Parameter	Sokal score	Hasford score	EUTOS score
CCyR at 12 months	Sig = 0,126	Sig = 0,737	Sig = 0,037
MMR at 18 months	Sig=0,624	Sig = 0,465	Sig = 0,024
Survival at 24 months	Sig = 0,113	Sig = 0,221	Sig = 0,024
Survival at 36 months	Sig = 0,136	Sig = 0,147	Sig = 0,024
Survival at 48 months	Sig = 0,036	Sig = 0,099	Sig = 0,012
Survival at 60 months	Sig = 0,048	Sig = 0,193	Sig = 0,037
Survival at 72 months	Sig = 0,024	Sig = 0,101	Sig = 0,010
Survival at 84 months	Sig = 0,024	Sig = 0,101	Sig = 0,010
Survival at 96 months	Sig = 0,024	Sig = 0,101	Sig = 0,010

In our study, Sokal and Hasfordscores do not have statistical impact on CCyR at 12 months and MMR at 18 months achievement with the exception ofthe EUTOS score. The table below summarizes the statistical impact (Table 5).

Table 5. Statistical impact of Sokal, Hasford and EUTOS scores on CCyR, MMR and on survival during TKI treatment

	CP patients		
	Sokal score	EUTOS score	Hasford score
CCyR at 12 months	no	yes	no
MMR at 18 months	no	yes	no
Survival at 24 months	no	yes	no
Survival at 36 months	no	yes	no
Survival at 48 months	yes	yes	no
Survival at 60 months	yes	yes	no
Survival at 72 months	yes	yes	no
Survival at 84 months	yes	yes	no
Survival at 96 months	yes	yes	no

There is a statistical correlationbetween the CML phase at diagnosis and survival at 24, 36, 48, 60, 72, 84 and 96 months during TKI treatment.(Sig < 0,001). The following table represents a synthesis of statistical impact (Table 6).

Table 6. The impact of the CML phase at diagnosis on survivalduring TKI treatment

Period		AP	BP	CP	Total	Sig
24 months	Death	2	9	14	25	<0,001
	Survival	12	0	152	164	
	Total	14	9	166	189	
36 months	Death	2	9	19	30	<0,001
	Survival	12	0	147	159	
	Total	14	9	166	189	
48 months	Death	3	9	21	33	<0,001
	Survival	11	0	145	156	
	Total	14	9	166	189	
60 months	Death	3	9	24	36	<0,001
	Survival	11	0	142	153	
	Total	14	9	166	189	
72 months	Death	4	9	25	38	<0,001
	Survival	10	0	141	151	
	Total	14	9	166	189	
84 months	Death	4	9	25	38	<0,001
	Survival	10	0	141	151	
	Total	14	9	166	189	
96 months	Death	4	9	25	38	<0,001
	Survival	10	0	141	151	
	Total	14	9	166	189	

Median survival time during TKI treatment was correlated with CML phase at diagnosis: 85 months in CP, 77 months in AP and 4.66 months in BP.

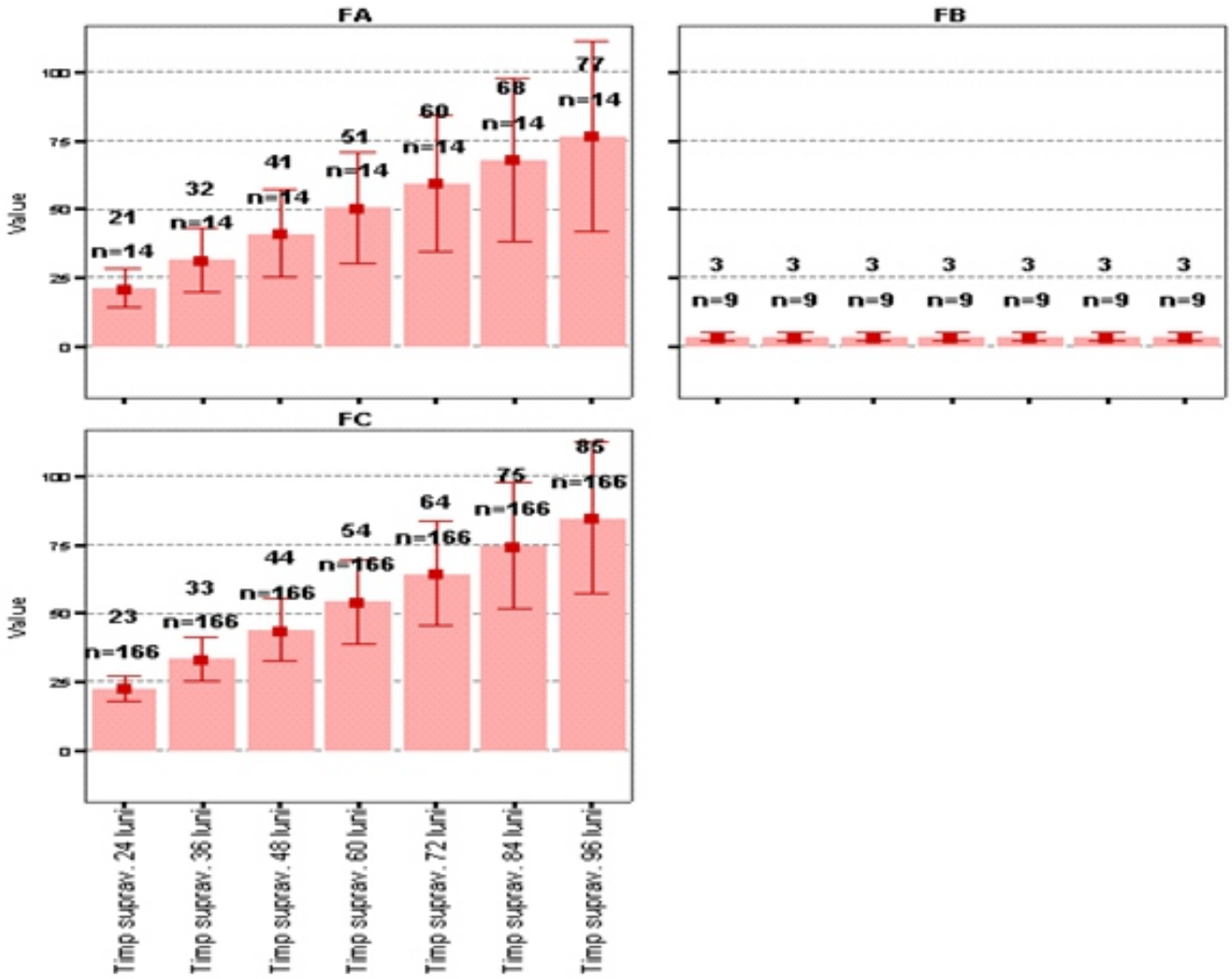


Figure 6. Survival during TKI in CP, AP and BPat 24, 36, 48, 60, 72, 84 and 96 months

During the analysis of 2015, 151 (79.9%) patients were alive and 38 (20.1%) patients were dead. Kaplan-Meier analysis estimated an average survival period of 98.5 months.The events (deaths) were associated with progression tothe advances phase.

Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
189	38	151	79,9%

Means and Medians for Survival Time

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
98,470	3,136	92,324	104,617	.	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

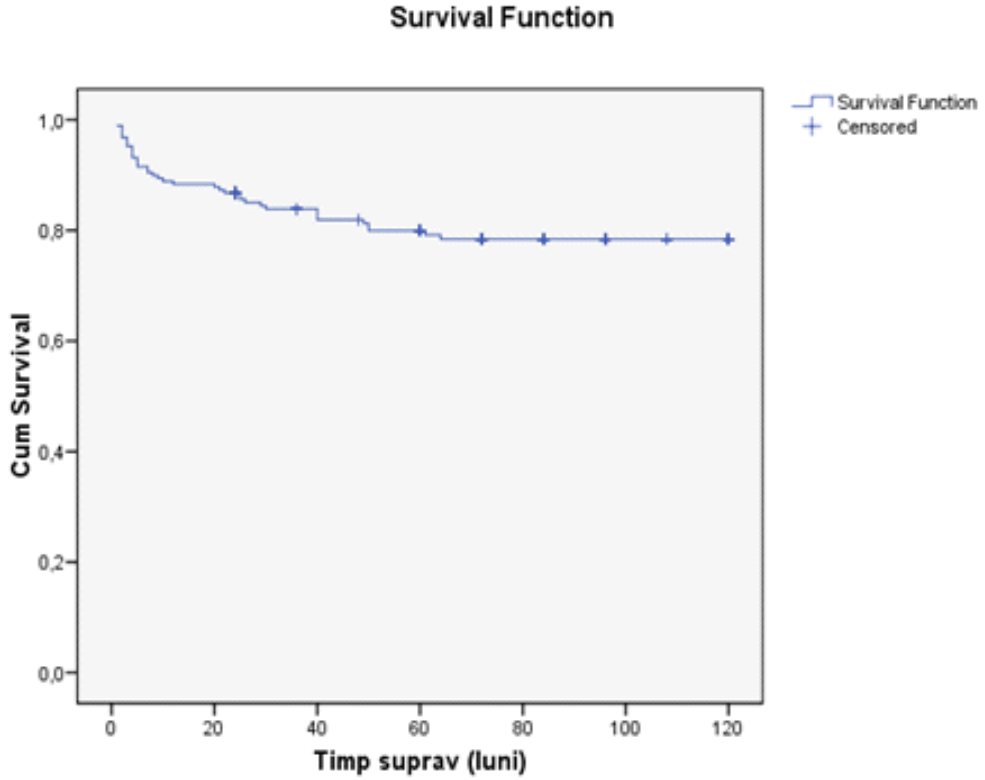


Figure 7. Group analysis according tomean, median and overall survival and events (deaths)

Discussions:

IRIS[1] (International Randomized Study of Interferon and STI571) patients' distribution was in favor of the male gender (61.8% versus 38.2%) with an averageage at diagnosis of 50 years. Sokal score was low for 26.3%, intermediate for 20.1% and high for 12.8% patients.

In a GIMEMA (Gruppo Italiano Malattie E Matologichedell'Adulto) study[2] who enrolled 559 CML patients in CP, the median age at diagnosis was 52 years, Sokal score was low for 39 %, intermediate for 39 % and high for 22%patients and Hasford score was low for 43%, intermediate for 50% and high for 7%patients.

A Hammersmith study[3] which enrolled 282 newly diagnosed CML patients treated with Imatinib used EUTOS score to evaluate prognosis and showed that 88.8% were low and 11.2% were high risk.

A MD Anderson study[5] which enrolled 1569 CML patients diagnosed before and during TKI era suggested that 73.16% were in CP, 11.15% in AP and 15.69% in BP at diagnosis. Median survival time during the TKI era in CP was of 105, in AP of 56 and in BP of 6 months.

The first CML study in our center[4] enrolled 350 CML patients before the TKI era. The patients' characteristics were predominance of male gender (54% versus 46%), average age at diagnosis of 45.5 years and Sokal score was low in 31% of the patients, intermediate in 30% of the patients and high in 39%of the patients. The average survival period was 63, 42 and 36 months in low, intermediate and high risk Sokal score. Average survival time in CP was 24 months and in BP was 3.6 months. The events (deaths) were associated with progression to BP and 59.6% progressed into BP without AP.

In our study, the patients' characteristics were in favor of the male gender (52.38% versus 47.61%), average age at diagnosis for females was 48 years and for males 50 years. At diagnosis, 87.8% were in CP, 7.4% were in AP and 4.8% were in BP.Sokal score was lowin 27.71%, intermediate in 30.76% and high in 32.53%patients,Hasford score was low in 32.53%, intermediatein 43.37% and high in 24.10% and EUTOS score was low in 84.94% and high in 15.6% patients.Median survival time during TKI treatment in CP was 85 months, in AP was 77 months and in BP was 4.66 months. The events (deaths) were associated with progression to advance phase.

Our results are similar to all three international studies and demonstrated that EUTOS is the most influent score.

