Bifenotipik Lösemi Tanı ve Tedavi

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Mikst fenotipik akut lösemi (MFAL)

- Birden fazla hücre dizisine ait antijenler taşıması nedeni ile tek bir hücre dizisi ile kesin bağlantısı kurulamayan lösemiler

  ° İki ayrı hücre dizisine ait farklı blast toplulukları (eski tanıma göre bilineage veya bilineal)

  ° Tek bir blast topluluğunda farklı hücre dizilerine ait çok sayıda antijen taşıyan akut lösemiler (eski tanıma göre bifenotipik)

  ° İkisinin karışımı olabilir

  ° Bilineal ve bifenotipik löseminin ayırımı sıklıkla net değil-2 farklı popülasyon tek bir kök hücrenin alt klonundan kaynaklanabilir. Ayırım genellikle tanısal yaklaşım veya tedaviyi etkilemez

WHO 2008

Acute leukemias of ambiguous lineage

- Acute undifferentiated leukemia
- Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*
- Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
- Mixed phenotype acute leukemia, B-myeloid, NOS
- Mixed phenotype acute leukemia, T-myeloid, NOS
- *Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma*

B lymphoblastic leukemia/lymphoma

- B lymphoblastic leukemia/lymphoma, NOS
- B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
  - B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2);*BCR-ABL 1*
  - B lymphoblastic leukemia/lymphoma with t(v;11q23);*MLL* rearranged
  - B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1*)
  - B lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B lymphoblastic leukemia/lymphoma with hypodiploidy
  - B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH*
  - B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*

T lymphoblastic leukemia/lymphoma

- Akut indifferansiye lösemi
- Mikst fenotipik akut lösemi, t(9;22)(q34;q11.2); BCR-ABL1 ile birlikte
- Mikst fenotipik akut lösemi, t(v;11q23); MLL yeniden düzenlenmesi ile birlikte
- Mikst fenotipik akut lösemi, B/miyeloid, ayrıca tanımlanmamış
- Mikst fenotipik akut lösemi, T/miyeloid, ayrıca tanımlanmamış
- *Doğal öldürücü (NK) hücre lenfoblastik lösemi/lenfoma*

WHO 2016

WHO myeloid neoplasm and acute leukemia classification
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Arber DA et al. Blood. 2016;127:2391-405

EGIL 1995 Skorlama Algoritm

Table 1. European Grou
Characterization of A
Algorithm for

Points	B
2	
1	
	13
	CD33
	CDw65
	CD14
	CD15
	CD64

[a]Ac ia (BAL) is diagnosed when scores are >2 for the myelo marker is considered positive if more than 20% of cells stain posi y; a lower threshold of 10% was set for MPO, CD3, CD79a and TdT.

Güncel sınıflamada miyeloid, T-lenfoid ve B-lenfoid komponentleri tanımlamak için kullanılacak kriterler önemli derecede değiştirilmiştir: CD13, CD33 ve CD117 MFAL tanısı için miyeloid seriye özgü kabul edilmemektedir

Bene MC et al. Leukemia. 1995;9:1783-1786

MFAL Sınıflandırılması

Sitogenetik bulgulara göre

- **Ph-pozitif MFAL:**
  t(9;22)(q34.1;q11.2) ve/veya *BCR-ABL1* ile ilişkili MPAL

- **Ph-nega**

  Diğer tü
  MFAL olgu

WHO 2016 ka öre

Tek bir
po

İmmünfenotipik özelliklerine göre birden fazla hücre dizisine özgü antijenleri taşıyan bazı miyeloid lösemiler eğer genetik veya klinik olarak tekrarlayan t(8;21), t(15;17) inv(16), FGFR1 mutasyonu, t(AML), kompleks karyotip, MDS ilişkili AML (monozomi 5, 7) gibi başka bir kategoriye giriyorsa MFAL kabul edilmez. Kronik miyeloid löseminin blastik fazı da MFAL'ye dahil edilmez

mün histokimya veya sitokimya ile)

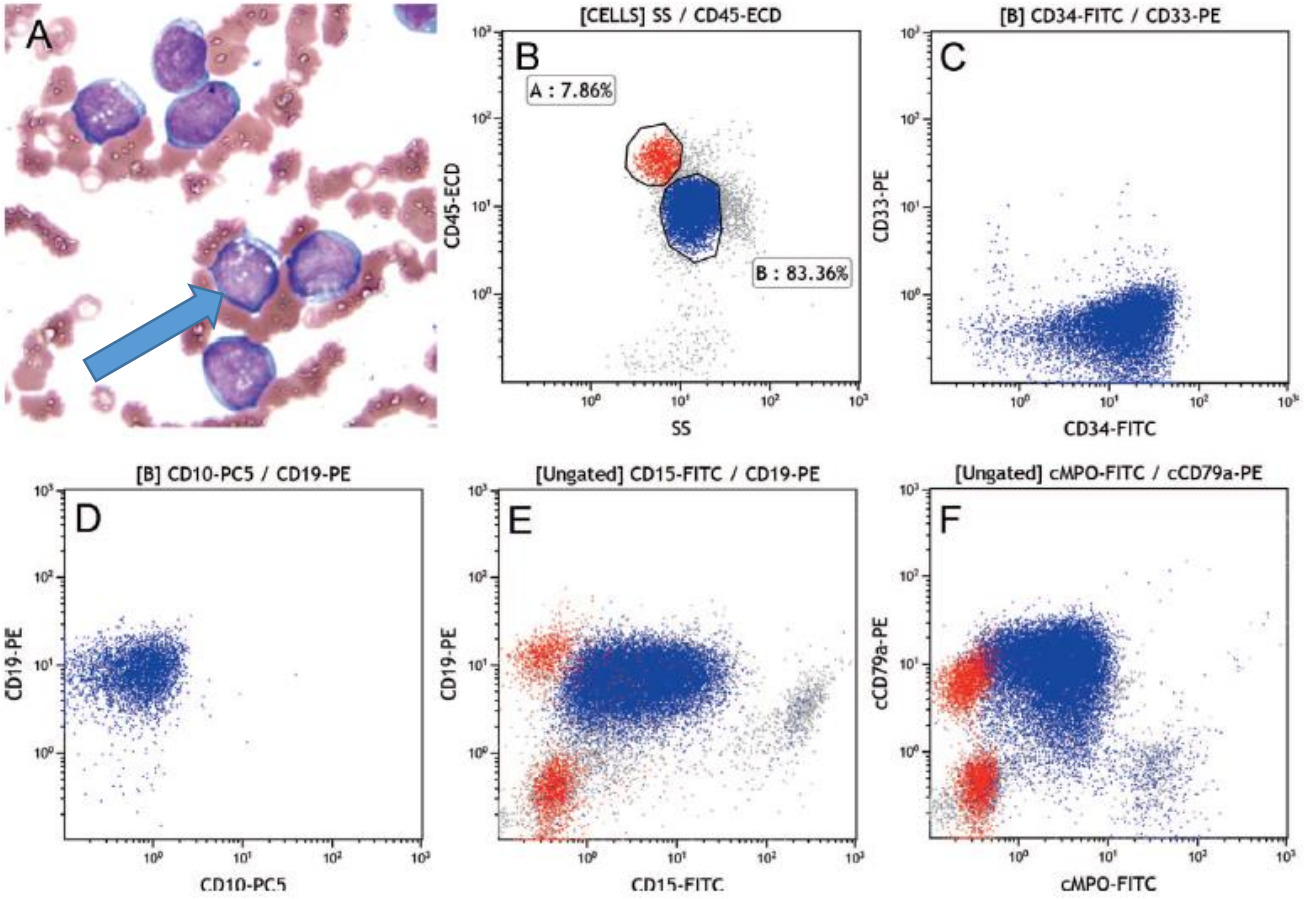
spesifik esteraz, CD11c, CD14, CD64 ve lizozimden en az

zmik CD3
veya
Yüzey CD3 (mikst fenotip akut lösemide nadir)

- B hücre dizisi (birden fazla antijen gerekir)

Kuvvetli CD19 ile CD79a, sitoplazmik CD22 veya CD10'dan en az biri kuvvetli olarak
veya
Zayıf CD19 ile CD79a, sitoplazmik CD22 ve CD10'dan en az ikisi kuvvetli olarak

MFAL, B/miyeloid (Bifenotipik)



Periferik yayma: düzensiz nükleer çekirdek ve nadir stoplazmik vakuol içeren çeşitli büyük blastlar

FCM: güçlü CD19, sCD79(+), miyeloid marker CD15(+), cMPO(+)

MFAL-Sitogenetik anormallik

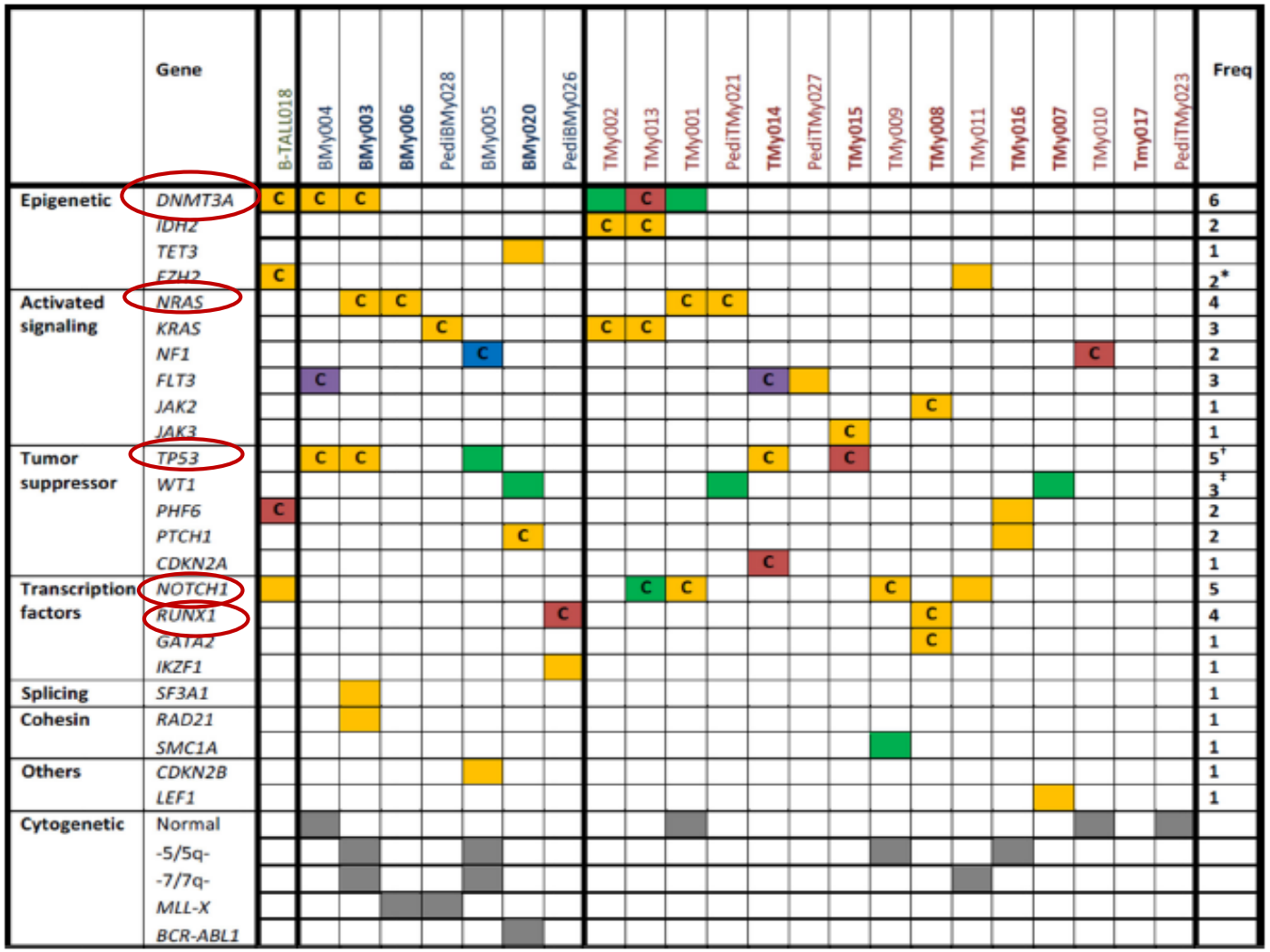
Table II. Recurrent cytogenetic abnormalities in MPAL in relation to genes involved, age groups, immunophenotype, prognosis and diagnostic criteria.

