Erişkin ALL'de Risk Tanımlaması, Tedavi Yönlendiriciliği

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İç Hastalıkları - Hematoloji BD.

- 1,6 / 100.000
  - Çocuklukta ve 50 yaş civarında pik

- 5 yıllık OS:
  - Çocuklarda: %86-89
  - AYA'da: %42-63
  - Erişkinlerde: 40-59 yaş; %24,1
    60-69 yaş: %17,7

- Risk değerlendirmesi – tedavi
  - farklı tedavi rejimleri (PETHEMA, CALGB, hyper-CVAD….)
  - kök hücre nakli

- Prognoz değerlendirmesi ALL tedavisi için esastır

- Prognostik faktörler
  - Yaş - lökosit sayısı
  - SSS tutulumu – ekstramedüller hastalık
  - İmmünofenotipik / sitogenetik alt tipler
  - İndüksiyon tedavisine yanıt (MRD)

- Artan yaşla prognoz kötü*
  - >60 yaşta uzun süreli sağkalım %10-15
  - kötü biyolojik özellikler de artan yaşla artar (Ph kromozomu, hipodiploidi, kompleks karyotip)
  - eşlik eden hastalıklar

- Lökosit sayısı*
  - B-ALL'de >30x10^9
  - T-ALL'de >100x10^9

*Rowe JM, Blood 2005

- **Ph (-) ALL'de* yaşa ve lökosit sayısına göre**
  - Düşük risk
    - Risk faktörü yok
    - 5 yıllık OS: %55
  - Orta risk
    - Yaş>35 veya artmış lökosit sayısı
    - 5 yıllık OS: %34
  - Yüksek risk
    - Yaş >35 ve artmış lökosit sayısı
    - 5 yıllık OS: %5

*Rowe JM, Blood 2005

- 15-21 yaş vakaların pediatrik protokollerle tedavisi ile EFS'de iyileşme[1]

- Erişkin protokoller, pediatrik protokollere göre;
  - ilik baskılayıcı olmayan tedavi daha az oranda kullanılıyor
  - intratekal kemoterapi yoğunluğu daha az
  - allonakil oranları daha fazla

- AYA vakalarının pediatrik rejimlerle tedavisi ile veriler daha iyi, ancak <10 yaşa kıyasla sonuçlar hala daha kötü
  - hastalık biyolojisi
    - iyi risk genetik anormallikler AYA hastalarında daha az
    - erişkinlerde sitogenetik sonuçlar, lökosit sayısını bağımsız risk faktörü olmaktan çıkarır

[1]Seibel NL, Hematology Am Soc Hematol Educ Program 2008

- **Klinik bulguların yanında sitogenetik özellikler de risk belirlemede önemli**
  - t(9;22) %15-50 sıklıkta (+), yaşla artar[1]
    - TKI öncesi 1 yıllık OS: %10
  - Ph-benzeri ALL[2]
  - Diğer kötü prognostik sitogenetik bozukluklar[3]
    - t(4;11)
    - *KMT2A* translokasyonu
    - t(8;14)
    - kompleks karyotip: ≥5 kromozomal anormallik
    - low hipodiploidi (30-39 kromozom) / near triploidi (60-78 kromozom)
  - İyi prognostik sitogenetik bozukluklar[4]
    - hiperdiploidi
    - del9p

[1]Faderl S, Cancer 2017
[2]Roberts KG, NEJM 2014
[3]Rowe JM, Blood 2005
[4]Moorman AV, Blood 2007