Conclusions:

Before the TKI era our first CML analysis showed that the patients' gender distribution was in favor of men (54% versus 46%), average age at diagnosis was 45.5 years and Sokal score was low in 31% of the patients, intermediate in 30% of the patients and high in 39%of the patients. Average survival period was 63, 42 and 36 months in low, intermediate and high risk Sokal score. Averagesurvival period in CP was 24 months and in BP was 3.6 months. The events (deaths) were associated with progression to BP and 59.6% progressed to BP without prior AP.

In our TKI era CML analysis, the patients'gender distribution was in favor of men (52.38% versus 47.61%), average age at diagnosis for womenwas 48 years and for menwas 50 years,Sokal score was low in 27.71% of the patients, intermediate in 30.76% of the patients and highin 32.53%of the patients, Hasford score was low in 32.53% of the patients, intermediatein 43.37% of the patients and highin 24.10% of the patients and EUTOS score was low in 84.94% of the patientsand high in 15.6% of the patients.Sokal and Hasfordscores do not have statistical impact onthe achievement of CCyR at 12 months, MMR at 18 months and overall survival with the exception of EUTOS score. The average survival period has been correlated with the CML phase: 85 months in CP, 77 months in AP and 4.66 months in BP.

The first generation of TKIhadimproved prognosis, progression free and overall survival but it did not cure CML. Second generation TKIwere developed for patients who do not obtain and/or lose optimal response and/or are intolerant to first generation TKI.

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Gaucher Disease - one center experience

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Abstract:

Gaucher disease (GD) is one of the most frequent lysosomal diseases, specific for several ethnic groups and transmitted in an autosomal recessive manner.The quality of life for GD patientssince enzyme replacement therapy (ERT) has become similar to that of the general population andwas confirmed by our two patients: first case was diagnosed during childhood when ERT was not yet available and secondcase was diagnosed during adult life and started ERT at diagnosis.

Key words: *Gaucher disease= GD, bone mineral density= BMD, enzyme replacement therapy= ERT*

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Introduction:

Gaucher disease is a lysosomal storage disorder, transmitted by an autosomal recessive manner, characterized by the deficiency of the beta-glucocerebrosidase enzyme which results into accumulation of the glycolipid substrate glucocerebroside in the monocyte-macrophage system. The diagnosis is confirmed by the low level of leukocyte glucocerebrosidase activity compared to baseline activity in healthy subjects and molecular biology testscan identify the genotype of patients. There are 300 point mutations ingluco-cerebrosidase gene, located on the 1q21 chromosome and the most frequent are N370S and L444P.

Gaucher disease features include multiple organ dysfunction such as bone marrow, skeletal, nervous, renal and reproductive systems. The clinical findings are hepatosplenomegaly, osteopenia/osteoporosis with pathological fractures or osteonecrosis, anemia, thrombo-cytopenia and, less frequently, pulmonary infiltration. One specific feature of diseaseis elevated chitotriosidase levelwith an unknown significance. The clinical findings of Gaucher disease subtypes are summarized in Table 1.

Table 1. Characteristics of Gaucher disease types[1]

	TYPE I		TYPE II		TYPE III		
Subtype	Asymptomatic	Symptomatic	Neonatal	Infantile	3a	3b	3c
Genotype	N370S/ N370S	N370S/ other	Unfavourable mutations		None	L444P/ L444P	D409H/ D409H
Ethnic predilection	Ashkenazi Jews	Ashkenazi Jews	none	none	None	Norbottnians, Arabs, Asians	Palestinian Arabs, Japanese
Onset	none	Hepatospleno megaly, hypersplenis,bleeding, bone pains	Hydropsfetalis; ichthyosis	Supranuclear gaze palsy (SNGP), strabismus, opisthotonus,trismus	SNGP; myoclonic seizures	SNGP; hepatosplenomegaly, growth retardation	SNGP; cardiac valves' calcification
CNS Involvement	none	none	Lethal	Severe	SNGP; slowly progressive neurological deterioration	SNGP; gradual progressive neurological deterioration	SNGP; brachycephalus
Bone involvement	none	Variable	none	none	Mild	Moderate to severe; kyphosis	Minimal
Pulmonary involvement	none	Variable(rarely severe)	severe	Severe	Mild tomoderate	Moderate to severe	Minimal
Life expectancy	normal	Near normal	Neonatal death	Death before age 3 years	Death during childhood	Death in mid-adulthood	Death in early adulthood

In the Western part of word, the most frequent GD subtype is I, whereas in Asia and the Arab countries is III[2].

Before enzyme replacement therapy (ERT), treatment was supportive: blood transfusions and splenectomy in selected cases.In 1991, first specific treatment for GD was approved by theFDA and consisted in Alglucerase, an enzyme analogue obtained from human placenta. Today, enzymes are obtained by recombinant DNA technology such as imiglucerase, velaglucerase alpha and taliglucerase alpha. ERTs tend to normalize blood count parameters, normalizeorganomegaly diameters, control bone pain, prevent osteonecrosis and increase bone mineral density[3].Nonetheless, some patients still develop irreversible bone lesions such as femoral head aseptic necrosis. Those patients and/or patients who develop osteonecrosis during treatment are recommended for arthroplasty.[4]

Case1: A 3 yearsold girl was seen due to epistaxis, abdominal left side discomfort and bilateral knee pain. At clinical exam, patient had medium pallor, liver at 3cm below costal margin, spleen at 10 cm below costal margin and no neurologic deficits.

The blood count showed: Hb= 7.7 g/dl, Ht=22%, MCV=78 fL, WBC=3400/mmc, PLT= 69000/mmc,Ret= 1% and differential: Bands=1, Segmented=55,Eosinophils=1, Basophils=1, Lymphocytes=38, Monocytes=4. Biochemical, coagulation, biocatabolites,tumoral and viral markers were negative. Imaging assays confirmed the presence of hepatosplenomegaly and showed small osteolytic lesions in the knee joints bilaterally.

In order to establishdiagnosis, bone marrow trephine was performed and showed a hypercellular marrow with Gaucher cells infiltration.

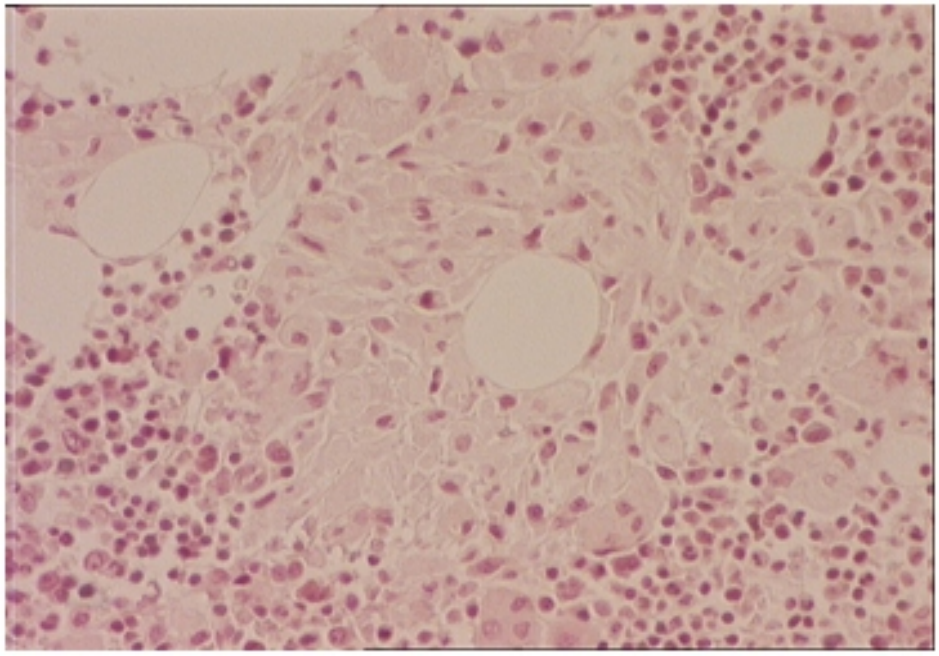

Figure 1:

Bone marrow trephine exam showingGaucher cells which are large, with eccentric nucleus and cytoplasm resembling "crumpled paper" (Hematoxylin Eosin stain; Objective20x)

The diagnosis was confirmed by testing glucocerebrosidase activity which was 50% of thereference range. Molecular testing revealed presence of N370S and L444P mutations.The chitotriosidase level was high.

Table 2. Patient`s diagnosis test panel

Betaglucocerebrosidase	Reference range	Chitotriosidase	Reference range	Genotype
3 nmol/h/mg proteins	6-25 nmol/h/mg proteins	29 000 nmol/h/ml plasma	170- 5 700 nmol/h/ml plasma	N370S/L444P

The patient was diagnosed astype I of GD, received red blood cell transfusions followed by splenectomy few years later in order to improvehypersplenism. At the age of 12, patient presented left coxo-femoral joint pain, the MRI confirmed presence offemoral head aseptic necrosis and a total hip replacement was performed. Annual BMD showed maintained osteopenia with a minimum score of -1.4 on the lumbar spine region.

At the age of 13, imiglucerasewas started andthe dosewas of 60 IU/kg every two weeks. ERTimproved blood count parameters, reduced risk of bleeding, reduced hepatomegaly and improved bone structure. Annual BMD showed that maintained osteopenia with a minimum score of -1.4 on the lumbar spine region.Patient gave birth by cesarean section to a healthy fetus in January 2015.

Table 3. Osteodensitometry (BMD: bone mineral density)

	T score	Z score	BMD
Lumbar spine	-1.4	-0.9	1.013
Right femur	-0.9	-0.6	0.894
Left femur	Hip arthroplasty		

Table4. Patient`s response to ERT

	Before ERT	After ERT
Hemoglobin	7.7 g/dl	12.3 g/dl
Platelets	69 000/mm3	459 000/mm3
WBC	3 500/mm3	6 800/mm3
Bleeding	Epistaxis	Absent
Hepatic volume	1227cc (1.78xN)	1353 cc (1.05xN)
Bone pain	Bilateral knee	Rare (lumbar spine, right hip)
Bone crisis	Left hip (12 years old)	Absent
Bone MRI	Left femoral head aseptic necrosis (12 years old), medullary infiltration of bilateral distal tibial epiphysis (Dusseldorf 5,Terk 3b)	Medullary infiltration distal metaphysis and bilateral femur lytic lesions (Dusseldorf 3, Terk 1b)

Case 2:

The 47 years old female was seen in our clinic in December 2014 for early satiety and abdominal left side pain. During clinical examination, the patient had no pallor, no hemorrhagic signs, liver at 8 cm below costal margin, spleen at 18 cm below costal margin and no neurologic signs. The blood count showed Hb= 12.4g/dl, Ht= 38.3 %, MCV=90 fL, WBC=6790/µl, PLT= 69000/µl with following differential: Bands=1, Segmented=58, Eosinophils=2, Basophils=1, Lymphocytes=33, Monocytes=5. The biochemical, coagulation, viral and tumoral tests were negative. The abdominal ultrasound revealed liver with prerenal diameter of 21.4 cm with infiltrative aspect; portal vein= 14.5 cm; spleen with a diameter of 28 cm. The hepatic fibrosis grade was evaluated by Fibroscan: 6.3 kPa, F1 Metavir score.

The abdominal CT scan confirmed marked hepatosplenomegaly with multiple splenic lesions and portal hypertension.

We performed a bone marrow exam which confirmed the presence of Gaucher cells.