Chromosome abnormality	Genes involved	Age groups	Immunophenotypic features	Prognosis	Criteria	Occurs also in AML or ALL
del(1)(p32)	*STIL-TAL1*	Adults and children	M+B	Unknown	WHO 2008/EGIL	T-ALL
t(2;5)(p13;p13–15.3)	NA	Children	M+B, M+T	Rather good	WHO 2008/EGIL	None
t(3;11)(q13;p15)	*NUP98-IQCG*	Adults	M+T	Unknown	WHO 2008/EGIL	AML
Trisomy 4	Multiple	More common in children than adults	M+T, M+B, M+B+T	Rather good	WHO 2008/EGIL	Mainly in AML but also in ALL
t(4;11)(q21;q23)	*MLL-MLLT2*	More common in infants and children than adults	Most M+B but also M+T or B+T	Poor	WHO 2008/EGIL	Mainly in ALL but also in AML
t(4;12)(q12;p13)	*ETV6* rearrangement	Children	B+M	Poor	EGIL	AML
−5/del(5q)	Multiple	Adults and children	B+T, M+T	Poor	WHO 2008/EGIL	AML
del(6q)	Multiple	Children and young adults	M+T, M+B, M+B+T	Rather good	WHO 2008/EGIL	Mainly in ALL
t(6;14)(q25;q32)	NA	More common in children than adults	M+T	Not bad	EGIL	ALL
Monosomy 7	Multiple	More common in adults	M+B, M+T	Rather poor	WHO 2008/EGIL	AML
del(7q)	Multiple	More common in children	M+B, M+T	Unknown	WHO 2008/EGIL	AML
abn(7p)	Multiple	Children and adults	M+T or M+B	Unknown	WHO 2008/EGIL	AML & ALL
t(7;12)(q36;p13)	*HLXB9-TEL*	Infants	M+T	Poor	WHO 2008/EGIL	AML
Trisomy 8	Multiple	Children and adults	M+T, B+M	Rather good	WHO 2008/EGIL	AML
Polysomy 8	Multiple	Adults	M+B	Unknown	WHO 2008/EGIL	AML
t(8;12)(q13;p13)	*ETV6 – NCOA2*	Children	M+T	Decent	EGIL	AML
t(8;14)(p21;q32)		Children	M+T	Unknown	WHO 2008/EGIL	ALL
t(8;21)(q22;q22)	*RUNX1-RUNX1T1*	Most common in adults	M+B	Worse than AML	EGIL	AML
t(9;11)(p22;q23)	*MLL-MLLT3*	Children, infants and adults	M+B	Poor	WHO 2008/EGIL	AML
t(9;22)(q34;q11.2)	*BCR-ABL1*	More common in adults than in children	Most B+M, also M+T or M+B+T	Poor	WHO 2008/EGIL	Mainly in ALL but also in AML
t(10;11)(p12;q23)	*MLL-MLLT10*	More common in children and infants	M+B and M+T	Poor	WHO 2008/EGIL	AML
t(10;11)(p15;q21)	*PICALM/MLLT10*	Adults	M+T and B+M	Unknown	WHO 2008/EGIL	ALL & AML
t(v;11q23)	*MLL*	More common in children/infants than in adults	Most B+M but also M+T or B+T	Poor	WHO 2008/EGIL	ALL & AML
t(11;19)(q23;p13)	*MLL-MLLT1*	More common in children/infants and young adults	Most B+M but also B+T	Poor	WHO 2008/EGIL	More common in AML than in ALL
del(12p)	*ETV6*	Children	Most M+T, also B+M or B+T+M	Poor	WHO 2008/EGIL	ALL & AML
t(12;21)(p13;q22)	*ETV6-RUNX1*	Children	NA	Good	WHO 2008/EGIL	ALL
t(12;22)(p13;q12)	*EWSR1 – ZNF384*	More common in adults than children	M+B	Rather poor	EGIL	ALL
add(14)(q32)	*IGH*	Children	Most M+T but also M+B+T	Good to intermediate	WHO 2008/EGIL	ALL
i(17)(q10)	Multiple	Children and adults	M+T	Unknown	WHO 2008/EGIL	AML & ALL
Trisomy 19	Multiple	Children and young adults	M+T	Unknown	WHO 2008/EGIL	AML
Trisomy 21	Multiple	Children and adults	M+B	Unknown	EGIL	AML & ALL
Polysomy 21	Multiple	Adults	M+T and M+B	Unknown	WHO 2008	ALL & AML
Hyperdiploidy	Multiple	Children	M+B, M+T or B+T+M	Good	WHO 2008/EGIL	ALL
Complex karyotypes	Multiple	More common in adults than children	M+B, M+T and less frequently with B+T	Poor	WHO 2008/EGIL	AML & ALL

Sitogenetik anormallik: %59-91

MFAL-Artmış somatik mutasyon

Eckstein OS et al. Exp Hematol. 2016;44(8):740-4.



23 pediatrik+erişkin MPAL: 6/23 DNMT3A mutasyonu (%26), TP53 mutasyonu %22, NOTCH1 mutasyonu %22, NRAS mutasyonu:%17, RUNX1 mutasyonu:%17

MFAL Epidemiyolojisi

- ✓MPAL nadir
- ✓Gerçek insidensi bilinmiyor
- ✓Retrospektif çalışmalara göre tüm akut lösemilerin <%3'ünde
- ✓MPAL yetişkinlerde çocuklara göre daha sık
- ✓Bimodal yaş dağılımı: 19 yaş ve ≥60 yaş
- ✓Erkeklerde daha sık (1.5:1)
- ✓MPAL B/miyeloid, NOS: MPAL'ın 2/3'ü
- ✓Ph-pozitif MPAL: MPAL'ın 1/4'ü

Phelan KW et al. Curr Hematol Malig Rep. 2018;13:289-299

Weinberg ve Arber retrospektif derlemesi

Table 5 Analysis of the frequency of EGIL biphenotypic AL and MPAL using WHO criteria in prior studies

Study	*Total number of cases*[a]	*Number of biphenotypic AL patients using EGIL criteria*	*Number of MPAL patients using the 2008 WHO criteria (prevalence %)*	*Adults, pediatric or both*
Killick *et al.* [34]	693	25	18 (2.6)	Both
Legrand *et al.* [40]	287	23	7 (2.4)	Adults
Weir *et al.* [2]	1477	19	13 (0.9)	Both
Xu *et al.* [36]	452	21	10 (2.2)	Both
Owaidah *et al.* [35]	676	23	7 (1.0)	Both
Rubnitz *et al.* [38]	1855	35	19 (1.0)	Pediatric
Lee *et al.* [39]	1554	43	34 (2.2)	Adults
Al-Seraihy *et al.* [33]	633	24	11 (1.7)	Pediatric
	7627	213	119 (1.6)	

7627 pediatrik+adult erişkin akut lösemi
EGIL skorlaması: %2.8 BAL, WHO 2008: %1.6 MPAL

Weinberg OK et al. Leukemia. 2010;24(11):1844-1851.

MFAL Prognostik Faktörler

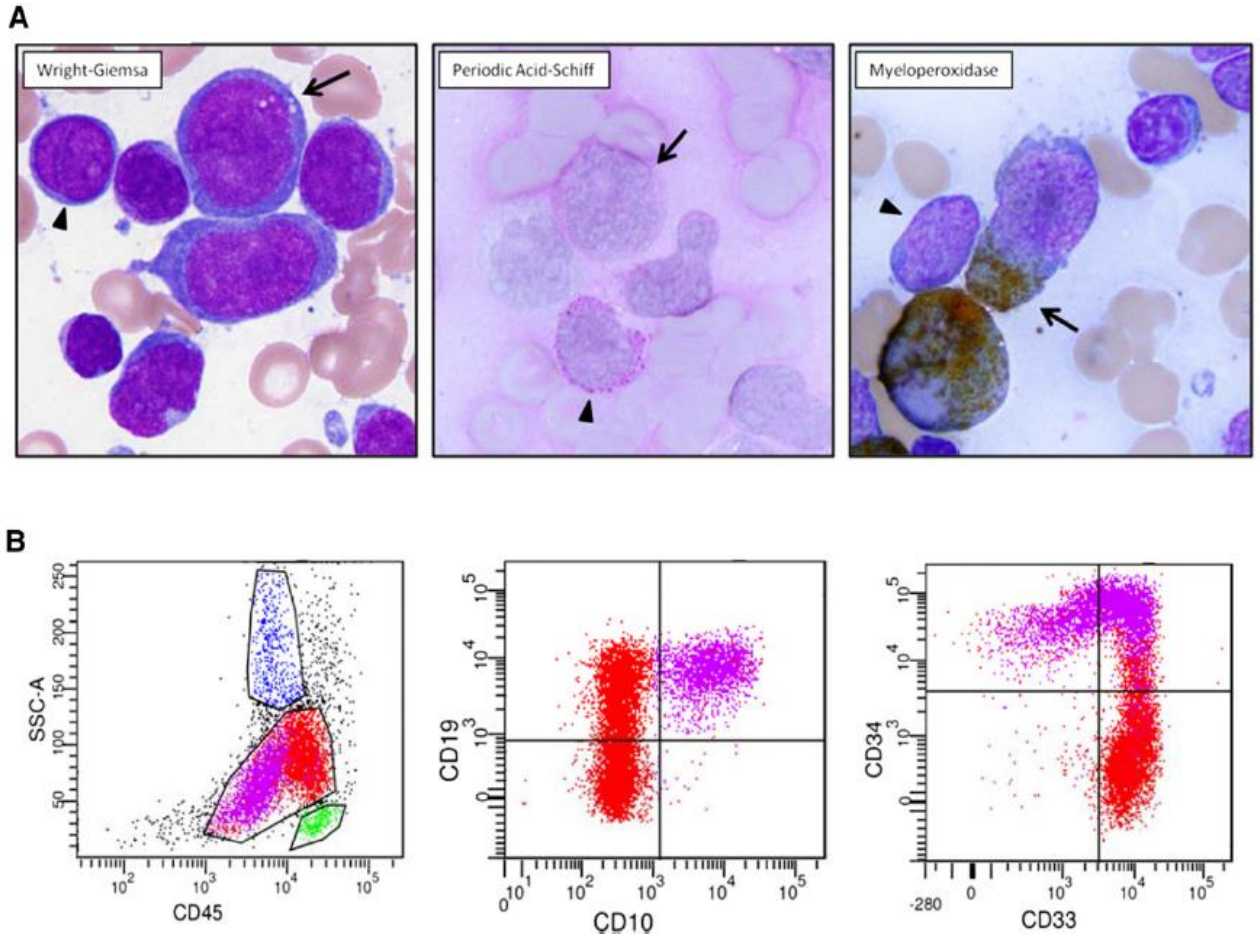
- İleri yaş
- Tanıda yüksek lökosit sayısı
- Kötü sitogenetik ve KMT2A rearanjmanı varlığı
- Remisyon elde edilememesi
- Bir yazıda T/miyeloid MFAL; B/miyeloid MFAL'a göre daha kötü prognozlu

Ph(+) MFAL'da TKI varlığında prognostik önem belirsizdir

Matutes E, et al. Blood 2011;117:3163
Lee JH, et al. Leuk Lymphoma 2008;49:700
Getta BM, et al. Biol Blood Marrow Transplant 2017; 23:1879
Legrand O, et al. Br J Haematol 1998;100:147

Olgu

- 51 yaşında erkek hasta
- Şikayeti: 2 haftadır egzersiz dispnesi
- Kan sayımı: lökosit: 280.000/mm^3 (%76 blast), trombosit:91.000/mm^3, Hgb 9 g/dl



Kemik iliği aspirasyonu: 2 ayrı morfolojik/sitokimyasal blastik popülasyon (MPO ve PAS pozitif)

Akım sitometri: 2 atipik blast popülasyonu (1) B lenfoid belirteçlerinden CD19 ve CD10 pozitif, CD34 pozitif ve değişken derecede miyeloid belirteç CD33 pozitif, (2) CD33, CD34 , değişken derecede CD19 pozitif, CD10 negatif

- Kemik iliği sitogenetik: 20 metafazda t(9;22)(q34;q11.1) translokasyonu
- Moleküler analiz: e1a2 BCR-ABL transkripti (p190)

TEDAVİ?