Subtype	Prevalence (%)*	Comment
B-cell precursor ALL		
Hyperdiploidy with >50 chromosomes	20-30	Excellent prognosis
Hypodiploidy with <44 chromosomes	2-3	Poor prognosis; high frequency of Ras pathway and Ikaros gene family mutations
t(12;21)(p13;q22) translocation encoding *ETV6-RUNX1*	15-25	Excellent prognosis
t(1;19)(q23;p13) translocation encoding *TCF3-PBX1*	2-6	Increased incidence in African-Americans; generally excellent prognosis; association with CNS relapse
t(9;22)(q34;q11.2) translocation encoding *BCR-ABL1*	2-4	Historically poor outcome; improved with addition of imatinib and/or dasatinib to intensive chemotherapy
Ph-like ALL	10-15	Multiple kinase-activating lesions; associated with older age, elevated white blood cell count, and *IKZF1* alteration; potentially amenable to TKI therapy
t(4;11)(q21;q23) translocation encoding *MLL-AF4* fusion	1-2	Common in infant ALL (especially age <6 mo); poor prognosis
t(8;14)(q24;q32), t(2;8)(q12;q24), t(2;8)(q12;q24) encoding; *MYC* rearrangement	2	Favorable prognosis with short-term high-dose chemotherapy
CRLF2 rearrangement (*IGH-CRLF2; P2RY8-CRLF2*)	5-7	Common in Down syndrome–associated and Ph-like ALL (~50% each); associated with *IKZF1* deletion and/or mutation and *JAK1/2* mutation and poor prognosis in non–Down syndrome–associated ALL
ERG-dysregulated ALL	~7	Distinct gene expression profile; the majority have focal ERG deletions and favorable outcome despite *IKZF1* alterations
PAX5 rearrangement	~2	Multiple partners, commonly from dic(7;9), dic(9;12), and dic(9;20)
iAMP21	~2	Complex structural alterations of chromosome 21; rarely associated with a constitutional Robertsonian translocation rob(15;21)(q10;q10)c; poor prognosis

Hunger SP, Blood 2015

T-lineage ALL		
t(1;7)(p32;q35) and t(1;14)(p32;q11) translocations and interstitial 1p32 deletion; *TAL1* dysregulation	15-18	Generally favorable outcome
t(11;14)(p15;q11) translocation and 5′ *LMO2* deletion; LMO2 dysregulation	10	Generally favorable outcome
t(10;14)(q24;q11) and t(7;10)(q35;q24) translocations; *TLX1 [HOX11]* dysregulation	7	Good prognosis
t(5;14)(q35;q32) translocation; *TLX3* dysregulation	20	Commonly fused to *BCL11B*, also a target of deletion and/or mutation; poor prognosis
t(10;11)(p13;q14) translocation; *PICALM-MLLT10 [CALM-AF10]*	10	May have poor outcome
MLL-MLLT1 [MLL-ENL]	2-3	Superior prognosis to other types of *MLL*-rearranged leukemia
9q34 amplification encoding *NUP214-ABL1*	6	Potentially amenable to TKIs, also identified in high-risk B-ALL; other kinase fusions identified in T-ALL include *EML1-ABL1*, *ETV6-JAK2*, and *ETV6-ABL1*
t(7;9)(q34;q34) translocation	<1	Rearrangement of *NOTCH1*; also sequence mutations in >50% T-ALL
Early T-cell precursor ALL	10-15	Immature immunophenotype; expression of myeloid and/or stem cell markers; historically poor outcome, although improved in recent studies; genetically heterogeneous with mutations in hematopoietic regulators, cytokine, and Ras signaling, and epigenetic modifiers