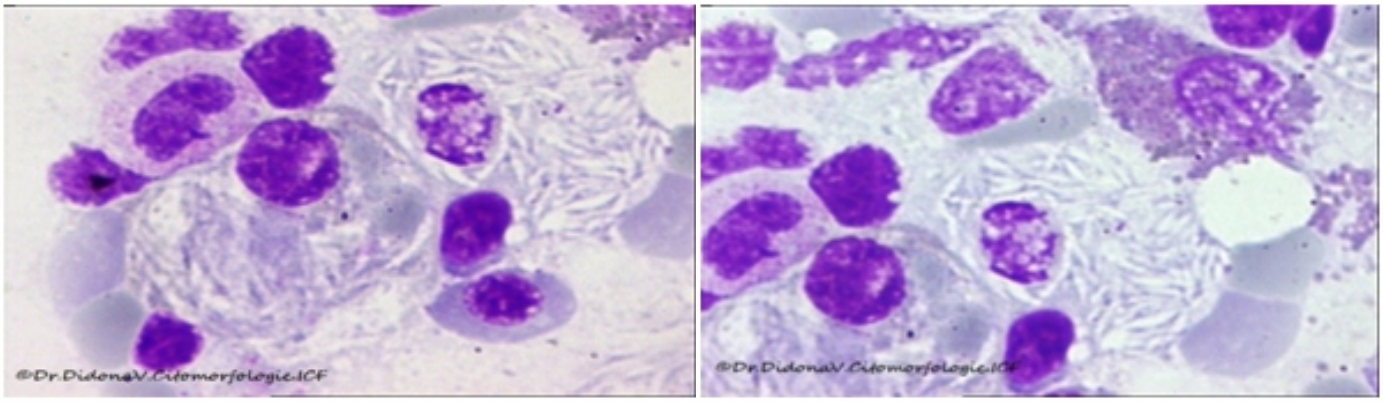

Figure 2. Gauchercells in bone marrow aspirate smear: large cell,excentric nucleus, fibrillary aspect of the cytoplasm (Panoptic stain, 100x objective)

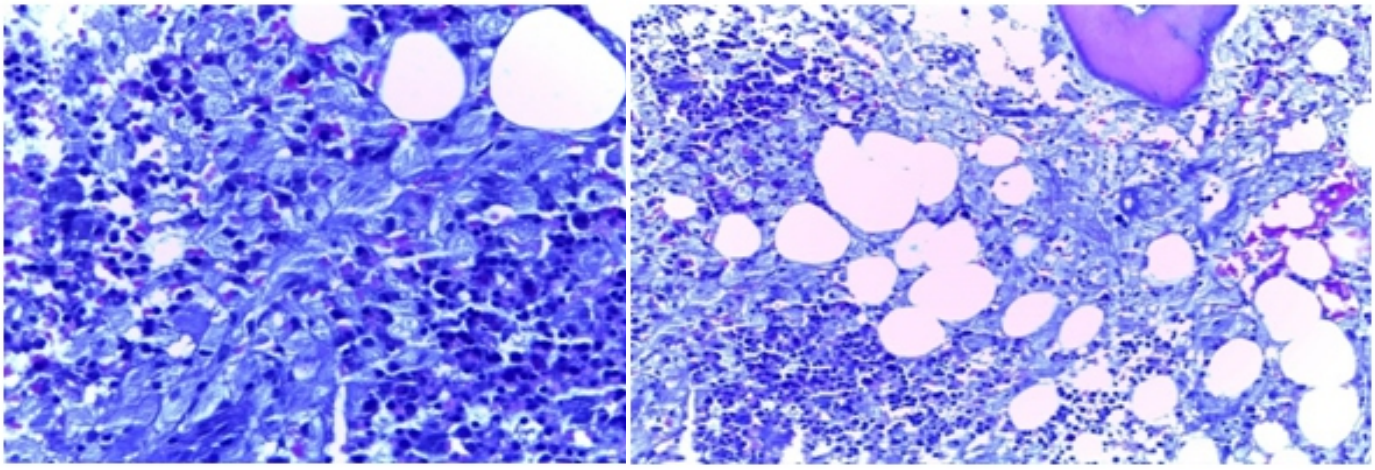

Figure 3. Bone marrow trephine showing frequent groups of hystiocytes with rich cytoplasm resembling "crumpled paper" (Gaucher cells); diminished normal hematopoiesis (Hematoxylin – Eosin stain, 40x, respectively 20x objective)

Furthermore, we tested the activity of β-glucocerebrosidase=21.78 (Reference range= 200-2000 pmolls/spot). Molecular testing revealed presence of 126A>G N409S mutation.

The patientwas diagnosed as type I of GD. Imiglucerasewas started with a dose of 50 IU/kg every two weeks. 12months after starting ERT, platelet count normalized and spleen size was reduced by 30%. For response evaluation, we have usedcriterias detailed in Table 5.

Table 5. Response criteria for ERT

Before ERT		1 year after ERT	2 years after ERT	5 years after ERT
Hemoglobin		Normal range	Normal range	Normal range
Platelet count	Unsplenectomized patients with PLT>60 000/mmc	Increase 1.5- 2 fold	Progressive increase (even if not reaching normal range)	
	Unsplenectomized patients with PLT< 60 000/mmc	Increase 1.5 fold	Progressive increase (even if not reaching normal range)	
	Splenectomized patients with PLT< 120 000/mmc	Increase in 6 months and normal range in 1 year	Progressive increase (even if not reaching normal range)	
Hepatic volume		Decrease 20%- 30%	Decrease 30%- 40%	
Spleen volume		Decrease 30%- 50%	Decrease 50%- 60%	
Bone crisis		Reduction/remission of bone pains Disappearance bone crisis Prevention of osteonecrosis	Increase in bone mineral density	

Discussions:

In Romania, the only available ERT is imiglucerase, a glucocerebrosidase analogue obtained by genetic engineering and with a very good safety profile. One ofthe disadvantages is that it does not penetrate the hematoencephalicbarrier thus it does not provide clinical benefit in types II and III of GD. In February 2010,velaglucerase alpha received FDA approval for therapeutic use, has the advantage of being produced in human cell lines and is identical to the wild-type enzyme (unlike imiglucerase which differs from glucocerebrosidase by an aminoacid at position 495) causing less hypersensitivity reactions. There are studies involving the use of taliglucerase alpha which is an enzyme analogue produced on plant cell lines[6]. In terms of efficiency, velaglucerase and taliglucerase are similar to imiglucerase.[7,8]

Before ERT, the patients' quality of life was severely influenced by the presence of bone disease manifested by pain and functional impairment, fatigue due to anemia, bleeding due to thrombocytopenia and abdominal discomfort due to massive splenomegaly. Weinreb et al. evaluated the quality of life for 32 patients with bone disease treated with imiglucerase and results showed that quality of life improved after 2 years of therapy.[9]
In order to prevent bone disease, ERT is crucial.

The patient diagnosed during childhood developed femoral head aseptic necrosis before starting ERT andunderwent total hip replacement before ERT. The patient with late onset of GD started imiglucerase at diagnosis, with a favorable impact on the quality of life and did not develop bone pain.

A study which evaluated 150 GD patientsduring pregnancy suggests beneficial effects of imiglucerase by reducing risks of

menorrhagia, spontaneous abortion, complications during delivery or postpartum[10] and with no teratogenic effect on the fetus.[11] Our patient underwent treatment with imiglucerase during the entire course of pregnancy, did not experience any complications and gave birth to a healthy fetus through cesarean section.

ERT changed the natural history of GD, allowing normal growth and development of affected children. In terms of life expectancy, one study conducted on patients treated with ERT from International Collaborative Gaucher Group Gaucher Registry (ICGGGR) estimated an average 68 years life expectancy compared to 77 years in the reference population.[12]

Conclusions:

GD is a rare disorder in Romania with 80known patients. Once a lethal disease with a poor prognosis on supportive treatment, it has become a manageable disease since ERT and affected individuals can lead quasi-normal lives.

Abbreviations:

GD: Gaucher disease; ERT: enzyme replacement therapy; SNGP: supranuclear gaze palsy; FDA: food and drug administration; BMD: bone mineral density

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Relapsed/refractory multiple myeloma treatment: clinical cases

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Abstract

Relapsed/refractory multiple myeloma (RRMM) patients represent a real therapeutic challenge. Current strategies are based on patient or disease related prognostic factors, including preexisting toxicities, comorbidities, initial response, aggressive disease and cytogenetic exam. We present two cases of RRMM that had important bone diseases and early relapse after the first line of therapy and received treatment with KRd as the second line. The first case is of a young anaplastic MM patient that has multiple adverse prognostic factors, but no cytogenetic high risk, that received PAD regimen as first line, followed by ASCT with HD-Cyclophosphamide and radiotherapy. He had an early relapse of the bone disease and was administered the KRd regimen, with a very good response. The second case is that of a patient with cardiovascular comorbidities which interfered with the treatment for MM and adverse cytogenetic factors (del 17p and t (14;16)), that received first line therapy with PAD regimen, could not perform ASCT due to cardiovascular comorbidities and a long delay of the harvesting after the cardiologic reevaluation. He wasn't eligible for radiotherapy because of the vast extension of the bone lesions so he continued with Vd, maintenance waiting for the transplant. Unfortunately, he had progressive bone disease, liver plasmacytoma and needed to start the second line of therapy. He received KRd and radiotherapy on the largest bone lesions, but had disease progression during this treatment. As a conclusion, it is essential to perform ASCT at the right moment, after the induction, especially for those patients with adverse prognostic factors, because the delay of harvesting and transplantation may very well lead to passing by the optimal moment, the moment with the real utility in the treatment of multiple myeloma.

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Introduction

Relapsed/refractory multiple myeloma (RRMM) patients represent a real therapeutic challenge. This heterogeneous group of patients has been defined by The Multiple Myeloma International Work Group as having either a primary refractory, secondary refractory or relapsed and refractory disease.

Refractory myeloma is a disease that is nonresponsive on primary or salvage therapy, or progresses within 60 days since the last therapy. Nonresponsive disease is either failure to achieve minimal response or development of progressive disease (PD) while on therapy. Relapsed and refractory myeloma is defined as the disease that is nonresponsive while on salvage therapy, or progresses within 60 days since the last therapy in patients who have achieved minimal response or got better at some point. Primary refractory myeloma is the disease that is nonresponsive in patients who never achieved at least MR.[1]

Current strategies are based on patient or disease related prognostic factors, including preexisting toxicities, comorbidities, initial response, aggressive disease and cytogenetic exam.The RRMM treatmentis based on the alternative use of thalidomide, lenalidomide and bortezomib/carfilzomib.[4]

Some patients have de novo resistance to Bortezomib, and most of the rest develop drug

resistance following treatment.Research efforts are being carried out to identify novel biomarkers that can be used to select more effectively, customized treatment protocols for each patient.[2]
Carfilzomib is an irreversible proteasome 26S inhibitor that binds to a different site than Bortezomib on the proteasome and has shown efficacy in clinical studies of patients with relapsed and refractory multiple myeloma.[3]

For transplant ineligible patients it is recommended[4]:
- For standard cytogenetic risk (trisomy, t(11;14), t(6;14)): VRd x12 months, then Rd > 1 year
- For intermediary cytogenetic risk (t(4;14), +1q, high division rate): VRd x12 months, then Bortezomib based maintenance > 1 year
- For high cytogenetic risk (del17p, t(14;16), t(14;16), t(14;20)): KRd x12 months, then Bortezomib or Carfilzomib based maintenance > 1 year

For transplant eligible patients it is recommended[4]:
- Standard cytogenetic risk: VRd x4 cycles -> SC harvest -> ASCT or 4 more VRd cycles -> Rd > 1 year
- Intermediary cytogenetic risk: VRd x4 cycles -> SC harvest -> ASCT x2 ->Bortezomib based maintenance > 1 year
- High cytogenetic risk: KRd x4 cycles -> SC harvest -> ASCT x2 ->Bortezomib or Carfilzomib based maintenance > 1 year

It is essential to determine the cytogenetic risk, in order to decide which is the best way to treat each patient, as well asin order to obtain the best response with minimal toxicities.

