RARE B CELL LEUKEMIAS AND WALDENSTRÖMS DISEASE

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Roger °1929

- **HEMATOLOGIE**
  - Rode bloedcellen 5.00 10E6/µL 4.25-5.63
  - Hemoglobine 15.3 g/dL 12.9-17.3
  - Hematocriet 45.9 % 39.0-49.7
  - MCV 91.8 fL 82.3-96.4
  - **Witte bloedcellen H 220.42 10E3/µL 3.65-9.30**
  - **Bloedplaatjes L 83 10E3/µL 149-319**

Casus: Roger °1929

- **Differentiatie WBC op perifeer bloed**

Neutrofiele granulocyten	L **2.0**	%	**38.9-74.9**
Lymfocyten	*97.0 % merendeel met restnucleool*		
Monocyten	L **0.0**	%	**4.6-12.7**
Eosinofiele granulocyten	1.0	%	0.4-5.0
Basofiele granulocyten	L **0.0**	%	**0.2-1.0**
Normoblasten	<1.0	/100 WBC	<1.0
Lymfocyten	H **217833**	**/µL**	**1133-3105**

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- Flowcytometry *
- B-Lymfocyten (CD19+) H **95** % **6-19**
- CD 3 3 %
- CD 5 29 %
- CD 10 <1 %
- CD 20 >99 %
- CD 45 >99 %
- Kappa-ketens <1%
- Lambda-ketens >99 %

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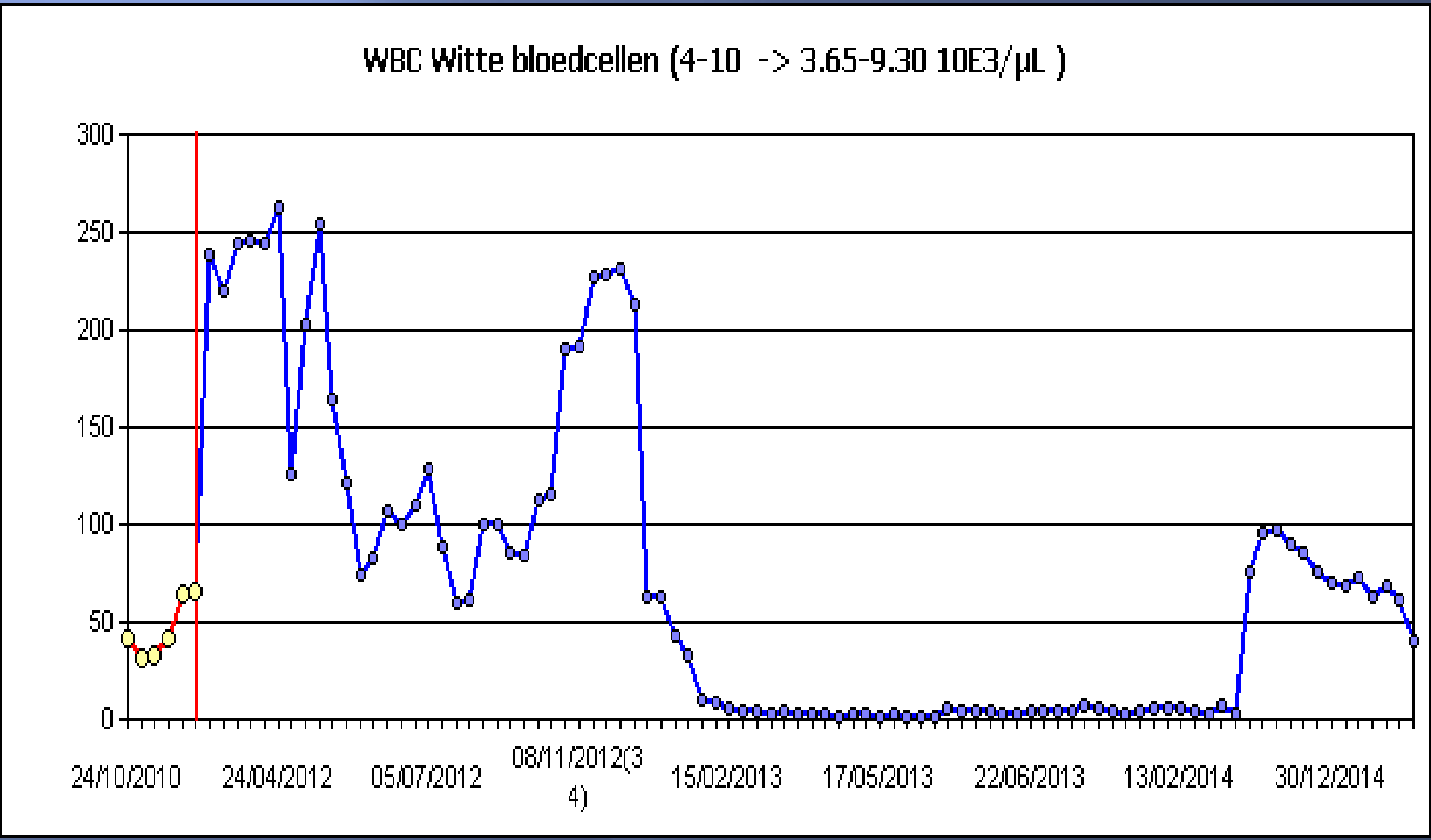


