Akut Promyelositer Lösemi: Güncel Tedavi Yaklaşımı ve MRD Takibi

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İç Hastalıkları ABD/Hematoloji BD Öğretim Üyesi

Ankara Onkoloji Eğitim ve Araştırma Hastanesi

Hematoloji Kliniği ve Kök Hücre Nakli Merkezi Sorumlusu

Akut promiyelositik lösemi

- FAB sınıflaması AML M3
- Bütün AML'lerin %10-15'i
- İnsidans 20-60 yaş aralarında plato , ortalama görülme yaşı 44
- Cinsiyet farkı yok
- Kemoterapiye sekonder tedavi ilişkili APL; özellikle topoizomeraz II inhibitörleri

AML WHO SINIFLAMASI

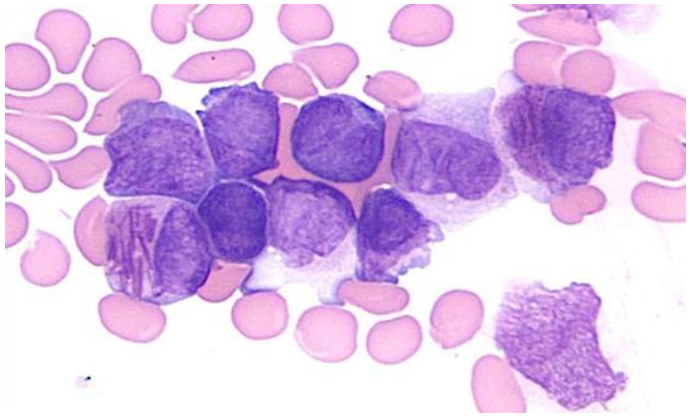
- **Sitogenetik translokasyonlarla birlikte olan akut myeloid lösemiler**
  - — T(8;21) (Q22;Q22), [AML1(CBF A)/ETO]
  - -Akut promyelositik lösemi [t(15;17)(q22;qll-12) ve varyant, PML/RAR a]
  - — ANORMAL KEMIK ILIĞI EOZINOFILLI AML [İNV(16)(PL3Q22) VEYA T(16;16)(QL3;QLL); CBFP/MYHLL]
  - — 11 Q23 ANOMALILI (MLL) AML
- **Multilineage displazili AML**
  - — Önceden MDS hikayesi olan
  - — ÖNCEDEN MDS HIKAYESI OLMAYAN
- **Tedaviyl e il işkil i AML veya MDS**
  - — Alkilleyici ajanlarla ilgili
  - — EPİPODOFİLOTOKSİNLERLE İLİŞKİLİ (TOPOİZOMERAZ II İNHİBİTÖRLERİ İLE İLİŞKİLİ)
  - — Diğer tipler
- **Diğer şekillerde kategorize edilmeyenler**
  - — Minimal diferansiye AML (minimal farklılaşma gösteren AML)
  - — Matürasyon göstermeyen AML (olgunlaşma göstermeyen AML)
  - — Matürasyon gösteren AML
  - — Akut myelomonositik lösemi
  - — Akut monoblastik ve monositer lösemi
  - — Akut eritroid lösemi
  - — Akut megakaryositik lösemi
  - — Akut bazofilik lösemi
  - — Akut myelofibrozis ile panmyeloz lösemi
  - — Granülositik olgunlaşma gösteren akut myeloblastik lösemi
  - — RARA rearranjmanı göstermeyen APL
  - — Myeloid sarkom

Morfoloji

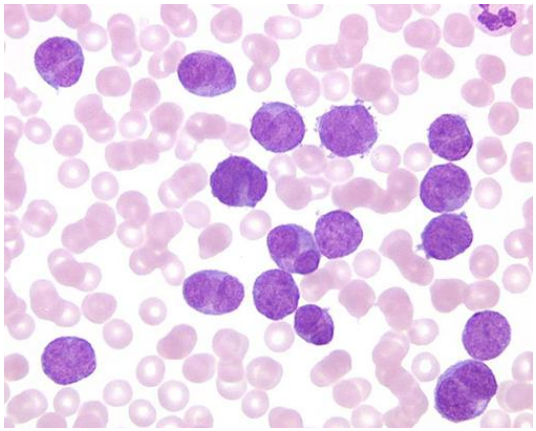
- –**Kemik iliğinde Blast >%20
- –***Kemik iliğinde %30'un üzerinde promyelosit
- –**Stoplazmada yoğun dens granüller ve belirgin,
- –Fazla miktarda-küme şeklinde auer rod'lar = **"fagot hücre"** görülebilir

Morfoloji

- Hipergranüler form(%80)

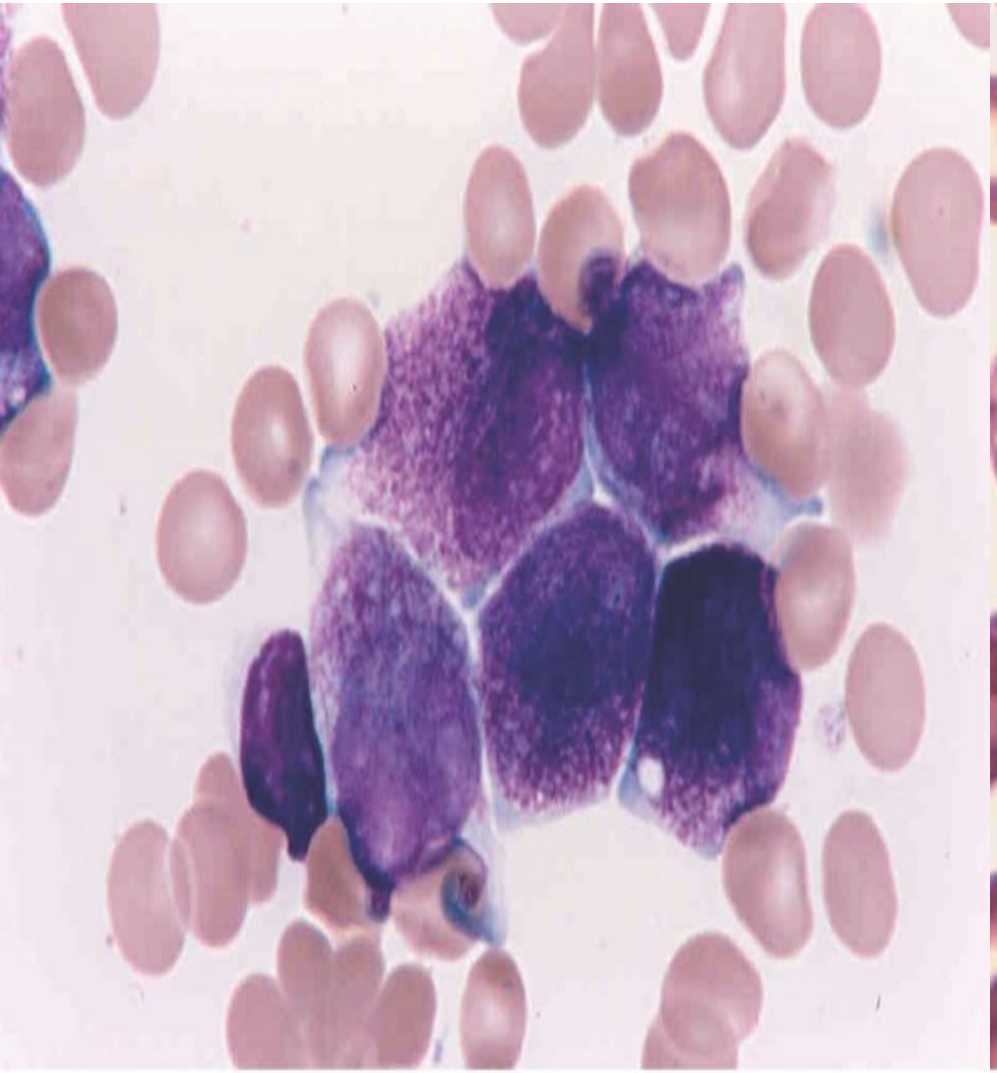


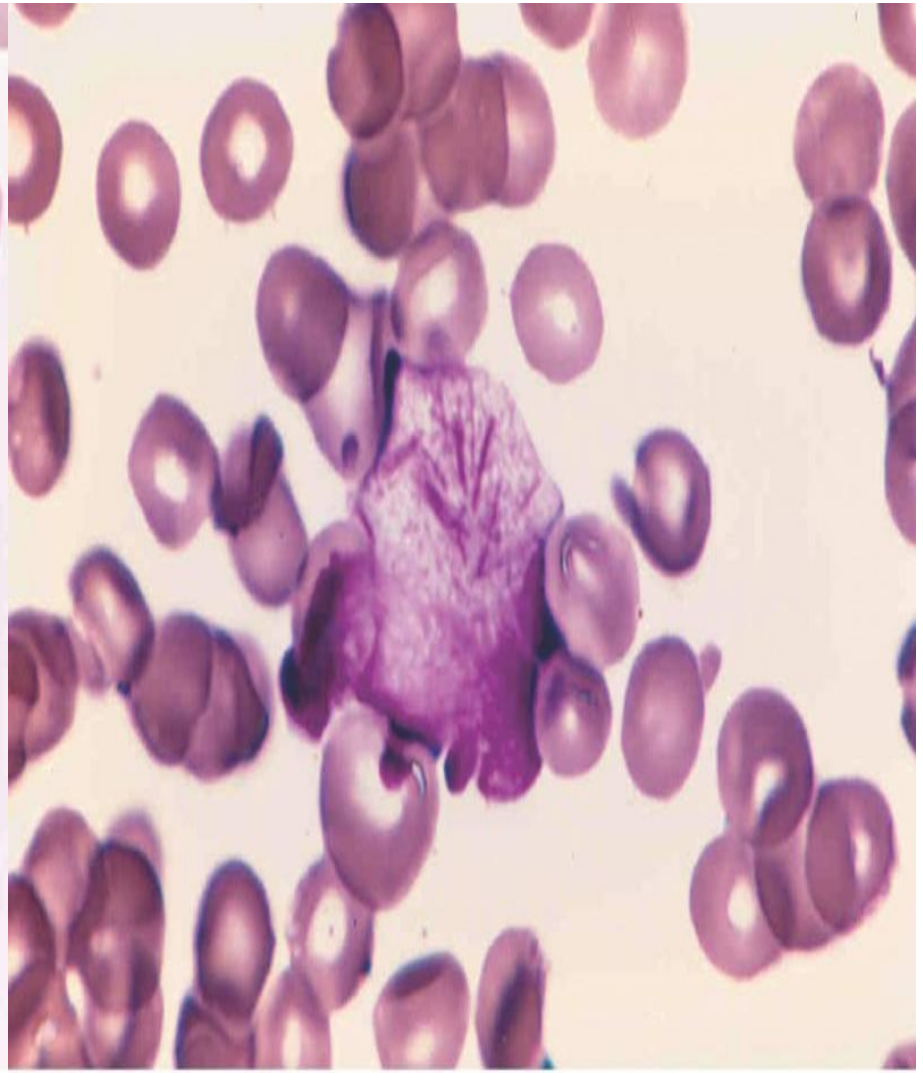
- Mikrogranüler varyant(%20)



