EHA-ROHS-NHS Tutorial on "Real world challenges and opportunities in diagnostics and management of onco-hematological patients today"

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EUROPEAN HEMATOLOGY ASSOCIATION

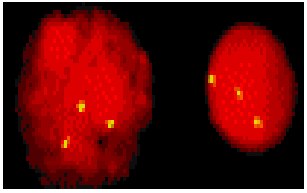
Male, 47 years

2007 | 2008 | 2009 | 2010

July 2007

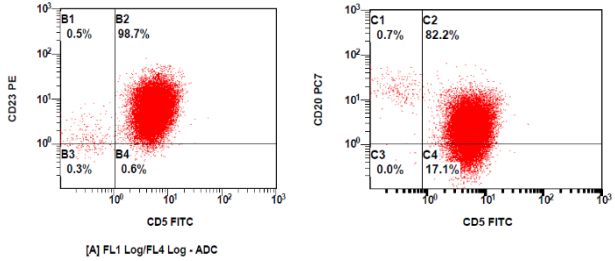
Haemoglobin	Platelets	WBC	Neutrophils
115 g/l	145 × 10^9/l	82 × 10^9/L	3.2 × 10^9/l

- Bone marrow biopsy: **lymphocytosis 97%,** represented by mature lymphocytes
- FISH – trisomy 12 in 70% of metaphases



- IGHV-gene mutation status - unknown

Immunophenotype of peripheral blood lymphocytes: **CD19+, CD20+, CD5+, CD23+, CD38 > 30%**



September 2007

Indications to start treatment according to iwCLL criteria:

- Growth of lymph nodes, spleen
- B-symptoms

October 9-12

1 cycle of **«FCR» in standard doses**

Response: regression of lymph nodes and spleen

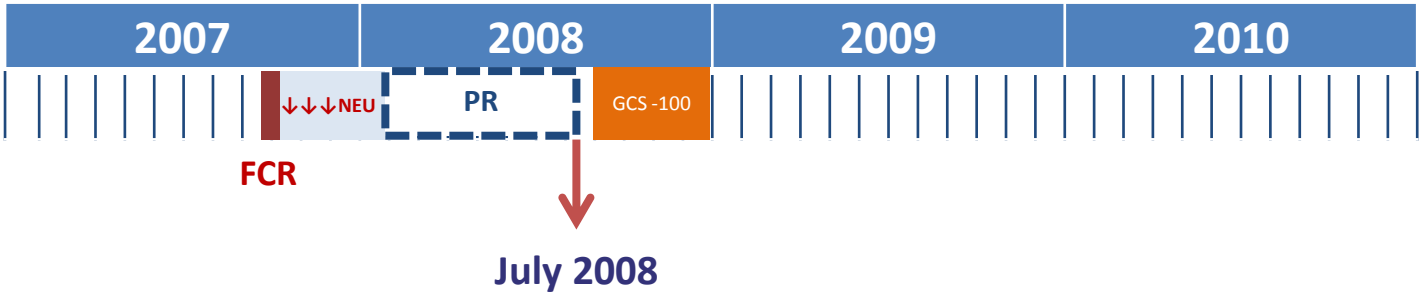
January 2008

- Haemopoiesis restored
- Response estimated as partial remission.

Genesis of cytopenia:

- Tumour infiltration?
- Post-cytotoxic aplasia?

