Universitas Indonesia

2019

LEUKEMIA KRONIK

MODUL HEMATOLOGI-ONKOLOGI

Narator

dr. Fikri Ichsan Wiguna

Narasumber

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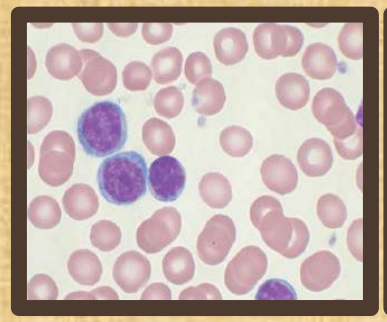
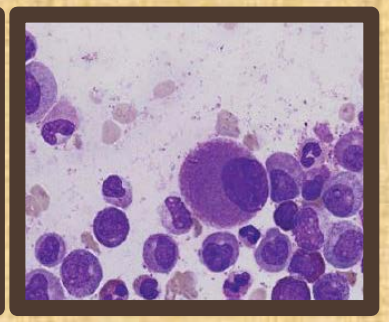




Sumber:

- Davis, A. S., Viera, A. J., & Mead, M. D. (2014). Leukemia: An overview for primary care. *American Family Physician*, *89*(9), 731–738.

TUJUAN PEMBELAJARAN

- Peserta didik mampu memahami definisi, dan etiologi dari leukemia kronik
- Peserta didik mampu memahami perbedaan antara kedua tipe leukemia kronik
- Peserta didik mampu mengenali manifestasi klinis dan memahami diagnosis leukemia kronik
- Peserta didik mampu mengetahui prinsip dasar terapi leukemia kronik