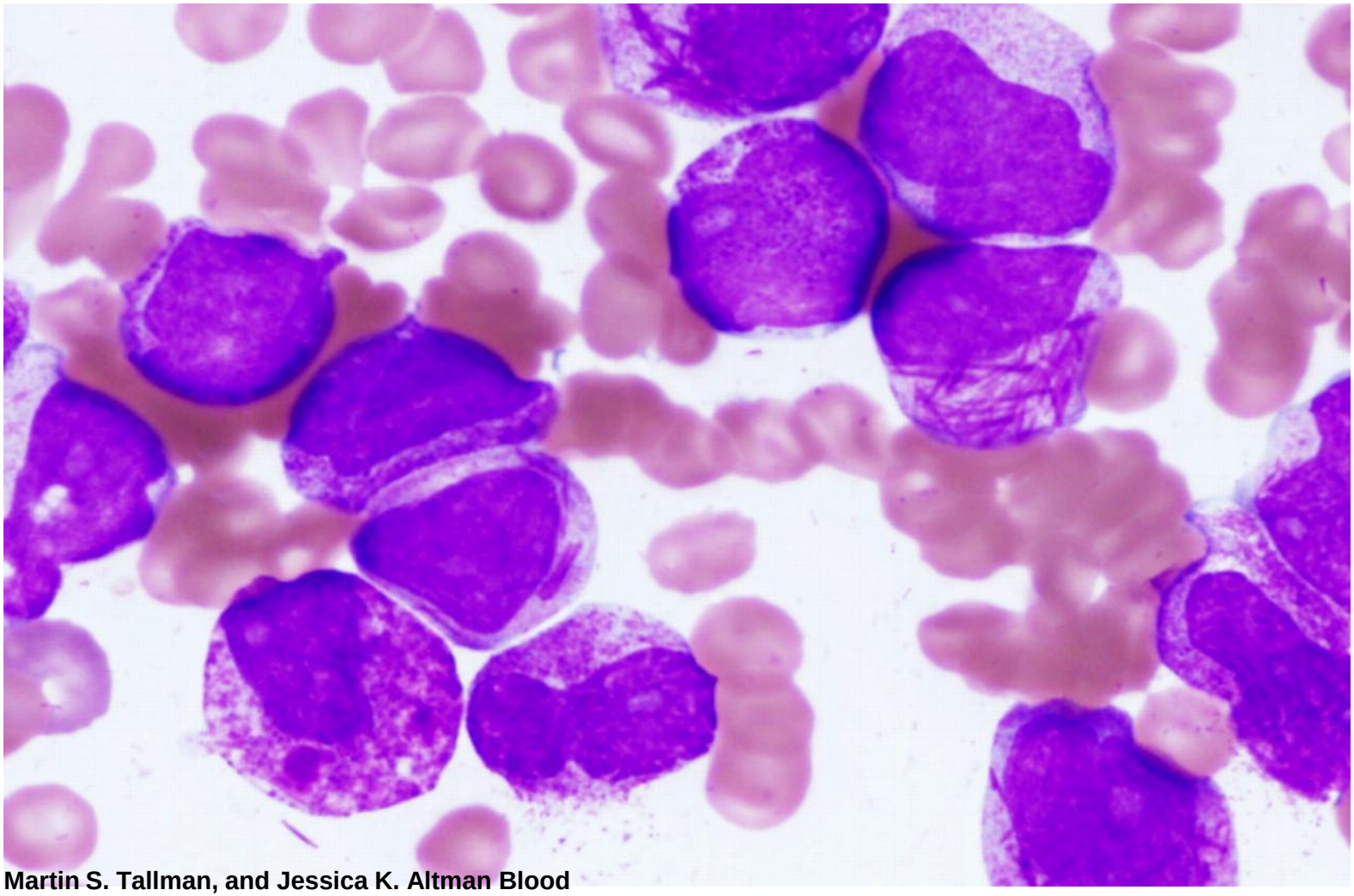
- t(11;17) ve diğer varyantlar

Morfoloji



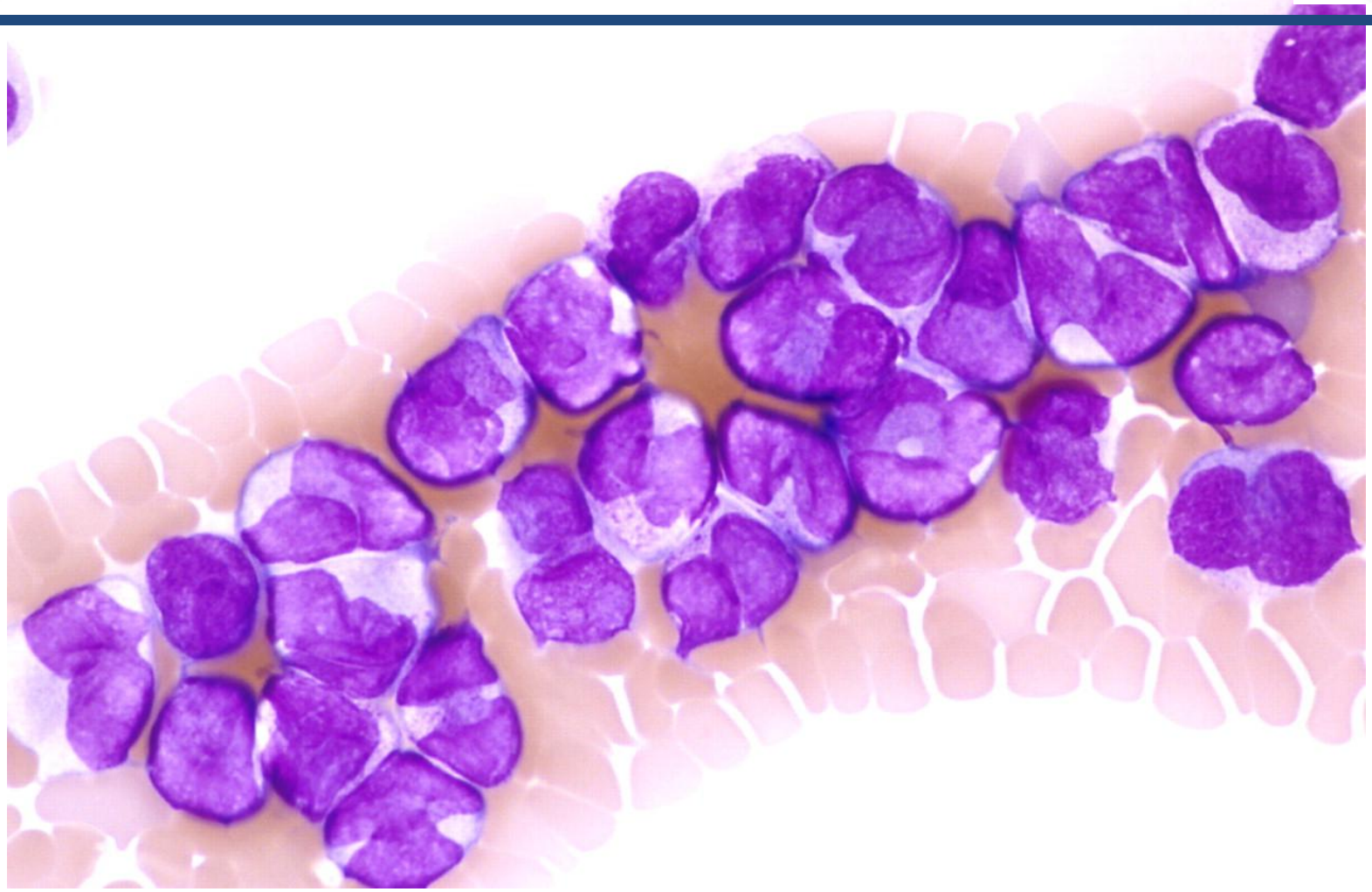


Morfoloji



Martin S. Tallman, and Jessica K. Altman Blood 2009;114:5126-5135

Morfoloji- M3v



Martin S. Tallman, and Jessica K. Altman Blood 2009;114:5126-5135

blood

İmmunhistokimya-İmmunfenotiplendirme:

- –**MPO ile kuvvetli boyanma vardır
- –Naftol-ASD- kloroasetat esteraz boyası pozitif (spesifik esteraz)
- **CD13(+) ve ** CD 33 (+) , ***HLA-DR (-)
- –***CD34 (-), ve TdT (-)
- -***CD 11b (-),***CD 117 zayıf veya değişken

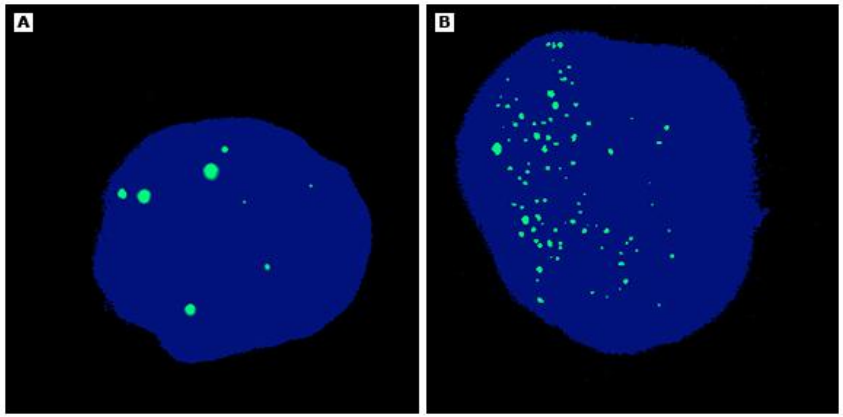
Genetik

- **Konvansiyonel karyotip**;
  - Yüksek derecede spesifik, kriptik translokasyonlar kaçırılabilir.
  - Nadir moleküler subtipler [t(11;17), t(5;17) ve diğer ek beraber bulunan sitogenetik anormallikler] tespit edilebilir.
- **FISH**
  - Daha kolay bir yöntem
  - Sensitivitesi kullanılan proba göre değişir
  - PML-RARA izoformu hakkında bilgi vermez, takipte kullanılmaz

Genetik

- **RT-PCR**
  - Tanı teyidinde **Gold Standart**
  - PML kırılma noktası belirlenebildiği için MRD takibinde kullanılabiliyor.