Prolymphocytic leukemia

- less than 1 percent of B cell leukemias
- initially described as a variant form of B-cell CLL
- comprised of so-called prolymphocytes: mature activated B cells
- De novo or in transformation from B- CLL

Clinical features

- mean age at presentation of between 65 and 70 years
- Rapidly rising white blood cell count >100,000/microL
- Anemia and thrombocytopenia are present in approximately 65 and 35 percent
- Massive splenomegaly, almost no adenopathies.
- B- symptoms are common
- Prognosis: 3 to 5 years despite therapy

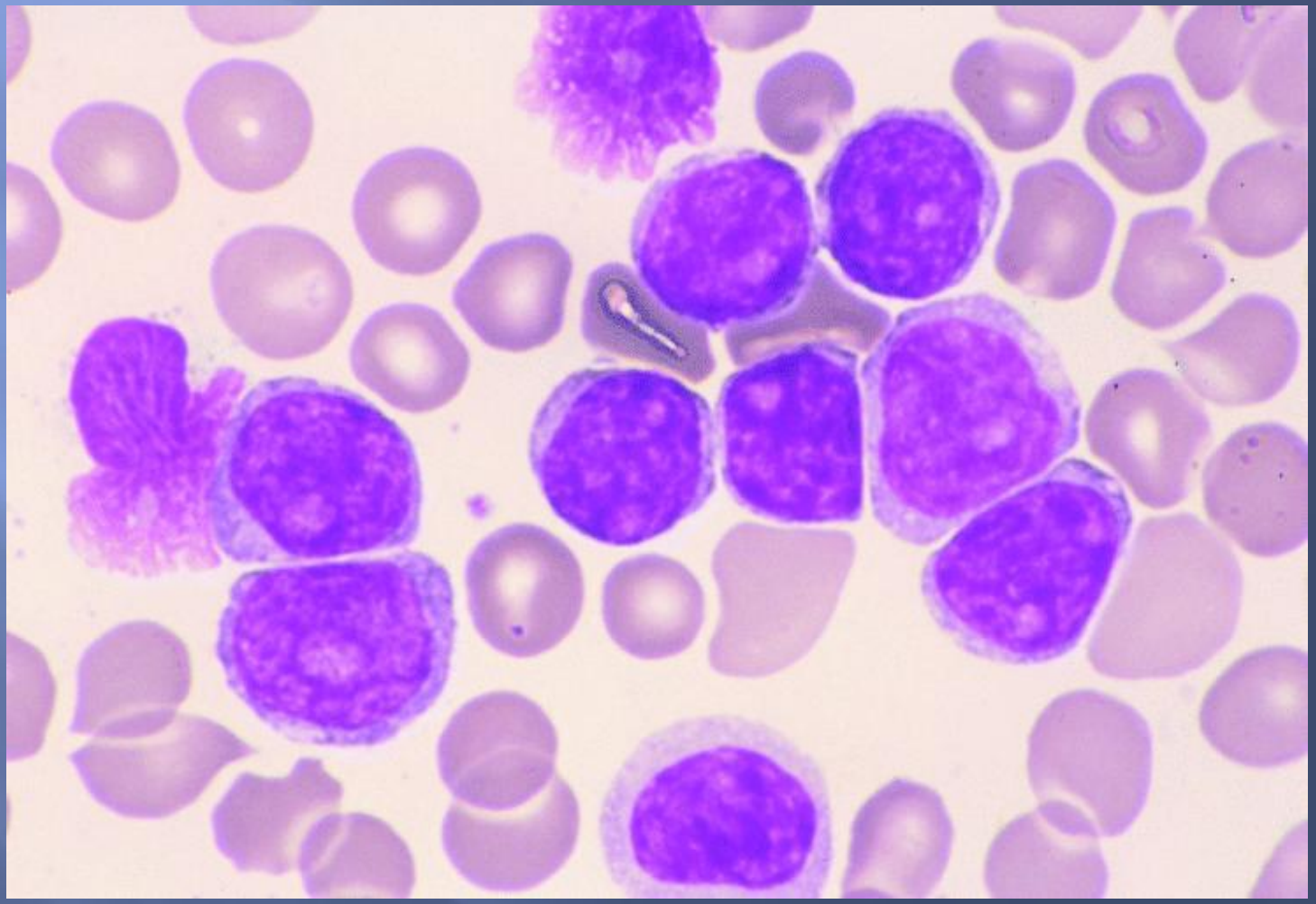
Diagnosis

- Blood examination:
  - more than 55 percent of the circulating cells in the peripheral blood are prolymphocytes
  - B-prolymphocyte has a characteristic large size, twice that of a small CLL lymphocyte
- Bone marrow examination
- Flowcytometry
- Cytogenetics

Diagnosis

- B-PLL should be distinguished from “CLL with increased prolymphocytes” (CLL/PL).
- A small proportion of patients with CLL undergo prolymphocytoid transformation, and PB morphology reveals the presence of a mixture of small mature CLL cells and prolymphocytes in contrast to typical B-PLL where the circulating cells are monomorphic prolymphocytes.