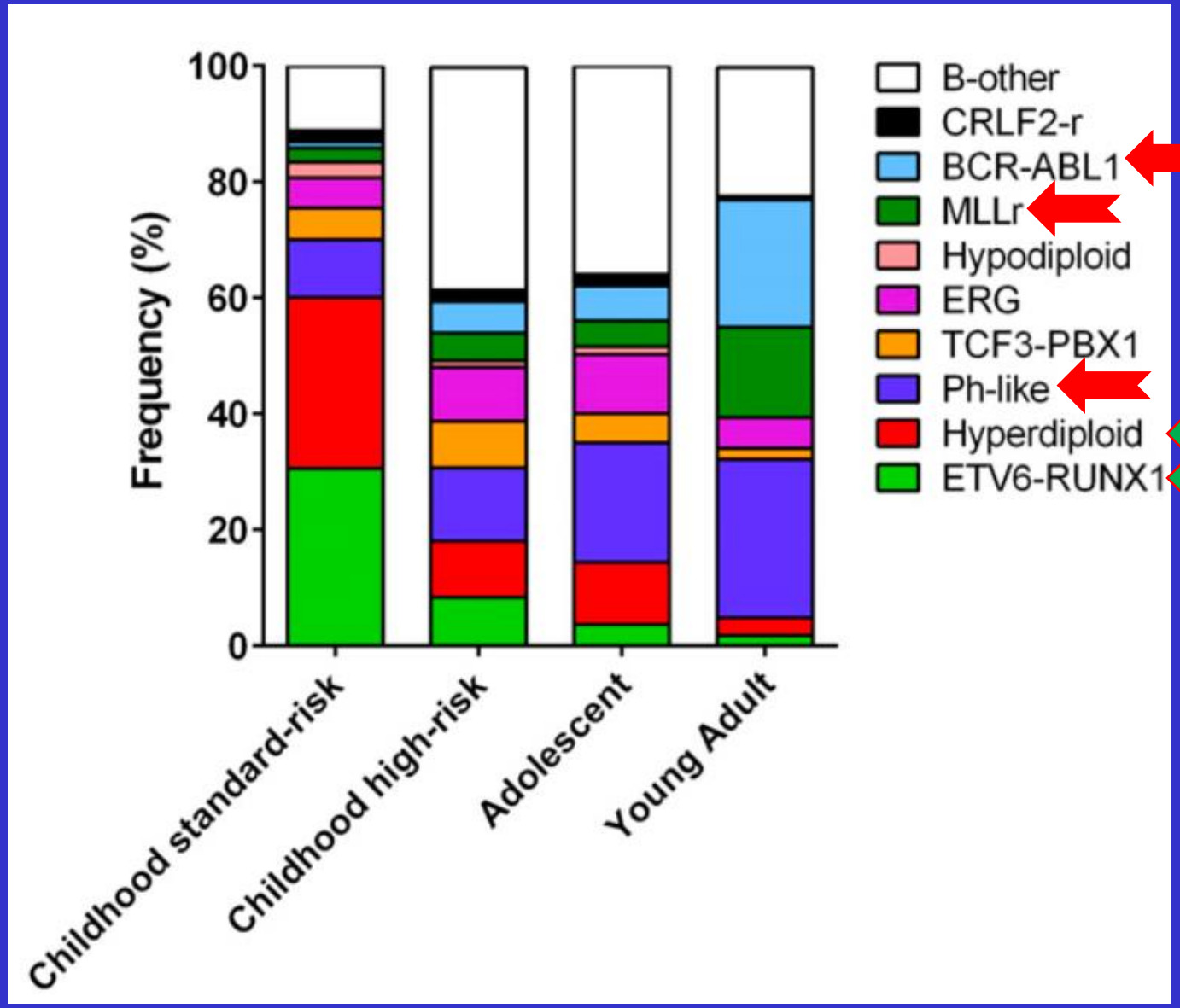
Hunger SP, Blood 2015

Chromosome / Genetic Abnormalities	Genes	Prognosis
t(12,21)(p13;q22)	*ETV6-RUNX1*	Excellent
t(1;19)(q23;p13)	*TCF3-PBX1*	Children: intermediate/good Adults: intermediate/poor Infants: very poor
t(17;19)(q22;p13)	*TCF3-HLF*	Extremely poor
MLL (11q23) translocations	*MLL* gene	Poor
t(9;22)(q34;q11.2)	*BCR-ABL1*	Very poor (unless treated with tyrosine kinase inhibitors)
IGH (14q32) translocations	*IGH* gene	Poor
CRLF2 alterations	*CRLF2* gene	Children: Intermediate/ poor Adolescents & young adults: poor
iAMP21		Very poor (unless treated on high risk protocol)
Complex karyotype (> 4 chr abnormalities)		Very poor
Near haploidy (<30 chrs)		Very poor
Low hypodiploidy/ near triploidy (30-39/ 60-78 chrs)		Very poor
High hyperdiploidy (51-65/67 chrs)		Excellent