DAFTAR ISI

PEMAHAMAN DASAR

DEFINISI

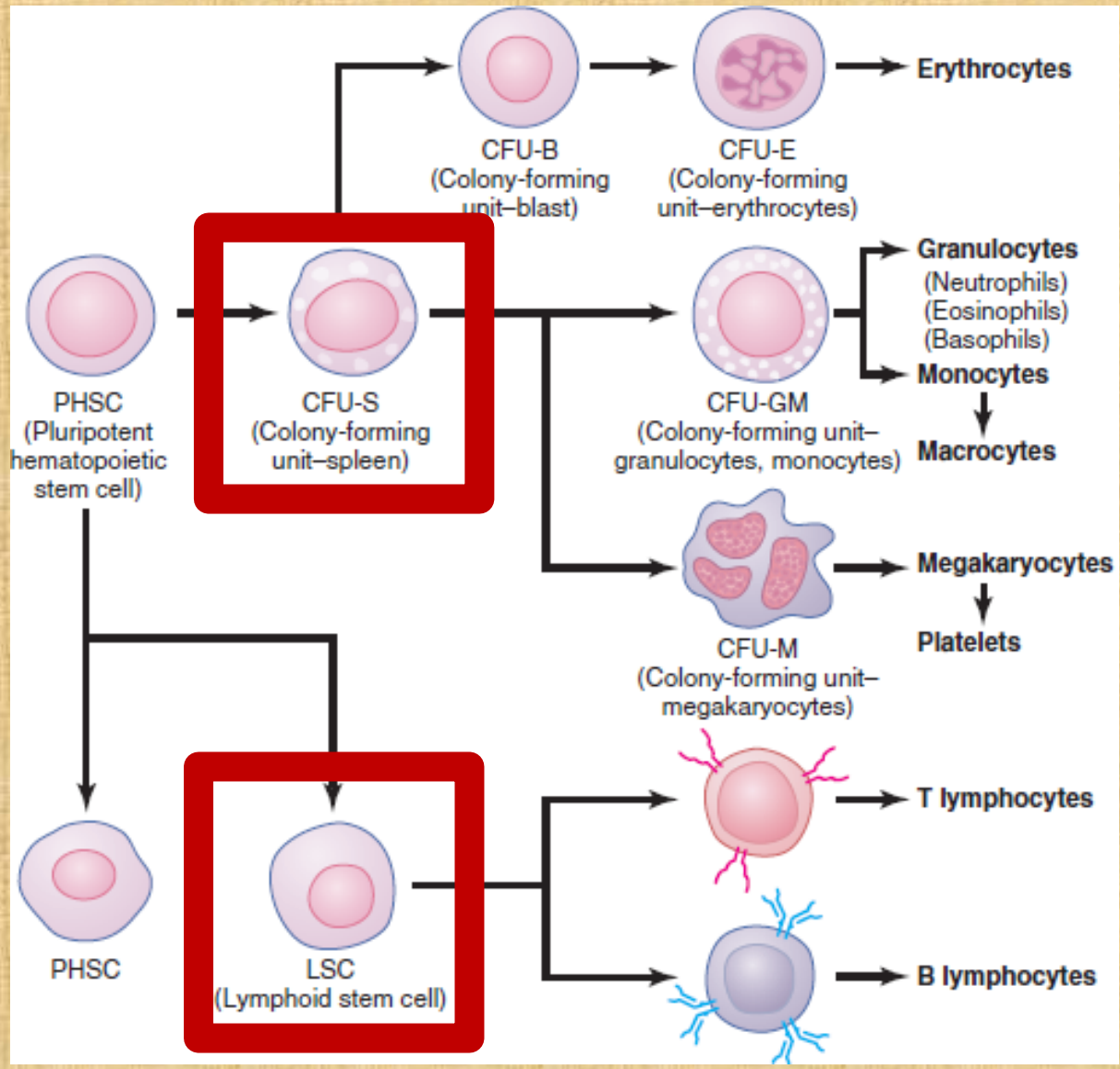
↑ Leukosit

↓

↑ Sel hematopoietik

↓

Sel Matur



Sumber:

1. Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's principle of internal medicine. 19th ed. McGraw-Hill Education; 2015.
2. Hall JE. Textbook of medical physiology. 13th ed. Elsevier, Inc. Philadelphia: Elsevier Inc; 2016.

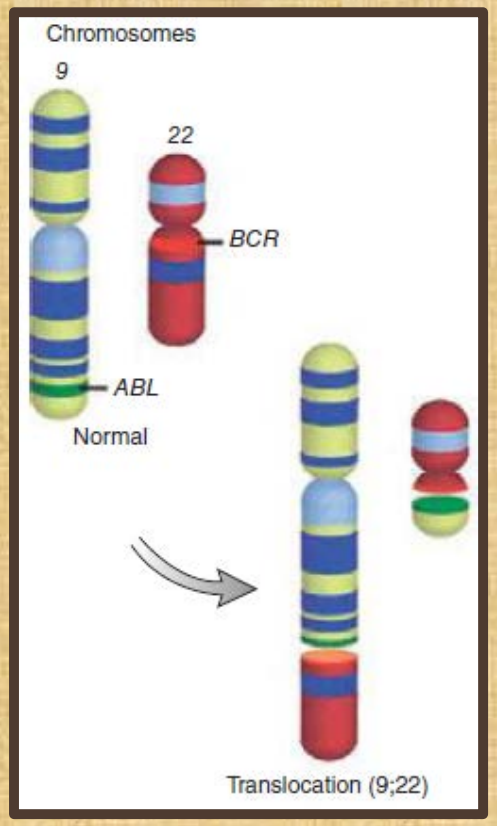
KLASIFIKASI-ETIOLOGI

Sumber:
2. Hall JE. Textbook of medical physiology. 13th ed. Elsevier, Inc. Philadelphia: Elsevier Inc; 2016.

Chronic

Myeloid Leukemia

CML



CLL Lymphocytic Leukemia

?