CYTOLOGY



Flowcytometry

Disease	Immunophenotype
HCL	CD11c, CD25, CD103, CD123, annexin A1^{+}, CD20^{bright}
Hairy cell variant	CD11c, CD103, CD25^{-}
SMZL/SLVL	CD11c, CD25, CD24, CD79b
Chronic lymphocytic leukemia	CD5, CD19, CD23
B-prolymphocytic leukemia	CD19, FMC7, CD79b, CD20, and CD22^{bright}

Genetic features

- Largely unknown
- Complex karyotypic changes are common
- Deletions of 17p and TP53 mutations are found in more than half of cases
- Deletions of 13q14 in 25%
- monoallelic 11q23 deletions
- t (11, 14) should be excluded ! Those cases are leukemic forms of MCL

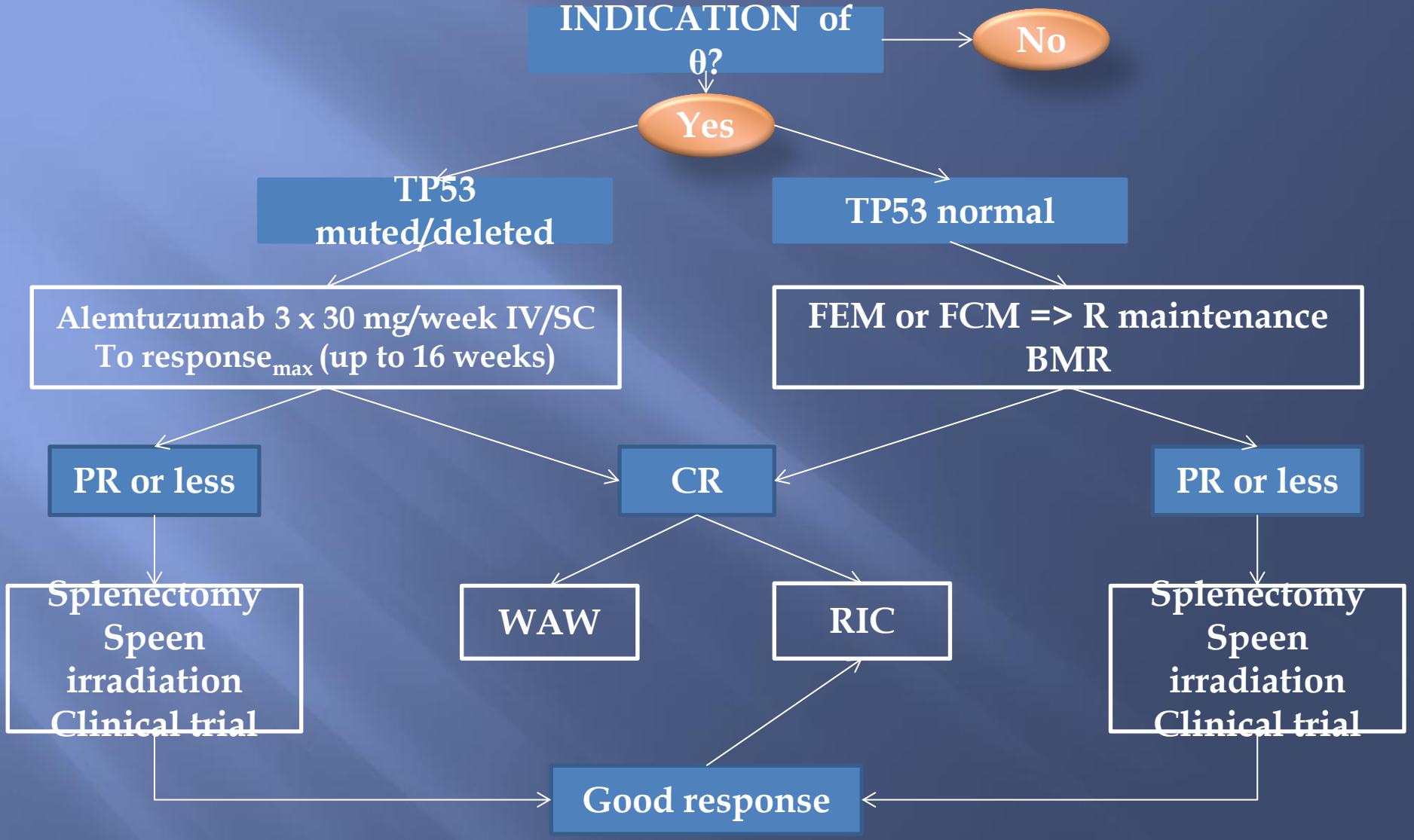
Genetic features

- Gene expression profiling demonstrated that B-PLL has a signature quite distinct from that of CLL or CLL/PL
- Chromosomal translocations involving 8q24 [eg, t(8;14)] have been reported in cases of B-PLL, suggesting that *C-MYC* alterations may be important in the pathogenesis of a subset of these cases.