Meng CY, Int J Biomed Sci 2015

Cytogenetics	Gene	Frequency in Adults	Frequency in Children
Hyperdiploidy (>50 chromosomes)	--	7%	25%
Hypodiploidy (<44 chromosomes)	--	2%	1%
t(9;22)(q34;q11): Philadelphia chromosome (Ph)	*BCR-ABL1*	25%	2%–4%
t(12;21)(p13;q22)	*ETV6-RUNX1 (TEL-AML1)*	2%	22%
t(v;11q23) [eg, t(4;11), t(9;11)], t(11;19)	*MLL*	10%	8%
t(1;19)(q23;p13)	*TCF3-PBX1 (E2A-PBX1)*	3%	6%
t(5;14)(q31;q32)	*IL3-IGH*	<1%	<1%
t(8;14), t(2;8), t(8;22)	*c-MYC*	4%	2%
t(1;14)(p32;q11)	*TAL-1*[a]	12%	7%
t(10;14)(q24;q11)	*HOX11 (TLX1)*[a]	8%	1%
t(5;14)(q35;q32)	*HOX11L2*[a]	1%	3%
t(11;14)(q11) [eg, (p13;q11), (p15;q11)]	*TCRα and TCRδ*	20%–25%	10%–20%
BCR-ABL1-like	*various*[b]	10%–30%	15%
ETP	*various*[a]	2%	2%
Ikaros	*IKZF1*	50%	12%–17%

[a]Abnormalities observed exclusively in T-cell lineage ALL; all others occur exclusively or predominately in B-cell lineage ALL. [b]See text for more details.



Hunger SP, Blood 2015

CYTOGENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	CYTOGENETICS
Good risk	Hyperdiploidy (51–65 chromosomes; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): ETV6-RUNX1
Poor risk	Hypodiploidy (<44 chromosomes); t(v;11q23):t(4;11) and other KMT2A rearranged t(--;11q23); t(9;22)(q34;q11.2): BCR-ABL1 (defined as high risk in the pre-TKI era); complex karyotype (5 or more chromosomal abnormalities); Ph-like ALL; intrachromosomal amplification of chromosome 21 (iAMP21)

NCCN, 2.2017

WHO - 2016

B-cell lymphoblastic leukemia/lymphoma, not otherwise specified

B-cell lymphoblastic leukemia/lymphoma, with recurrent genetic abnormalities

- B-cell lymphoblastic leukemia/lymphoma with hypodiploidy
- B-cell lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-cell lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2)[*BCR-ABL1*]
- B-cell lymphoblastic leukemia/lymphoma with t(v;11q23)[*MLL* rearranged]
- B-cell lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22)[*ETV6-RUNX1*]
- B-cell lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3)[*TCF3-PBX1*]
- B-cell lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32)[*IL3-IGH]*
- B-cell lymphoblastic leukemia/lymphoma with intrachromosomal amplification of chromosome 21 (iAMP21)[b]
- B-cell lymphoblastic leukemia/lymphoma with translocations involving tyrosine kinases or cytokine receptors ('BCR-ABL1–like ALL')[b]