Case presentation

Case 1

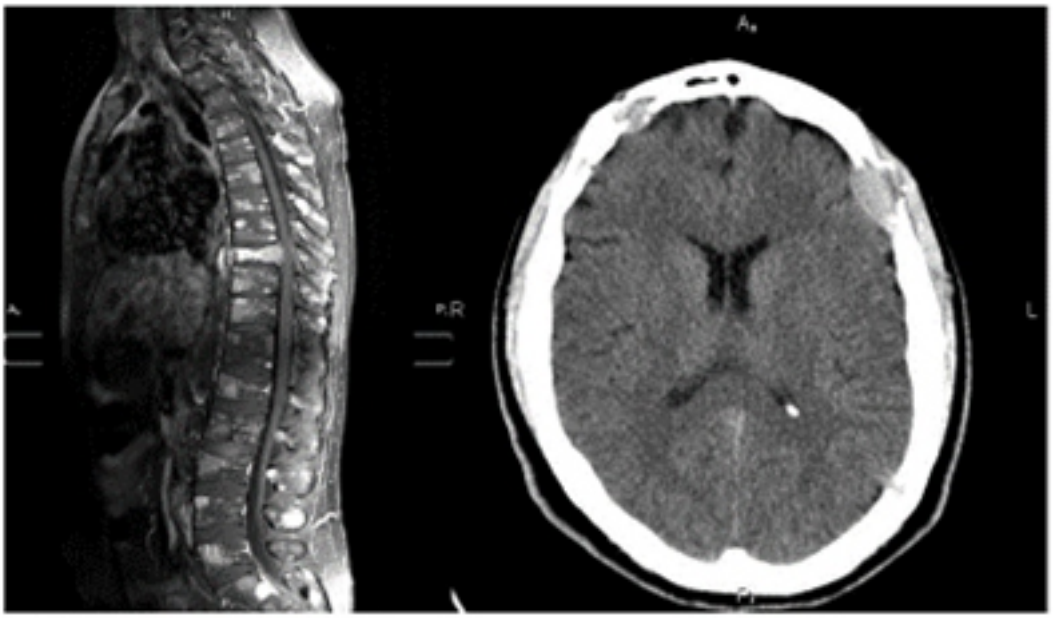


***Fig. 1**: Spine IRM (Feb.2016)- myeloma lesions at IT9 level and spinal cord compressions*

***Fig. 2**: Skull CT - multiple osteolytic lesions, largest in the left frontal bone (Feb. 2016)*

A 36-years-old male patient came to our Hospitalwith thoracic and lumbar, clavicular and dental pain that had started in November 2015. He had previously been admitted to a Neurosurgical Clinic (Bagdasar Hospital), where the thoraco-lumbar spine MRI showed multiple myeloma lesions (Fig. 1) and skull CT: multiple osteolytic lesions (Fig.2). Anterior decompression and vertebral reconstruction of T9 vertebra.

He was then transferred to our Clinic (Fundeni Clinical Institute – Hematology Department), with paraparesis, ECOG 3 and acute pain of the thoracic, lumbar and pelvic areas. Lab results showed anemia, rouleaux formation, hypercalcemia, nitrogen retention, LDH 277mmol/l (135mmol/l-225 mmol/l), β2-microglobulin 12.6 mg/l (0.85mg/l-1.68 mg/l); no M-protein; Ig G= 508 mg/dl; Ig A= 85.3 mg/dl; Ig M =53.6 mg/dl; Free κ= 13.90 mg/dl; Free λ= 2490 mg/dl; κ/λ ratio <0.01; SPEP positive for λ chain, 50% anaplastic myeloma cells infiltrate.

A medullary FISH exam was performed – negative for t (14;16); t (4;14) and del 17p. Skeletal X-ray showed multiple osteolytic lesions; nodular masses in the Vth right costal arch and the VIIth left costal arch. Myeloma score: Skull >3 lesions; spine – 0; rib cage >3 lesions; pelvis > 3 lesions.
He is diagnosed with anaplastic micromolecular multiple myeloma stage IIIB (Durie-Salmon)/III (ISS); T9 vertebra and costal plasmacytomas.

At that time, intravenous Melphalan was absent in Romania, and therapeutic options for relapsed/refractory multiple myeloma were limited.

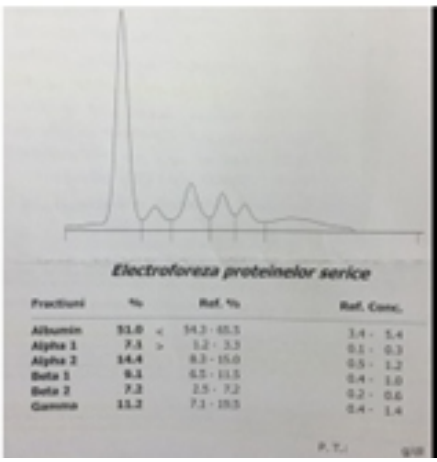


***Fig. 3**: Serum protein electrophoresis*

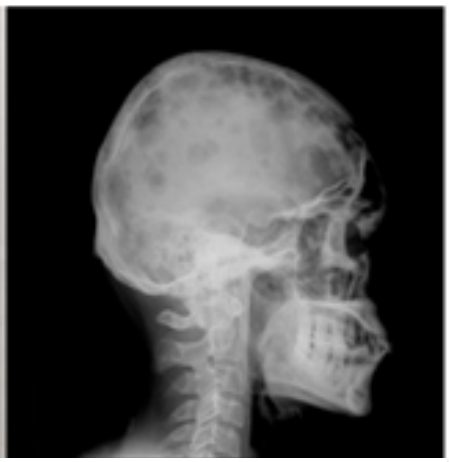


***Fig. 4**: Skull radiography: multiple osteolytic lesions*

He received a CyBorD regimen, with favorable clinical response, but he had a progressive supraclavicular mass (Fig. 5) during the treatment. He was then switched to a PAD regimen. After 3 cycles, he had a good clinical response, decreased pain, 1-2% medullary plasma cells, and on June 15th, 2016, 4.3x10 ^ 6 CD34/kg stem cells were harvested (without HD cyclophosphamide). He further received 2 more PAD regimens, waiting for ASCT. On August 20th, 2016 he received conditioning regimen with Melphalan 200 mg/m^2 and then ASCT, using ½ of the collected SC. Treatment was continued with Radiotherapy at T9 level (TD 30 Gy). During radiotherapy, new pain appeared in the pelvis and vertebrae.

On November 2nd, 2016 he was admitted again in our Clinic, with severe pain, pallor(Hb 9.9 g/dl), LDH 301 mmo/l (135mmol/l-225 mmol/l), β2–macroglobulin 9.4 mg/l(0.85mg/l-1.68 mg/l), low immunoglobulin levels, free λ = 54,7 mg/l, 2% medullary plasma cells; negative medullary FISH exam.

He was diagnosed with RRMM – early relapse after ASCT. KRd treatment was started and 5 cycles were performed between November 2016 and March 2017. Intermediary assessment (after 3 cycles): no bone pain, no serum M-protein, free κ 1.46 mg/l; free λ 12.7 mg/l; 1-2% medullary plasma cells.

Fig.5 *-March 2016 CT*
Multiple clavicular osteolytic lesions with fracture lines in pathologic bone

Fig.6 *-April 2016 CT*
T9 paravertebral tumor mass with vertebral body invasion

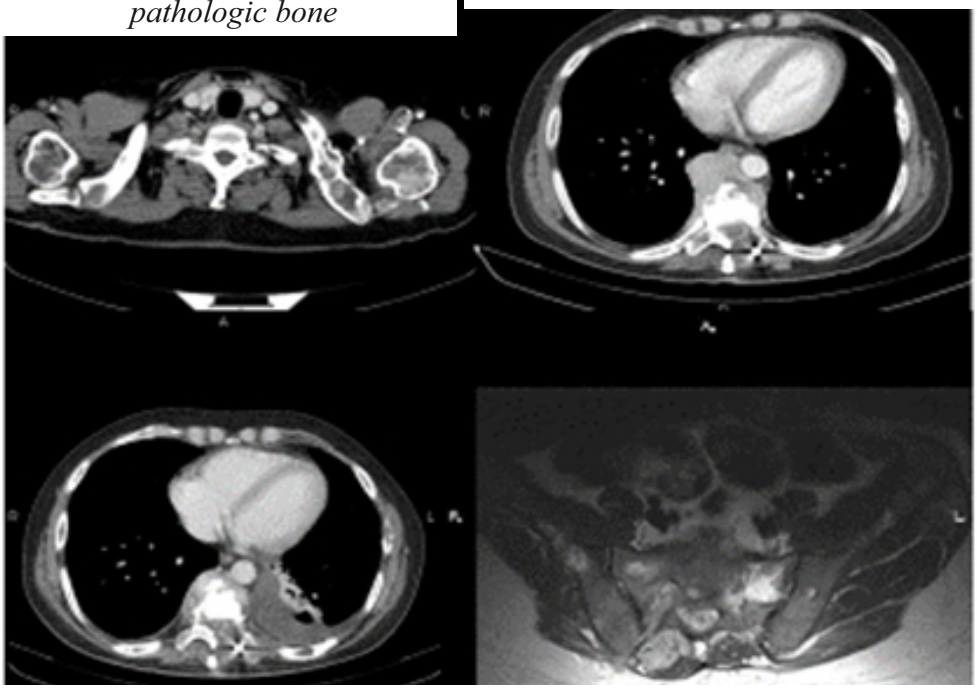


Fig.7 *-August 2016 CT*
Smaller myeloma lesion with partial sclerotic conversion, except for the lesion in T9 vertebral body, which is larger

Fig.8 *-Oct. 2016 RMN*
Extensive myeloma lesions on the spine, pelvis and rib cage. Sacroiliac masses that invade the soft tissue.

Case 2

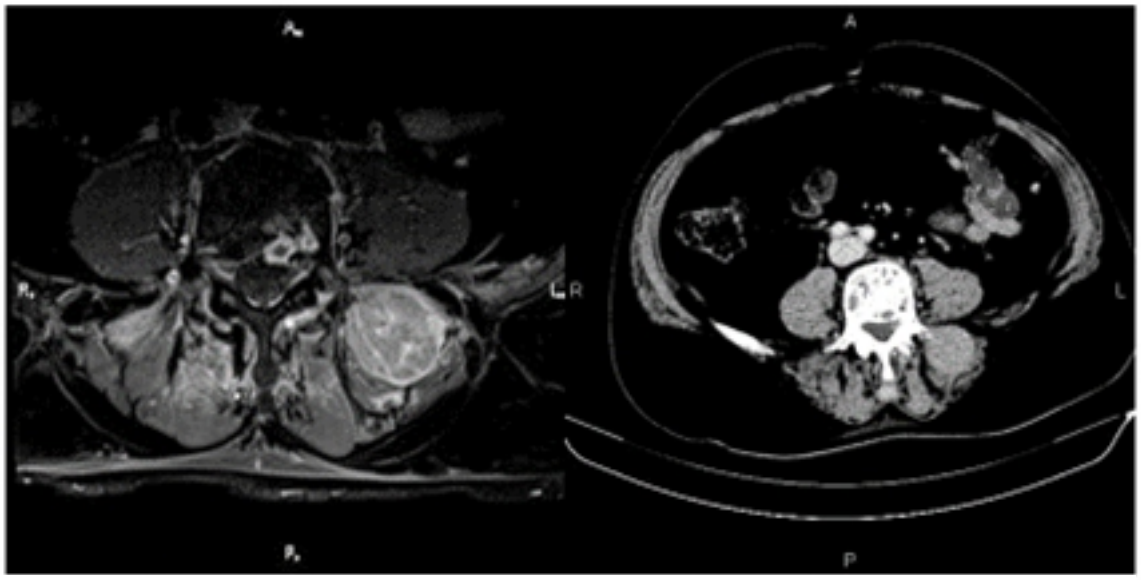


Fig. 9 *-March 2016 IRM.*
L4 level: swelling of the posterior wall and severe spinal stenosis, more pronounced on the left (ap. diameter of spine-6mm), severe foraminal stenosis L4-L5 and diffuse infiltration of the bone marrow

Fig. 10 *-Apr. 2016 axial CT*
Lesion of the L4 left transverse process with extension to the paravertebral muscle

A 50-years-old male had the onset of the disease in December 2015 with thoracic and lumbar pain that appeared after coughing during an upper respiratory tract infection. The MRI showed multiple compressed vertebrae in the thoracic and lumbar areas, fracture tracts in L1 and L4 vertebrae, diffuse infiltration of the bone marrow, nodular lesions at S1 and S2 level (maximum of 23/25/19 mm in S1 vertebral plateau). He had no indication for neurosurgery. He was then transferred to our Clinic with paraparesis, ECOG 4, urinary retention and urinary catheter, acute pain, slight anemia and thrombocytopenia, hypercalcemia, LDH 419 U/L (135mmol/l-225 mmol/l), β2-microglobulin 12.9 mg/l (0.85mg/l-1.68 mg/l); hypoalbuminemia, total protein 9.6 g/dl, M-protein in γ1 of 5.5 g/dl, IgG 5550 mg/dl, free kappa 151 mg/l, free lambda 3.55 mg/l, κ/λ 42.53, 18% plasma cells medullary infiltrate, FISH exam of the marrow was positive for t(14;16) and del 17. Because he was hypertensive he had a cardiologic exam and echocardiography that showed a 54% ejection fraction of LV and interventricular septum of 13/17 mm. CT whole body low dose: small nodule in the VIIth segment of the liver, multiple vertebral tumors, multiple bone plasmacytomas (L4, T7 with invasion of the medullary canal) and a myeloma score: skull >3; cervical spine – 1, thoracic spine>3, lumbar spine> 3, rib cage – 0, pelvis – 2.