Treatment

- Combination regimens, such as CHOP: respons in up to one-third of cases.
- A phase 2 trial using fludarabine and cyclophosphomide showed an ORR of 50% with a median survival of 32 months
- Case reports with rituximab
- Alemtuzumab ?
- Stem cell transplantation should also be considered in younger, fit patients who have responded to their initial therapy

B-PLL: TREATMENT



<u>Unfit patient with splenomegaly</u>: spleen irradiation or splenectomy

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Casus: Andre ° 1939

- **HEMATOLOGY**

RBC	L	**3.62**	**10E6/µL**
Hemoglobin	L	**12.1**	**g/dL**
Hematocrit	L	**36.4**	**%**
MCV	H	**100.6**	**fL**
MCH		33.4	pg/cel
MCHC		33.2	g/dL RBC
WBC	L	**1.69**	**10E3/µL**
Platelets	L	**44**	**10E3/µL**

Casus: Andre ˚1939

Differentiation WBC peripheral blood

Neutrofiele granulocyten	44.0 %	40-74
Neutrofiele staafkernigen	1 %	0-5
Lymfocyten	52.0 %	19-48
Plasmacellen	0 %	0
Hairy	H **2** %	**0**
Monocyten	L **1.0** %	**3.5-9**
Eosinofiele granulocyten	0.0 %	0-7
Basofiele granulocyten	0.0 %	0.-3

Casus

- Bone marrow examination:
  - Invasion by a lymphoproliferative population, morfolgical suggestive for hairy cell leukemia.
- Flowcytometry:
  - kappa clonal population
  - CLL score 1/5: CD 19+, CD 20+, CD 10+, CD 5-, CD79b -, FMC7 +
  - CD11c+, CD103+, CD22 +, CD25 +, CD24-

Casus

- Ultrasound abdomen
  - Enlarged spleen up to 14 cm
- Treatment
  - 2 CDA

Hairy cell leukemia

- less than 1 percent of lymphoid neoplasms
- US: estimated incidence: 3/milj/year.
- Strong male predominance (4/1).

Clinical features

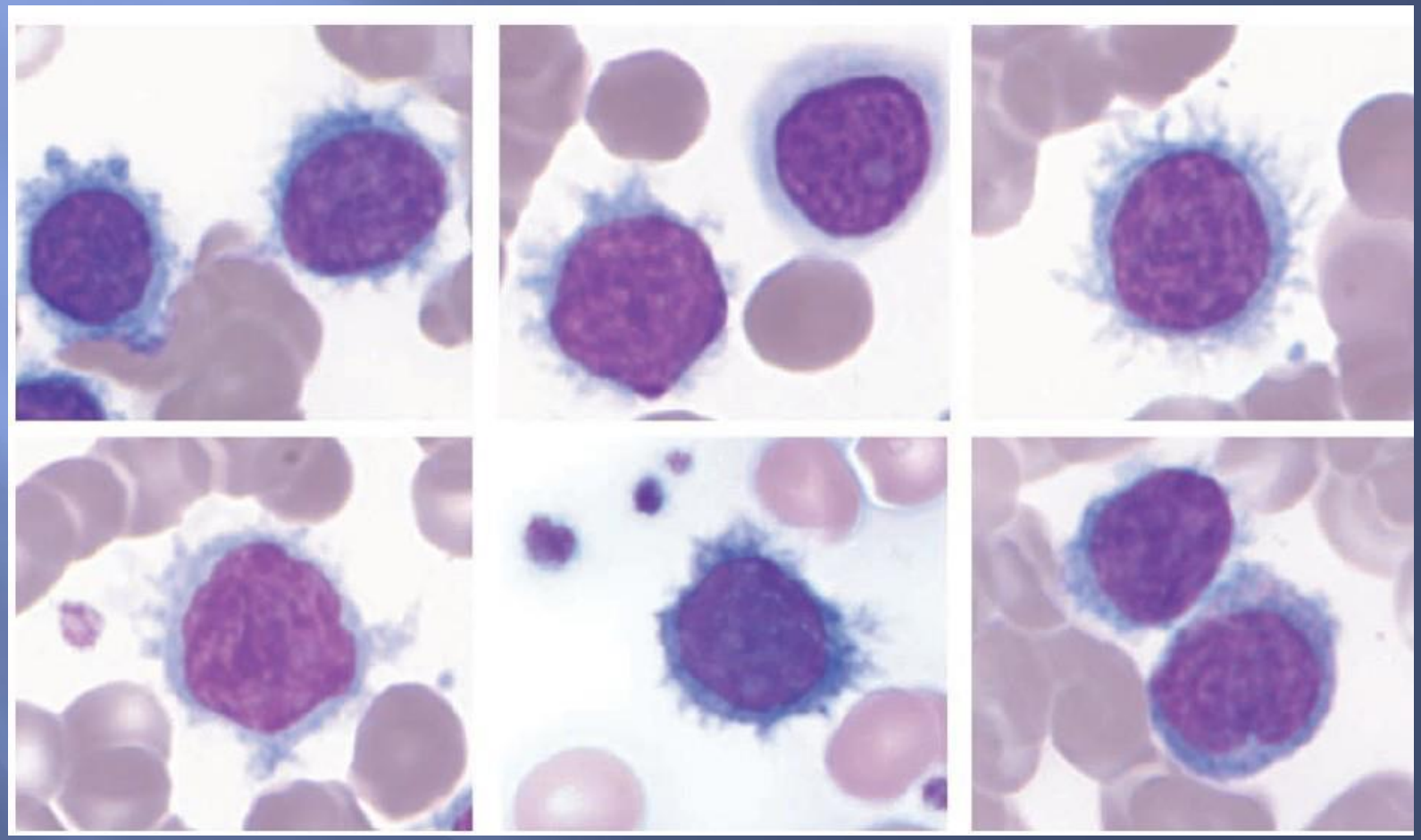
- 1 /4 patients is asymptomatic
- Splenomegaly in 80-90% of the patients.
- Symptoms due to trombocytopenia, anemia
- fatigue, weakness, and weight loss. Patients do not usually complain of fever or night sweats.
- autoimmune manifestations
- Lab findings: 60 to 80 percent of patients with HCL present with pancytopenia