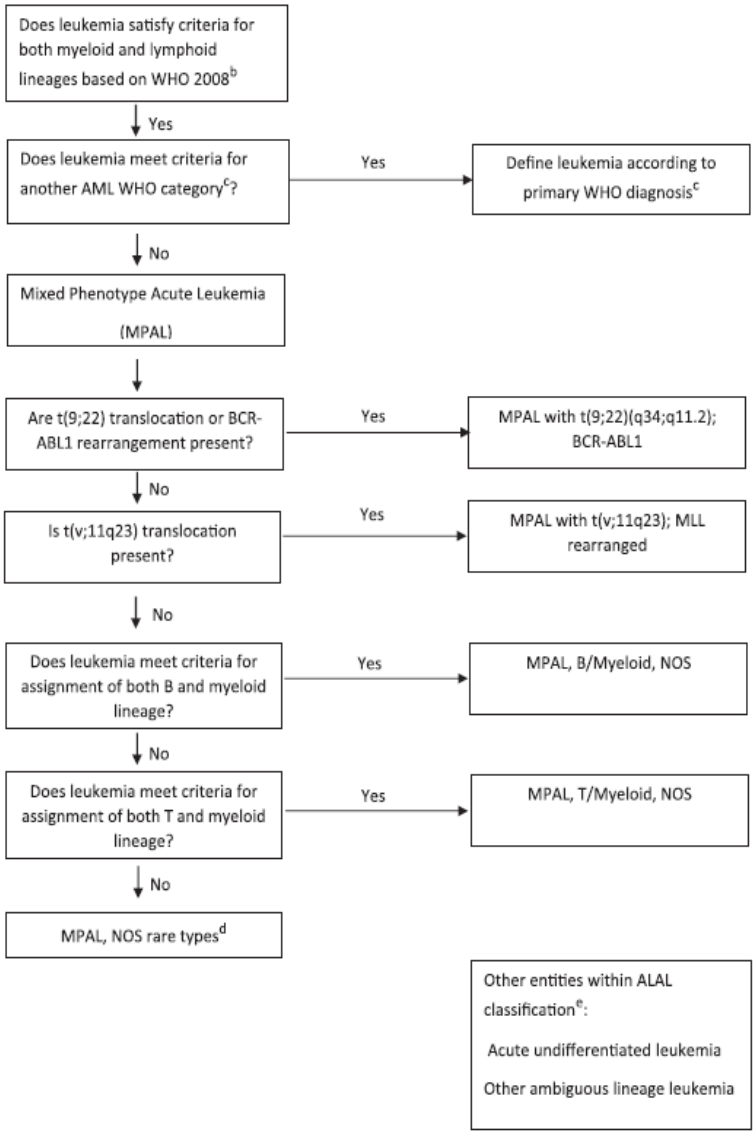
MFAL Optimal Tedavisi bilinmiyor

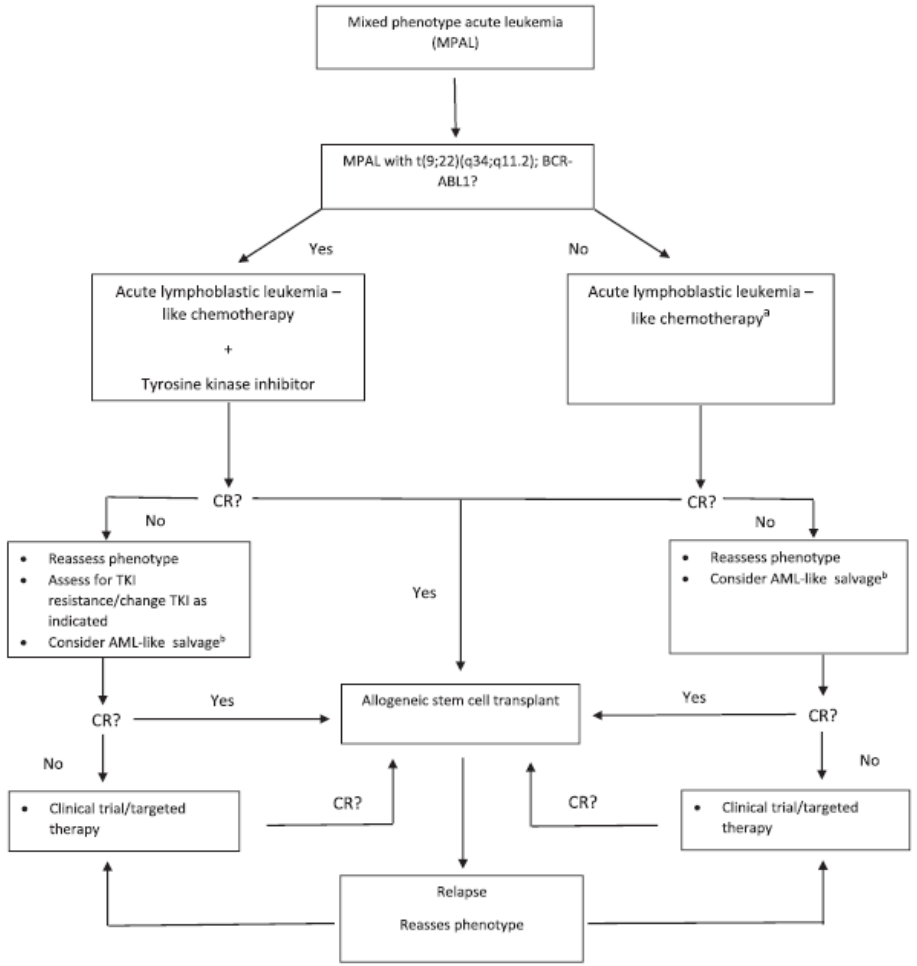
- Nedenleri
- Sınıflandırmadaki zorluklar
- Tedavi sonuçlarını karşılaştıran prospektif veri yokluğu
- TR1'de allogeneik nakil yapılması konsolidasyon kemoterapisi ile karşılaştırıldığında artmış sağkalım ile ilişkili

Wolach O et al. Curr Opin Hematol. 2017;24(2):139-145.

MFAL Tedavi Algoritması

Wolach O et al. Blood. 2015;125(16):2477-85.





[a]Consider pediatric inspired protocol if <40 years old (in which case transplant in first remission not generally indicated)

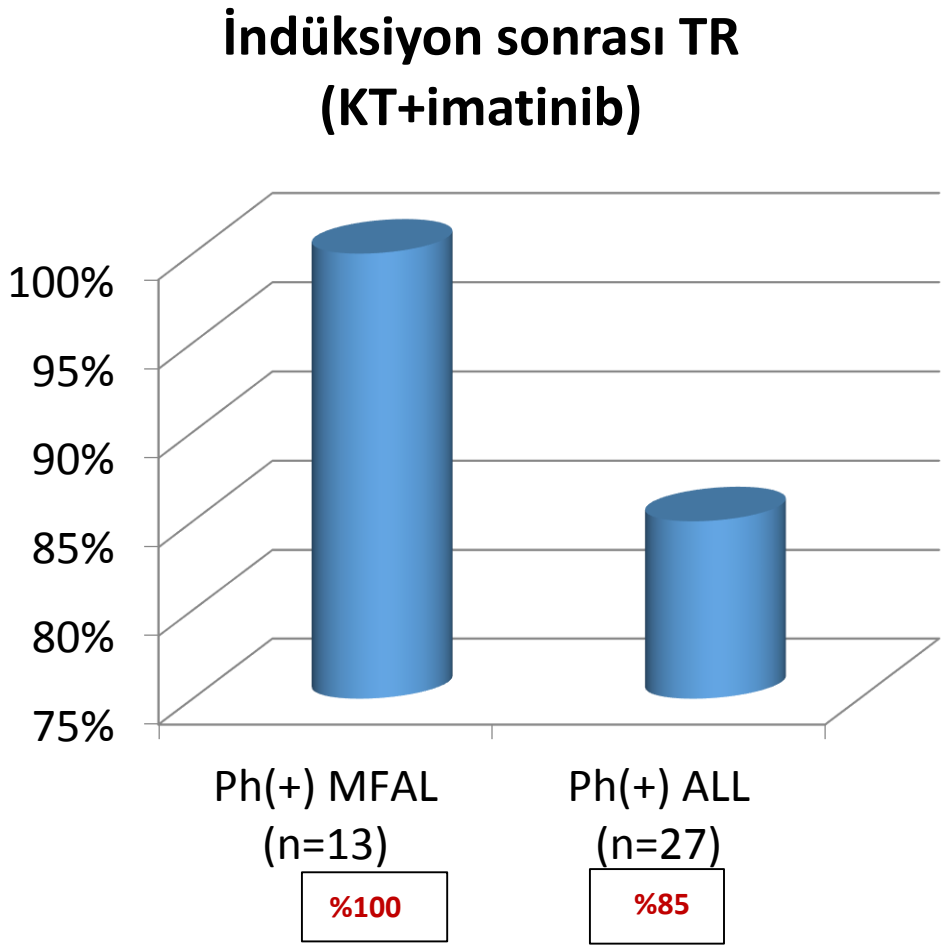
[b]For example High-dose cytarabine and mitoxantrone (HAM).

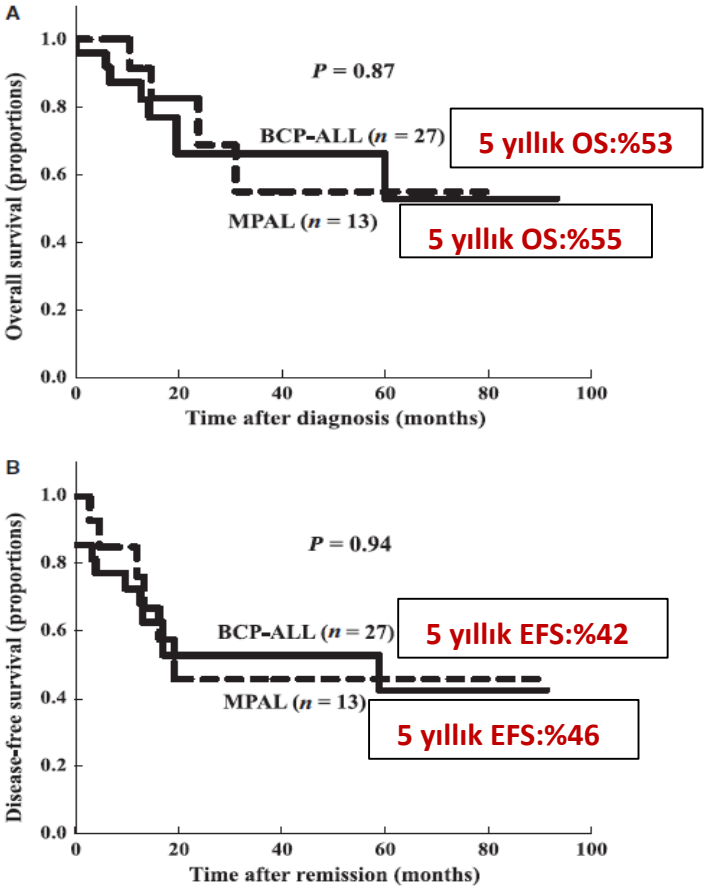
ALL'de Yaş Tanımı

- Çocuk: <15 yaş
- AYA: 15/21-**15/39** yaş
- Erişkin: 40/64 yaş
- Yaşlı: ≥65 yaş

Fit ALL için yaş sınırı 65 olmakla beraber performans durumu, uç organ fonksiyonu ve uç organ rezervi önemlidir

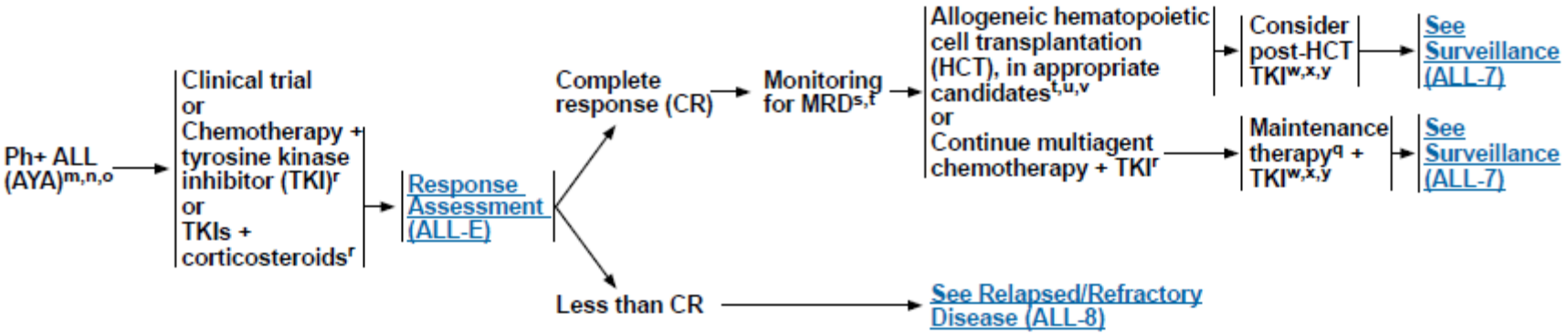
Ph(+) MFAL ile Ph(+) ALL sağkalımı benzer…





Shimizu H et al. Eur J Haematol 2014; 93:297

Ph(+) MFAL tedavisi
çoğunlukla Ph(+) ALL çalışmalarına dayalı



[m]Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.

[n]For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

[o]It is reasonable to approach the initial treatment of blast phase CML with similar strategies to Ph+ ALL, with a goal of proceeding to HCT.

[p]All ALL treatment regimens include CNS prophylaxis.

[q]See Principles of Supportive Care (ALL-C).

[r]See Principles of Systemic Therapy (ALL-D).

[s]See Minimal/Measurable Residual Disease Assessment (ALL-F).

[t]Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.

[u]Data suggest that for younger patients (aged ≤21 y), allogeneic HCT may not offer an advantage over chemotherapy + TKIs. Schultz KR, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. J Clin Oncol 2009;27:5175-5181; Schultz KR, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia 2014;28:1467-1471.

[v]Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

[w]See Discussion for use of different TKIs in this setting.

[x]The recommended duration of TKI after HCT is at least one year. The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy. The optimal duration of TKI is unknown in both settings.

[y]Consider periodic MRD monitoring (no more than every 3 months) for patients with complete molecular remission (undetectable levels). Increased frequency may be indicated for detectable levels.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TKI varlığında Ph(+) ALL seyri

- İmatinib veya dasatinib+standard çoklu ajan kemoterapisi: uzun süreli PFS:%40-60 (Erişkin Ph(-) ALL ile benzer)

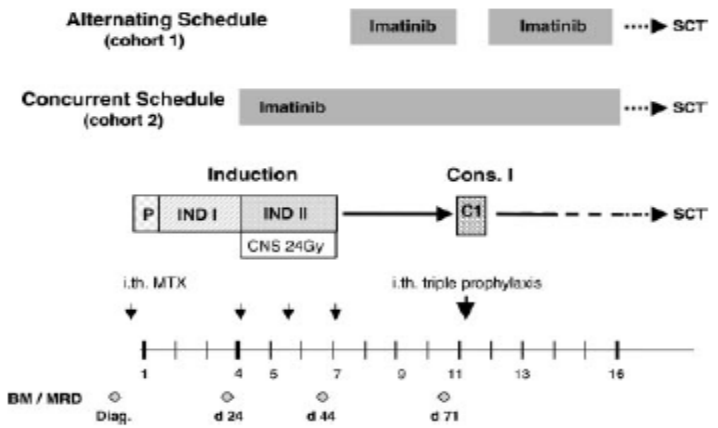


Figure 1. Study design indicating the 2 schedules of imatinib administration in conjunction with the GMALL protocols 06/99 and 07/03. P indicates prephase; INDI, induction phase 1; INDII, induction phase 2; C1, consolidation phase 1; SCT, stem cell transplantation; CNS 24 Gy, CNS irradiation, scheduled by protocol in patients having achieved a CR after INDI; ith, intrathecal chemotherapy; MTX, methotrexate; BM, bone marrow analysis; MRD, minimal residual disease analysis; and diag, diagnosis.

Wassmann B et al. Blood. 2006;108(5):1469-1477.

Thomas DA et al. Blood. 2004;103(12):4396-4407.
Ravandi F et al. Blood. 2010;116(12): 2070-2077.