He was diagnosed with Multiple Myeloma IgG κ stage IIIA (Durie-Salmon)/III(ISS) and was started on PAD regimen. After 4 courses, he had regained sphincter control and gait,

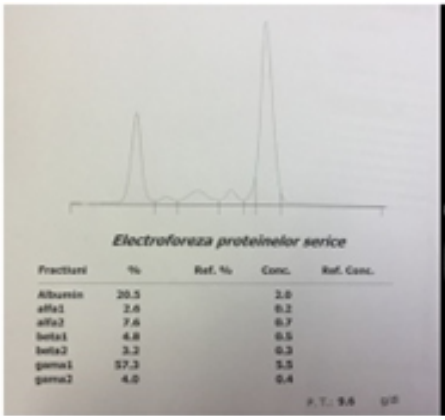


Fig. 11 *- serum protein electrophoresis - peak in y1globulins (5,5 g/dl)*

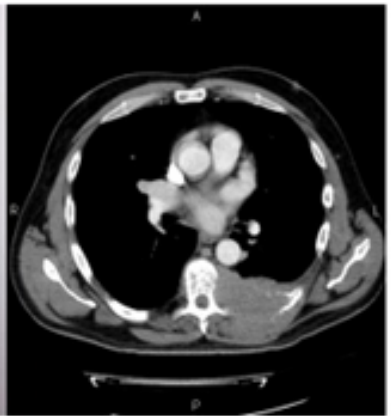


Fig. 12 *- April 2016 CT exam Osteolytic lesion in the left VII-th rib, with extension to the T7 and T6 transverse proces, increase in size of the soft tissue next to the thoracic wall at this level and apperent extension to the spinal cord (6.7/5 cm axial diameter)*

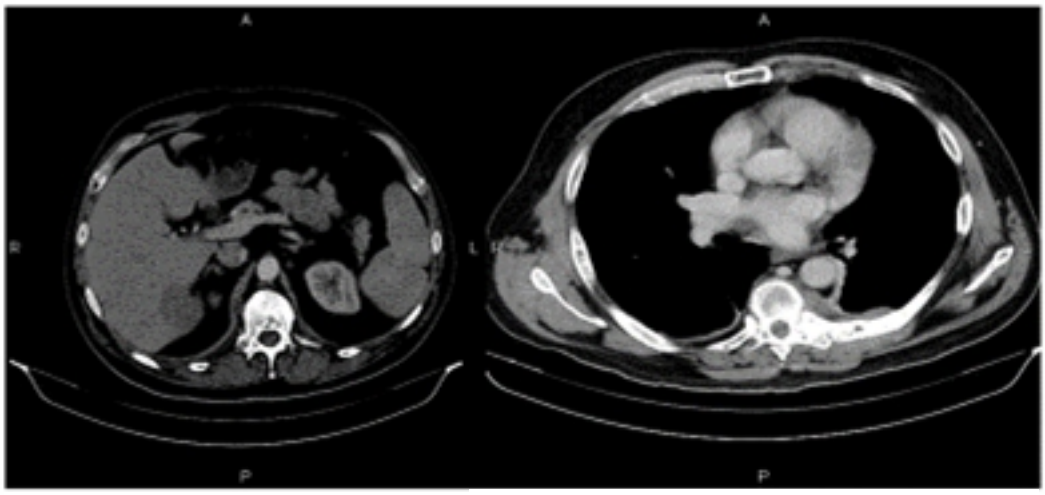


Fig. 13 *- Nov. 2016 Two new level masses (segment VI and VIII)*

Fig. 14 *- Nov. 2016 CT Regression of thoracic and lumbar paravertebral masses; epidural collection at T7-T9 level*

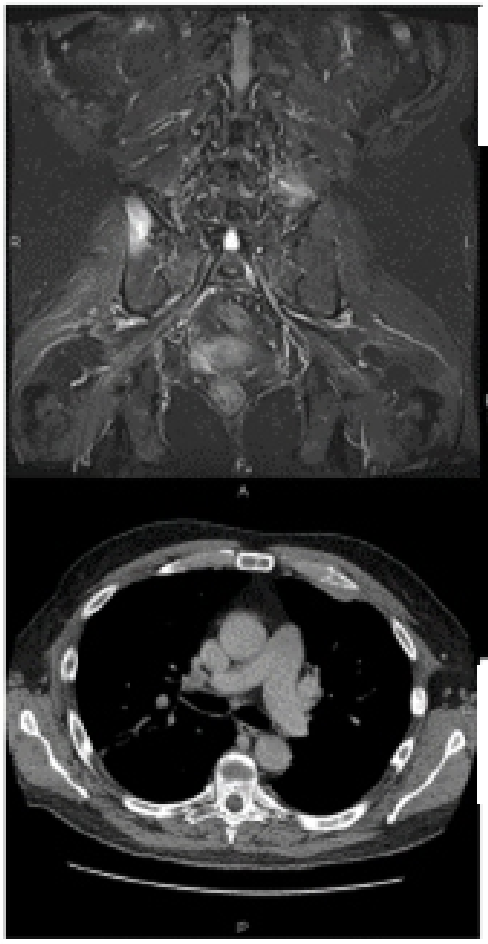


Fig. 15 *- Jan. 2017 RMN*
Regression of left paravertebral lesion and stable right iliac lesion

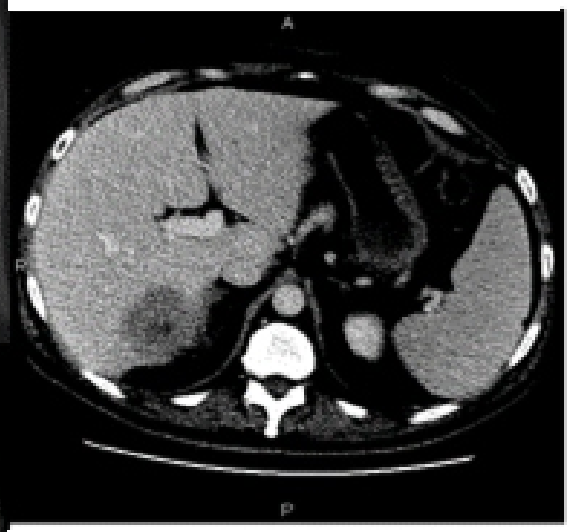


Fig. 16 *- Feb. 2017 CT*
Progression of the liver mass in segment VI (52 mm diameter). Absence of liver lesion in segment VIII

Fig. 17 *- Feb. 2017 CT*
New lesion in the anterior left rib arch

the pain was under control with Fentanyl patch, but had grade 1 neuropathy secondary to Bortezomib. The serum M-protein was reduced from 5.5 g/dl to 1.3 g/dl and IgG from 5550 mg/dl to 1900 mg/dl and he had 2% plasma cells on the bone marrow aspirate. This was considered a partial response to treatment.

In July 2016, he was admitted to the Bone Marrow Transplantation Department for stem cell harvesting, but he was refused due to uncontrolled hypertension and a 22 mm interventricular septum on the echocardiography performed in the Cardiologic Emergency Department. Afterwards he was reevaluated with ECG Holter and echocardiography that showed a 13 mm interventricular septum and controlled hypertension that would allow SC harvesting and ASCT. Unfortunately, he was rescheduled for SC harvesting with great delay so he continued treatment with 2 PAD regimens and a Vd regimen, after which he had 1% bone marrow plasma cells and no serum M-protein.

In October 2016 peripheral SC were harvested, without HD-Cyclophosphamide and, due to the absence of Melphalan in Romania at that time, the ASCT was postponed and Vd maintenance was started. Radiotherapy consult was done, but he could not receive this treatment due to the vast extension of the bone lesions.

On November 23rd, 2016, he came to our Clinic with new thoracic pain and accentuated paresthesia of the lower limbs. The CT exam performed showed regression of the thoracic and lumbar paravertebral tumors, epidural mass at T7-T9 level and 2 new liver lesions (segment VI and VIII). An MRI was performed, that showed multiple thoracic, lumbar, pelvic, costal masses (there was endothoracic and to the soft tissue spread of the costal mass, largest at T7-T8 level, with the involvement of the spinal canal and spinal cord affection).

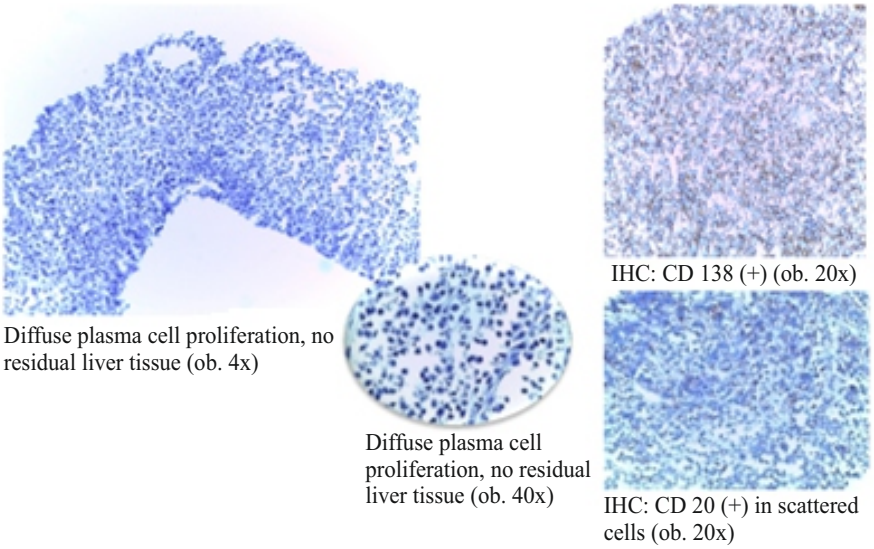
He was once again considered without neurosurgical indication.

In November 2016, he was diagnosed with RRMM, without ASCT and had 2 liver masses (suspected to be plasmacytomas), progressive bone disease and T7-T8 spinal cord compression, paraplegia, urinary retention and serum M-protein

of 0.5 g/dl. At this point he was past ASCT. We decided to continue with KRd treatment [December 2016-February 2017]. After one KRd regimen he is without spinal cord invasion and smaller paravertebral tumor masses.

In February 2017, after 2 KRd courses he has a complete regression of the T7- T9 paravertebral masses, absence of segment VIII liver mass, but progression of the liver mass in segment VI (that reached 52 mm in diameter). Clinically, he showed some improvement, with

Fig. 18 *- Liver biopsy - plasmacytoma*



Diffuse plasma cell proliferation, no residual liver tissue (ob. 4x)

Diffuse plasma cell proliferation, no residual liver tissue (ob. 40x)

IHC: CD 138 (+) (ob. 20x)

IHC: CD 20 (+) in scattered cells (ob. 20x)

Table 1. Characteristics of the 2 cases

	Case 1	**Case 2**
Hemoglobin (g/dl)	8.5	8.3
Calcium (mg/dl)	15.17	11.56
Creatinine (mg/dl)	2.18	1.56
LDH (U/L)	277	419
B2-microglobulin (mg/l)	12.6	12.9
Albumin (g/dl)	3.9	2.5
Total proteins (g/dl)	6	9.6
SerumM-protein (g/dl)	absent	5.5
MM type	λ	IgG κ
Medullary plasma cells (%)	50%	18%
FISH exam (medullary)	0	T (14;16) +; del17p +
First line of therapy	PAD -> TMO-> RT	PAD
Second line of therapy	KRd	KRd
Response to second line	PR	PD
ASCT	Yes	No
Comorbidities	No	Yes

the regain of sphincter function, paraparesis, but a new sternal palpable mass.