Bone marrow histology: hypoplasia of granulocyte and megakaryocyte lineages

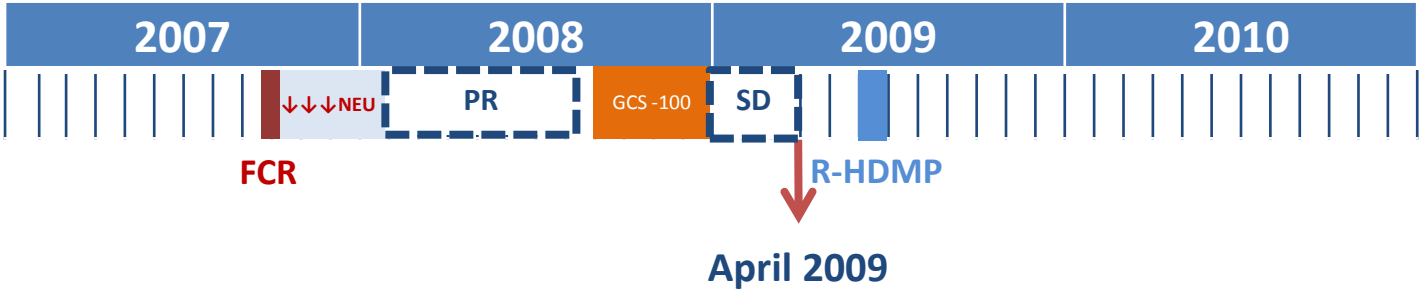


Progression – increase of leukocytosis, peripheral lymph nodes, anaemia and thrombocytopenia grade 1-2.

Patient included in PR – CS 008 trial, from August 2008 to January 2009 **received 8 cycles of GCS-100**.

Response: stable disease.

AEs: diarrhoea, rash.

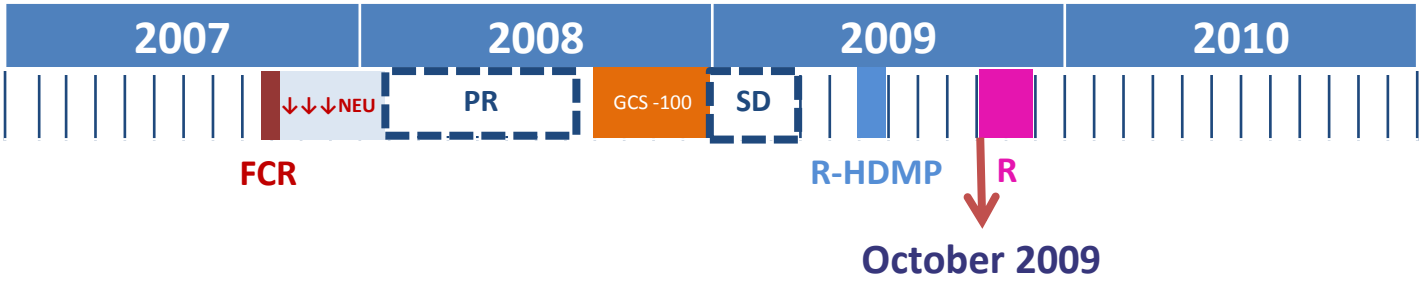


- **Progression** – growth of lymph nodes

Haemoglobin	Platelets	WBC	Neutrophils
80 g/l	60 × 10^9/l	30 × 10^9/l	Neutropenia grade 4

- Bone marrow biopsy – total infiltration of bone marrow by tumour lymphocytes.
- June 2009 – therapy with **R-HDMP no. 1**

AEs – invasive aspergillosis, bacterial sepsis (*Steno maltophilia*, sensitive to ticarcillin)
Therapy: voriconazole, ticarcillin, G-CSF
Treatment interrupted to October 2009



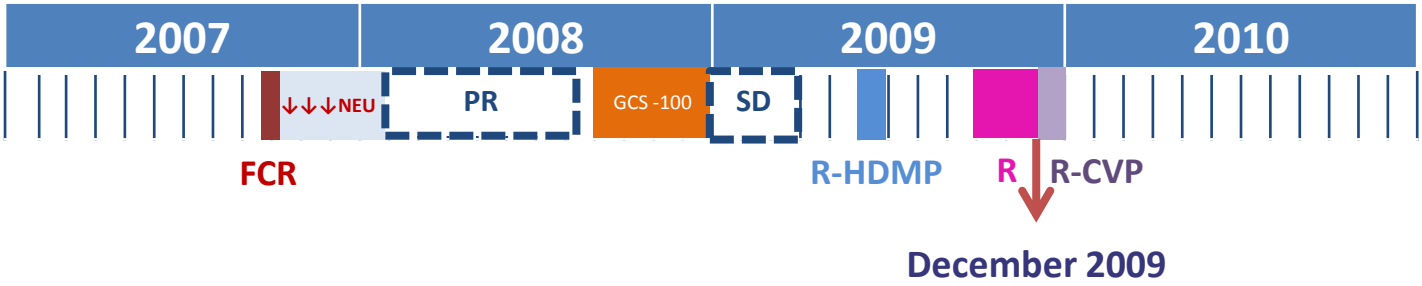
- Progression: fatigue, intoxication, fever up to 38°C in the evenings, enlargement of all groups of peripheral lymph nodes and spleen (according to ultrasonography 200 × 170 × 130 mm)