PRINCIPLES OF SYSTEMIC THERAPY

INDUCTION REGIMENS FOR Ph-POSITIVE ALL[a]

Protocols for AYA patients:

- EsPhALL regimen: (imatinib, dasatinib); and a backbone of the Berlin-Frankfurt-Münster regimen[2,3]
- TKIs (ponatinib, imatinib, dasatinib) + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4–8]
- TKIs (imatinib, nilotinib, dasatinib) + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)[9-13]
- TKIs (imatinib, dasatinib, nilotinib)[14,15] + corticosteroids[b]
- TKIs (imatinib, dasatinib, nilotinib) + vincristine + dexamethasone[16,b]

Adult patients:

- TKIs (ponatinib, imatinib, dasatinib) + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4–8]
- TKIs (imatinib, nilotinib) + multiagent chemotherapy (daunorubicin, vincristine, prednisone, and cyclophosphamide)[9-13]
- TKIs (imatinib, dasatinib, nilotinib)[14,15] + corticosteroids[b]
- TKIs (imatinib, dasatinib, nilotinib) + vincristine + dexamethasone[16,17,b]

Treatment of Older Patients (≥65 y) with ALL

Maintenance regimens:

- Add TKIs (imatinib, dasatinib, nilotinib, ponatinib) to maintenance regimen; optimal duration is unknown.
- Monthly vincristine/prednisone pulses (for 2–3 years). May include weekly methotrexate + daily 6-mercaptopurine (6-MP) as tolerated.[c,d]

Induction Regimens for Ph-Negative ALL
References

[a]All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[b]These regimens are used for induction therapy and additional therapy is needed.
[c]For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.
[d]Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MINIMAL/MEASURABLE RESIDUAL DISEASE ASSESSMENT

- The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate.
- MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.
- MRD is an essential component of patient evaluation over the course of sequential therapy. If patient is not treated in an academic center, there are commercially available tests available that should be used for MRD assessment.
- Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements during and after initial induction therapy.[1]
- The most frequently employed methods for MRD assessment include at least 6-color flow cytometry assays[2,3] specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (eg, *BCR-ABL1*), and next-generation sequencing (NGS)-based assays, to detect clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes.
- Current 6-color flow cytometry can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells (MNCs).[2,3] PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $< 1 \times 10^{-6}$ (<0.0001%) bone MNCs.[4,5] The concordance rate for detecting MRD between these methods is generally high.
  - Timing of MRD assessment:
    - Upon completion of initial induction.
    - Additional time points should be guided by the regimen used.
    - Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.

[1]Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult lymphoblastic leukemia. JAMA Oncol 2017;3:e170580.
[2]Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. Haematologica 2012;97(10):1582-1593.
[3]Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2013;27:635-641.
[4]Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. Leukemia 2010;24:521-535.
[5]Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2010;2010:7-12.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY - Treatment of Older Adults with ALL

- Older adults (defined as those aged 65 years and older) benefit from therapy, in spite of higher treatment-related morbidity and mortality.
- Careful assessment of comorbid conditions, performance status, and ability to attend to activities of daily living (ADLs) and instrumental ADLs (IADLs) is important when deciding treatment intensity.
- Dose reduction of pegylated asparaginase (1000 IU/m²), anthracycline (50% dose), and/or other myelosuppressive agents may be warranted.
- The categorization of regimens as low, moderate or high intensity is based on two factors: 1) the presence or absence of myelosuppressive cytotoxic agents, and 2) the relative dose intensity of the included agents.
- All regimens should include CNS prophylaxis, antimicrobial prophylaxis, and growth factor support.
- For appropriate fit individuals achieving remission, consideration of autologous or reduced-intensity allogeneic SCT may be appropriate.

See the NCCN Guidelines for Older Adult Oncology. Discussion of ALL in the elderly can be found on OAO-C page 2 of 7.

INDUCTION REGIMENS for Ph-negative ALL – Adults aged ≥65 y

- Low intensity
  - Vincristine + prednisone[1]
  - Prednisone, vincristine, methotrexate, and 6-mercaptopurine (POMP)[2]
- Moderate intensity
  - GMALL: Idarubicin + dexamethasone + vincristine + cyclophosphamide + cytarabine ± rituximab[3]
  - PETHEMA-based regimen[4]
    - ALLOLD07 regimen: vincristine, dexamethasone, idarubicin, cyclophosphamide, cytarabine, methotrexate, and L-asparaginase
  - GRAALL: doxorubicin + vincristine + dexamethasone + cytarabine + cyclophosphamide[5]
  - Modified DFCI 91-01 protocol: dexamethasone, doxorubicin, vincristine, methotrexate, cytarabine, L-asparaginase, and IT chemotherapy[6]
- High intensity
  - Hyper-CVAD[7] with dose-reduced cytarabine to 1 g/m²
  - CALGB 9111[8] (cyclophosphamide, daunorubicin, vincristine, prednisone, and pegaspargase)

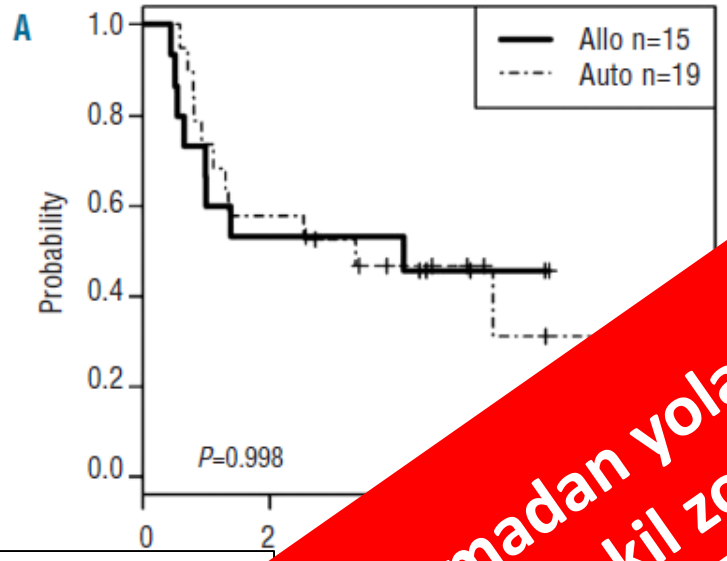
INDUCTION REGIMENS for Ph-positive ALL – Adults aged ≥65 y

- Low intensity
  - TKI (imatinib, dasatinib, nilotinib) ± corticosteroids[9-12]
  - TKI (dasatinib, imatinib) + vincristine + dexamethasone[13-15]
- Moderate intensity
  - EWALL: TKI (dasatinib, nilotinib) with multiagent chemotherapy (vincristine, dexamethasone, methotrexate, cytarabine, asparaginase)[16]
- High intensity[17,18]
  - TKI (dasatinib, ponatinib) + HyperCVAD with dose-reduced cytarabine to 1 g/m²

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Remisyon elde edilen Ph(+) ALL'de Otolog ile Allogeneik Nakil sonuçları benzer…



Bu çalışmadan yola çıkarak Ph(+) MFAL'da allogeneik nakil zorunluluk mu?

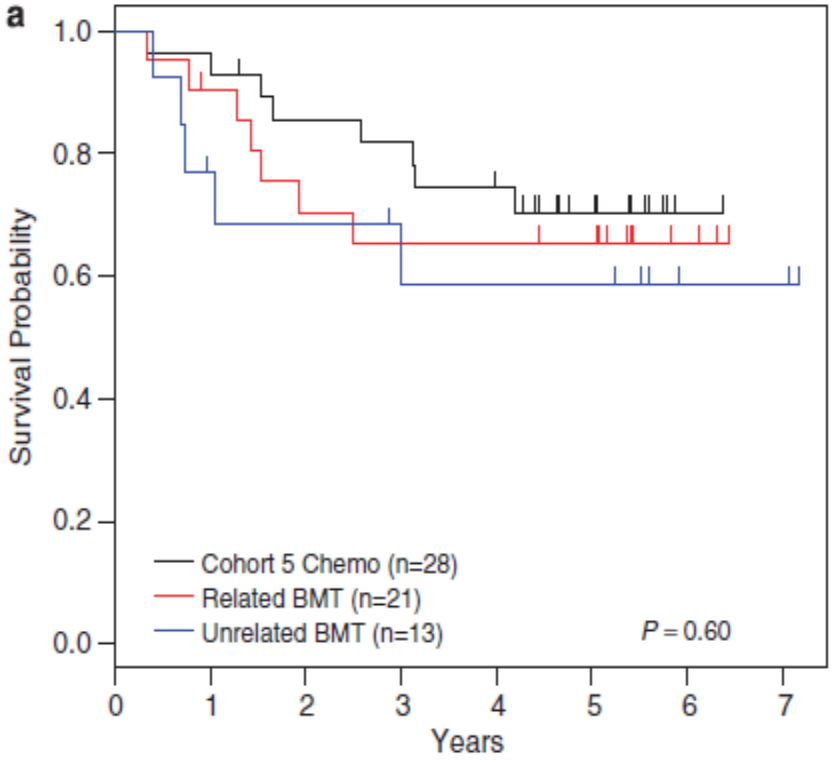
Ort. PFS:3.5 vs 4.1 yıl (otolog vs allogen

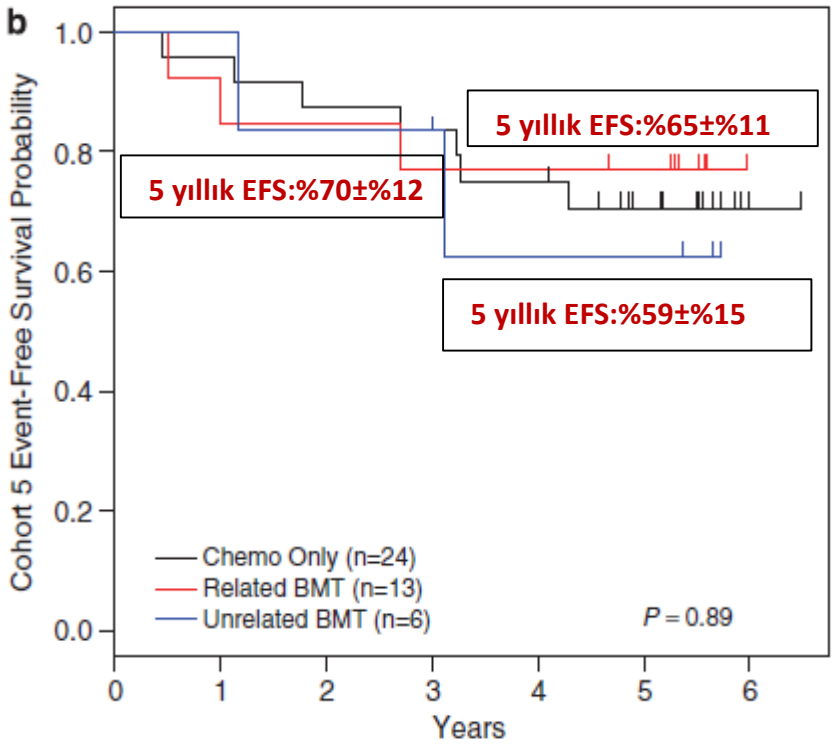
Ort. OS:6 yıl vs ulaşılamamıştır (otolog vs allogeneik)

CALGB çal yumlu kardeş donörü bulunmayanlard otolog alternatif tedavi olabilir (İmatinib+KT ciddi lösemi yükünü azalttıktan sonra)

Wetzler M, et al. Haematologica. 2014;99(1):111-115.

≤21 yaş **Ph(+) ALL'de AHKHN'nin KT+TKI'ne** avantajı olmayabilir...





Schultz KR et al. Leukemia. 2014 Jul;28(7):1467-71.

Orta yaşlı Ph(+) ALL-HyperCVAD+imatinib

Treatment of Philadelphia chromosome–positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate

- Tek merkezli çalışma
- 20 yeni tanı Ph(+) ALL, ortanca yaş 42 (17-75), Nisa
- 11 de novo (%55), 4 standard indüksiyon KT'
, 5 hastada 1 indüksiyon KT'si sonrası CR (%25)
- %70 erkek

Uygun hastalara konsolidasyon amaçlı allogeneik kök hücre nakli yapıldı

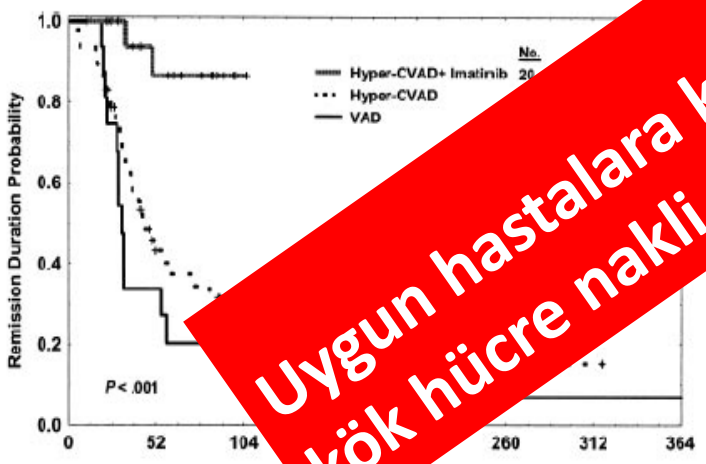


Figure 1. Disease-free survival o tients treated with hyper-CVAD and imatinib mesylate compared with those treated with non–imatinib mesylate–containing hyper-CVAD and VAD regimens. Note: a long-term survivor at 15 years in the VAD group is not shown.