In March 2017, we performed a CT guided liver biopsy and the histopathological and immunohistochemistry result was liver plasmacytoma. He started radiotherapy on the bone plasmacytomas and continued treatment with Rd. He soon had progressive disease and we decided to start palliative care.

Discussions:

We presented 2 cases of RRMM in young transplant eligible patients, that have adverse prognostic factors, important bone disease and early relapse after the first line of therapy.

The first case is that of a young anaplastic MM patient that has multiple adverse prognostic factors (ECOG 3, high involved light chain, extramedullary disease, LDH and β2-microglobulin), eligible for ASCT and allotransplantation. Unfortunately, his brother is not compatible, and therapeutic options were drastically limited due to the absence of Melphalan at that time and no modern treatment alternatives, other than Bortezomib. Considering the early relapse, the progressive disease during radiotherapy, the switch to the second line is imperative. The KRd regimen is started with a donation of Carfilzomib. A few questions are raised at this moment, regarding the future therapeutic approach: what is the optimal number of KRd cycles, is the Lenalidomide maintenance adequate and is a mini-allotransplantation useful, and if so which would be the best moment for it?

The second case is that of a young patient with low performance status, cardiovascular comorbidities which interfere with the treatment for MM, adverse cytogenetic factors (del 17p and t (14;16)), a high involved light chain, extramedullary disease and early relapse after the first line of therapy. He is eligible for ASCT, Bortezomib maintenance and even tandem transplantation. Sadly, the circumstances are the same as for the first case, without available Melphalan for ASCT and very limited treatment options for the relapsed multiple myeloma. The evolution was impressive after the PAD regimen, but the relapse was early, with bone and liver plasmacytomas. Despite the loss of the ASCT moment, he has the chance of a second line treatment with KRd and a very good clinical, biological and plasmacytoma response (important regression of the vertebral and a few of the liver plasmacytomas). Still, the response is short, and there is a fast relapse of the liver and bone plasmacytoma during chemotherapy and radiotherapy. The disease is refractory to Bortezomib, Carfilzomib, Lenalidomide and Radiotherapy, and the patient is given palliative care. The different evolution of the liver and bone plasmacytomas suggests that this disease had more than one plasma cells clones growing simultaneous.

Conclusions:

An important conclusion of these 2 cases is that it is essential to perform ASCT at the right moment, after the induction, especially in those patients with adverse prognostic factors, because the delay of harvesting and transplantation may very well lead to passing by the optimal moment, the moment with the real utility in the treatment of multiple myeloma.

Clinical trials showed an improved survival for cytogenetic high risk patients that received double ASCT followed by one year of Bortezomib maintenance. We should take into consideration this treatment alternative for young myeloma patients in Romania. Allotransplantation performed within clinical trials is another treatment alternative for eligible RRMM patients.

The patient with adverse cytogenetically factors had an obviously worse course of the disease and extramedullary plamacytoma, with a short response to therapy and rapidly acquired resistance to Bortezomib, Carfilzomib and Lenalidomide.

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Refractory cytopenia with multilineage dysplasia in a young patient with multiple poor prognostic factors: a case report

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Abstract:

We present the case of a 42 years old man known with congenital bilateral hip dysplasia, who came to our clinic with severe pancytopenia. Following the bone marrow and cytogenetic exams, he was diagnosed with refractory cytopenia with multilineage dysplasia, and high risk (IPSS-R: 6, WPSS: 4), 7q22 deletion and grade II myelofibrosis. Taking into consideration the age, diagnosis and the poor prognostic factors,tests were initiated to identify a suitable stem cell donor in the family. Meanwhile the patient received substitution therapy, but he went into anaphylactic shock during a platelet transfusion and required intensive care support. Irregular antibody and antiplatelet antibodywere found. Given the adverse reaction to platelets transfusion he received only erythrocytes, fresh frozen plasma transfusions(with only mild reactions), erythrocytes stimulating agents, granulocyte stimulating agents and iron chelators. Death occurred 6 months after diagnosis due to gastrointestinal bleeding.

Key words: myelodysplastic syndrome, myelofibrosis, del (7q,22)

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Introduction:

Myelodysplastic syndromes (MDS) are a group of heterogeneous disorders characterized by cytopenias, cytogenetic alterations and an increased risk of leukemic evolution[6].Most often in MDS del(5q), -7 or del(7q) (in up to 10% of the cases), trisomy 8, del(20q), and loss of the Y chromosome are encountered. 7q(-) deletion is considered to have an intermediary prognosis according to the Revised International Prognostic Scoring System (IPSS-R) and poor prognosis according to WHO Classification-based Prognostic Scoring System (WPSS)[8].

Bone marrow fibrosis is encountered in up to 20% of MDS cases and is associated with severe thrombocytopenia and poor prognosis for low and high risk MDS[1].

Case presentation:

The patient, a 42 yearold man, non-smoker, known with congenital bilateral hip dysplasiawith multiple surgical interventions, presented in our clinic in October 2014with severe pancytopenia for investigations and treatment.

One week prior the patient developed fever, cough, progressive fatigue, intense paleness, perspirations and dyspnea for which standard blood tests were performed that revealedsevere

pancytopenia. Hewas referred to our hospital for further investigations.

The initial clinical examination showed: malaise, gum bleeding, intense paleness, generalized cutaneous petechial hemorrhage, no swollen lymph nodes, mild hepatomegaly and tachycardia.Fig 1.Bone marrow biopsy – hipercelularity, panmielosis, (H & E) stain, OM 20x);

The blood count revealed severe pancytopenia (hemoglobin 4 g/dl, platelets 12000/µl, white blood cell 970/µl, granulocytes 230/µl, MCV 73,3fl, MCH 22,3 pg). Ham and sucrose tests were negative. The other blood tests showed only high level of uric acid. Ferritin, folic acid and vitamin B12 levels were normal. The tests for hepatitis B, C, and HIV were negative.

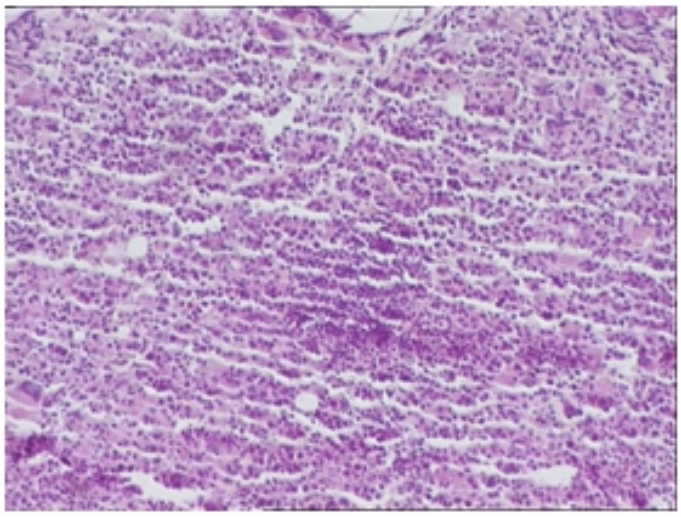

Fig 1. Bone marrow biopsy – hipercelularity, panmielosis, (H & E) stain, OM 20x);

A bone marrow biopsy was performed and showed: hipercellularity, dismegacariopoesys, blast cells < 5% and grade II myelofibrosis. The bone marrow aspiration was unsuccessful and so was the cytogenetic exam.A FISH exam from peripheral blood was positive for the deletion (7q,22).

The final diagnosis was: refractory cytopenia with multiliniage dysplasia, high risk (IPSS-R:6, WPSS: 4), del (7q, 22)and grade II myelofibrosis.Fig 2. Bone marrow biopsy – grade II myelofibrosis, (argentic stain, OM 10x),Taking into consideration the severe pancytopenia, grade

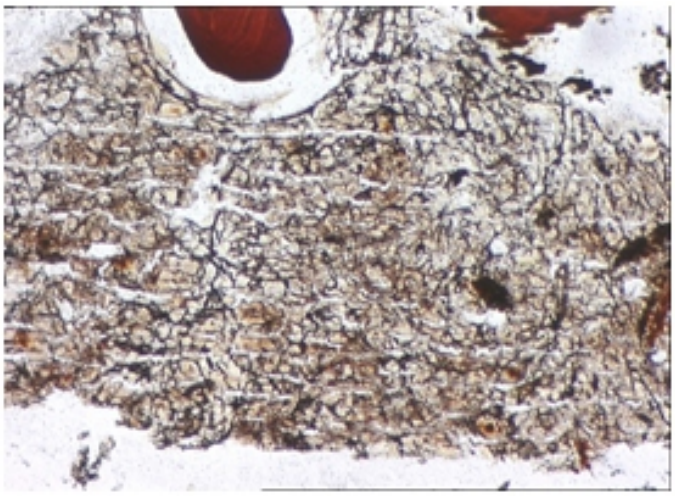

Fig 2. Bone marrow biopsy – grade II myelofibrosis, (argentic stain, OM 10x),

II myelofibrosis, 7q deletion, age at diagnosis,the choice treatment was ahematopoietic stem cell transplantation so HLA compatibility testswere performed.

Meanwhile the patient received erythropoietin stimulating agents (ESAs), substitution treatment(red blood cells (RBCs) and platelet transfusion).

In the second month from diagnosis, duringplatelet apheresis transfusionthe patient experienced profuse perspiration, dyspnea, facial edema and hypotension, in two separate occasions. Immediate intensive care measures were taken both times with a rapid recovery.

After the transfusions,blood tests were performed and thepatient was found with irregular antibodies and antiplatelet antibodies. Further on he receivedonly compatibilized RBCs.

The hypothesis of anaphylaxis to citrate, the anticoagulant used for the platelet apheresis, was taken into consideration and repeated tests were performed, but they were inconclusive due to the patient's granulocyte depletion. An allergist was consulted, who considered that further administration of platelets aphaeresis would be too dangerous for the patient.

Given the above, the search for a compatible hematopoietic stem cell donor was stopped (he would require subsequent platelets transfusion). The patient received: treatment with erythropoietin stimulating agents (ESAs) and substitution treatment with compatibilized RBCs (7 U/month)

and fresh frozen plasma. He presented with minor adverse reactions during subsequent transfusions like fever and chills.
Five months from diagnosis iron chelators were started due to the high ferritin levels (high transfusion requirement) and granulocyte stimulating factors were added in an attempt to improve the response to the ESAs, with no result.
Six months from diagnosis exitus occurred due to gastrointestinal bleeding.

Discussions:

The patient presented above was diagnosed at a young age with refractory cytopenia with multiliniage dysplasia, high risk (IPSS-R:6, WPSS: 4) del (7q, 22), (classified on the FISH examination), and grade II myelofibrosis. We stress the fact that the cytogenetic examination can't be replaced by the FISH exam and the possibility of a complex karyotype can't be overlooked. This would put the patient in the very high risk category[6]. He also associated severe pancytopenia and myelofibrosis which is a poor prognostic factor for both low risk and high risk MDS. Myelofibrosis in MDS patients is also associated with more severe thrombocytopenia than seen in patients with MDS without fibrosis[1,5].

In this situation the appropriate treatment would have been allogenic stem cell transplantation, but that would require substitution therapy including platelet transfusion. Because the patient presented severe adverse reaction on twooccasions during platelet transfusion,that was no longer possible.

Allergic reactions to platelet transfusions varies between 0.9 and 21%. It appears that allergic reactions are more common in platelet transfusion than in the rest of the blood components. Their severity is also variable from urticaria and fever to anaphylactic shock[2,4].