Diagnosis

- Blood examination
- Bone marrow examination
- Flow cytometry
- Genetic features

Diagnosis

- Peripheral blood examination:
  - Careful examination of peripheral blood films will show the characteristic hairy cells, which are approximately twice as large as normal lymphocytes and have a round, oval or kidney-shaped nucleus and a loose chromatin pattern
  - Monocytopenia



Diagnosis

- Bone marrow biopsy
  - Aspirate often negative or dry tap
  - Trephine biopsy necesseray!
  - Immunohistochemistry: CD20, TRAP, DBA44
- Flow cytometry:
  - B-cell panel: CD19, CD20, CD22, SmIg
  - HCL panel: CD11c, CD25, CD103, CD123

Diagnosis

- Whole exome sequencing of HCL cells in parallel with normal cells has recently revealed the presence of the *BRAF V600E mutation*
- Cytogenetic studies and BRAF V600E mutation testing is not necessary for diagnosis. It may be useful in cases of diagnostic uncertainty or when therapeutic management is difficult.

Prognosis

- Leucocytosis > 10.10^{9}__/l
- Bulky spleen > 10 cm below costal margin
- Unmutated IgVH gene profile ≥98 %
- Use of the VH4–34 repertoire
- Mutation of the TP53 gene

Treatment

- **Indications for treatment**
  - Symptomatic splenomegaly
  - Cytopenia : Hb < 10 g/dl, Platelets < $100x10^{9}/l$, ANC < $1x10^{9}/l$
  - Recurrent or severe infections
- In the absence of treatment, clinical monitoring and monitoring of the blood count are necessary every 3 months for the first year and then every 6 months.

Treatment

- There are no data in the literature proving the superiority of one drug over the other
  - 2CDA
  - Pentostatin (not available in Belgium)
  - Rituximab (no reimbursement in Belgium)
  - IFN alfa
- Prevention of Pneumocystis and Herpes zoster infections !!!

Treatment

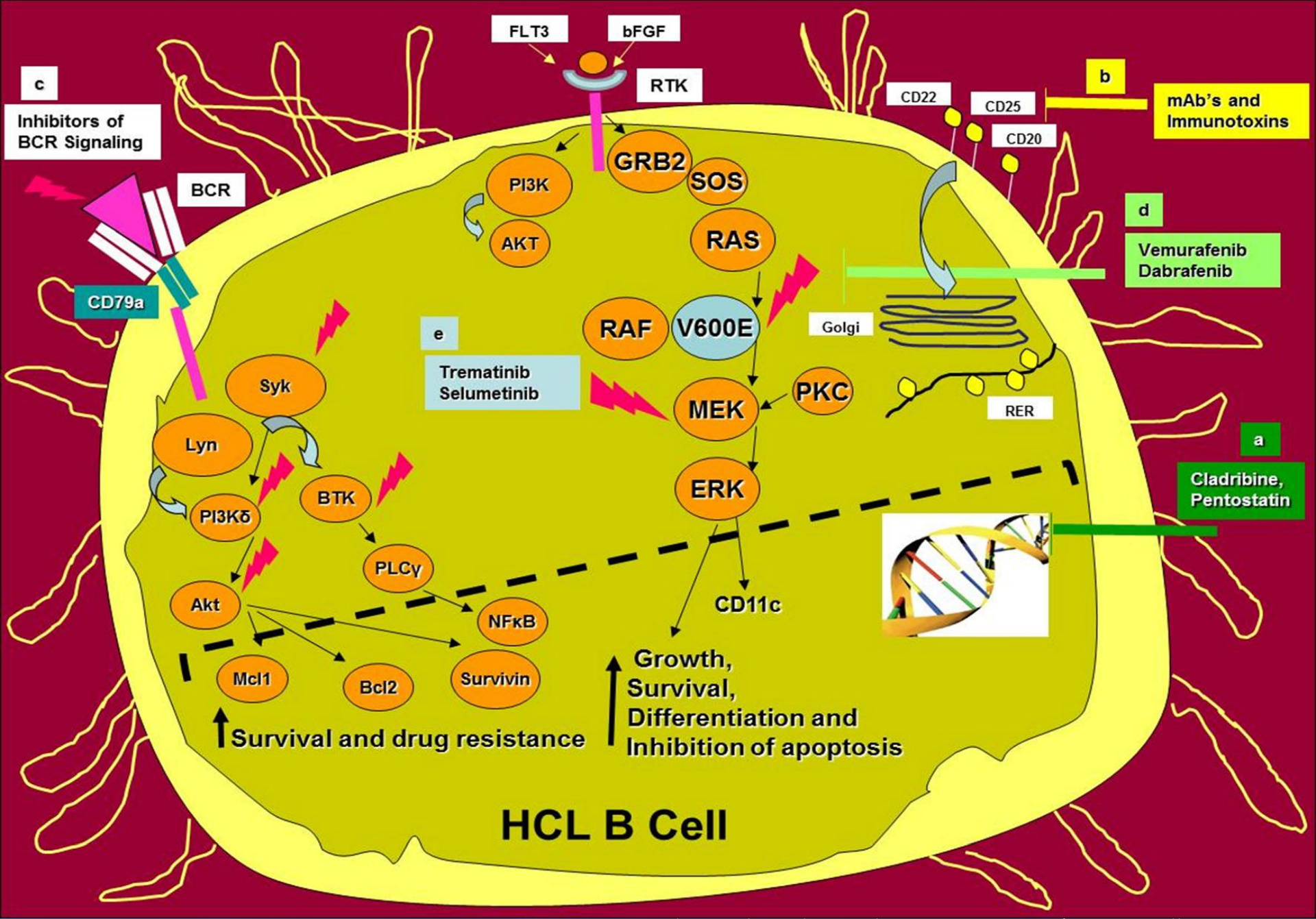
- Based on purine analogs: 2CDA
  - 0.1 mg/kg/day as a continuous IV infusion for 7 days
  - The dosage must be repeated in the absence of CR at 6 months