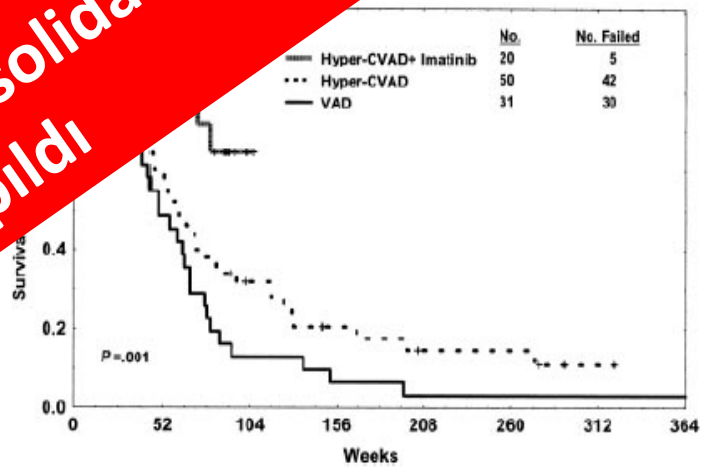
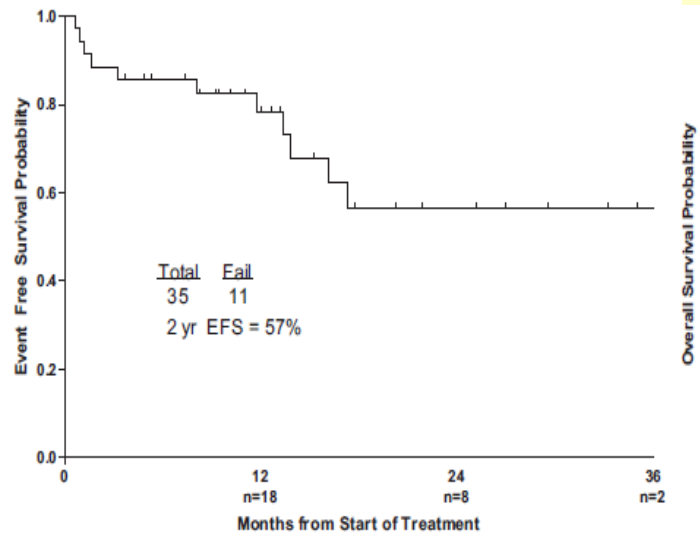


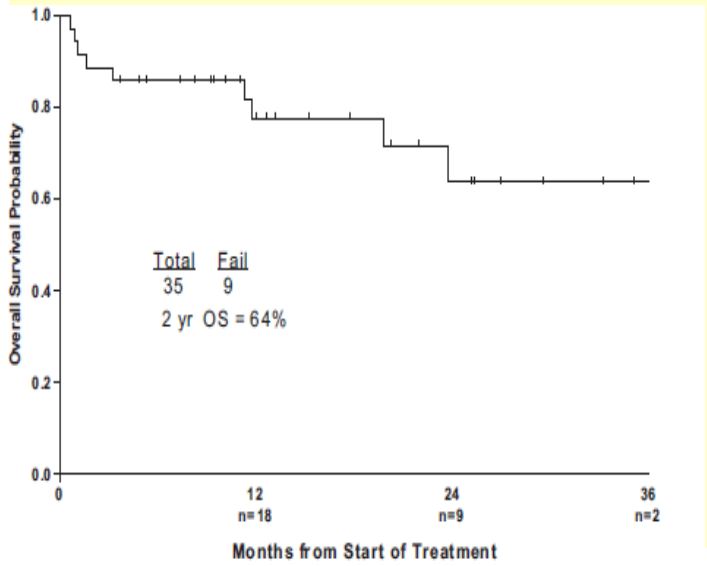
Figure 2. Overall survival of patients treated with hyper-CVAD and imatinib mesylate compared with those treated with non–imatinib mesylate–containing hyper-CVAD and VAD regimens. Curves represent intention to treat, without censoring for allogeneic SCT. Differences remain significant with exclusion of the 5 patients in CR at start of hyper-CVAD and imatinib mesylate (not shown). Note: a long-term survivor at 15 years in the VAD group is not shown.

Orta yaşlı Ph(+) ALL-HyperCVAD+dasatinib

First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome–positive (Ph^+) acute lymphoblastic leukemia

- **Tek merkezli çalışma**
- **35 yeni tanı Ph(+) ALL, ortanca yaş 53 (21-79), %11'inde tanıda SSS tutulumu**
- **33 hastada ilk kürden sonra TR (%94)**
- **Ortanca takip süresi 14 ay (4-37), ortanca tedavi kür sayısı 6 (1-8)**

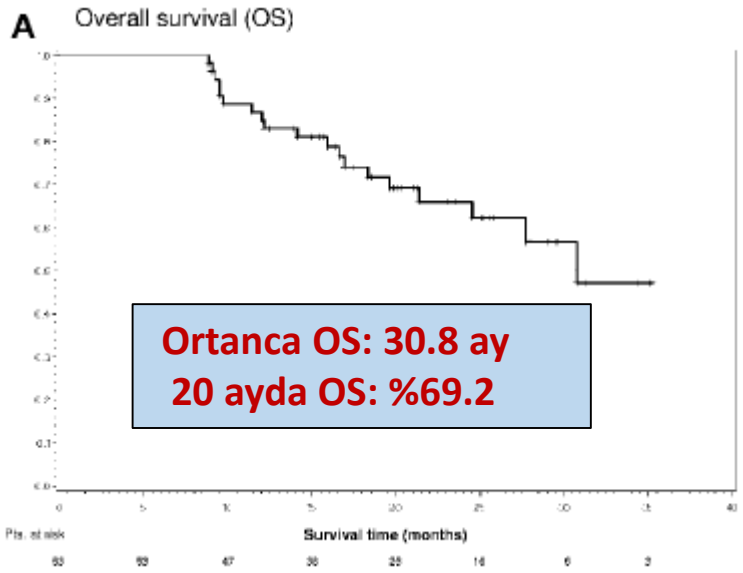




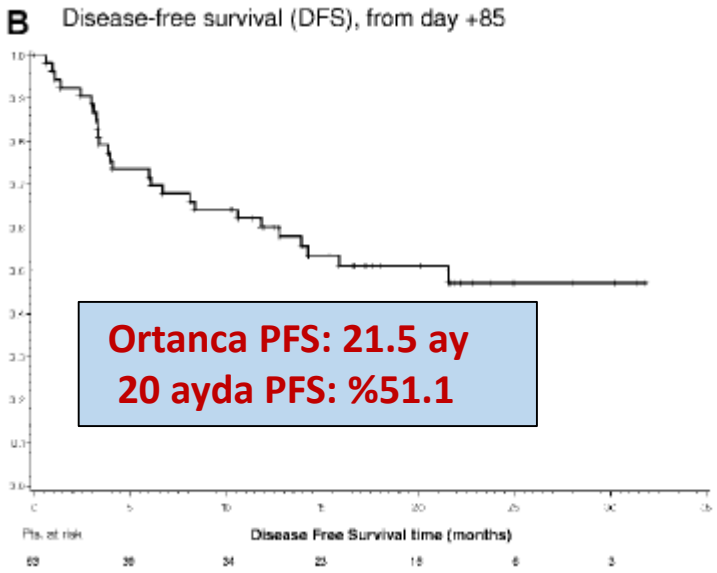
Protokol:
Dasatinib 2x50 mg/gün 8 siklus boyunca her siklüs ilk 14 gününde

Yaşlı erişkinlerde dasatinib+steroid+İT KT ile kısa dönem sonuçlar oldukça iyi...

Ortanca yaş:53.6 (23.8-76.5)



Ortanca OS: 30.8 ay
20 ayda OS: %69.2



Ortanca PFS: 21.5 ay
20 ayda PFS: %51.1

Protokol: 7 günlük steroid prefazı (oral prednizon 10-60 mg/m^2), indüksiyon tedavisi (oral dasatinib 2x70 mg 84 gün boyunca, prednizon 60 mg/m ^{2} /gün 24.güne kadar-sonra azaltılıp 32.günde kesilir, İT metotreksat 22. ve 43.günlerde)

Fo`a R,et al. Blood. 2011;118(25):6521-6528..

Ph (+) MFAL Öneriler

- t(9;22) ile birlikte olan MFAL'da

  Yaşa uygun ALL kemoterapisi

  ° Orta yaş: HyperCVAD

  ° Daha ileri yaş: Foa rejimi
- TKI

  ° İmatinib

  ° Dasatinib
- Takiben uygun hastalarda allogeneik kök hücre nakli

Wolach O et al. Blood. 2015;125(16):2477-85.

Ph(+) MFAL-Olgu

- 51 yaşında erkek hasta
- Şikayeti: 2 haftadır egzersiz dispnesi
- Kan sayımı: lökosit: 280.000/mm^3 (%76 blast), trombosit: 91.000/mm^3, Hgb: 9 g/dl
- Kemik iliği sitogenetik: 20 metafazda t(9;22) (q34;q11.1) translokasyonu
- Moleküler analiz: e1a2 BCR-ABL transkripti (p190)

- Tedavi:HyperCVAD+dasatinib
- Yanıt: 1B sonrası hematolojik tam yanıt, 2B sonrası bcr-abl:%0.01
- MA HR ardından AHKHN
- Naklin 3.ayında remisyonda

Ph(-) MFAL Tedavisi-Optimal Tedavi Bilinmiyor

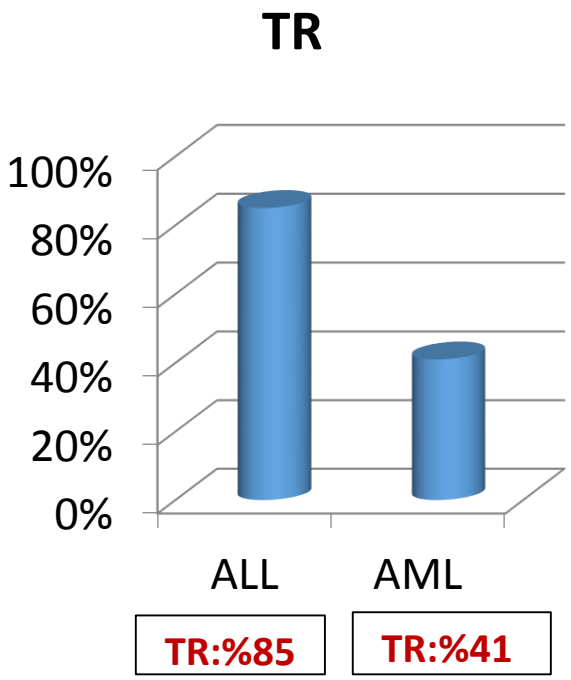
Ph (-) MFAL-Genel Görüş

- **Prospektif çalışma yok-kısıtlı sayıda retrospektif çalışma**
- **ALL benzeri indüksiyon rejimi AML benzeri rejime göre daha iyi sonuç, daha az toksisite**
- **<40 yaş: Pediatrik bazlı rejim**
- **≥40 yaş: Erişkin tip ALL rejimi**
- **Tüm hastalara SSS profilaksisi yapılmalı**
- **R.İ hemen sonrası +29.günde kemik iliğinde akım sitometri ve PCR ile MRD bakılmalı**
- **CR1'da gözlem veya konsolidasyona kıyasla AKHN daha iyi sonuç ve kabul edilebilir toksisite**

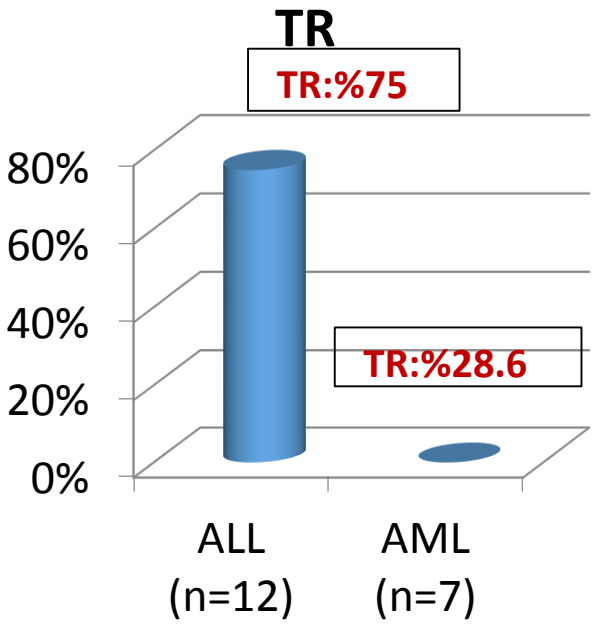
Heesch S et al. Ann Hematol 2013; 92:747.
Tian H et al. Leuk Res 2016; 45:40.
Munker R et. Biol Blood Marrow Transplant 2016; 22:1024.

Çalışmaların çoğunda ALL tipi rejim ile TR oranı daha yüksek...

100 pediatrik+erişkin MFAL

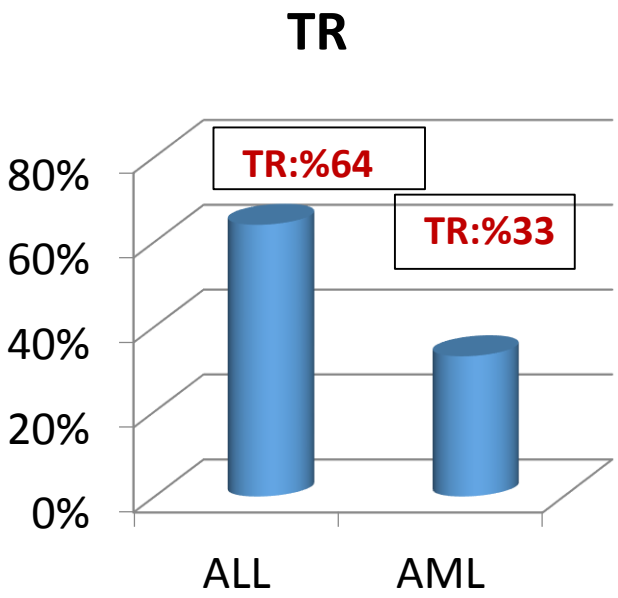


Matutes et al. Blood. 2011;117:3163-3171.