EPIDEMIOLOGI

CLL

4,2:100.000 /tahun

>30:100.000 /tahun (>80yo)

72 tahun

CML

10-15:1.000.000 /tahun

60 dan 65 tahun

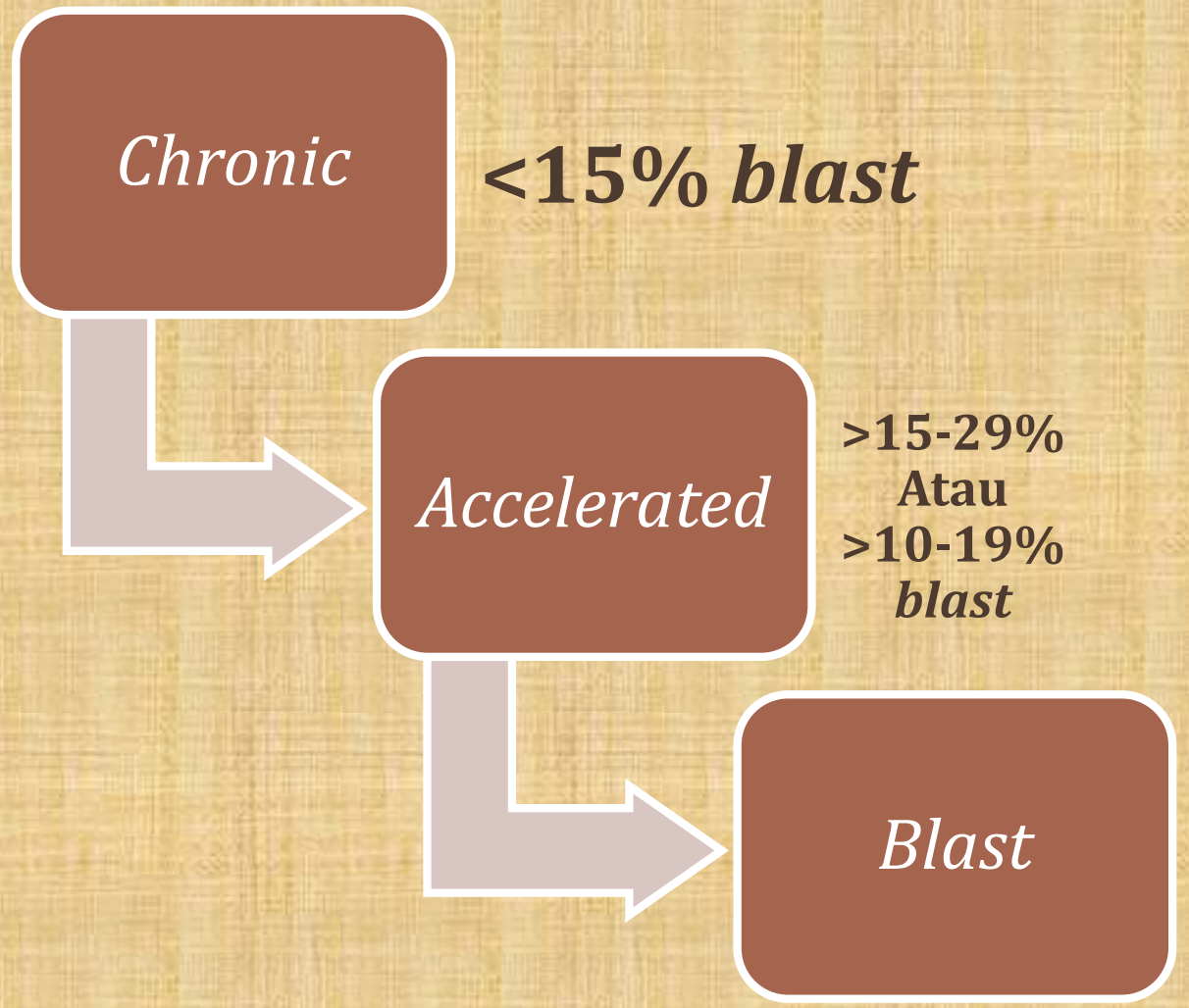
Sumber:

3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.
4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

DIAGNOSIS

Chronic Myeloid Leukemia

FASE-CML



BCR-ABL1

Tidak stabil

Faktor

- Mutasi titik domain kinase
- Kelainan sitogenetik tambahan

Sumber:

3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.
4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

FASE-CML

Table 1. Clinical and haematological criteria for the definition of AP and BP according to WHO [ ] and ELN [6]

	Accelerated phase		Blast phase	
	WHO	ELN	WHO	ELN
Spleen	Persisting or increasing splenomegaly unresponsive to therapy	–	–	–
WBC count	Persisting or increasing WBC count (> 10 x 10^9/L) unresponsive to therapy	–	–	–
Blast cells[a]	10%–19%	15%–29%	≥ 20%	≥ 30%
Basophils[a]	> 20%	> 20%	–	–
Platelet count	> 1000 x 10^9/L uncontrolled by therapy < 100 x 10^9/L unrelated to therapy	– Yes	– –	– –
CCA/Ph+	Any new clonal aberration during therapy Additional clonal chromosomal abnormalities in Ph cells at diagnosis that include 'major route' abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype or abnormalities of 3q26.2	Present	–	–
Extramedullary involvement[b]	–	–	Present	Present
'Provisional' response-to-TKI criteria	Haematological resistance to the first TKI (or failure to achieve a complete haematological response[c] to the first TKI) or Any haematological, cytogenetic or molecular indications of resistance to 2 sequential TKIs or Occurrence of 2 or more mutations in BCR–ABL1 during TKI therapy			

The criteria of AP are different, reflecting the difficulty of making the diagnosis of this transitory phase. The criteria of BP differ only for the percent of blast cells. Only one of the listed criteria is sufficient for the diagnosis of AP or BP.

[a]In peripheral blood or in BM.

[b]Excluding liver and spleen, including lymph nodes, skin, CNS, bone and lung.

[c]Complete haematological response: WBC < 10 × 10^9/L; platelet count < 450 × 10^9/L, no immature granulocytes in the differential and spleen non-palpable.

AP, accelerated phase; BM, bone marrow; BP, blast phase; CCA/Ph+, clonal chromosome abnormalities in Ph+ cells; CNS, central nervous system; ELN, European LeukemiaNet; Ph, Philadelphia; TKI, tyrosine kinase inhibitor; WBC, white blood cell; WHO, World Health Organization.

Sumber:
4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

MANIFESTASI KLINIS = Asimptomatik !

Chronic Phase	*Accelerated Phase*	*Blast Phase*
Fatigue, berat badan berkurang, malaise, merasa penuh /nyeri pada kuadran kiri atas Anemia, splenomegali	Anemia yang memburuk, splenomegali, infiltrasi organ	Gejala konstitusional yang memburuk, perdarahan, demam, dan infeksi

Sumber:
4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

PENGUKURAN RISIKO

Chronic Myeloid Leukemia

PENGUKURAN RISIKO

Table 3. Calculation of the relative risk of a patient with CML using clinical and haematological data obtained before any treatment [8]

	Sokal	EURO	EUTOS	ELTS
Age (years)	0.116 (age - 43.4)	0.666 when age > 50	N/A	$0.0025 \times (age/10)^3$
Spleen size[a] (cm)	0.345 × (spleen - 7.51)	0.042 × spleen	4 × spleen	0.0615 × spleen
Platelet count ($\times 10^9$/L)	$0.188 \times [(platelets/700)^2 - 0.563]$	1.0956 when platelets ≥ 1500	N/A	$0.4104 \times (platelets/1000)^{-0.5}$
Blood blast cells (%)	0.887 × (blast cells - 2.10)	0.0584 × blast cells	N/A	0.1052 × blast cells
Blood basophils (%)	N/A	0.20399 when basophils > 3%	7 × basophils	
Blood eosinophils (%)	N/A	0.0413 × eosinophils	N/A	
Relative risk	Exponential of the total	Total × 1000	Total	Total
Low	< 0.8	≤ 780	≥ 87	≤ 1.5680
Intermediate	0.8–1.2	781–1480	N/A	1.5680–2.2185
High	≥ 1.2	≥ 1480	≥ 87	≥ 2.2185
Endpoint	Survival	Survival	CCyR	CML-specific survival