Haemoglobin	Platelets	WBC	Neutrophils	
70 g/l	20 × 10^9/l	30 × 10^9/l	0.2 × 10^9/l	30% prolymphocytes

- Bone marrow biopsy: sample is hypercellular, 70% of lymphocytes, 27% of prolymphocytes, other lineages are suppressed. Immunophenotype of tumour cells remains the same.
- Until December 2009 – **rituximab monotherapy 500 mg/m^2/week.**

- Considering the continuously relapsing course of CLL, **we decided to carry out an allogeneic stem cell transplant (alloSCT)**

- No related donors.
- Search for HLA matched donor, found a full match in international registry.



- Patient still has constitutional symptoms – fatigue and fever without signs of infection
- Progressive splenomegaly, peripheral lymphadenopathy up to 3 cm

Haemoglobin	Platelets	WBC	Neutrophils
75 g/l	15 × 10^9/l	30 × 10^9/l	Neutropenia grade 3

- December, 2009: 1 cycle of **R-CVP** in standard dose – with anti-tumour inhibiting effect

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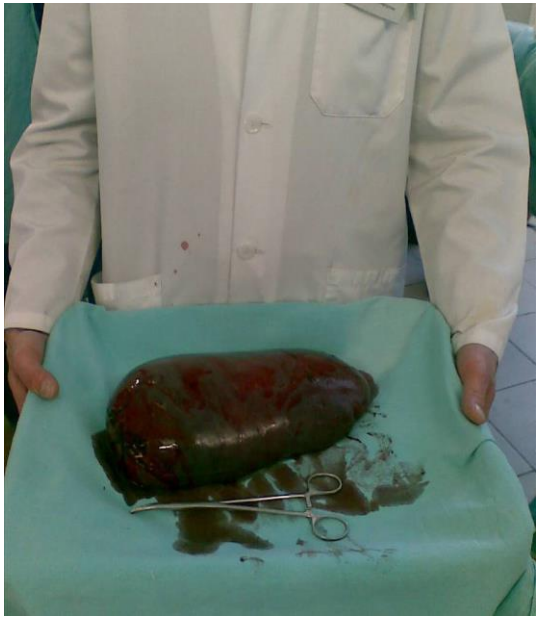
21.01.2010 surgery – splenectomy

- Removed spleen: weight – 3 kg, size 25 × 20 × 15 cm
- Complications – massive abdominal bleeding from the bed of the spleen (overall loss of blood 5 L), reoperate 22.01.2010
- Efficacy – overall status significantly improved, disappearance of fever, anaemia and thrombocytopenia decreased.



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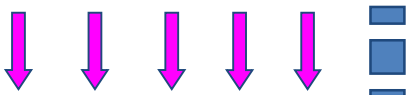
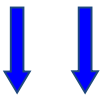
Conditioning regimen

Drug	Days (25.03.10 – 29.03.10)	**Dosage**
Fludarabine 30 mg/m^2		250 mg
Busulfan 4 mg/kg		648 mg
Cyclosporine 3 mg/mg		
Mycophenolate mofetil 20 mg/kg		