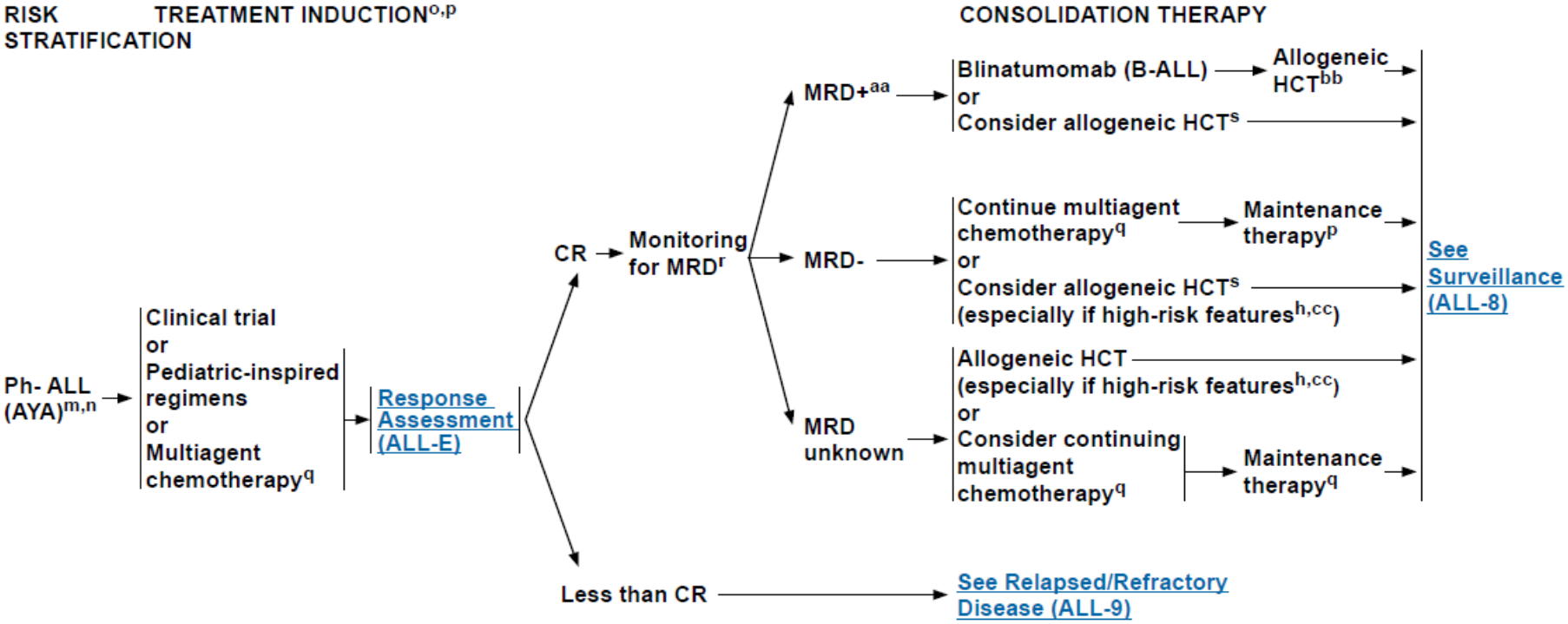


Zheng C et al. Haematologica. 2009;94:1778-1780

51 bifenotipik lösemi



Zhang Y, et al. Acta Haematol. 2011;125(4):210-218.



[h]See Cytogenetic Risk Groups for B-ALL (ALL-A).
[m]Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.
[n]For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult Oncology.
[o]All ALL treatment regimens include CNS prophylaxis.
[p]See Principles of Supportive Care (ALL-C).
[q]See Principles of Systemic Therapy (ALL-D).
[r]See Minimal Residual Disease Assessment (ALL-F).
[s]Optimal timing of HCT is not clear. For fit patients, additional therapy may be considered to eliminate MRD prior to transplant.

[aa]The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evalution for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible. (See Discussion)
[bb]Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.
[cc]High WBC count (≥30 x 10^9/L for B lineage or ≥100 x 10^9/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY (2 of 6)

INDUCTION REGIMENS FOR Ph-NEGATIVE ALL[a,e]

AYA patients:

- **Regimens based on data from multi-institutional or cooperative group studies:**
  - **CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (ongoing study in patients aged <40 years)[15,f]**
  - **COG AALL0232 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (patients aged ≤21 years)[16,f]**
  - **COG AALL0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, and pegaspargase; nelarabine added to consolidation regimen[17,f]**
  - **DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase (ongoing study in patients aged <50 years)[18,f]**
  - **GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <60 years), with rituximab for CD20-positive disease[19,f]**
  - **PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <30 years)[20,f]**
- **Regimens based on data from single-institution studies:**
  - **Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease[21]**
  - **USC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase (patients aged 18–57 years)[22,f]**
  - **Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase[23]**

Adult patients: Treatment of Older Patients (≥65 y) with ALL (ALL-D 6 of 6)

- **CALGB 8811 Larson regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide; for patients aged ≥60 years, reduced doses for cyclophosphamide, daunorubicin, and prednisone[24]**
- **GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide (patients aged <60 years) with rituximab for CD20-positive disease[19,e]**
- **Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with or without rituximab for CD20-positive disease[21,25]**
- **Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase[23]**
- **MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, and pegaspargase (induction phase I); and cyclophosphamide, cytarabine, and 6-MP[c] (induction phase II)[26]**

Maintenance regimen:

- **Weekly methotrexate + daily 6-MP[c] + monthly vincristine/prednisone pulses (duration based on regimen)**

Induction Regimens for Ph-Positive ALL (ALL-D 1 of 6)
References (ALL-D 5 of 6)

[a]All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[c]For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP.
[e]There are data to support the benefit of rituximab in addition to chemotherapy for CD20-positive patients (especially in patients <60 years).
[f]Pediatric-inspired regimen.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC THERAPY (6 of 6)
Treatment of Older Adults with ALL

Induction therapy for older adults with ALL (defined as aged 65 years and older) remains challenging. For those patients with advanced age, multiple comorbidities, and/or poor functional status, lower dose chemotherapy consisting of vincristine and steroids have effectively been used for decades. In older individuals with adequate functional status, intensive multi-agent chemotherapy regimens (such as hyper-CVAD and pediatric-inspired protocols) have resulted in high remission rates. Despite this, many more older than younger ALL patients succumb to treatment-related mortality and morbidity, specifically myelosuppression and infectious complications. G-CSF does not ameliorate toxicity of these regimens, thereby prompting the development of newer treatment regimens specifically for older patients, which include decreased drug doses and/or omission of some drugs. For instance, asparaginase has been removed from induction, and anthracycline doses have been reduced by 50% or omitted in some regimens. Similar to younger patients, MRD status appears to be a reliable predictor of clinical outcome following therapy. Whether rituximab improves upon chemotherapy in older adults with Ph-negative CD20+ ALL remains controversial. In contrast to younger patients, older patients with Ph-positive ALL may have improved overall survival and outcomes as compared with Ph-negative ALL due to the availability of well-tolerated, highly effective *BCR-ABL1* TKI therapy. For appropriate fit individuals achieving remission, consideration of autologous or reduced-intensity allogeneic stem cell transplantation may be appropriate. See the NCCN Guidelines for Older Adult Oncology. Discussion of ALL in the elderly can be found on OAO-C page 2 of 32.

INDUCTION REGIMENS for Ph-negative ALL – Adults aged ≥65 y

- **Vincristine + prednisone[1] (low intensity)**
- **GMALL: Idarubicin + dexamethasone + vincristine + cyclophosphamide + cytarabine ± rituximab[2,3] (moderate intensity)**
- **Hyper-CVAD[4] with dose-reduced cytarabine to 1 gm/m² (High intensity)**
- **CALGB 9111[5] (high intensity)**

INDUCTION REGIMENS for Ph-positive ALL – Adults aged ≥65 y

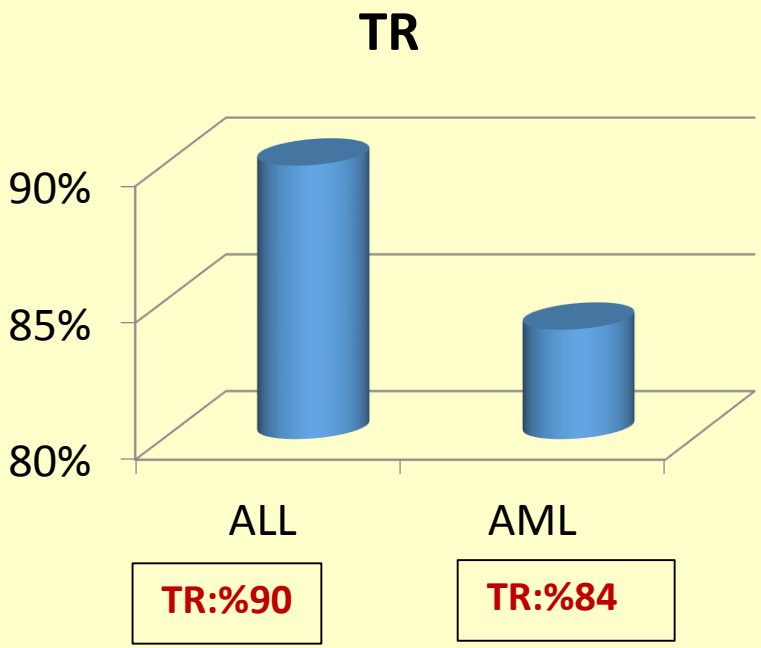
- **TKI (imatinib, dasatinib, nilotinib) ± steroids[6-9]**
- **TKI (dasatinib) + vincristine + dexamethasone[10,11]**
- **TKI (imatinib) + steroids followed by multi-agent chemotherapy[12]**
- **GRAALL: doxorubicin + vincristine + dexamethasone + cytarabine + cyclophosphamide[13]**

[1]Hardisty RM, McElwain TJ, and Darby CW. Vincristine and prednisone for the induction of remissions in acute childhood leukaemia. Br Med J 1969;2:662-665.
[2]Gokbuget N, Beck J, Bruggemann M et al. Moderate intensive chemotherapy including CNS prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German multicenter study group for adult ALL (GMALL). Blood 2012;120:1493.
[3]Ribera JM, Garcia O, Oriol A et al. PETHEMA group: Feasibility and results of subtype-oriented protocols in older adults and fit patients with acute lymphoblastic leukemia : results of three prospective parallel trials from the PETHEMA group. Leuk Res 2016;41:12-20.
[4]O'Brien S, Thomas DA, Ravand F et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone in elderly patients with acute lymphocytic leukemia. Cancer 2008;113:2097-2101.
[5]Larson RA, Dodge RK, Linker CA et al. A randomized control trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB 9111. Blood 1998;92:1556-1564.
[6]Ottmann OG, Wassmann B, Pfeiffer H et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Ph-chromosome positive acute lymphoblastic leukemia. Cancer 2007;109:2068-2076.
[7]Foa R, Vitale A, Vignetti M, et al Dasatinib as first-line treatment for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. Blood 2011;118:6521-6528.
[8]Vignetti M, Fazi P, Cimino G et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-3678.
[9]Papayannidis C, Fazi P, Piciocchi A, et al. Treating Ph+ acute lymphoblastic leukemia (ALL) in the elderly: the sequence of two tyrosine kinase inhibitors (TKI) (nilotinib and imatinib) does not prevent mutations and relapse. Blood 2012;120:Abstract 2601.
[10]Rousselot P, Coude MM, Gokbuget N et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood 2016;128:774-82.
[11]Rousselot P, Coude MM, Huguet F, et al. Dasatinib and low intensity chemotherapy for first-line treatment in patients with de novo Philadelphia Positive ALL aged 55 and over: final results of the EWALL-Ph-01 study [abstract]. Blood 2012;120:Abstract 666.
[12]Delannoy A, Delabesse E, Lheritier V et al. Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRAALL AFR09 study. Leukemia 2006;20:1526-1532.
[13]Hunault-Berger M, Leguay T, Thomas X, et al. A randomized study of pegylated liposomal doxorubicin versus continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study. Haematologica. 2011;96(2):245-252.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Tek merkezli bir çalışmada ALL ile AML benzeri rejimlerinin CR oranı benzer…

- 23 erişkin, 13 pediatrik MFAL (toplam 36 hasta)
- ALL tipi rejim: L-asparaginaz, kortikosteroid içerir (11 hasta)
- AML tipi rejim: ARA-C, antrasiklin (25 hasta)
- Erişkinlerin hepsi ilk CR'da nakle alındı



Getta BM et al. Biol Blood Marrow Transplant 2017; 23:1879.

MPO ekspresyonu varlığında 3+7 mi kullanılmalı?

What is the optimal treatment for biphenotypic acute leukemia?

Changcheng Zheng, Jingsheng Wu, Xin Liu, Kaiyang Ding, Xiaoyan Cai, and Weibo Zhu

- **Prospektif bir çalışma**
- **Akım sitometri ile >%20 MPO ekspresyonu olan 7 hastada AML tedavisi uygulandı**
- **AML rejimleri:**
  - **DA** (daunorubicin 45 mg/m^2 d1-3, cytarabine 150 mg/m^2 d1-7)
  - **HA** (homoharringtonin 2 mg/m^2 d 1-7, cytarabine 150 mg/m^2 d1-7)
- **CR oranı:2/7 (%28.6)**

ALL+AML kombinasyon tedavilerinin Ph (-) MFAL'da avantajı olur mu?

ALL+AML kombinasyon tedavileri

- **Yapı taşı: ALL protokolü steroid+vincristin bazlı rejim + AML için antrasiklin/ARA-C**
- **Kombine rejimler ile ALL protokolü kullananlarda remisyon oranları benzer**
- **Yan L et al. : 117 MFAL'ın 24'üne kombinasyon rejimi uygulandı: MOAP/IOAP/DOAP (daunorubisin, idarubisin veya mitoksantron+ ARA-C ile kombine olarak vincristine veya vindesine+prednizon)**
- **Yan L et al. : TR oranı: 14/24 (%58)**
- **Bazı yazılarda kombine rejimler daha toksik (solunum yetersizliği, intrakranial kanama vb)**

Wolach O et al. Blood. 2015;125:2477-2485
XuXQ et al. Hametologica 2009;94:919-927
Yan L et al. Haematologica. 2012;97(11): 1708-1712.