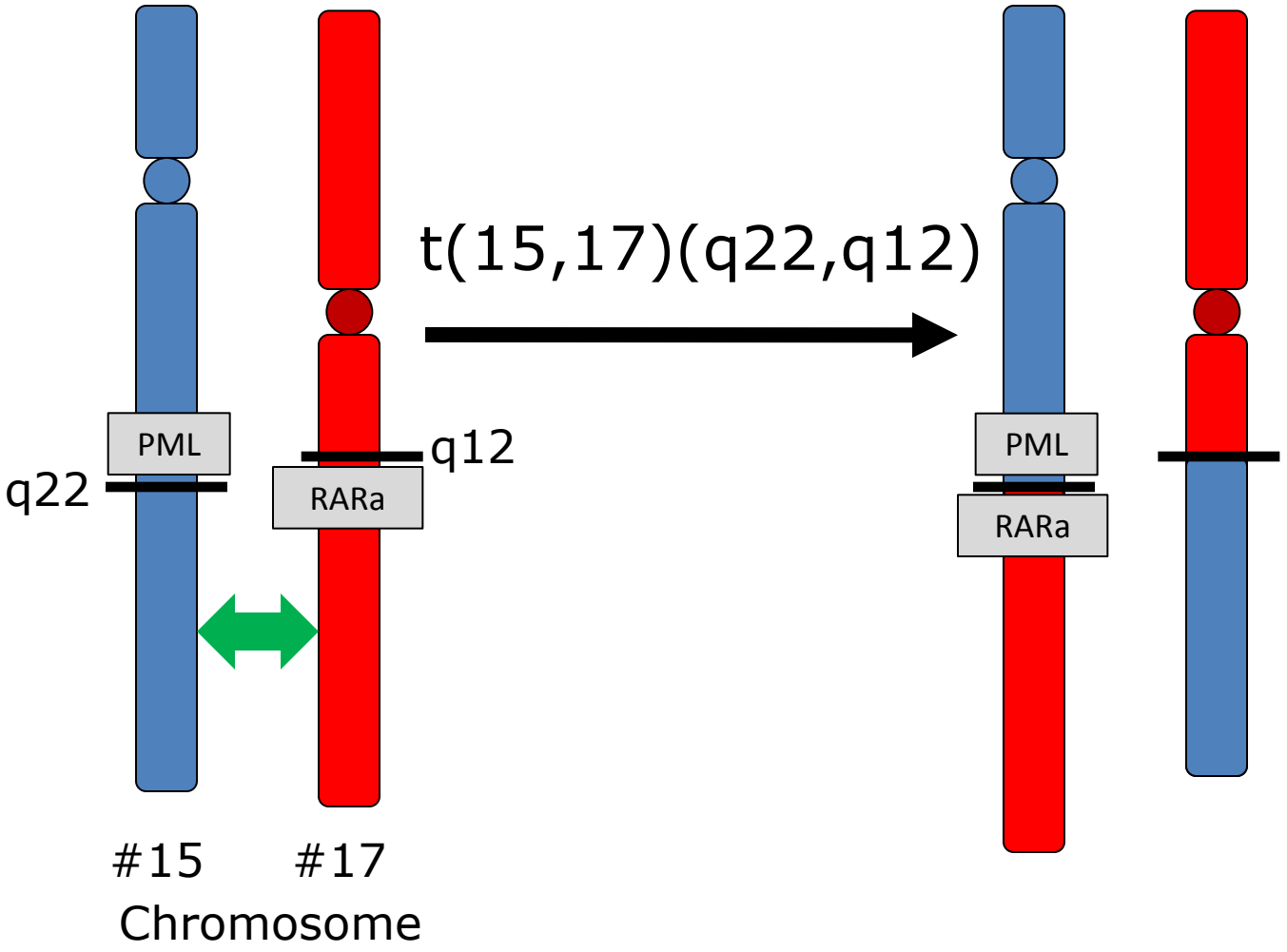
- Anti-PML monoklonal antikorlar
  - Saatler içinde sonuç alınabilir.



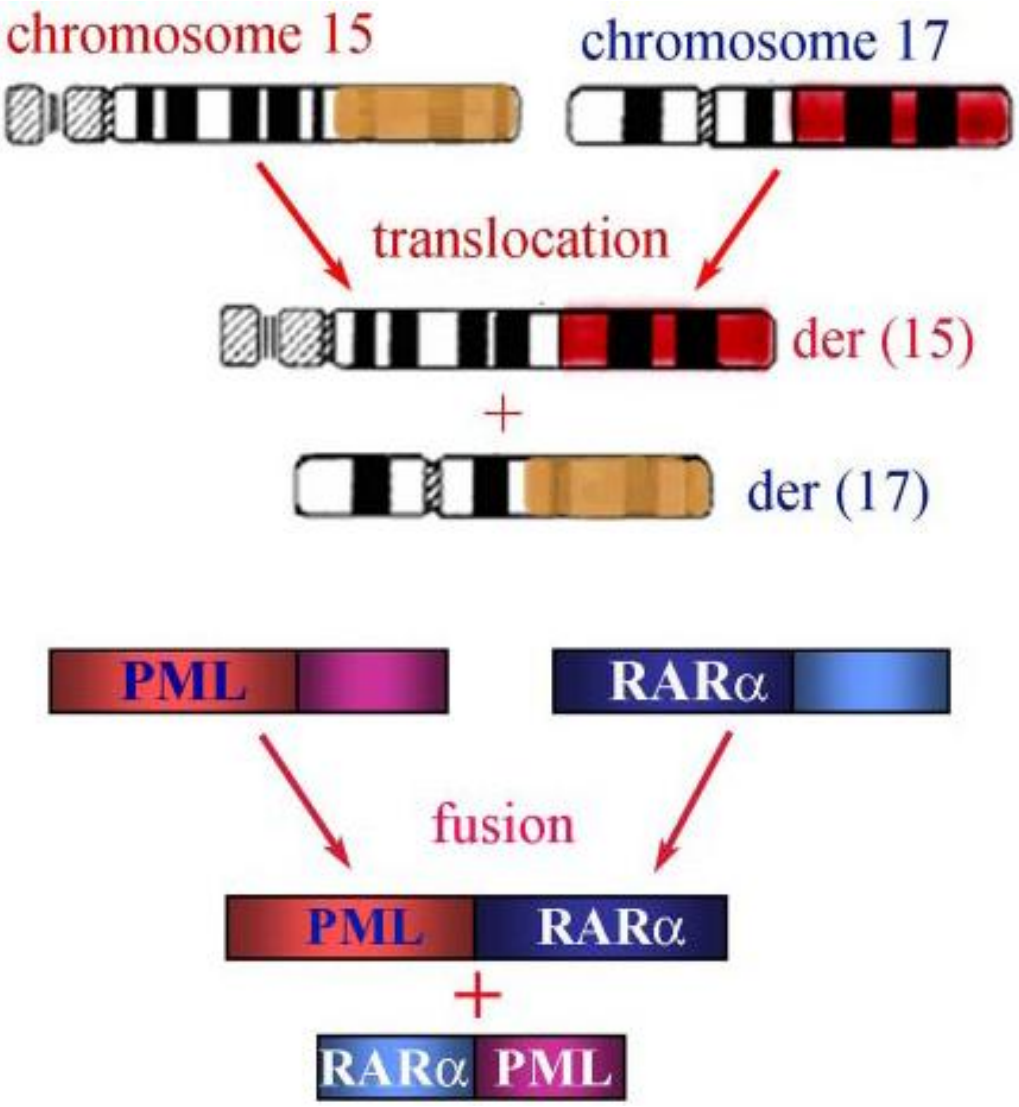
Genetik

- **Varyant RARA translokasyonlu AML**
  - t(11;17)(q23;q21) — PLZF/RARa, sıklıkla CD13+, CD56+→**ATRA tedavisine dirençli**
  - t(5;17)(q35;q21) — NPM1/RARa, sıklıkla CD13-, CD56-
  - t(11;17)(q13;q21) — NuMA/RARa