Treatment in relapse disease

- In cases of late relapse (>60 months), PNAs may be used again.
- In cases of intermediate relapse (24–60 months), the second-line treatment also PNA ‘s in combination with rituximab?
- Relapse < 24 months: diagnosis of HCL must be confirmed and *BRAF* V600E mutation testing must be performed.
  - Vemurafemib !

Treatment

- Novel insights in the biology of HCL have led to the development of novel agents with mechanisms of action very different from that of purine analogues.
  - recombinant immunotoxins targeting CD22 such as moxetumomab pasudotox
  - *BRAF inhibitors* such as vemurafenib
  - B cell receptor signaling kinase inhibitors such as ibrutinib, which is a Bruton's tyrosine kinase (BTK) inhibitor.



Update on the Biology and Treatment Options for Hairy Cell Leukemia
Preetesh Jain et al.

Hairy cell variant

- 10% of the HCL
- CD11C-, ***CD25^{-},CD103^{-},CD123^{+}***
- No monocytopenia !
- **Bad response to purine analogues and worse prognosis**
- **no BRAF mutation**
- **Treatment: splenectomy?, rituximab?, alemtuzumab?, HA22?, BL22?, translpantation?**

Morbus Waldenström

- Overall incidence : 3 milj new patients every year
- Median age at diagnosis: 65 years
- Men > women
- Caucasian

symptoms

- Asymptomatic
- Symptoms due to proliferation of lymphoplasmocytic cells
  - Adenopathy
  - Hepatomegaly and splenomegaly
  - Anemia
- Symptoms due to IgM
- B symptoms

Table 1: morbidities mediated by the monoclonal IgM protein in WM

Diagnostic condition/ Property of IgM monoclonal protein	Clinical manifestations
Hyperviscosity	Headaches, blurred vision, epistaxis, retinal hemorrhages, leg cramps, impaired mentation, intracranial hemorrhage
Cryoglobulinemia	Raynaud phenomenon, purpura, cold urticaria, arthralgias, renal failure
Peripheral neuropathies (antibodies to myelin-associated glycoprotein (MAG), ganglioside M1(GM1), cryoglobulinemia)	Sensorimotor neuropathies, painful neuropathies,ataxia
Cold agglutinins	Hemolytic anemia, Raynaud phenomenon, livedo reticularis
Tissue deposition as amorphous aggregates	Bullous skin disease, papules, Scnitzler syndrome, diarrhea, malabsorption, proteinuria, renal failure
Amyloidosis	Fatigue, weight loss, edema, hepatomegaly, macroglossia, organ dysfunction: heart , hepatic and renal failure, peripheral and autonomic neuropathy

Diagnosis

- Bloodexamination:
  - Cytopenia
  - Monoclonal IgM
- Bone marrow examination
- Flowcytometry:
  - Positive for CD19, CD20 and CD22
  - Lack CD23, CD10, CD5 and cytoplasmic Ig. Variations from this phenotypic profile can occur and up to 20% of cases may express CD5, CD10, or CD23