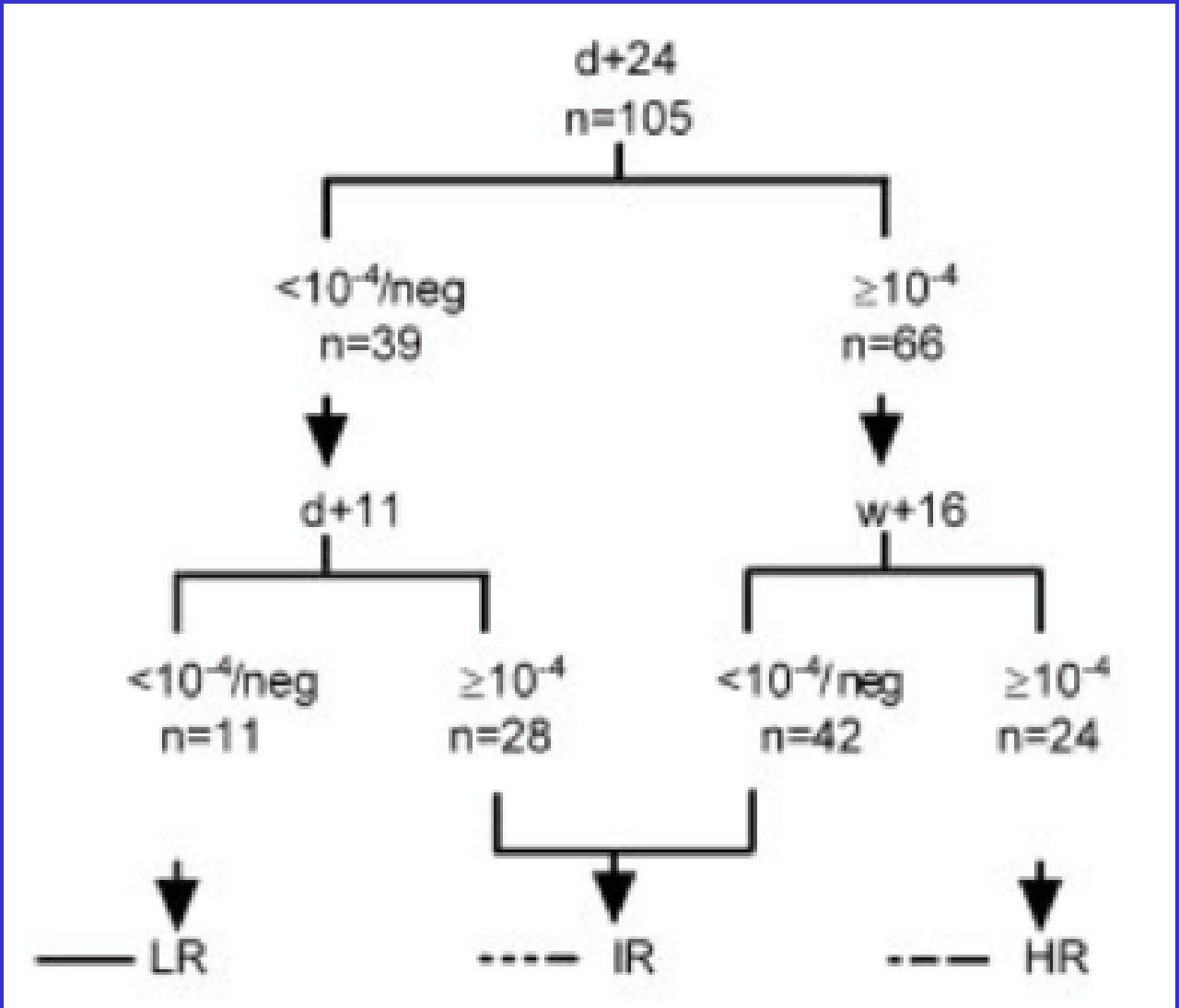
T-cell lymphoblastic leukemia/lymphomas

- Early T-cell precursor lymphoblastic leukemia[b]