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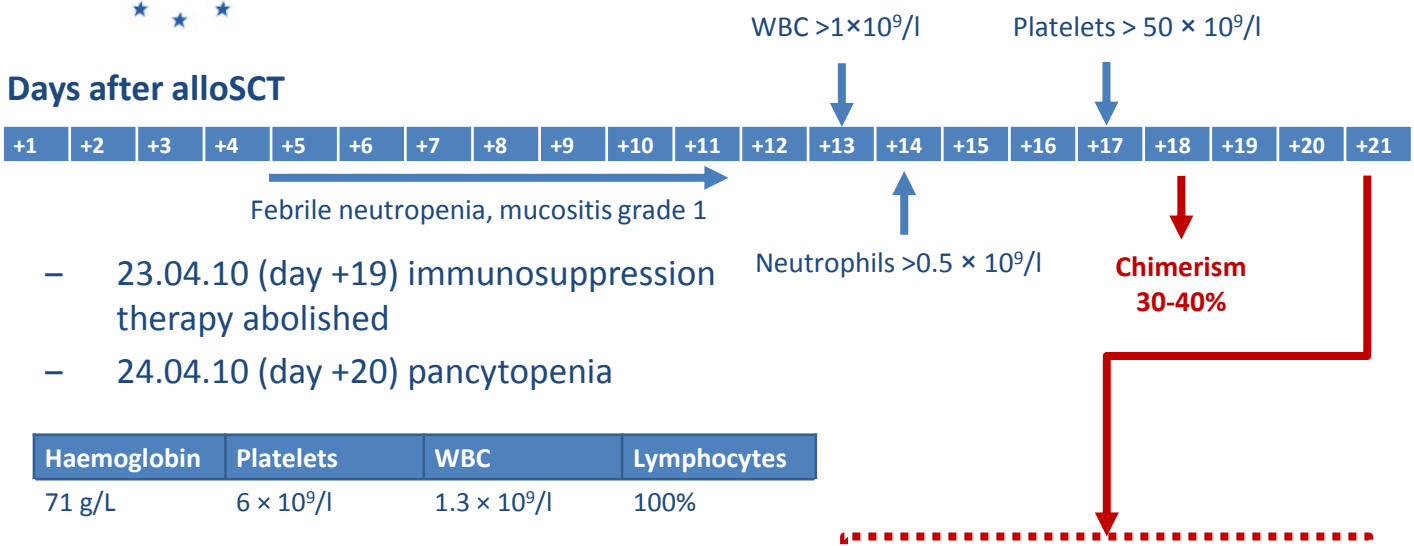
Post-transplant period



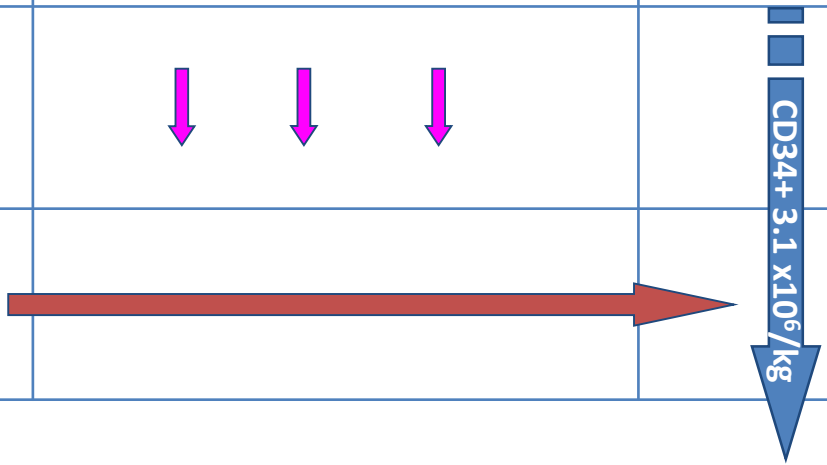
- 23.04.10 (day +19) immunosuppression therapy abolished
- 24.04.10 (day +20) pancytopenia

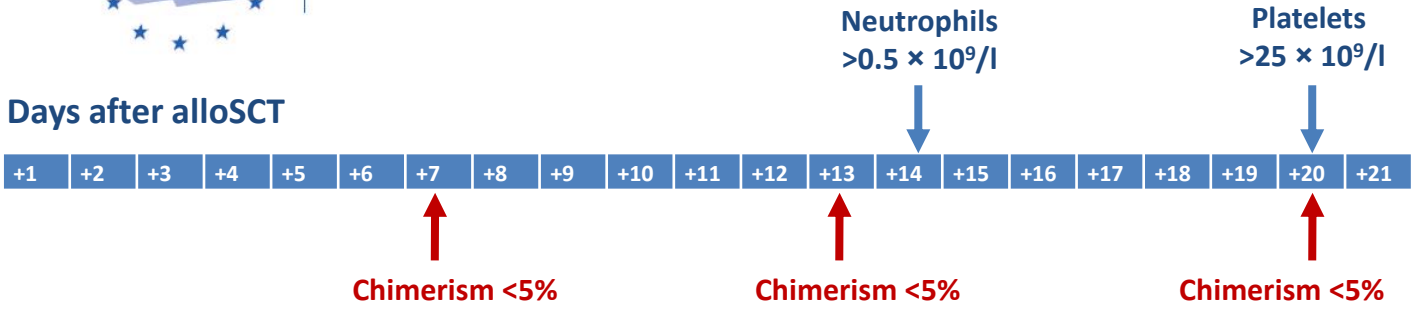
Haemoglobin	Platelets	WBC	Lymphocytes
71 g/L	6 × 10^9/l	1.3 × 10^9/l	100%