[a]Spleen size is measured by manual palpation and expressed as maximum distance perpendicular from costal margin.
CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; ELTS, EUTOS Long-Term Survival; EUTOS, European Treatment and Outcome Study; N/A, not applicable.

Sumber:
4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

TERAPI

Chronic Myeloid Leukemia

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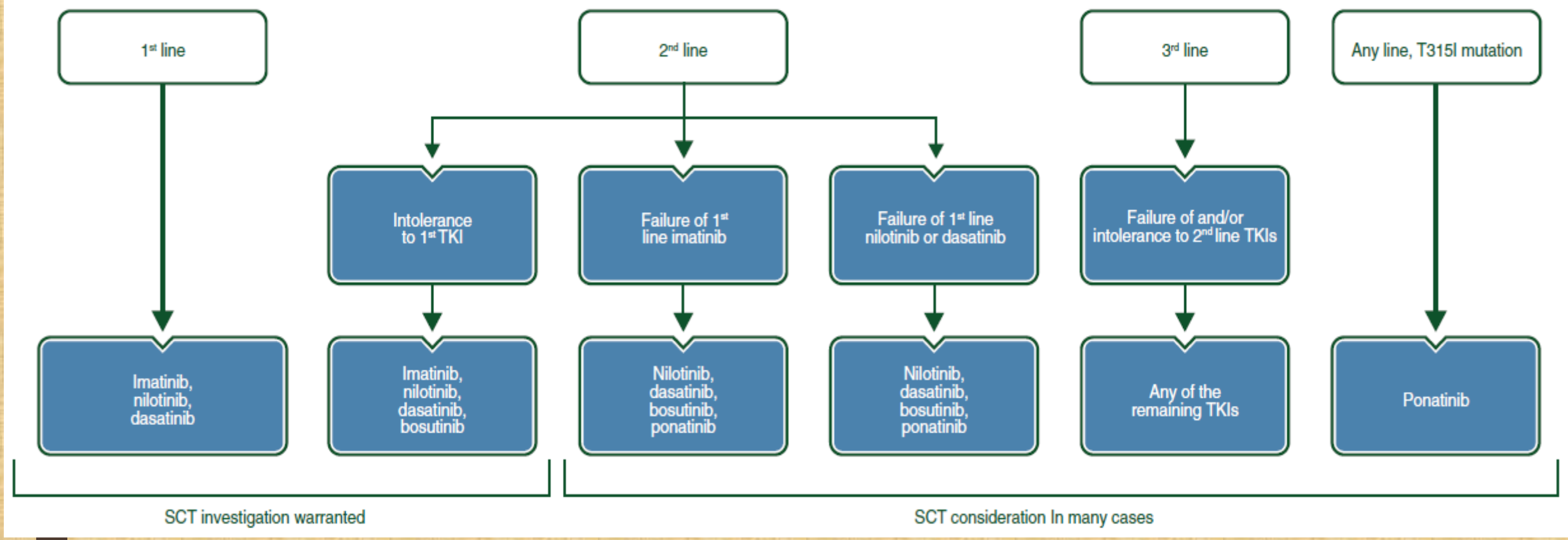

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4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

DIAGNOSIS

Chronic Lymphocytic Leukemia

DIAGNOSIS

Kriteria Diagnosis

Sel monoklonal B ≥5000 limfosit/µL

- Konfirmasi dengan *flow cytometry*

Apusan darah tepi

- Karakteristik sel: Kecil, limfosit matur, batas sitoplasma tipis, nukleus padat, kromatin teragregasi sebagian

Small lymphocytic lymphoma (SLL)

- Splenomegali / limfadenopati
- Limfosit B <5000/µL
- Dikonfirmasi dengan biopsy
- kelenjar getah bening

Monoclonal B-Lymphocytosis (MBL)

- Tanpa limfadenopati, organomegali, sitopenia, dan gejala
- Limfosit B <5000/µL

Sumber:
3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.