Patogenez



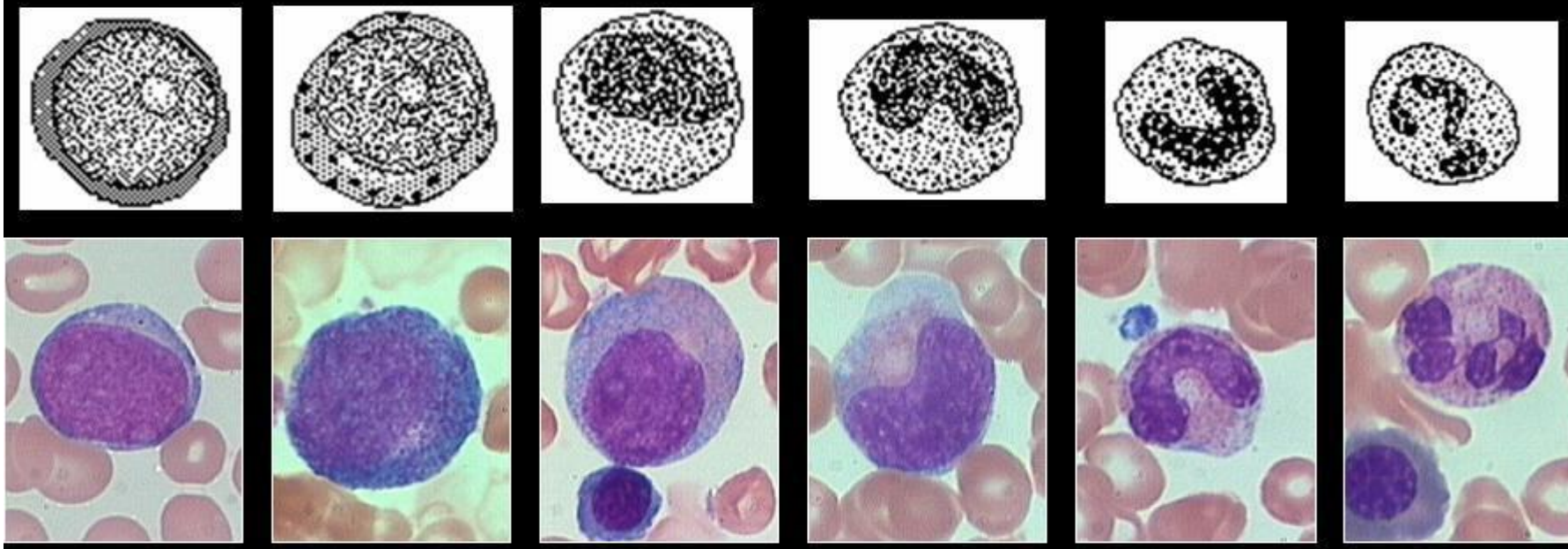
Patogenez



Maturasyon duraklaması

Myeloid maturasyon

myeloblast | promyelosit | myelosit | metamyelosit | band | nötrofil



MATURASYON DURAKLAMASI

KLİNİK BULGULAR

- Sitopenilere bağlı komplikasyonlar
- Diğer AML'lerden farklı olarak kanama komplikasyonları daha fazla
  - **DIC**→tanı anında veya kemoterapi başlayınca
    - **Doku faktörü** salınımı
    - Faktör X'u direkt aktive eden **kanser prokuagulanı**
    - Lösemik promiyelositlerde **annexin II reseptör ekspresyonu**

Koagülopati

Pathogenesis of Coagulopathy in APL

Mechanism	Putative Mediators
DIC	Tissue factor
	Cancer procoagulant
	Cytokines (IL-1, TNF)
Fibrinolysis	tPA, uPA, PAI-1
	Annexin
Proteolysis	Elastases (targets include fibrinogen and vWF)

Lösemik hücrelerde anneksin II'nin yüksek düzeyde ekspresyonu plazmin üretimini artırır

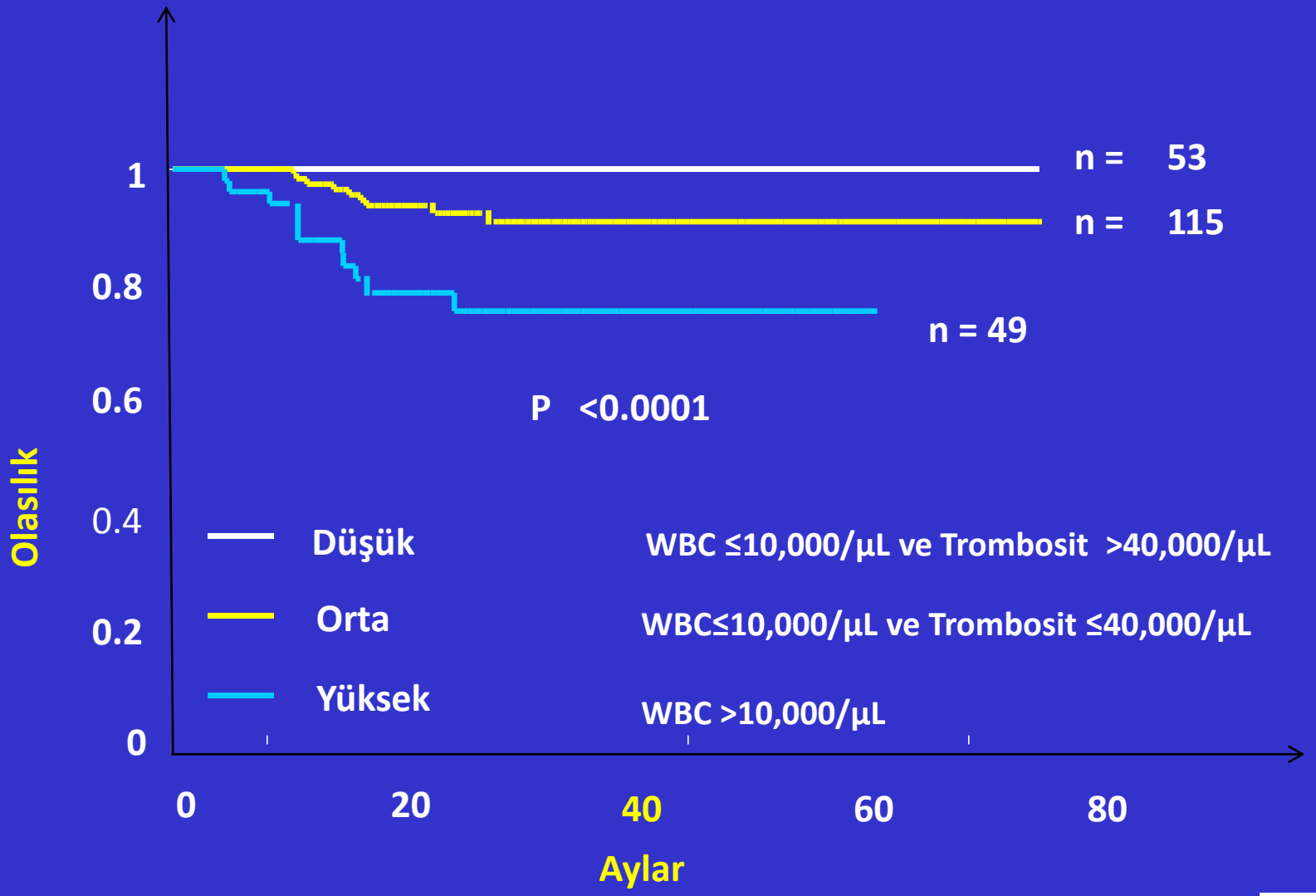
- AML-M3'de erken ölüm eşlik eden koagülopatinin bir sonucu olarak kanamadan kaynaklanır
  - TDP/KRYO, trombosit ile tedaviyi gerektirir.

Risk Sınıflaması

	Trombosit	WBC	3-yr relapse-free survival
Düşük Risk	**>40.000 mm^3**	**<10.000 mm^3**	**98%**
Intermediate	**<40.000 mm^3**	**<10.000 mm^3**	**89%**
Yüksek Risk	**<40.000 mm^3**	**>10.000 mm^3**	**70%**