There are studies regarding the role of platelets in hypersensitivity reactions, including anaphylaxis. It has been shown that platelets express receptors for Ig E and may be capable of releasing different inflammatory mediators following antigen-specific activation. Moreover, activated platelets were suspected of anaphylactic reactions in transfusions[3].

Allergic reaction to citrate phosphate dextrose/adenine (CPD/CPDA), the anticoagulant used for preserving blood products, was suspected. There are cases of donors that presented severe allergic reactions to this anticoagulant while donating blood after several donations. Tests were performed, but were inconclusive due to granulocytic depletion and the patient continued to receive blood products (but no platelets) that were stored by using the same anticoagulant only with minor adverse reactions[7].

Conclusion:

We presented the case of a young patient diagnosed with refractory cytopenia and multiliniage dysplasia, high risk (IPSS-R: 6, WPSS: 4), deletion (7q,22), grade II myelofibrosis and severe pancytopenia (adverse prognostic factors) that required hematopoietic stem cell transplantation, but due to severe adverse reaction to platelet transfusionhe received only palliative care. Death occurred 6 months after diagnosis due to gastrointestinal bleeding.

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The new tyrosine kinase inhibitor Ponatinib (Iclusig®) provides new hope for CML patients when other therapies fail

Katharina Miedzinska, Msc

The third-generation tyrosine kinase inhibitor (TKI) ponatinib is a new agent that can be effective in chronic myeloid leukemia (CML) where other therapies fail. Within the scope of an expert panel, international experts discussed various therapeutic approaches for all stages of CML. In addition tothe safety and efficacy of different TKIs, the discussion focused in particular on multiple resistancemechanisms, diagnostic criteria, and stem-cell transplantation (SCT).

With an incidence rate of one to two cases per 100,000 adults (1), CML is one of the most frequent types of leukemia. CML results from a genetic aberration in the stem cells of the bone marrow that is known as Philadelphia chromosome. The natural course of CML is divided into three stages: the chronic phase (CP-CML; <15% abnormal white blood cells in blood and bone marrow; median duration: 4-6 years), the accelerated phase (AP-CML; 15%-30% abnormal white blood cells in blood and bone marrow; median duration: 3-9 months), and the blast crisis phase (BP-CML; >30% abnormal white blood cells in blood and bone marrow; median duration: 3-6 months)(1).

Therapy with tyrosine kinase inhibitors, and the mechanism of resistance to them

Prof. Elias Jabbour, MD, Department of Leukemia,
University of Texas MD Anderson Cancer Centerpresented an overview of the current treatment strategies for CML.Most patients are diagnosed inthe chronic phase of CML. “Up until some 15 years ago, successful treatment of CML was limited to SCT. With the introduction of TKIs, the prognosis and overall survival of patients with CML improved greatly, so that today this represents the recommended standard therapy in the chronic phase of CML. After long-term TKI treatment, approximately 90% of patients are still alive”, explains
Prof. Jabbour.

In 2001, imatinib was the first TKI to be introduced for the treatment of CML, and it was followed by the second-generation TKIs nilotinib and dasatinib, and more recently, bosutinib. Then in 2013, ponatinib was the first third-generation TKI to be approved by the European Medicines Agency. Ponatinib is indicated for the treatment of patients withCP-CML, AP-CML, BP-CML, and Philadelphia-positive acute lymphocytic leukemia (Ph+ ALL) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib,and for patients who have the T315I mutation, or where subsequent treatment with imatinib is clinically not appropriate.

Multiple resistance mechanisms

After 18 months of treatment with imatinib, more than 95% of patients randomized in an international approval study for imatinib were free from disease progression.(2) However, longer follow-up showed significant discontinuation rates among these patients. A significant proportion of patients had point mutations at the ATP-binding site of the ABL-kinase domain (3). With the development of the second-generation TKIs nilotinib and dasatinib, most mutations can be overcome, except for T315I (1). However, although dasatinib overcame several imatinib-resistant mutations (4), additional mutations such as T315A

are resistant to dasatinib, while nilotinib was less effective against mutations such as Y253H and E459K (5). Studies have shown that over time, therapies with imatinib, dasatinib, and nilotinib fail in a significant proportion of patients, substantiating the need for new therapeutic options.

Ponatinib phase I trial

Ponatinibwas designed to overcome all types of BCR-ABL mutations, including T315I. It has been shown that the active component of ponatinib has anti-angiogenetic and antineoplastic qualities and inhibits tyrosine kinases other than BCR-ABL1, such as FLT-3, FGFR, VEGFR, PDGFR, and c-Kit. To determine its safety, activity, and maximum tolerated dose, 48 patients with refractory leukemia were enrolled in a phase I trial(6).The dose levels were ponatinib at 2, 4, 8, 15, 30, 45, and 60mg. After evaluation of the interim results, ponatinib 45mg became the recommended dose for future studies. Complete cytogenetic response (CCyR) was achieved in 63% of the patients with CP-CML, with major molecular response (MMR) in 44%.

PACE trial

The open-label, multinational, phase II PACE(Ponatinib Ph+ ALL and CML Evaluation) trial (7) included 449 heavily pretreated patients with CML or Ph+ ALL with resistance to, or unacceptable side effects to, imatinib, nilotinib and/or dasatinib, or with the BCR-ABL T315I mutation. The patients were divided into six cohorts (Figure 1). At the latest cut-off reported, the median follow-up for the entire population was 34 months (38 months in the CP-CML cohort) (8).The patients received ponatinib 45mg once daily. In patients with CP-CML, the primary endpoint was major cytogenetic response (MCyR) within the first 12 months; in patients with AP-CML, BP-CML, and Ph+ ALL, the primary endpoint was major hematologic response within 6 months.

The efficacy of ponatinib was confirmed by the PACEtrial. In the CP-CML cohort, 56% of the patients achieved MCyR; 46% CCyR, and 34% MMR. The patients who had been less heavily pre-treated had better responses; in the 98 CP-CML patients who had two previous TKIs, MCyR was achieved in 67%, CCyR in 56%, and MMR in 36%. The responses were sustainable; during 2years of follow-up, 89% of responders had maintained response. Progression-free survival after 2 years was 67%, and overall survival was 86%. In the cohort of Ph+ ALL patients, 41% achieved major hematologic response, and 47% MCyR. Thrombocytopenia was observed in 37% of patients, and other common adverse events were rash (34%), dry skin (32%), and abdominal pain (22%). Serious arterial occlusive events were observed in 18% of patients. Recommendations for patient monitoring and dose reduction should be followed to minimize the risk for such events. In conclusion, ponatinib had clinically significant activity in patients with CML and in patients with Ph+ ALL.

The safety and efficacy of ponatinib are being further examined in two recently started international randomized open-label trials in patients with CP-CML. The objective of the first trial (OPTIC) is to characterize the efficacy and safety of ponatinib at a range of doses (15mg vs. 30 mg vs. 45mg). The second trial (OPTIC-2L)is investigating the efficacy and safety of ponatinib administered at two starting doses (15 mg vs. 30 mg), compared with nilotinib (400 mg BID), in patients who are resistant to imatinib.

Definition of optimal response to initial treatment

Prof. Thomas Lion, MD, PhD, Children´s Cancer Research Institute, Vienna, provided a comprehensive overview of diagnostic aspects in CML.

Regarding the diagnostic criteria in CML, Prof. Lion focused on the European LeukemiaNet recommendations for the management of CML. Following these recommendations (9), responses to initial treatment with imatinib, nilotinib, or dasatinib are assessed using standardized real-time quantitative polymerase chain reaction and cytogenetic examination at 3, 6 and 12 months. An optimal response is defined as BCR-ABL1 transcript levels ≤10% at 3 months, <1% at 6 months, and ≤0.1% from 12 months onward, as well as partial CyR at 3 months and CCyR from 6 months onward. Conversely, >10% CCyR at 6 months and >1% from 12 months onward, and no CyR (Ph+>95%) at 3 months, less than a partial CyR at 6 months, and less than CCyR from 12

months onward, define failure, and should serve as basis for changeof treatment. For responses to second-line therapies, similar definitions are provided, as well as special recommendations for patients with AP-CML and BP-CML, and for allogeneic SCT.

An analysis of mutations in CML is recommended for patients who become resistant or who show insufficient response (Figure 2). Routine analysis of the BCR-ABL1 kinase domain is not indicated for newly diagnosed patients with CP-CML, but should be conducted in patients with AP-CML or BC-CML. Specific mutations influence the choice of TKI treatment.

Stem cell transplantation

Prof. Jane Apperley, MD, Department of Haematology, Hammersmith Hospital, Imperial College London, presented facts and figures about SCT.

Over the past few years, the number of SCTs has decreased continuously. "Stem-cell transplantation is the only curative therapy for chronic myeloid leukemia, but due to its associated mortality and morbidity rates, it is no longer the first choice treatment," explains Prof. Apperley, while referring to data from the European Society of Blood and Marrow Transplantation. While in 2002 more than 1,000 patients with CML underwent SCT, in 2014, only 205 SCTs were conducted in CMLpatients. This tendency is seen for all stages of CML, and especially in CP1-CML. "Nevertheless, for some patients,stem-cell transplantation might be a good third choice, and this should be taken into consideration if TKIs do not have the desired effects", says Apperley, and adds,"As with tyrosine kinase inhibitors, the outcomes are very good today, and our aim should be to catch these few patients who would advance to blast crisis without intervention with stem-cell transplantation in the first place. In the chronic phase, all eligible patients failing one second-generation TKI treatment, and patients with a T315I mutation, should be referred to a transplant center for an early benefit discussion, although ponatinib should be initiated in patients with the T315I mutation."

Management of patients with vascular risk and under TKI treatment

Luigia Luciano, MD, Department of Haematology, 'Federico II' University of Naples, Naples, presented the cardiovascular effects associated with TKIs, and explained how to monitor patients with vascular risk under TKI treatment.

The individual cardiovascular risk has a decisive role in the management of patients on TKI. The occurrence of the adverse events with TKIs, such as edema, myalgias, diarrhea, and pancreatic enzyme elevation, has been shown in numerous studies in recent years. Indeed, as some TKIs can impinge upon vital organs in an irreversible way, such as the heart and the lungs, and especially when comorbidities are present, the overall management of the disease should take into account the variables related to the disease, the patient, and the TKI treatment.

Within the elderly population, cardiovascular disease is one of the most commonly seen comorbidities. Data from a national health and nutrition examination survey have shown that among the 40-59 age group, 34.4% of women and 40% of men are affected by cardiovascular disease. Furthermore, among patients aged ≥80, more than 80% suffer from some form of cardiovascular disease (11). The results of a retrospective analysis of 181 patients aged >75 years with CP-CML who were treated with imatinib indicate that concomitant comorbidities appear to influence their overall and event-free survivals, and thus evaluation of comorbidities at baseline should improve the initial decision making (12).

The cardiovascular adverse effects that are associated with TKIs include cerebrovascular disease, peripheral arterial disease, venous thrombosis, coronary heart disease, myocardial infarction, cardiomyopathy, congestive heart failure, and pulmonary arterial hypertension.The last one might especially affect patients treated with dasatinib, and can occur any time after initiation of therapy, including after more than 1 year. Thus patients with confirmed pulmonary arterial hypertension should permanently discontinue treatment with dasatinib.

Serious cardiovascular, cerebrovascular, and peripheral vascular events with a possible relation to treatment with ponatinib were observed in 6.7%, 5.6%, and 5.1% of patients in the PACEtrial, respectively (7,13)Dose reductions, which mightdecrease or prevent toxicities of TKIs, did not influence the responses to treatment with ponatinib. During the PACEtrial, reductions to ponatinib 30mg and 15mg were frequent and most patients were able to maintain their response.
For better overall management of comorbidities, thebasic measures at baseline include an extensive inquiry into the medical history of the patient, which will include details of their modifiable risk factors (e.g., smoking, dyslipidemia, diabetes, hypertension, obesity), nonmodifiable risk factors (e.g., previous cardiovascular events, age, gender, family history, chronic kidney disease) (14), life habits, family anamnesis, and pre-treatment with concomitant medications.