DIAGNOSIS

Table 1. Diagnostic and staging work-up

	Pretreatment evaluation	Response evaluation
History, physical examination and performance status	+	+
Complete blood count and differential	+	+
Serum chemistry including serum immunoglobulin and direct antiglobulin test	+	+
Cytogenetics (FISH) for del (17p)/ molecular genetics for *TP53* mutation	+	–
Marrow aspirate and biopsy	+[a]	+[b]
Hepatitis B and C, CMV and HIV serology	+	–

[a]Only if clinically indicated.
[b]Only for confirmation of CR within clinical studies.
FISH, fluorescence *in situ* hybridisation; CMV, cytomegalovirus; HIV, human immunodeficiency virus; CR, complete remission.

Sumber:
3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.

STAGING

Table 2. Staging systems for chronic lymphocytic leukaemia (CLL)

Stage	Definition	Median survival
Binet system		
Binet A	Hb ≥ 10.0 g/dl, thrombocytes ≥100 × 10^9/l, <3 lymph node regions	>10 years
Binet B	Hb ≥ 10.0 g/dl, thrombocytes ≥100 × 10^9/l, ≥3 lymph node regions	>8 years
Binet C	Hb < 10.0 g/dl, thrombocytes <100 × 10^9/l	6.5 years
Rai system		
Low risk		
Rai 0	Lymphocytosis >15 × 10^9/l	>10 years
Intermediate risk		
Rai I	Lymphocytosis and lymphadenopathy	>8 years
Rai II	Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy	
High risk		
Rai III	Lymphocytosis and Hb < 11.0 g/dl with/without lymphadenopathy/organomegaly	6.5 years
Rai IV	Lymphocytosis and thrombocytes <100 × 10^9/l with/without lymphadenopathy/organomegaly	

The overall survival times included in this table were adapted and have changed during the past 30 years [7].
Binet's lymphoid areas consist in: lymphadenopathy either uni- or bilateral in (1) cervical, (2) axillary, (3) inguinal areas, (4) spleen, (5) liver.
Hb, haemoglobin.

Sumber:
3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.

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Chronic Lymphocytic Leukemia