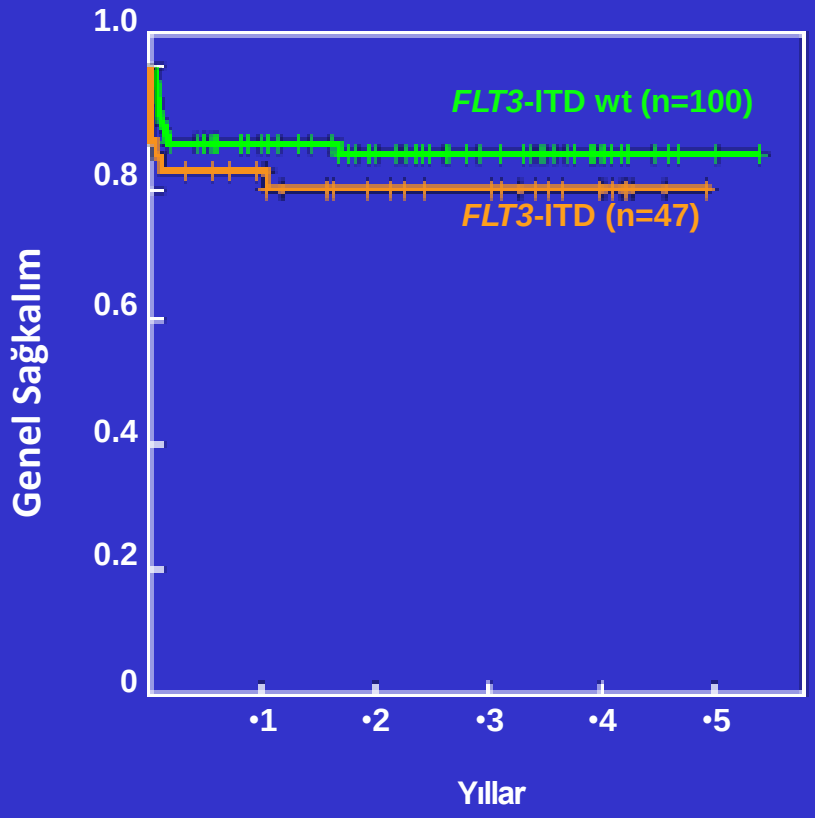
GIMEMA & PETHEMA ÇALIŞMASI

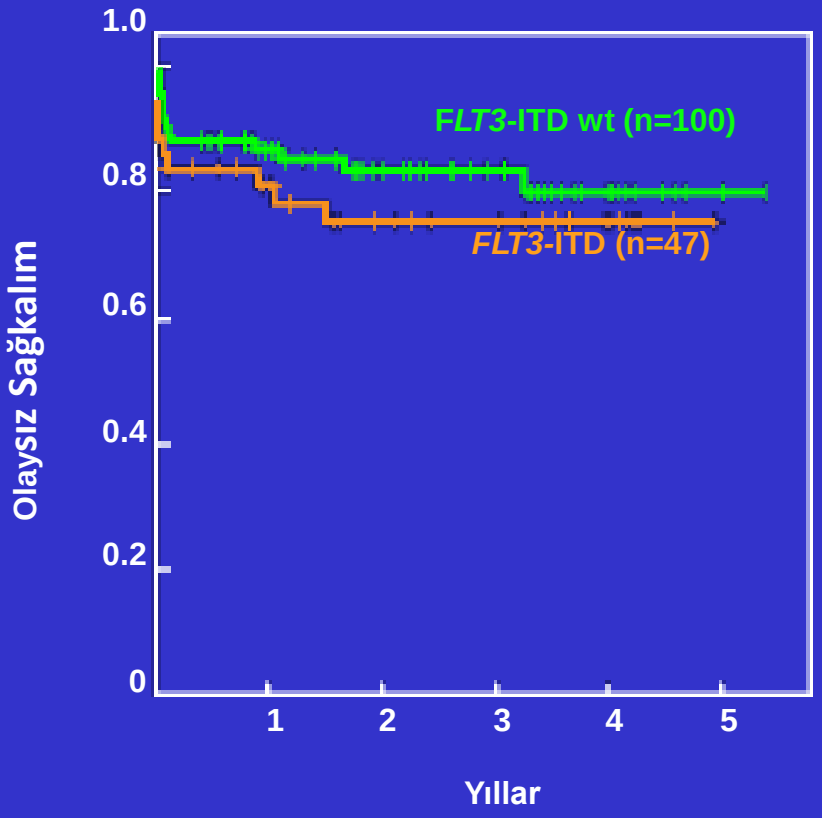
Sağkalım



Sanz et al. Blood, 2000

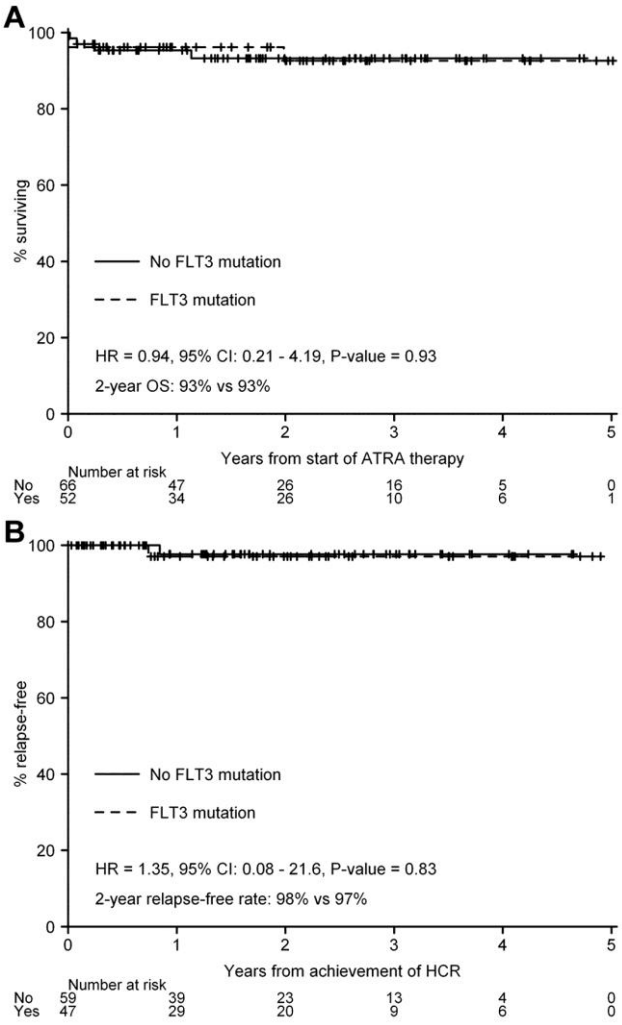
FLT3-ITD-Pozitif Hastalarda *FLT3*-ITD-Negatif Hastalara Kıyasla Genel Sağkalım ve Olaysız Sağkalım





Schnittger et al. Haematologica, 2011

Impact of FLT3 mutations on APML4 outcomes.



blood

Harry J. Iland et al. Blood 2012;120:1570-1580

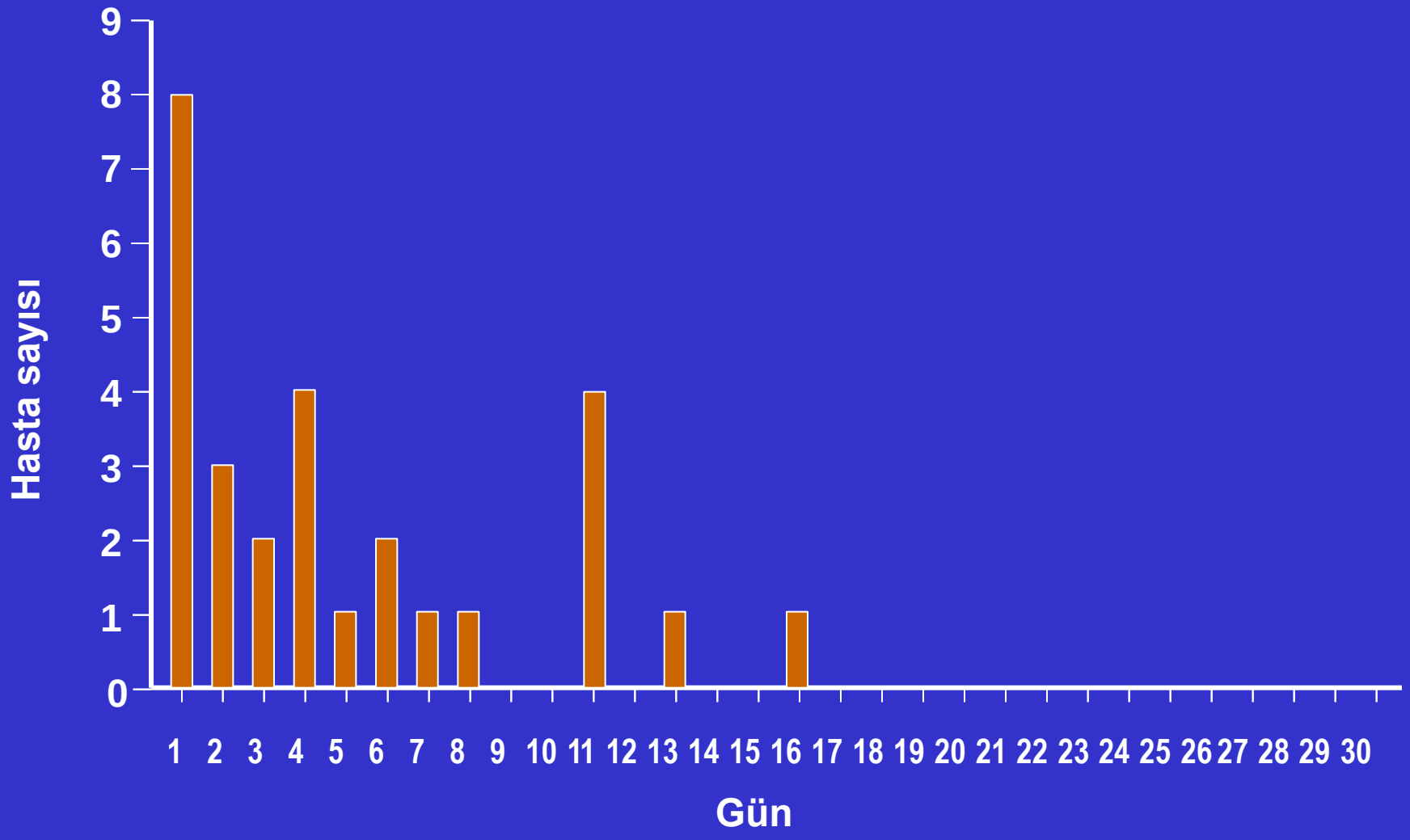
İndüksiyonda Farklı Özellikler

- Ek bir sitogenetik anormallik,tedavi ile ilişkili APL, FLT3 mutasyonu, CD56, PML izoform veya morfolojisine (M3V) dayalı **tedavi değişiklik yok**,
- Kemik iliği aplazisi zorlaması yok

- 14.Günde kemik iliği önerilmez
  - Yanlış yönlendirici olabilir, sıklıkla prognostik değeri olmadan hala molekül pozitif

- TR'da kemik iliği gerekmeyebilir
  - Primer direnç yok
  - TR1'e ilk olarak indüksiyonun sonunda ulaşıldığında sito/moleküler genetiğin prognostik önemi

Tanıdan Ölüme Kadar Geçen Süre



Lehmann et al. Leukemia, 2010

APL'de Erken Ölüm Oranı

İleriye Dönük Çalışmalar

Çalışma	N	İndüksiyon	TR %	EÖ %	Kanama nedeniyle EÖ %	DFS %
PETHEMA	732	ATRA + Ida	91	7	69	86
JALSG	283	ATRA/ida/ara-C	94	5	69	69
GAMLCG	142	ATRA/TAD/HAM	92	8	64	82

Sanz et al. Blood, 2008; Asou et al. 2007; Lengfelder et al. Leukemia, 2009 Blood,

APL'de Erken Ölüm

Popülasyon Tabanlı Çalışmalar

Çalışma	N	EÖ
Jeddi	41	%16
Lehmann	99	%31
Alizadeh	137	%14
Park	1,400	%18

Jeddi et al. Hematology, 2008; Lehmann et al. Leukemia, 2010; Alizadeh et al. ASH, 2009; Park et al. Blood, 2011

APL'de Erken Ölüm Oranı

- Klinik çalışmalarda bildirilenlerden daha yüksek
- APL'den ilk şüphe edildiğinde EÖ'lerde ATRA verilirse azaltılabilir
- Çok sayıda değişik alandan doktorun eğitilmesi öncelik taşımalıdır