Diagnosis

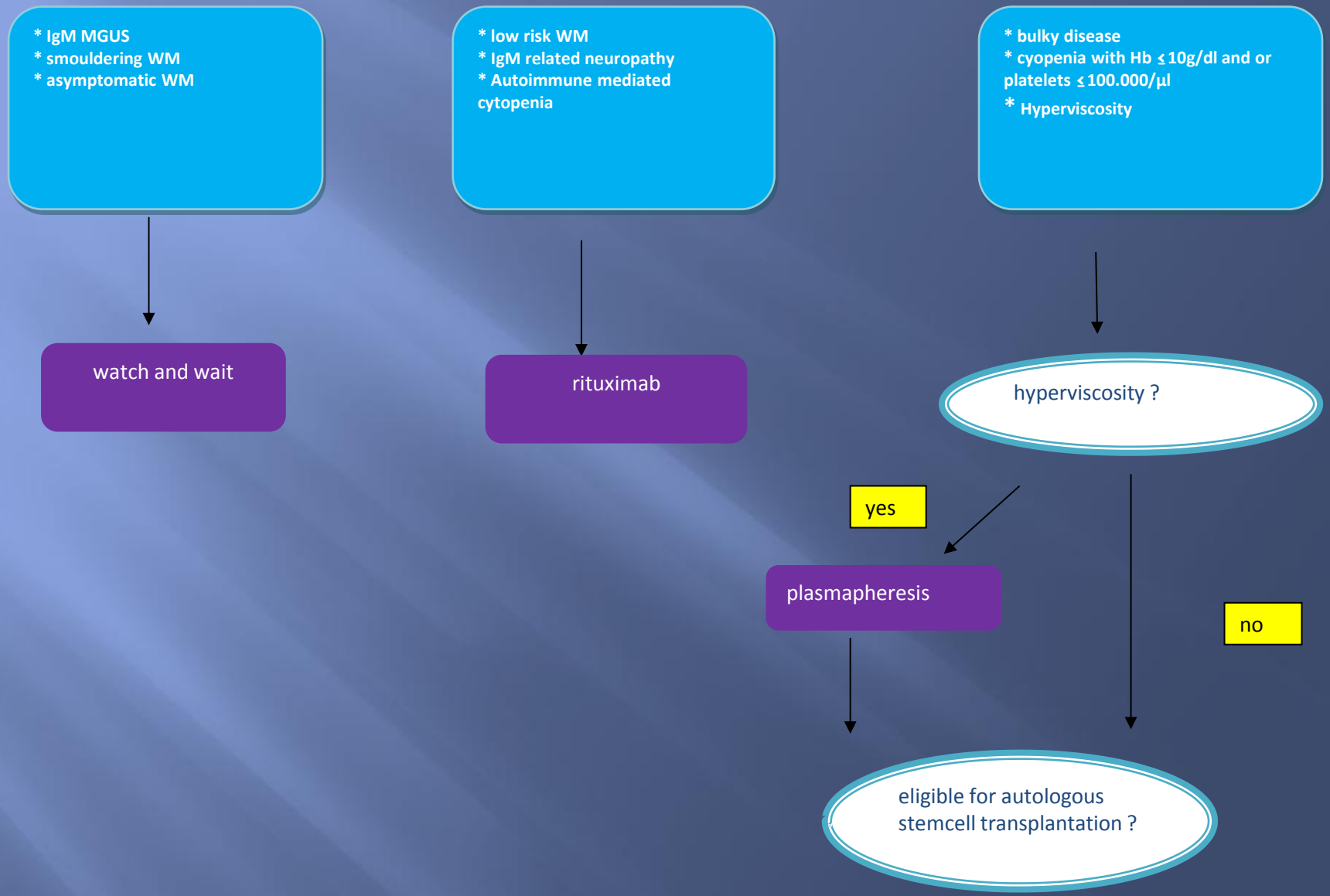
- Genetics:
  - Deletion of the long arm of chromosome 6 (6q-) up to 50% of patients. Meaning ? No routine testing advised.
  - single point mutation (L265P) in the myeloid differentitation primary response gene (*MYD88*) in 90% of patient with WM.
  - Deletion of *TP53* occurs in a minority of patients and appears to define patients with a poor outcome