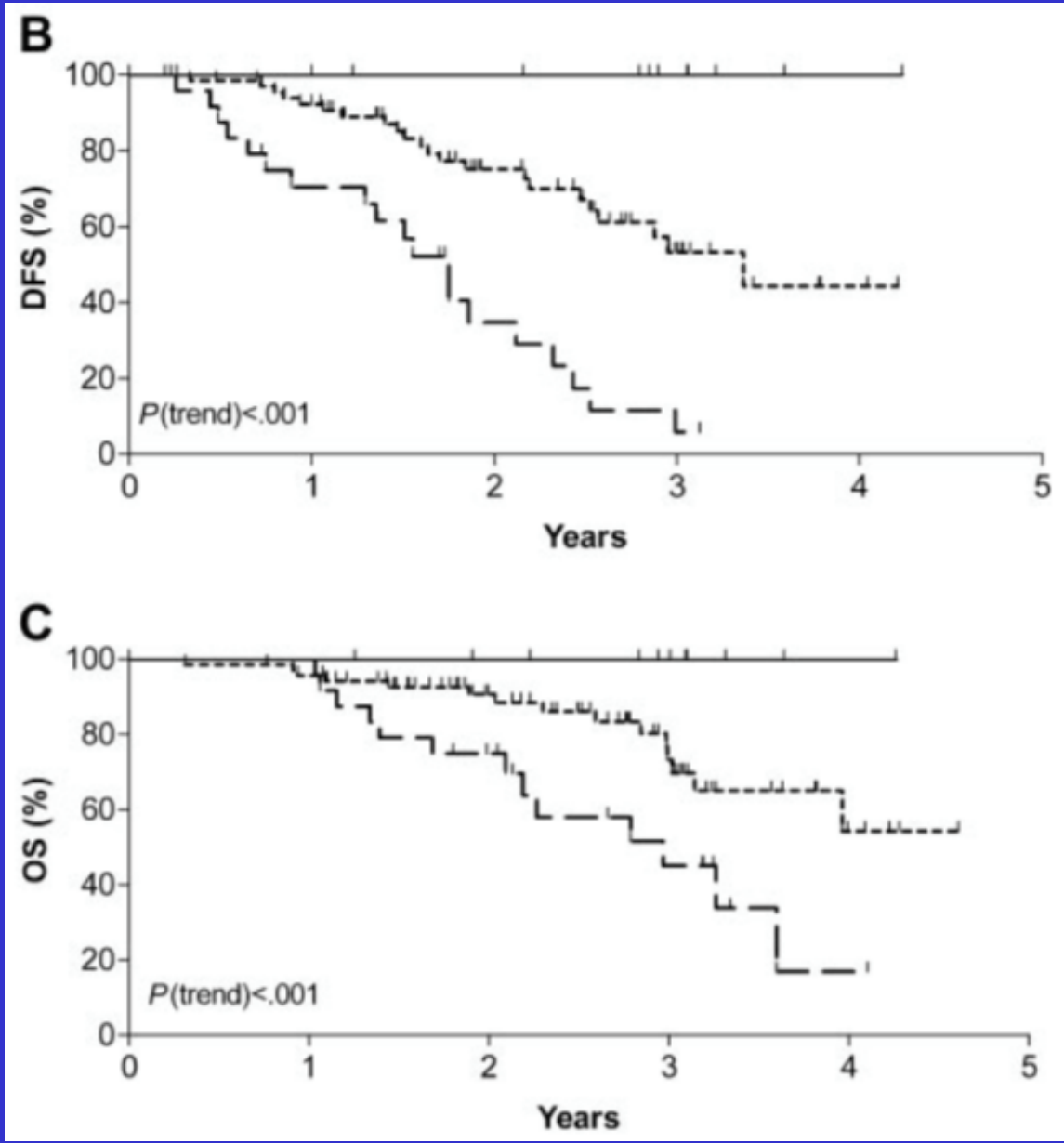
- **Başlangıç tedaviye yanıt - MRD**
  - Çok renkli akım sitometri – PCR
    - ikisinin kullanımı yanlış (-) sonuçları önleyebilir
  - Standart risk grubundaki hastalarda MRD, indüksiyon sonrası nüksün bağımsız göstergesidir

- AYA vakalarında COG AALL0232 çalışması[1]
  - 16-30 yaş vakalarda 1-15 yaş grubuna kıyasla indüksiyon sonrası MRD (-)'liği %59'a karşı %74 ($p<0.001$)
  - 15. günde kemik iliğinde M1 %67'ye karşı %80 ($p=0,015$)

[1]Raetz EA, J Clin Oncol 2010 (abstract)



*Brüggemann M, Blood 2006



*Brüggemann M, Blood 2006

Sonuç

- Hangi rejimi seçmeliyiz?
- Allo nakil ile konsolidasyonu kimlere yapmalıyız?
  - yaş, lökosit sayısı, sitogenetik inceleme, MRD
- Hastalar AYA – erişkin vakalar diye ayrılmalı!
  - sitogenetik alt gruplar belirlenmeli
- Sitogenetik analiz (Ph (-) / (+) ve diğer risk parametreleri)
  - Ph (-) olanlarda yüksek risk yaratan diğer sitogenetik alt tipler belirlenmeli
    - MLL, t(4;11), Ph-benzeri, kompleks karyotip…..
- MRD (+) ise yüksek risk olarak değerlendirilmeli


MEÜ TIP FAKÜLTESİ HASTANESİ