APL'de Erken Ölümün Önlenmesi

- İlk şüphe edildiğinde ATRA (klinik öykü ve periferik yaymaya dayalı), KEMİK İLİĞİNDEN ÖNCE, TANI TEYİT EDİLMEDEN ÖNCE
- ≥ 50,000/μL olacak şekilde sık trombosit transfüzyonu
- Fibrinojeni ≥150 mg/dL'de tutmak için kriyoterapi
- Rutin heparin yok
- Rutin antifibrinolitik yok

Rodeghiero et al. Blood, 1990; Tallman et al. Leukemia Res, 2004; Sanz et al. Blood, 2008

All-transretionik asit (ATRA)

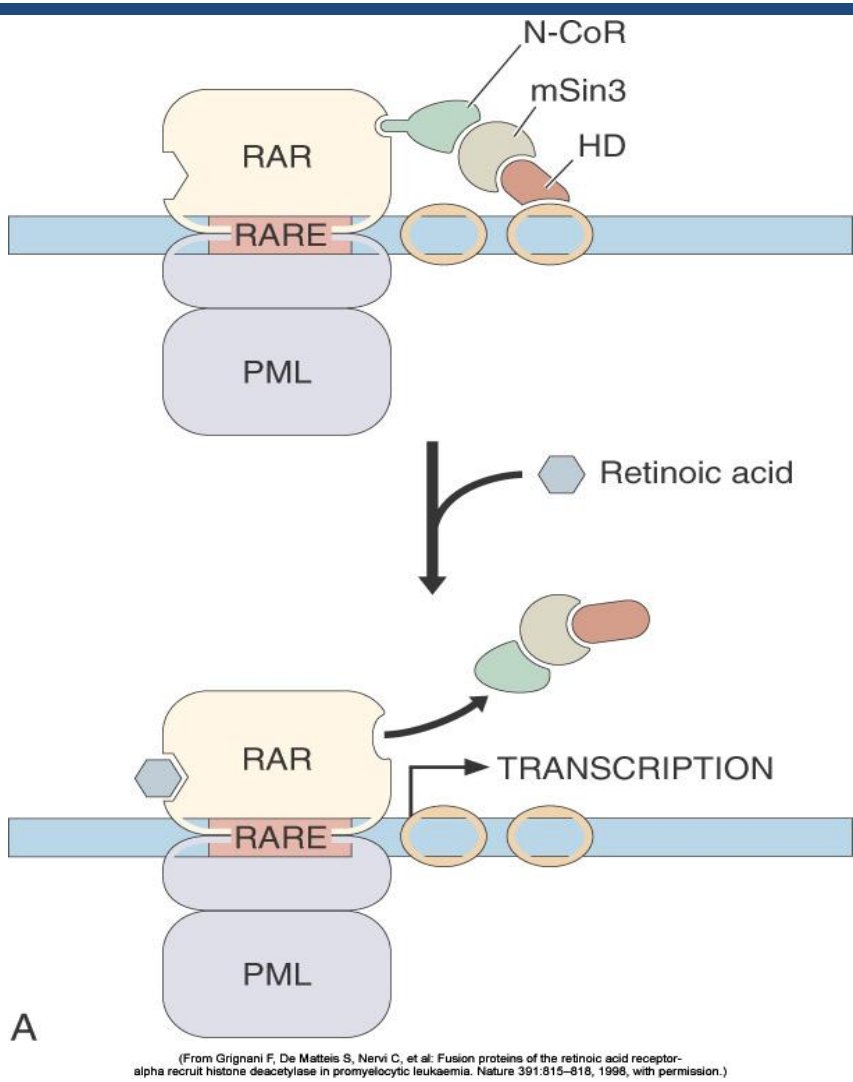
- ATRA tedavisi morfolojik olarak APL düşünüldüğünde başlanır.
- Sitogenetik sonucunu beklemeye gerek yok.
- Eğer t(15;17) negatif gelirse ATRA kesilir ve standart AML tedavisi başlanır.
- WBC sayısı <10.000 ise indüksiyon tedavisinden 2 gün önce ATRA başlanır (bu şekilde DIK gelişimi önlenir; Direkt ATRA ile DIK ihtimali daha düşük)
- ATRA diğer KT ajanlar gibi hızlı hücre yıkımına yol açmadığı hatta tedavinin başlangıcından itibaren 5-8.günlerde koagülopatide düzelmeler sağlayabilir.

Koagülopati tedavisi

- ATRA tedavisi ile tümör litik etkiden daha belirgin olarak prokoagülan etki görülebilir.
  - Pıhtılaşma bozukluğunu düzeltici bazı etkilere sahiptir.
  - Anneksin II RNA aşırı ekspresyonu ATRA tedavisinden sonra kaybolur.
    - Lösemik hücrelerde anneksin II'nin yüksek düzeyde ekspresyonu plazmin üretimini artırır.
    - Anneksin II'nin aşırı ekspresyonu hemorajik komplikasyonların bir mekanizması olabilir.
- Paradoksik olarak da; hiperkoagülabl bir pıhtılaşma eğilimi ATRA tedavisinin ilk aylarında görülebilir.

ATRA etki mekanizması

- ATRA selektif olarak PML-RAR-α bağlanıp diferansiasyonu suprese eden protein kompleksinin RARA'dan ayrılmasını sağlayarak etkisini inhibe eder.
- ATRA; PML-RARA füzyon proteinine bağlanınca nükleer transkripsiyonel represör kompleksi (N-CoR+mSin3A+HD) ayrılır ve
  - **Histon asetilasyonu artar**
  - **Kromatin yapımı artar**
  - **Transkripsiyonel aktivite yeniden artar**
  - **Sonuçta transkripsiyonel supresyonun ortadan kalkması ile hücre diferansiasyonu, apoptozis ve hemostazı sağlanır**



(From Grignani F, De Matteis S, Nervi C, et al: Fusion proteins of the retinoic acid receptor-alpha recruit histone deacetylase in promyelocytic leukaemia. Nature 391:815–818, 1998, with permission.)

APL Tedavi: KT, ATRA veya Kombine

- Tek başına Antrasiklin tabanlı KT (+ARA-C) ile TR= %70-80
  - Uzun süre sağkalım**= %35-45**
  - Tek başına KT koagülopatiyi tetikler; KT sonrası olguların **%10-15'inde öldürücü kanamalar**
- Tek başına ATRA (45 mg/m2/gün) oral uygulaması TR= %75-95
  - Hematolojik TR genelde 5-6 hafta arasında sağlanır
  - ATRA'nın sağladığı **TR geçici olup; tek başına kullanılırsa 3-12 ay içinde nüks gelişir**
  - Kronik oral ATRA kullanımı; plazma konsantrasyonunda aşamalı bir azalmaya ve sonuçta nüks gelişir.
- ATRA ile KT Kombinasyonu
  - Uzun süreli remisyon için (**ATRA'nın uyardığı TR'nun yoğun KT rejimleri ile konsolidasyonu)**
  - ATRA direnci önlemek için (retinoik asit bağlayan bir protein)
  - Uzun süreli yaşam beklentisi **%80'lerin üzerindedir**

ATRA tedavisi izlemi

- Tedavinin ilk 2 haftasında WBC yükselir.
- Serum ALT ve trigliserid düzeyi artar.
- Promyelositler 2-4 hafta içinde periferik kanda kaybolur ve normal bir kemik iliği 4-10 haftalarda izlenir.
- Anemi düzelir.
- ATRA ile **2. konsolidasyon tedavisinden sonra hastaların çoğunda PML-RAR-α PCR ile negatif** olur.

APL Farklılaşma Sendromu

- Ateş, nefes darlığı, sıklıkla WBC artışı, hipoksemi, plevral/perikardiyal efüzyonlara karşı tetikte olun

- Günde iki kez 10 mg Dxm, **İLK SEMPTOM VEYA BELİRTİ GÖRÜLÜR GÖRÜLMEZ, TANI KONMADAN ÖNCE**

- Hipoksemi şiddetli ise ATRA veya ATO'yu kesin; semptomlar/belirtiler steroidlerle çözümlendiğinde geri dönün

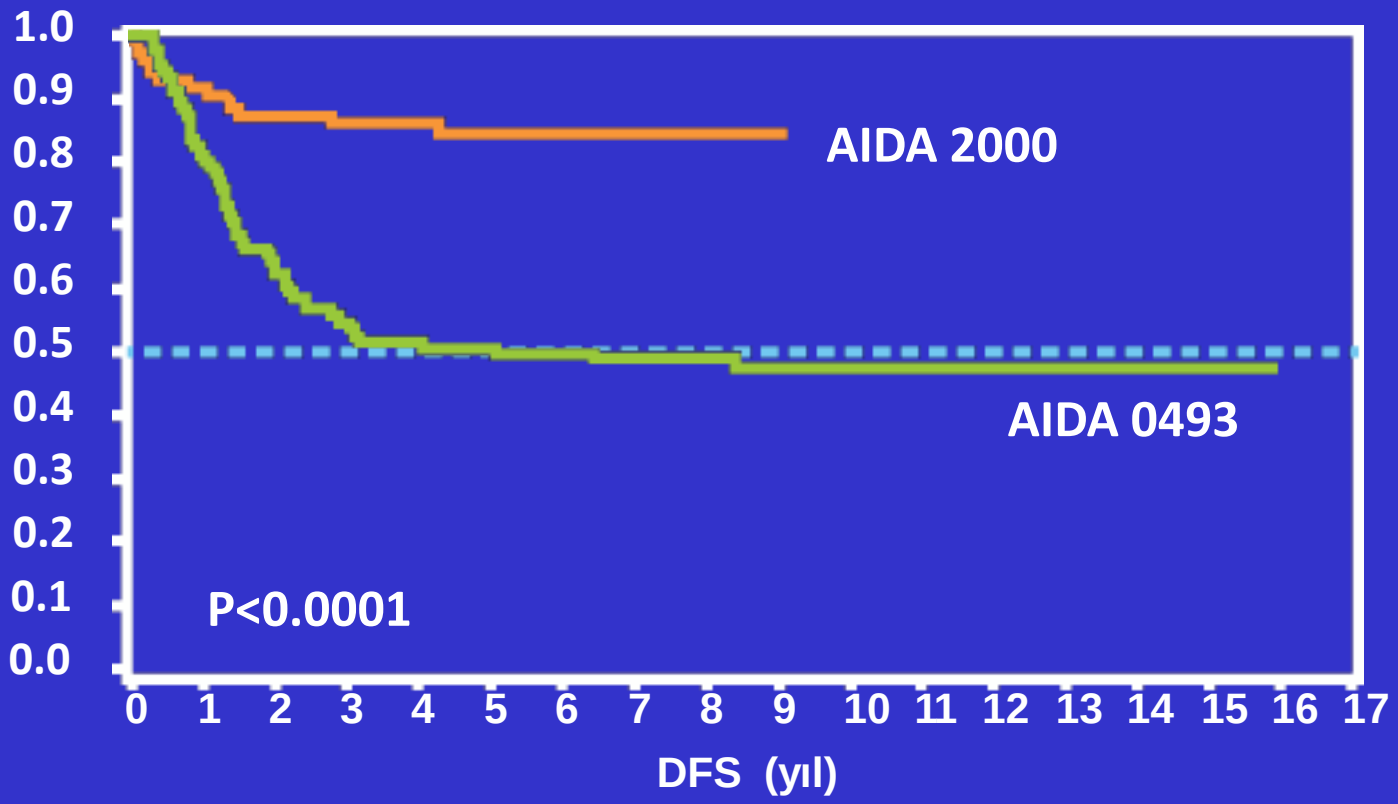
Wiley et al. Leukemia, 1995; Sanz et al. Blood, 2004; Tallman and Altman Blood, 2009