18-40 yaş arası ALL'de pediatrik bazlı rejimler ile erişkin tip rejimlere göre sağkalım daha yüksek (3 yıllık OS:%50-60 vs %30-40)

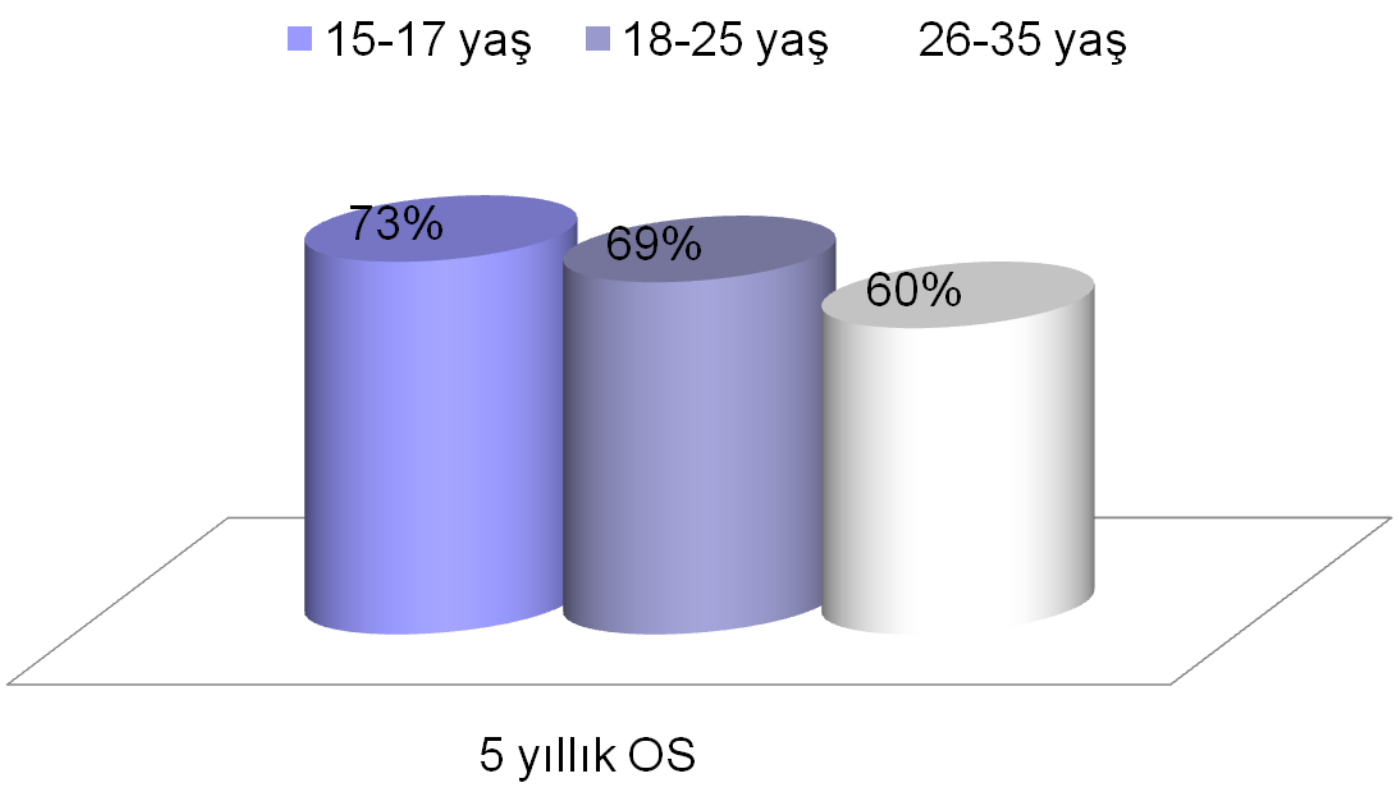
MFAL spesifik olarak bu çalışmalara dahil edilmemiştir

MFAL için de aynı yaklaşım düşünülebilir!

Larson RA et al. Blood.1998;92:1556-1564.
DeAngelo DJ et al. Leukemia. 2015;29:526-34.
Huguet F et al. J Clin Oncol. 2009;27:911-918.
Ram R et al. Am J Hematol. 2012;87:472-478.

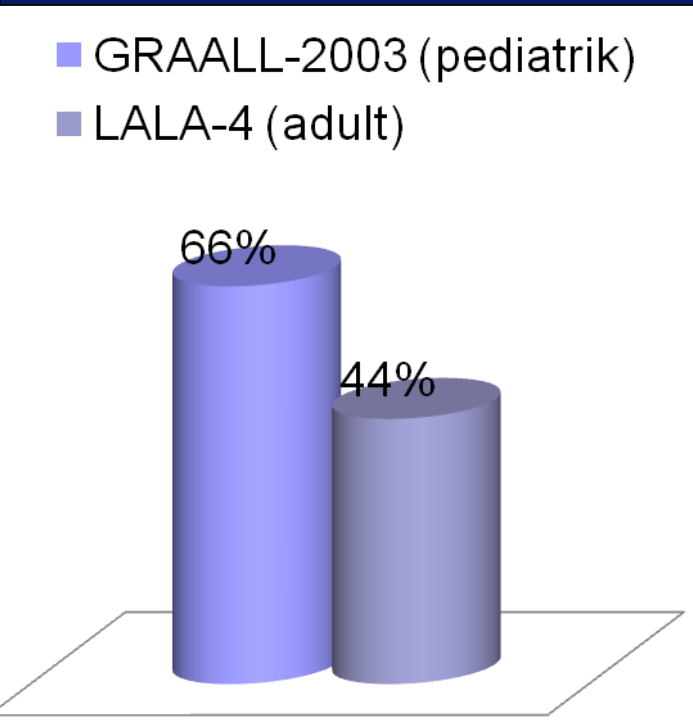
GMALL

En büyük pediatrik bazlı rejim deneyimi (n=1529, 15-35 yaş arası)



Gökbuget N. Blood.2013;122(121). Abstract 839

GRAALL Trial: Pediatrik bazlı tedavi 45 yaşına kadar sağkalımı olumlu etkiliyor…



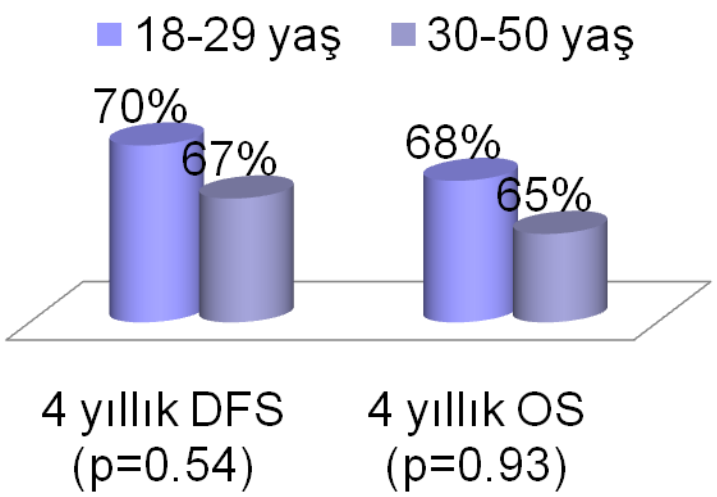
42.ay OS (p=0.001)

Remission induction	
Corticosteroid prephase	
PDN	60 mg/m²/d on days –7 to –1
IT MTX	15 mg between days –7 and –4
Induction course	
PDN	60 mg/m²/d on days 1-14
DNR	50 mg/m²/d on days 1, 2, and 3; 30 mg/m²/d on days 15 and 16
VCR	2 mg on days 1, 8, 15, and 22
L-asparaginase*	6,000 U/m²/d on days 8, 10, 12, 20, 22, 24, 26, and 28
CPM	750 mg/m²/d on day 1; 750 mg/m²/d on day 15 in good early responders; 500 mg/m²/12 h on days 15 and 16 in poor early responders
Lenograstim	150 μg/m²/d from day 17 to myeloid recovery
Salvage course	
IDA	12 mg/m²/d on days 1-3
Ara-C	2 g/m²/12 h on days 1-4
Lenograstim	150 μg/m²/d from day 9 to myeloid recovery
Consolidation blocks	
Blocks 1, 4, and 7	
Ara-C	2 g/m²/12 h on days 1 and 2
DXM	10 mg/12 h on days 1 and 2
L-asparaginase*	10,000 U/m² on day 3
Lenograstim	150 μg/m²/d on days 7-13
Blocks 2, 5, and 8	
MTX	3 g/m² continuous infusion on day 15
VCR	2 mg on day 15
L-asparaginase*	10,000 U/m² on day 16
6-MP	60 mg/m²/d on days 15-21
Lenograstim	150 μg/m²/d on days 22-27
Blocks 3, 6, and 9	
CPM	500 mg/m²/d on days 29 and 30
VP-16	75 mg/m²/d on days 29 and 30
MTX	25 mg/m² on day 29
Lenograstim	150 μg/m²/d from day 31 to myeloid recovery
Late intensification (between consolidation blocks 6 and 7)	
For patients in CR after the first induction course	
PDN	60 mg/m²/d on days 1-14
VCR	2 mg on days 1, 8, and 15
DNR	30 mg/m²/d on days 1-3
L-asparaginase*	6,000 U/m²/d on days 8, 10, 12, 18, 20, and 22
CPM	500 mg/m²/12 h on day 15
Lenograstim	150 μg/m²/d if neutrophils < 0.5 G/L to myeloid recovery
For patients in CR after the salvage course	
IDA	9 mg/m²/d on days 1-3
Ara-C	2 g/m²/12 h on days 1-4
Lenograstim	150 μg/m²/d from day 9 to myeloid recovery
Maintenance therapy	
PDN	40 mg/m²/d on days 1-7 monthly for 12 months
VCR	2 mg on day 1 monthly for 12 months
MTX	25 mg/m²/wk orally for 24 months
6-MP	60 mg/m²/d for 24 months
CNS therapy	
Prophylaxis	
Triple IT injections†	One at days 1 and 8 of induction; one at day 29 of each series of consolidation blocks; one at day 1 of late intensification
Cranial irradiation	18 Gy before maintenance therapy initiation; 6-MP 60 mg/m²/d during irradiation
Treatment of patients with initial CNS involvement	
Triple IT injections†	Eight between days –7 and 21 of induction; four during the first two consolidation blocks; one at day 29 of consolidation blocks 3 and 6
Cranial irradiation	15 Gy before SCT or 24 Gy before maintenance therapy initiation; 6-MP 60 mg/m²/d during irradiation

Huguet F et al. J Clin Oncol 2009; 27: 911–918.

Dana-Farber Cancer Institute (DFCI) ALL Consortium Protokolü 18-50 yaş arası güvenilir ve etkili…

DJ De Angelo et al.Leukemia 2015;29:526-34



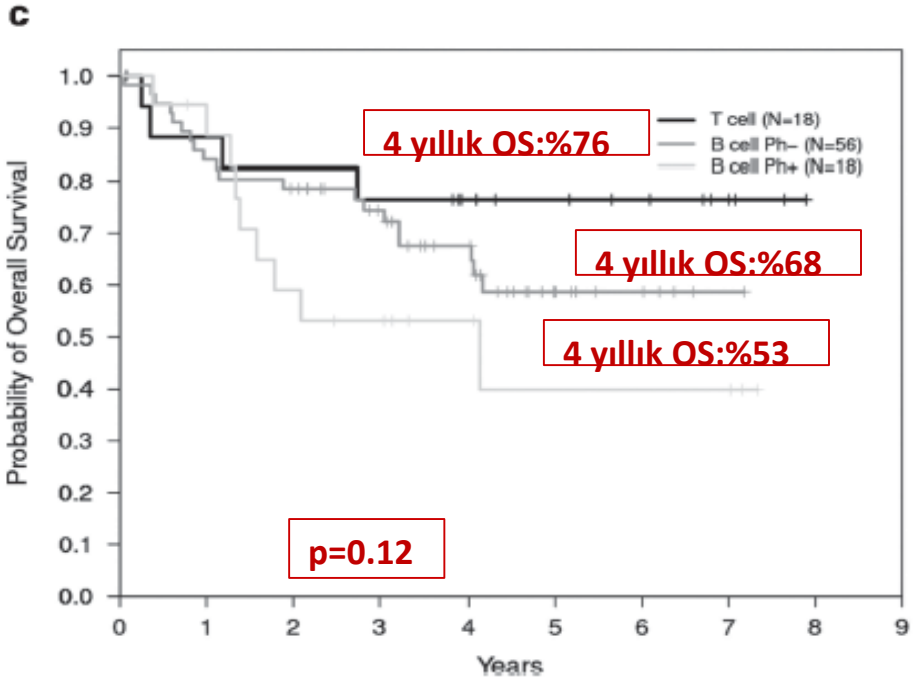


Table 1. Therapy on DFCI Adult ALL Consortium Protocol 01–175

Time Frame	*Treatment*
Induction 4 Weeks	Vincristine 2 mg weekly, days 1, 8, 15 and 22 Prednisone 40 mg/m^2/day, days 1–28 Doxorubicin 30 mg/m^2/dose, days 1and 2 Methotrexate 4 g/m^2 (8–24 h after doxorubicin) with leucovorin rescue on day 3 *E coli* L-asparaginase 25 000 IU/m^2 IM×1 dose, day 5 IT cytarabine 50 mg, day 0[a] (prior to initiation of systemic therapy) IT methotrexate/cytarabine/hydrocortisone,[b] days 15 and 29
CNS therapy 3 Weeks	Vincristine 2 mg×1 dose 6-mercaptopurine (6-MP) 50 mg/m^2/day orally, ×14 consecutive days Doxorubicin 30 mg/m^2×1 dose IT methotrexate/cytarabine twice weekly×4 doses Cranial radiation[c]
Intensification 30 Weeks	*Every 3-week cycles:* Vincristine 2 mg, day 1 Dexamethasone 18 mg/m^2/day b.i.d., orally, days 1–5 Doxorubicin 30 mg/m^2, day 1 of each cycle to a (cumulative dose 300 mg/m^2) 6-MP 50 mg/m^2/day orally×14 consecutive days *E. coli* asparaginase *Individualized dosing*: 12 500 IU/m^2/dose (starting dose)[d] Methotrexate 30 mg/m^2 i.v. or IM weekly, 1 day after asparaginase (no weekly methotrexate until doxorubicin completed). IT methotrexate/cytarabine/hydrocortisone at start of a cycle IT therapy consisting of methotrexate/cytarabine at start of a cycle every 18 weeks
Continuation 74 weeks	*Every 3-week cycles:* Same as intensification except no asparaginase and dexamethasone dose reduced to 6 mg/m^2/day