- 26.04.10 (day +22) infusion of donor lymphocytes 1 ×10^6/kg CD3+
- No effect from treatment (3-lineage cytopenia, neutropenia)

Graft rejection
Chimerism <5%
Small lymphocytes – 98% of bone marrow cells

Drug	Days of therapy -3, -2, -1	Infusion of stem cells
Methylprednisolone 750 mg		
Cyclosporin 1.5 mg/mg/day		

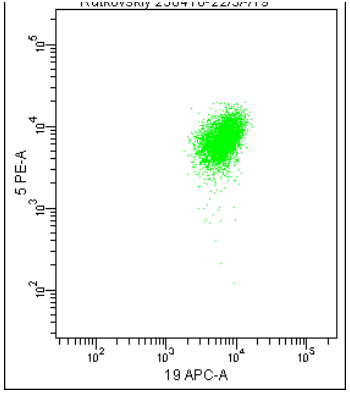




Recipient haemopoiesis recovered.

Graft rejection.

Immunophenotyping of peripheral blood (23.05.10): monoclonal population of B-lymphocytes, 34.5% of all lymphocyte count, immunophenotype CD19+, CD5+, CD22+ /κ-/ λ–. CD20 not evaluated.



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Course of post-transplant period – March 2011 (1 year after transplantation)

FBP

Hb	Platelets	WBC	Bands	Segments	Lymph.	Mon.	Eos.	Bas.
127 g/l	88 × 10^9/l	4.3 × 10^9/l	2%	45%	36%	14%	2%	1%

- Donor chimerism (10.03.11): <5% of cells are of donor origin
- Bone marrow morphology (04.03.11): lymphocytes 38%
- Bone marrow immunophenotyping (09.03.11): lymphocytes – 17.7%, of which 12% are B-cells (CD19+).
- Among the B-cells there are cells with a pathological immunophenotype CD19λ+ CD5+ CD79b dim+ CD38+ CD20dim+, which are 0.5% of nucleus-containing cells (8.7% of CD19+)

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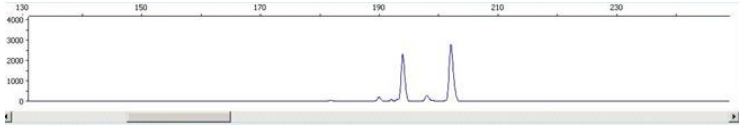
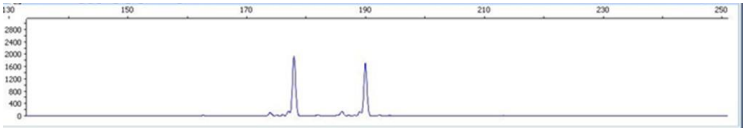
Chimerism after alloSCT