YÜKSEK-RİSK PROTOKOLLERİ

TEDAVİ PROGRAMI	İNDÜKSİYON	KONSOLİDASYON	İDAME
Amerika C9710	ATRA/D/Ara-C	C1: ATRA/ATO x 2	ATRA/6-MP/MTX
		C2: ATRA/D x 2	
PETHEMA LPA2005	ATRA/Ida	C1: ATRA/Ida/IDAC	ATRA/6-MP/MTX
		C2: ATR A/Mitox	
		C3: ATRA/Ida/SD Ara-C	
GIMEMA AIDA2000	ATRA/Ida	C1: ATRA/Ida/IDAC	ATRA/6-MP/MTX
		C2: ATRA/MTX/VP16	
		C3: ATRA/Ara-C/6-TG	
European APL2000	ATRA/D/Ara-C	D/Ara-C, sonra D/IDAC	ATRA/6-MP/MTX
• «Karıştırıp eşleştirmeyin» • Çoçuklarda ve ergenlerde düşük doz ATRA kullanın	• Profilaktik Deks	• İndüksiyondan sonra konsolidasyondan önce LP	

Protokole göre Hastalıksız Sağkalım

Yüksek-risk



Lo Coco et al. Blood, 2010

DÜŞÜK-RİSK PROTOKOLLERİ

TEDAVİ PROGRAMI	İNDÜKSİYON	KONSOLİDASYON	İDAME
Amerika C9710	ATRA/D/Ara-C	C1: ATRA/ATO x 2	ATRA/6-MP/MTX
		C2: ATRA/D x 2	
PETHEMA low-risk	ATRA	C1: ATRA/Ida	ATRA/6-MP/MTX
		C2; ATRA/Mitox	
		C3: ATRA/Ida	
GIMEMA APL0406	ATRA/ATO	C1: ATRA/ATO	Yok
		C2: ATRA/ATO	
European APL2000	ATRA/D/Ara-C	D/Ara-C sonra D/IDAC	ATRA/6-MP/MTX
	WBC>10,000 ise dxm ekle	Her konsolidasyon öncesinde kardiyak fonksiyonu değerlendir.	

MRD TAKİBİ

- Konsolidasyon sonrasında kemik iliğinden moleküler TR belgeleyin
- Düşük-risk: 5 yılda %1 Genel Sağkalım faydası
- Yüksek-risk: 5 yılda %10 Genel Sağkalım faydası
- Aşağıdaki durumlarda Periferden her 3 ayda bir 2 yıl süreyle MRH takip edin
    - yüksek-risk
    - hastalar > 60 yaş
    - Kesinti uygulanan ya da idameyi tolere edemeyen hastalar
- Düşük-risk: gerekli olmayabilir
- PCR pozitifse, 2-4 haftada tekrarlayın; pozitifse, relaps gibi tedaviyi uygulayın

Grimwade et al. J Clin Oncol, 2009; Grimwade and Tallman Leukemia Res, 2010

ARSENİK TRİOKSİT

- Mitokondrial/intrinsik yada ekstrinsik apoptoza neden olmakta
  - **Yüksek konsantrasyonda hücrelerde apoptozisi ve**
  - **Düşük konsantrasyonda maturasyonu uyarabilir**
- Hematolojik toksisitesi nisbeten az
  - Hücrenin G1 evresinde durmasıyla açıklanabilir
  - Hücreler için G1 siklus bloku, G2/M hücre siklusu blokuna göre daha az toksik ve geri dönebilir bir durum

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Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

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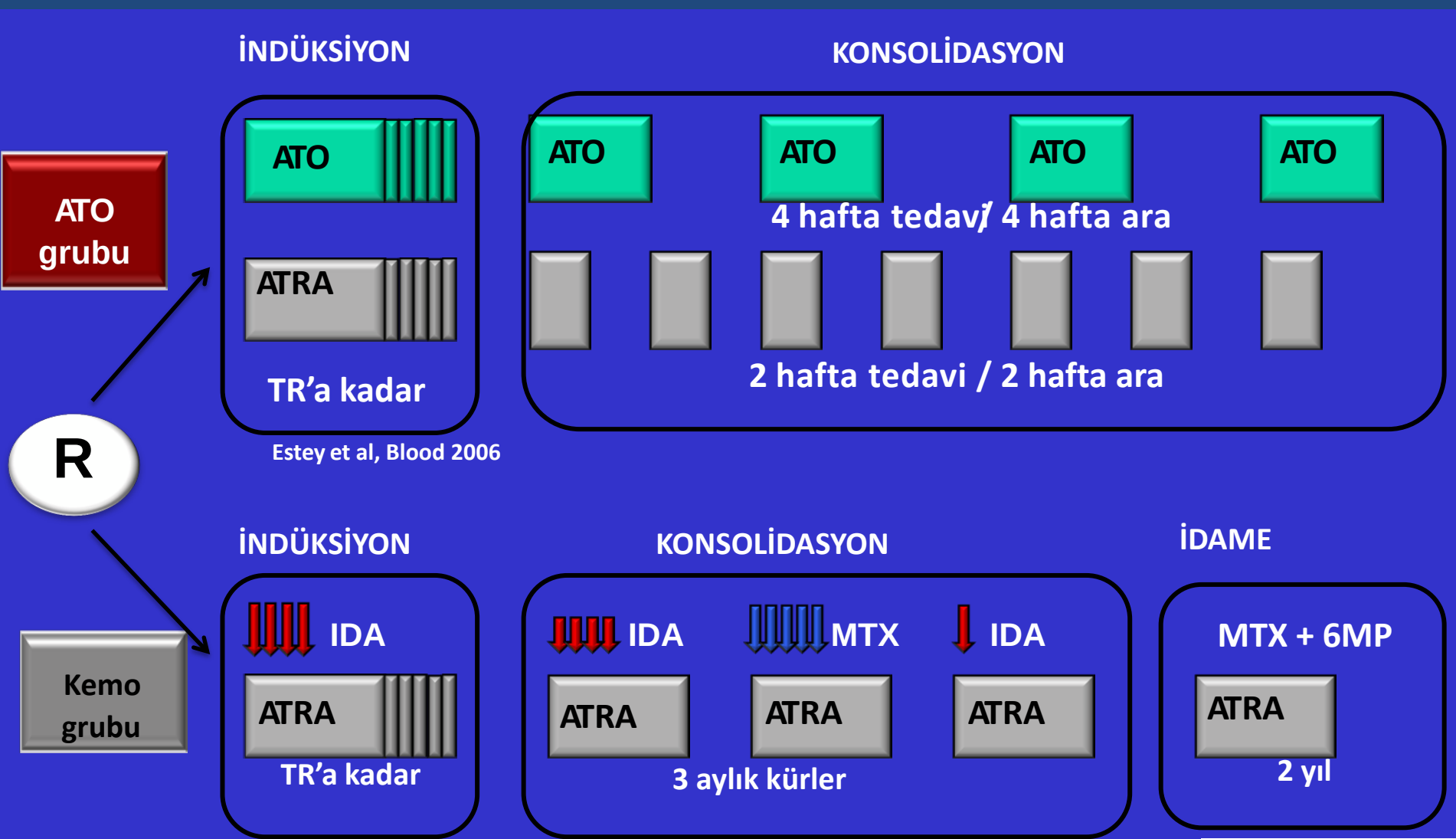
APL 0406 ÇALIŞMASI: TEDAVİ



Lo Coco et al. NEJM, 2013

APL 0406 Çalışması (GIMEMA/SAL)

Dahil Edilme Kriterleri

- Yeni tanı APL
- 18 - 70 yaşları arası
- WBC ≤10 x 10^9/L
- WHO performans durumu≤ 2