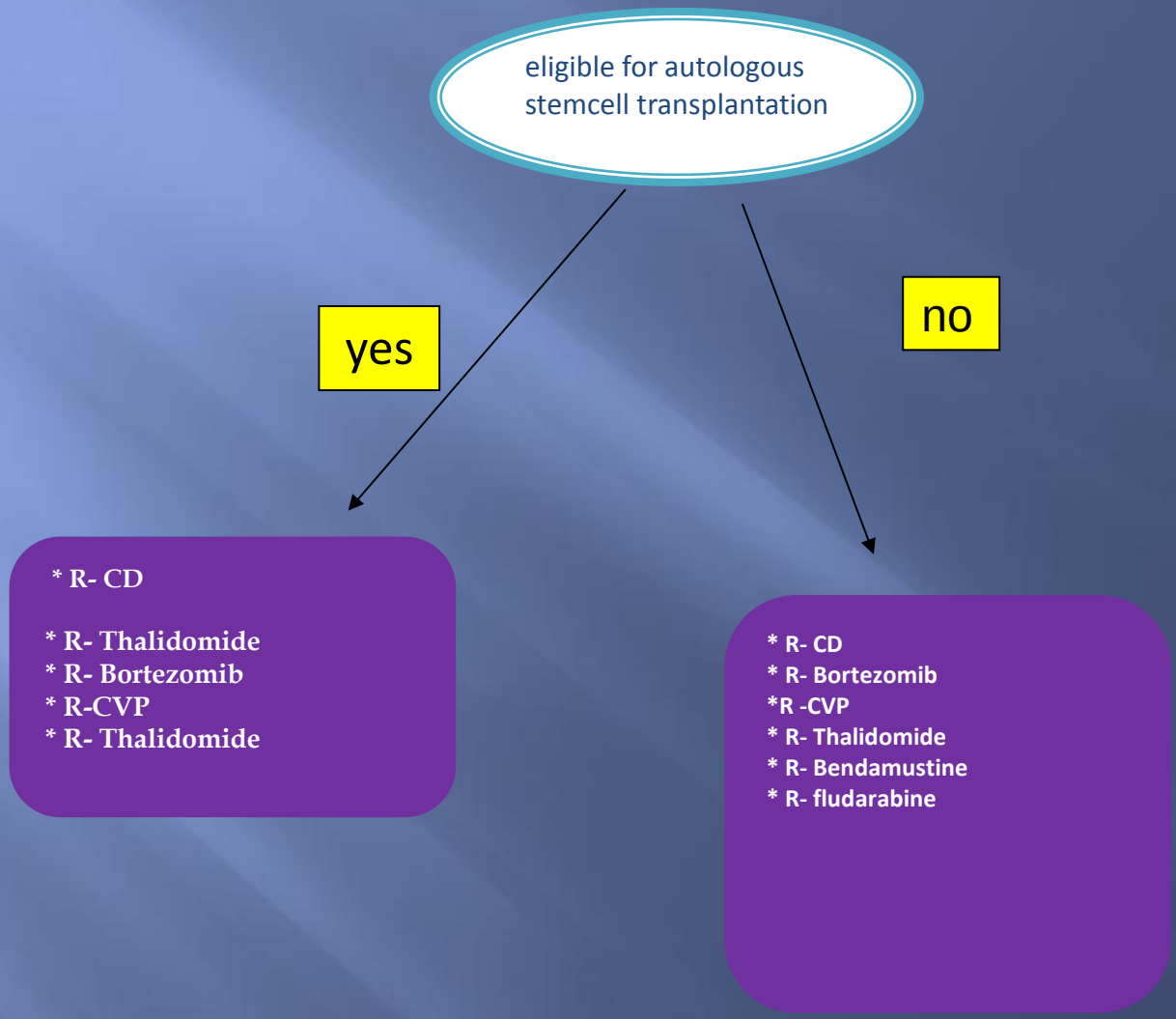
Prognosis

	Low risk	Intermediate risk	High risk
Age [redacted]	<65yr	>65 yr	>65 yr
Hemoglobin≤11,5g/dL	≤ 1 factor	2 factors	> 2 factors
Platelet≤100x10^9/L			
Beta2-microglobulin>3 mg/L			
IgM>7g/dL			
Survival at 5 yr	87%	68%	36%

treatment

- Watch and Wait
- Urgent treatment in case of hyperviscosity : plasmapheresis !!!
- Systemic treatment
- Flare up phenomenom !


* IgM MGUS
* smouldering WM
* asymptomatic WM
* low risk WM
* IgM related neuropathy
* Autoimmune mediated cytopenia
* bulky disease
* cyopenia with Hb ≤ 10g/dl and or platelets ≤ 100.000/µl
* Hyperviscosity
watch and wait
rituximab
hyperviscosity ?
yes
plasmapheresis
no
eligible for autologous stemcell transplantation ?


eligible for autologous stemcell transplantation
yes
no
* R- CD
* R- Thalidomide
* R- Bortezomib
* R-CVP
* R- Thalidomide
* R- CD
* R- Bortezomib
*R -CVP
* R- Thalidomide
* R- Bendamustine
* R- fludarabine

References

- **How I treat prolymphocytic leukemia.** Claire Dearden July 19,2012; Blood:120(3)
- Recommendations of the SFH (French Society of Haematology) for the diagnosis, treatment and follow-up of hairy cell leukaemia. Cornet E, Delmer A, Feugier P, et al. Ann Hematol. 2014 Dec;93(12):1977-83. doi: 10.1007/s00277-014-2140-y. Epub 2014 Jul 5.
- Novel Therapeutic options for Relapsed Hairy Cell Leukemia. Leuk Lymphoma 2015 Jan7: 1-30. [Epub ahead of print].
- Waldenström Macroglobulinemia.. Steven P. Treon*, Zachary R. Hunter,, Jorge J. Castillo, et al. Hematol Oncol Clin N Am 28 (2014) 945–970
- ***Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus.*** Meletios A. Dimopoulos, Efstathios Kastritis1, Roger G. Owen et al. Blood. 2014;124(9): 1404-1411.