This should be accompanied by serum chemistry (e.g., pancreatic enzymes, glycemia, bilirubin, cholesterol, liver enzymes) and instrumental examinations. Furthermore, during the first 3 months of treatment, patient biochemical parameters and vital signs should be monitored every month. Consistent active management of the modifiable risk factors of the patient may be a key factor in decreasing the risk of comorbidities, such as arterial occlusive events. Continuous patient monitoring is recommended during TKI treatment."It is especially the strengthened cooperation between hematologists, cardiologists, and angiologists that can optimize the management of patients with vascular risk and TKI treatment in the future," emphasizes Luciano.

A systematic literature review(15) was conducted to compare the efficacy of ponatinib and second-generation TKIs (i.e., bosutinib, dasatinib, nilotinib) in CP-CML with resistance or intolerance to one or more prior second-generation TKIs. Estimated probabilities of CCyR with second-generation TKIs range from 22% to 26%, compared to 60% with ponatinib.

Ponatinib is estimated to provide a higher probability of achieving MCyR and CCyR than bosutinib, dasatinib, and nilotinib **(Figure 3)**.

Prof. Elias Jabbour, MD
"A first-line therapy should be continued if a patient has achieved CCyR at 12 months; if not, other therapies should be taken into consideration. Sequencingwith second-generation TKIs (after failing prior 2nd generation TKI) is not promising, based on the available clinical data, due to the low probability of achieving CCyR. Patients with AP-CML and BP-CML, and patients with CP-CML with resistance to second-generation TKIs, will benefit from treatment with ponatinib, as well as patients with T315I mutations."

CML Case 1, presented by Daniela Žáčková, MD, Department of Internal Medicine, Hematology and Oncology, University Hospital Brno, Czech Republic: 66-year-old male patient with CP-CML and muliple comorbidities:

- First-line treatment: imatinib 400mg once, daily;
- Optimal response to treatment after 3 and 6 months, undetectable BCR-ABL transcripts after 18 months;
- Next molecular testing: rise in transcript levels; mutational analysis: T315I mutation;
- Change in therapy: ponatinib 45mg once daily;
- After 3/6 months: T315I mutation disappeared, MMR regained, and undetectable BCR-ABL transcripts;
- After 12 months: deep treatment response (CCyR; 0 ECOG; 0 SAE; 0 AE; MR 4.0).

CML Case 2, presented by Prof. Elias Jabbour, MD, Department of Leukemia, University of Texas MDAnderson Cancer Center: 65-year-old female patient with CP-CML:

- First-line treatment: imatinib 400mg once daily;
- After 3/12 months: achievement of complete hematologic response, transcript levels >10%, no kinase domain mutations;
- Change in therapy: dasatinib 100mg once daily;
- At 3 months: BCR-ABL ≤10% IS
- Quantitative PCR at 6 months: BCR-ABL levels 2%;
- After 12 months: loss of MCyR (BCR-ABL 15% IS);
- Change in therapy: ponatinib 45mg once, daily, prophylactic low-dose statins;
- Good therapy response: dose reduction to ponatinib 30mg once daily, then to ponatinib 15mg once daily;
- After 36 months: deep treatment response, BCR-ABL undetectable.

Summary

- Chronic myeloid leukemia is a potentially fatal disease.First-generation and second-generation TKIs provided major advances in therapy, but a proportion of these patients require other treatment options.
- Ponatinib was developed to fulfill this need, and it has proven to be highly effective in patients where the second-generation TKIs nilotinib and dasatinib fail.
- The benefit-to-risk ratio for ponatinib is high, although there is an increased risk of vascular occlusive events. Patient monitoring with active management of modifiable risk factors (e.g. hypertension, lipids), and decreasing the dose once optimal response is achieved is recommended.
- Stem-cell transplantation still remains a curative option to be considered, but morbidity and mortality are high.

Figure1: Process for assigning resistant/intolerant and the T315I cohorts (7)

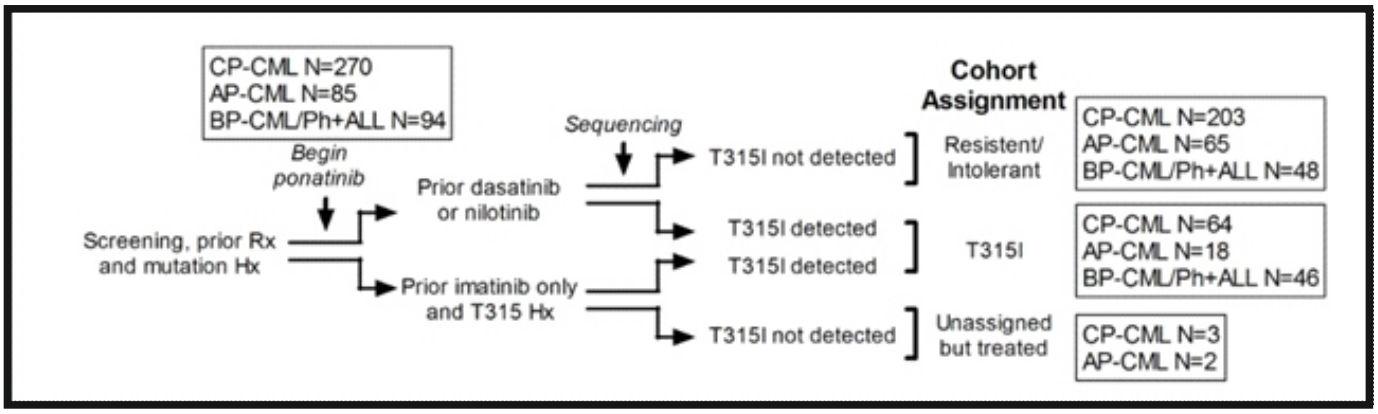


Figure 2: Summary of when mutation analysis is recommended in patients with CML (10)

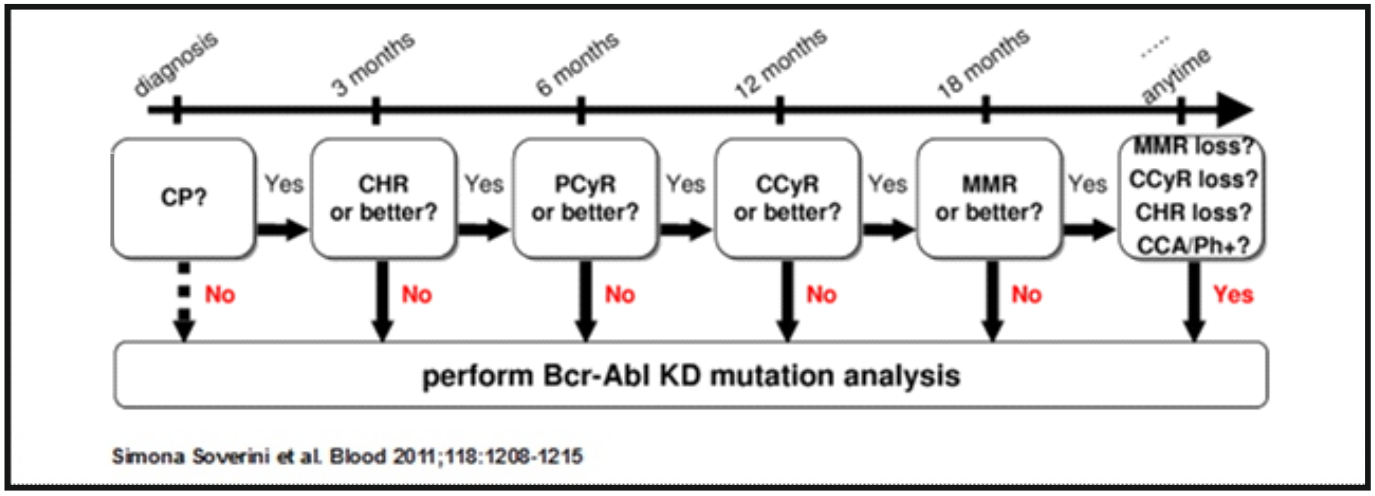
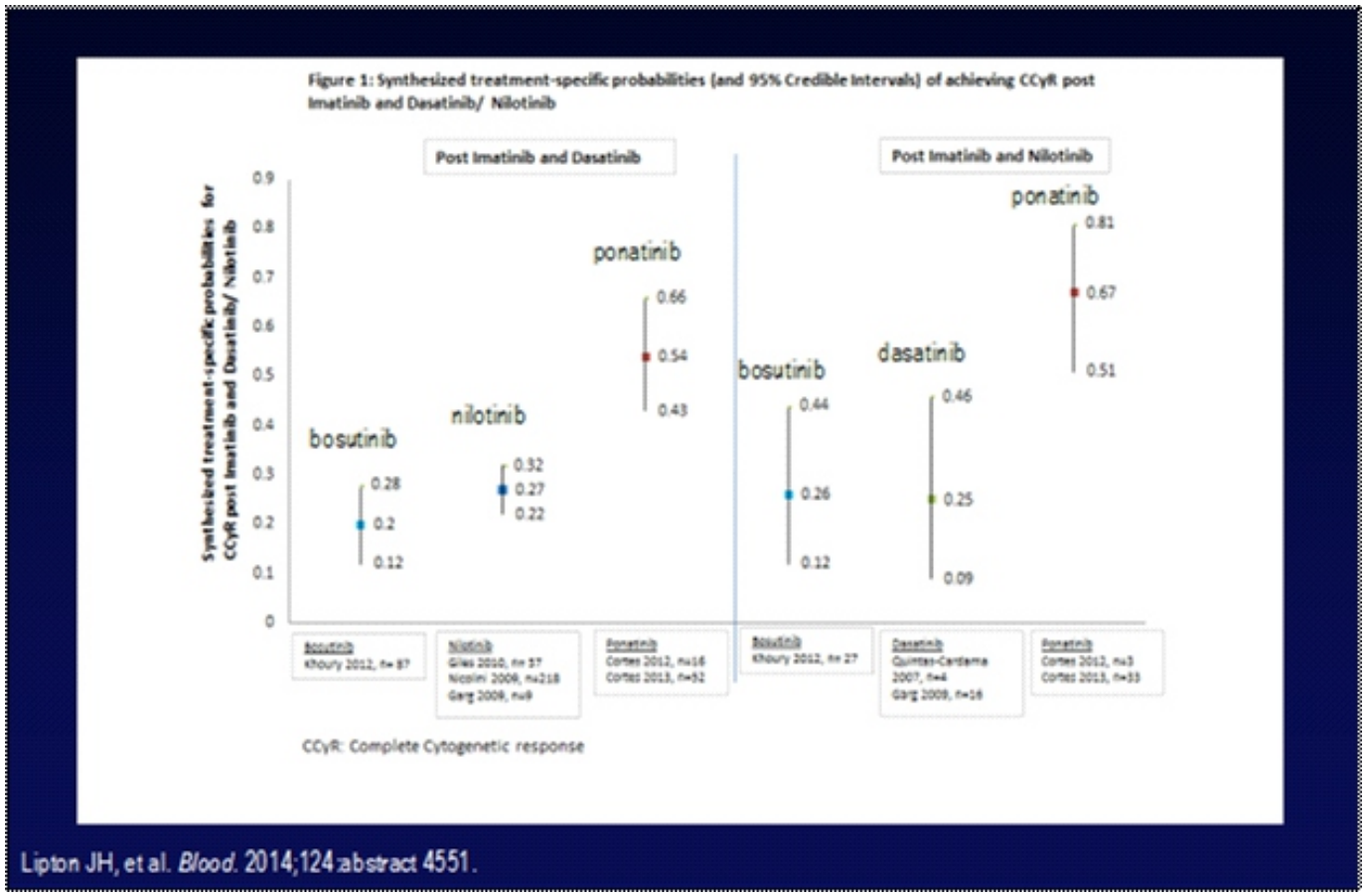


Figure 3: Comparative efficacy of third-line therapy after failure of imatinib and dasatinib or nilotinib (15)



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