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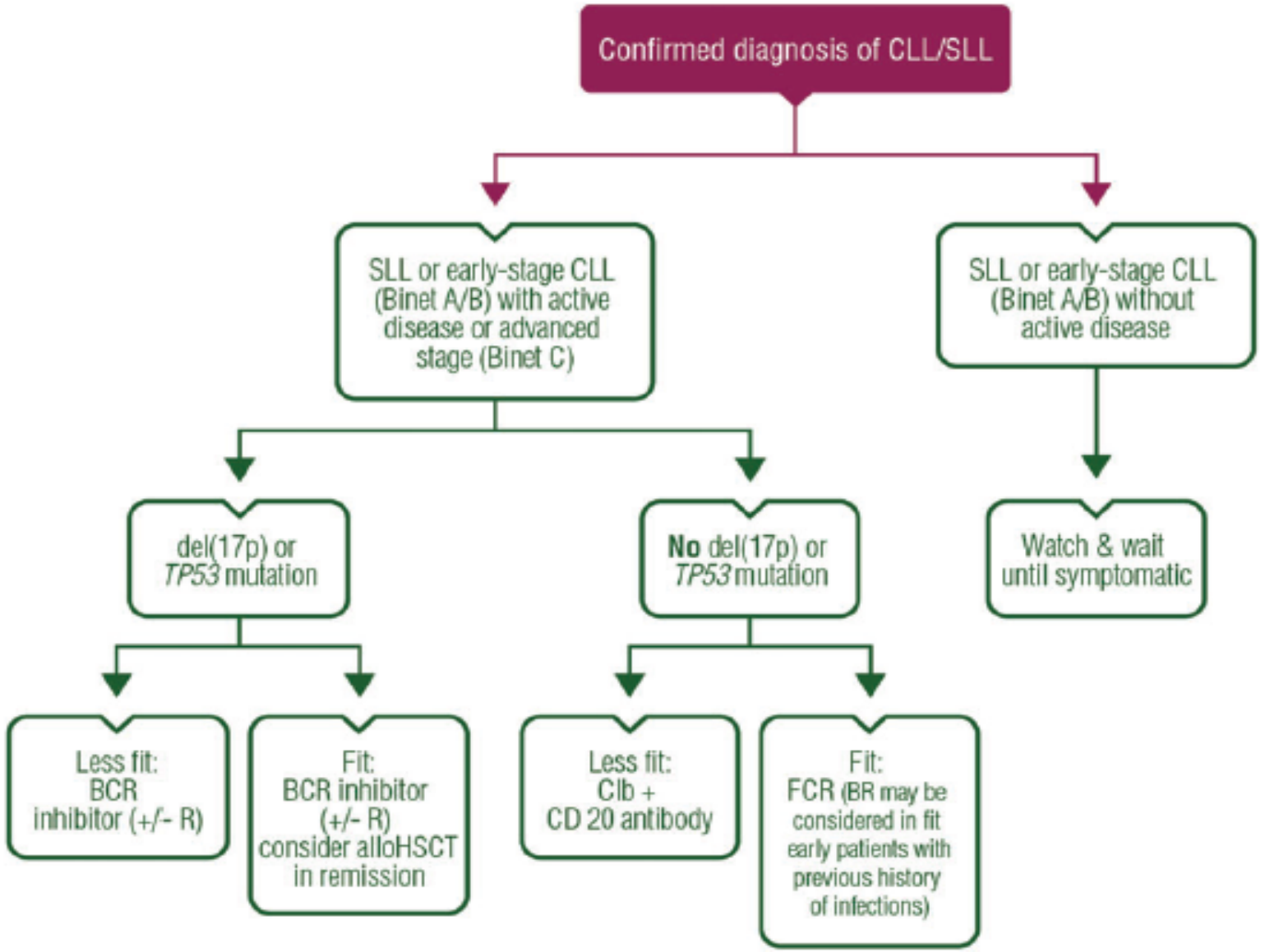

Figure 1. Front-line treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation; FCR, fludarabine, cyclophosphamide and rituximab; BR, bendamustine plus rituximab; Clb, chlorambucil.

Sumber:

3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.