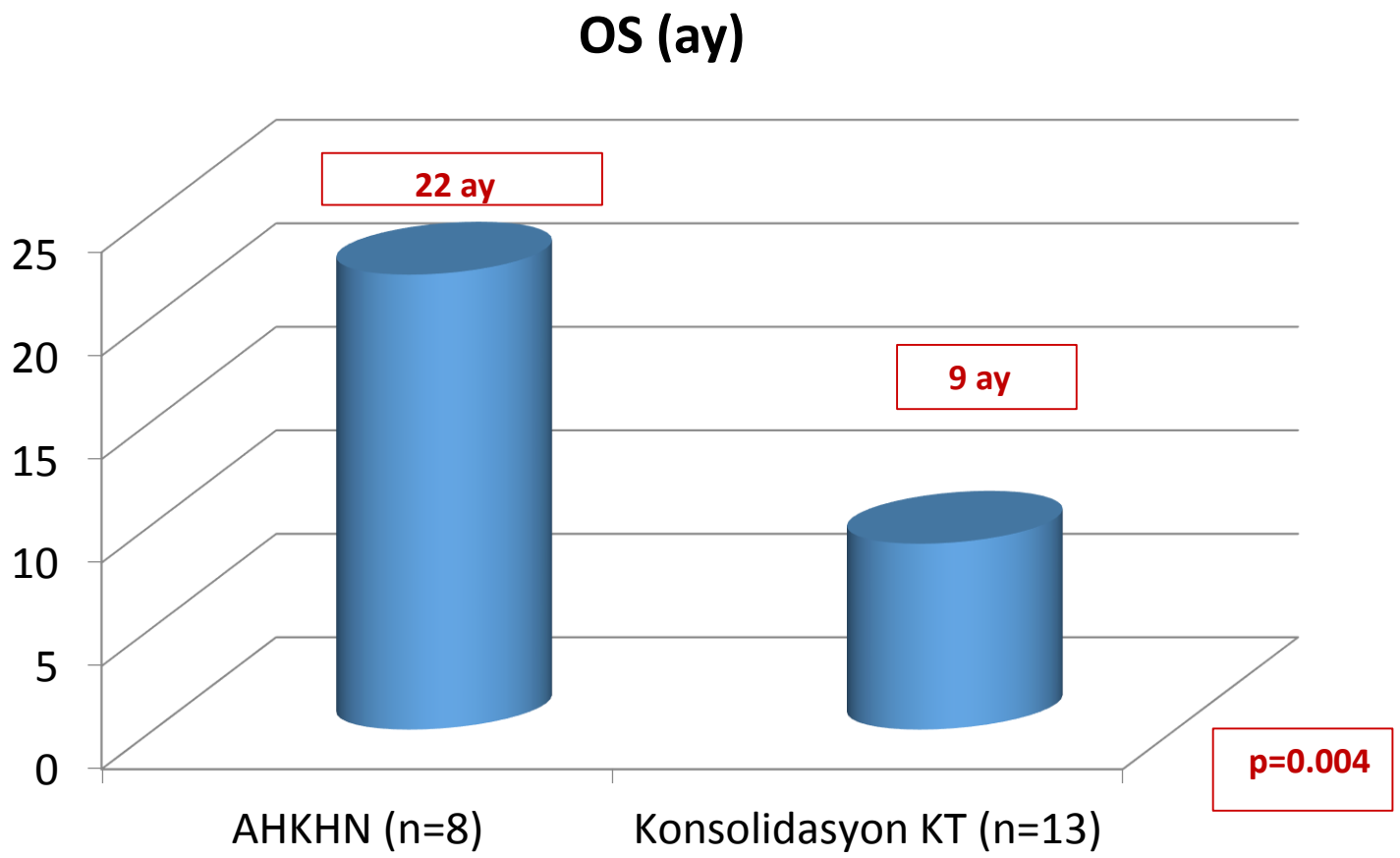
Pegile asparaginaz
40 yaş üzerinde güvenilirliği azalır, 55 yaş üzerinde belirgin toksisiteye neden olur…

- **UKALL 14 indüksiyon faz 1: PEG-ASP (1000 IU/m^2) 4. ve 18.günler, daunorubicin, vinkristin, deksametazon, IT MTX**
- **İndüksiyon faz 2: siklofosfamid, Ara-C, 6-MP, IT MTX**
- **25-65 yaş arası, toplam 91 ALL (çok merkezli, faz 3)**
- **PEG-ASP ilişkili non-fatal toksisite insidensi %36.7 (en sık hepatotoksisite (%24.5), koagülopati (%7.7) ve tromboz (%5.6))**
- **İndüksiyon mortalitesi %19.8 (18/91) (en sık sepsis+hepatotoksisite)**
- **PEG-ASP ilişkili olduğu düşünülen indüksiyon ölüm oranı:%61.1 (11/18)**
- **İndüksiyon ilişkili ölüm yaş ve Ph (+)liği ile ilişkili**
- **Bu çalışmadan yola çıkarak Ph(+) ALL'de PEG-ASP indüksiyon rejiminden çekildi**
- **ALL'de 40 yaşın üzerinde pek güvenilir olmadığı, özellikle 55 yaş üzeri toksik olduğu gösterildi**

Bella Patel et al. Blood 2013 122:3900

İlk Tam Remisyonda MFAL
Allogeneik Kök Hücre Naklinin Avantajı var mı?

MFAL'da Allogeneik Nakil uygulanırsa konsolidasyon KT'sine göre sağkalım daha iyi...



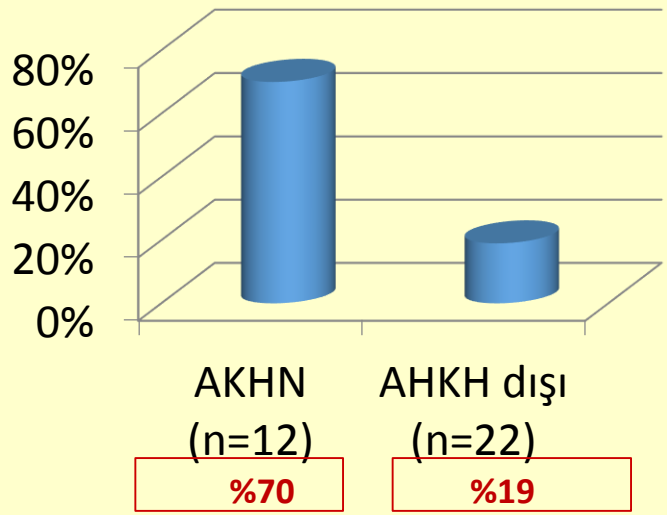
Yan L et al. Haematologica. 2012;97:1708-1712.

Acute leukemias of ambiguous lineage in adults: molecular and clinical characterization

Sandra Heesch · Martin Neumann · Stefan Schwartz · Isabelle Bartram · Cornelia Schlee · Thomas Burmeister · Matthias Hänel · Arnold Ganser ·

- Tek merkezli çalışma
- 26 bifenotipik lösemi (BAL), 16 farklılaşmamış lösemi (AUL)
- ALL bazlı rejim ile BAL/AUL'da %40 TR, AML bazlı rejim ile %22 TR
- Sadece 34 hastanın kayıtlardan nakil bilgisine ulaşıldı
- Uzun süreli sağkalım sadece AKHN uygulanan hastalar

5 yıllık OS



Heesch S et al .Ann Hematol. 2013;92(6):747-758.

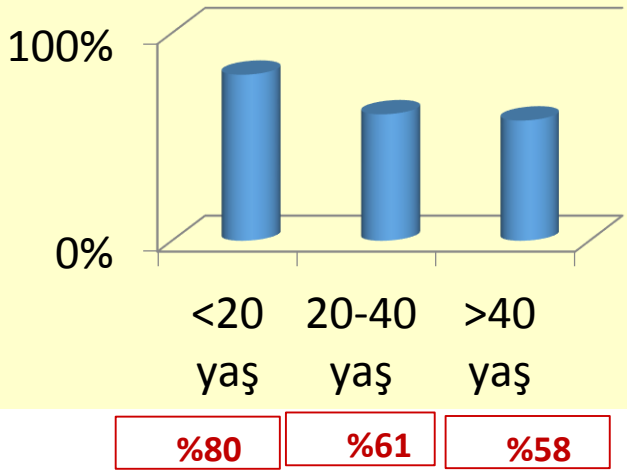
Allogeneic hematopoietic cell transplantation for patients with mixed phenotype acute leukemia

Reinhold Munker[1], Ruta Brazauskas[2], Hai Lin Wang[2], Marcos de Lima[3], Hanna J. Khoury[4],

- CIBMTR verisi (1996-2012)
- Ortanca yaş: 20 (1-68), %52 erkek, %58 MFAL; My+B, %33 MFAL;My+T)
- 78 CR1, 17 CR2

	AML (N = 375)	ALL (N = 359)	MPAL (N = 95)	
Outcomes	N Eval Prob (95% CI)	N Eval Prob (95% CI)	N Eval Prob (95% CI)	p-value
aGVHD	375	358	94	P_{Gray}=0.01
100-day	32 (27-37)%	38 (33-43)%	48 (37-58)%	0.01
cGVHD	368	352	95	P_{Gray}=0.02
1-year	33 (28-38)%	36 (31-41)%	44 (33-54)%	0.18
3-year	36 (30-41)%	42 (36-47)%	53 (42-63)%	0.02
5-year	36 (30-41)%	42 (36-47)%	53 (42-63)%	0.02

2 yıllık OS



3 yıllık OS:%67
LFS:%56
relaps:%29
NRM:%15

Comparison of outcomes in mixed phenotype acute leukemia patients treated with chemotherapy and stem cell transplantation versus chemotherapy alone

Hong Tian[a,b,c], Yang Xu[a,b,c], Liming Liu[a,b,c], Lingzhi Yan[a,b,c], Zhengming Jin[a,b,c],

- **Retrospektif çalışma**
- **66 hasta**
- **29 hasta AHKHN, 61 hasta KT ile konsolidasyon (5 hasta ilk indüksiyon sonrasında ex)**

TR1-Allogeneik Nakil

Table 1. Recent trials assessing allogeneic transplant for patients with MPAL in first remission

First author, year	Study context	*N*	Age (median, range)	Disease status at alloSCT	Outcomes	Comments
Munker, 2016 [33]	CIBMTR data on MPAL transplants 1996–2012	95	20 (1, 68)	CR1 – 82%; CR2 – 18%	3-year OS – 67%; 3-year LFS – 56%; 3-year RR – 29%; 3-year NRM – 15%	Outcomes comparable to AML and ALL controls
Tian, 2016 [42]	Single-center retrospective study	29	30 (12, 60)	CR – 72%; no CR – 28%	3-year OS – 77%; 3-year DFS – 68%; 3-year RR – 21%; 3-year NRM – 10%	Significantly better results as compared to chemo only group
Shimizu, 2015 [34]	Japanese transplant registry of MPAL cases	18	72% under age 50 years	CR – 72%; no CR – 28%	5-year OS – 48%; 5-year RFS – 40%; 5-year RR – 43%; 5-year NRM – 17%	Outcomes comparable to AML and ALL controls
Liu, 2013 [38]	Single-center retrospective study of ALAL patients	59	22–26 (12, 47)	CR – 58%; no CR –42%	3-year OS – 45%; 3-year RFS – 39%; 5-year RR – 53%; 5-year NRM – 22%	Better results with more intensive conditioning

Retrospektif çalışmalarda AHKHN ile uzun dönem sonuçlar iyi
MFAL grubundaki AHKHN sonuçları AML ve ALL ile benzer

Hücre dizisi belirsiz akut lösemide Hazırlama Rejiminin Farkı Var mı?

Allo-HSCT for acute leukemia of ambiguous lineage in adults: the comparison between standard conditioning and intensified conditioning regimens

Qi-Fa Liu · Zhi-Ping Fan · Mei-Qing Wu · Jing Sun ·

- Retrospektif bir çalışma, tek merkezli
- 59 ALAL (37 erkek, 22 kadın)
- Ortanca yaş: 23 (12-47)
- Nakil öncesi: CR1 (n=24), CR2 (n=10), CR olmayan (n=25)
- 24 hasta standard rejim (TBI+Cyc veya Bu+Cyc), 35 hasta yoğun rejim (TBI+Cyc+etoposid veya Flu+ARA-C+TBI+Cyc+etoposid)
- Standard rejim vs yoğun rejim: 5 yıllık TRM (%17.6, %25.5, p=0.38), 5 yıllık OS (%23.8, %64, p=0.029), 5 yıllık DFS (%16.7, %55.8, p=0.005), 5 yıllık relaps %80.8, %28.8, p<0.001)
- Sağkalımı arttıran faktörler: Genç yaş, nakil sırasında CR, yoğun HR

SONSÖZ

Ph (-) MFAL

- ✓ ALL indüksiyon tedavisi (Grade 2C)
- ✓SSS profilaksisi (Grade 2C)
- ✓CR1'de AHKHN (Grade 2B)

Ph (+) MFAL

- ✓ Tedavi tüm fazlarına TKİ eklenmeli (Grade 1B)
- ✓ Dasatinibin SSS geçişi daha iyi
- ✓ Yaşa uygun Ph(+) ALL rejimi (Grade 2C)
- ✓SSS profilaksisi (Grade 2C)
- ✓TR1'de AHKHN (Grade 2C)
- ✓Dasatinib devam tedavisi (Grade 2C)

Sabrınız ve beni dinlediğiniz için teşekkürler…