Initial data before alloSCT

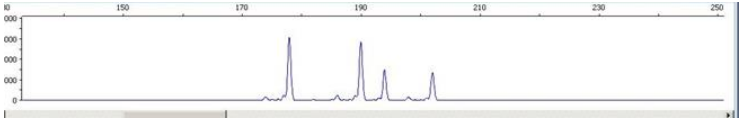


Donor

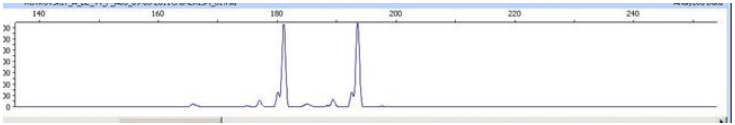


Recipient

After alloSCT



Recipient
3 weeks after alloSCT



Recipient
1 year after alloSCT

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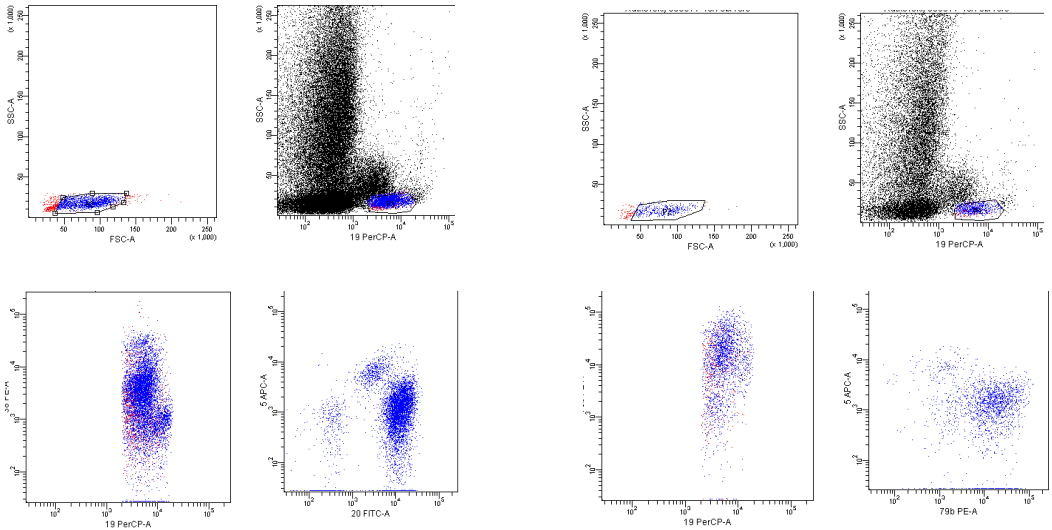
Immunophenotyping



Status after 8 years

NO THERAPY

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FBP: 01.03.2019				
Haemoglobin	140.9 g/l		(130-168)	
Erythrocytes	4.57 × 10^{12}/l		(4.0-5.0)	
Haematocrit	42.5%		(40-48)	
Platelets	255 × 10^{9}/l		(150-400)	
Leukocytes	6.0 × 10^{9}/l		(4.0-9.0)	
	Relative		**Absolute**	
Banded neutrophils	0 %	(1-6)	0	(0-0.3)
Segmented neutrophils	46 %	(45-72)	2.76 × 10^{9}/l	(2-5.5)
Eosinophils	4 %	(0-5)	0.24 × 10^{9}/l	(0-0.3)
Basophils	1 %	(0-1)	0,06 × 10^{9}/l	(0-0.1)
Monocytes	13 %	(3-11)	0.78 × 10^{9}/l	(0.1-0.7)
Lymphocytes	36 %	(19-37)	2.16 × 10^{9}/l	(1.20-3.2)

Ultrasonography, chest X-ray:
no signs of lymphadenopathy

Bone marrow morphology 01.03.2019		
Blasts	0 %	(0.1-1)
Promyelocytes	0 %	(1-4.1)
Myelocytes	1 %	(7-12.2)
Metamyelocytes	1 %	(8-15)
Banded neutrophils	5.6 %	(12.8-23.7)
Segmented neutrophils	38.8 %	(13.1-24.1)
Eosinophils	1 %	(0.5-5.8)
Monocytes	5.2 %	(0.7-3.1)
Lymphocytes	**42 %**	**(4.3-13.7)**
Plasma cells	0.4 %	(0.1-1.8)
Proerythroblasts	0 %	(0.2-1.1)
Basophilic normoblasts	0 %	(1.4-4.6)
Acidophilic normoblasts	4.8 %	(1.4-4.6)
Polychromatic normoblasts	0,.2 %	(8.9-16.9)
Megakaryocytes	0	
Conclusion: bone marrow is rich with cellular elements, granulopoiesis is well presented mostly with mature forms. Erythropoiesis is normoblastic. Lymphocytosis, and monocytosis. Megakaryocytes are not found.		

Evaluation of minimal residual disease in CLL:
Material: bone marrow
Cellularity 6.5 × 10^9/l

Percentage of all bone marrow lymphocytes:
B-lymphocytes 9.03%
CLL cells 6.55%

Chimerism:
Nucleotide sequence in bone marrow is identical to buccal epithelium

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Questions for expert

- What are current indications for stem cell transplantation in CLL?
- What should be treatment strategy be in this patient if CLL progresses?
- The patient is in MRD+ complete remission for 8 years without therapy. What are the possible mechanisms of anti-tumour effect?