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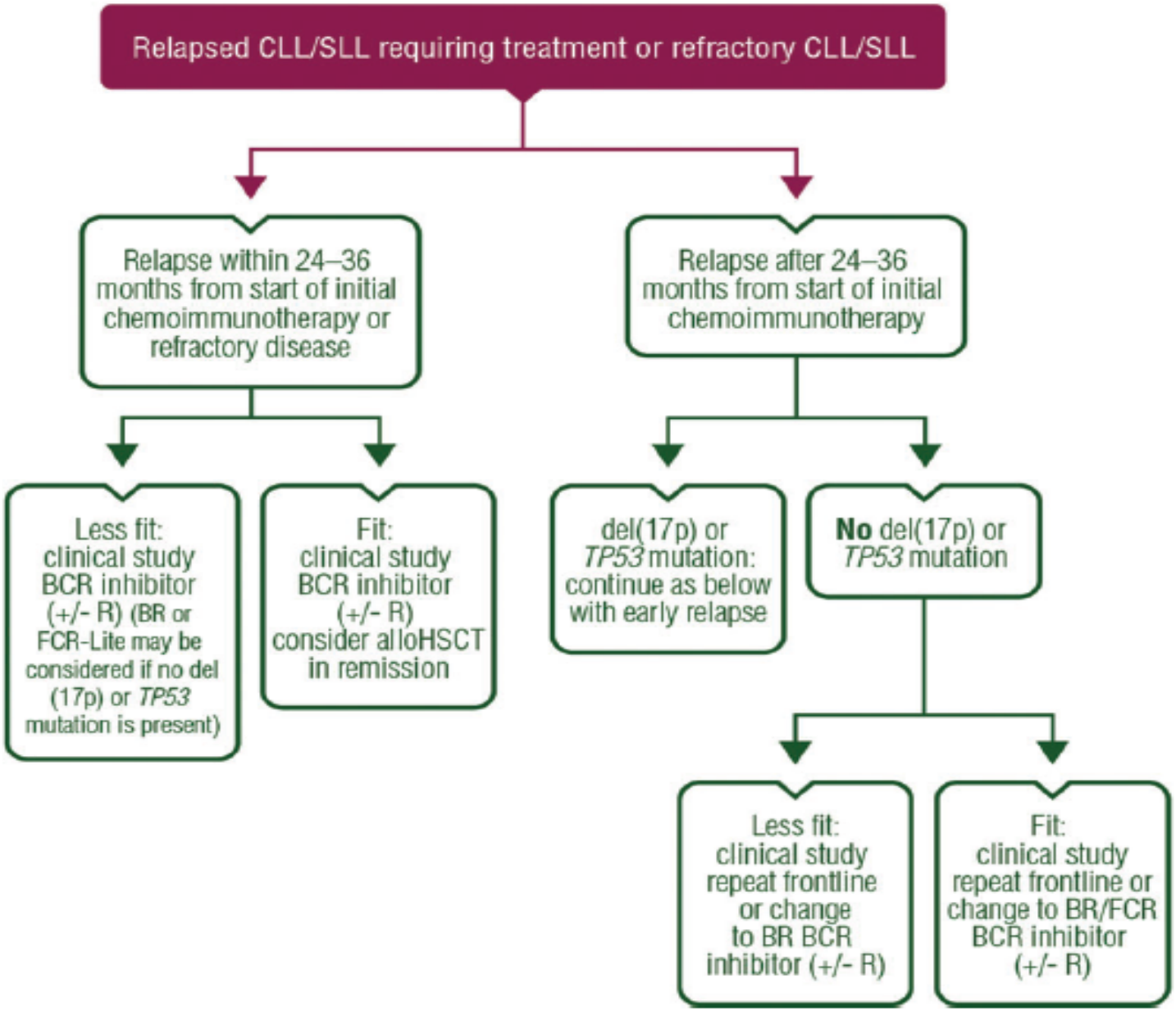

Figure 2. Relapse treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; BR, bendamustine plus rituximab; FCR, fludarabine, cyclophosphamide and rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation.

Sumber:

3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, et al. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26:v78–84.

KESIMPULAN

Leukemia kronik merupakan keganasan hematologi yang dapat dibedakan menjadi 2 tipe, yaitu CML dan CLL. Manifestasi klinis kedua leukemia tersebut tidak spesifik, sehingga memerlukan modal pemeriksaan lain. Terapi yang diberikan pun memerlukan pertimbangan-pertimbangan tertentu.

DAFTAR PUSTAKA

1. Kasper DL, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's principle of internal medicine. 19th ed. McGraw-Hill Education; 2015.
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4. Hochhaus A, Saussele S, Rosti G, Mahon F-X, Janssen J, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv41–51.

TERIMA KASIH

Jangan lupa untuk mengerjakan soal latihan ya!