Lo Coco et al. NEJM, 2013

APL 0406: İndüksiyon Sonucu

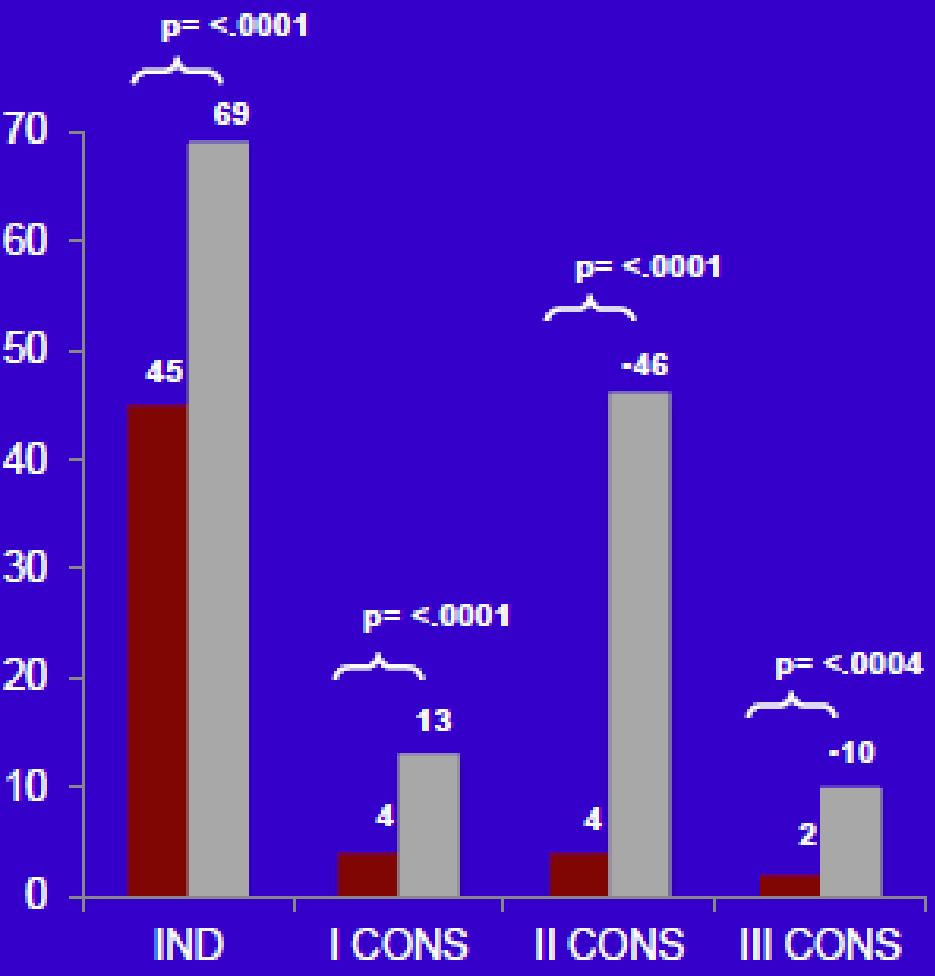
	ATRA + ATO	ATRA + KT
Hasta sayısı	75	79
TR	75 (%100)	75 (%95)
İndüksiyon ölüm	0	4*
Dirençli hastalık	0	0

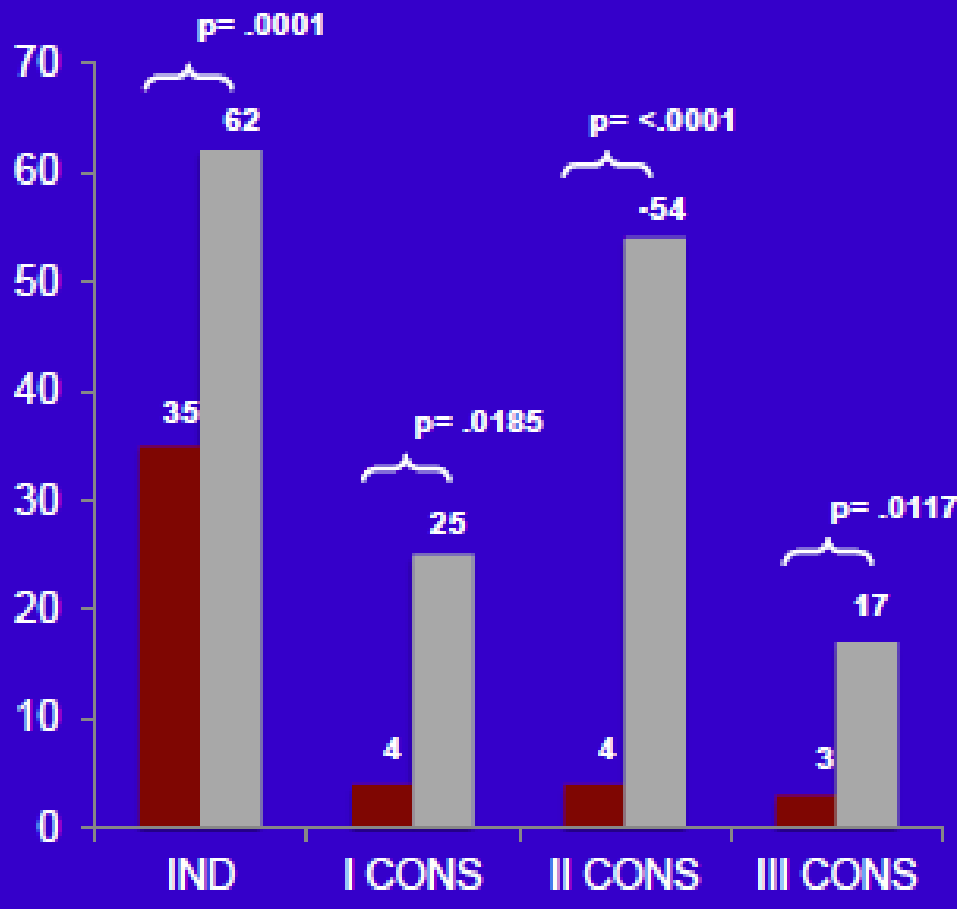
- *Farklılaşma sendromu (2), iskemik CVA (1) ve pnömoni (1)

Lo Coco et al. NEJM, 2013

APL 0406: Hematolojik Toksisite

- **Derece 3-4 trombositopeni > 15 gün**
- **Derece 3-4 nötropeni > 15 gün**





ATO Chemo

Lo Coco et al. NEJM, 2013

APL0406: Diğer Toksisiteler

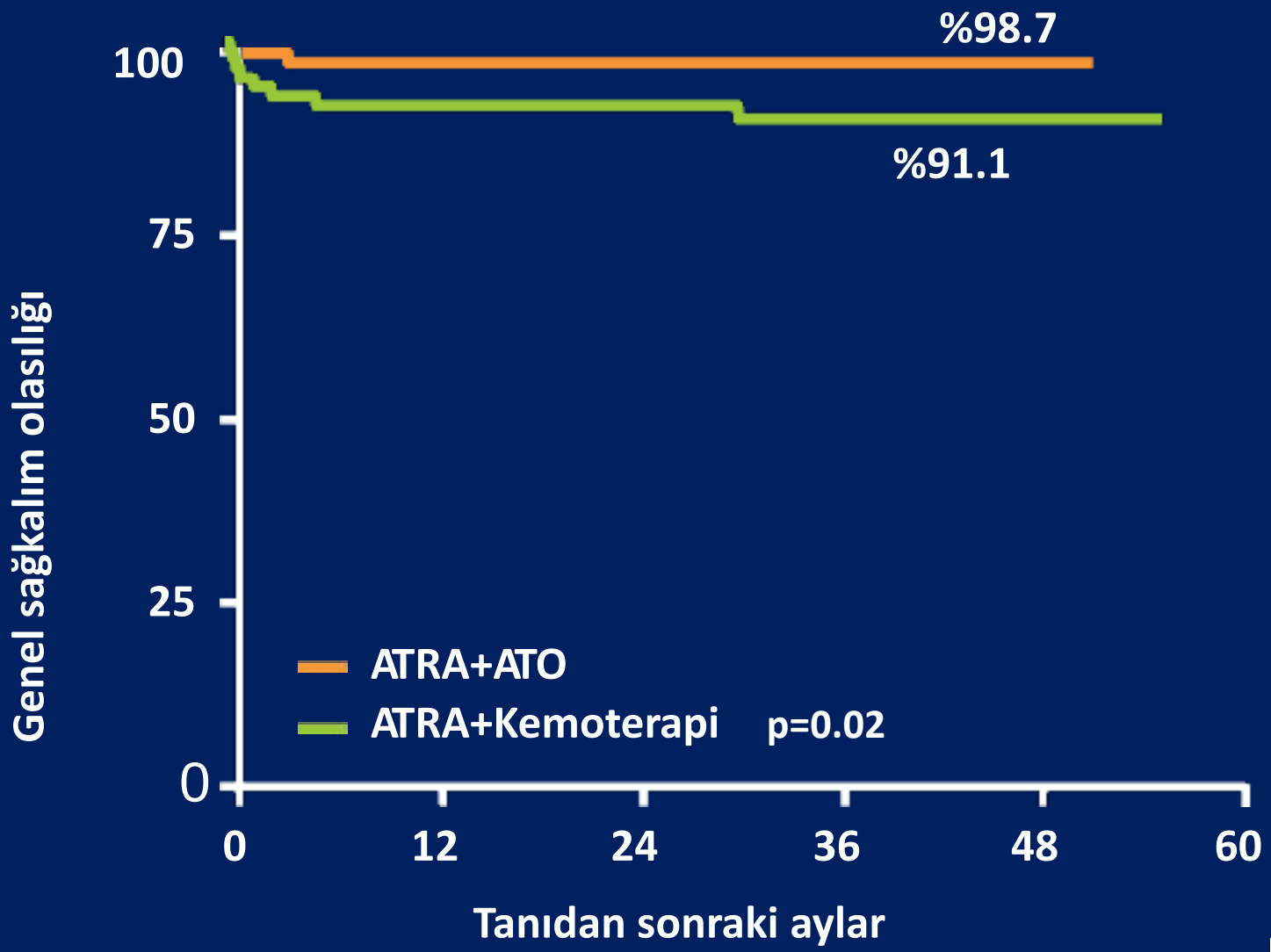
Toksisite	ATRA+ATO	ATRA+KT	P değeri
QTc uzaması[1],%	%13	0	0.0005
KcToksisite[1](Derece 3-4), %	%57	%5	<0.0001
Lökositoz[2](>10x10^9/L), %	%47	%24	0.007

1.ATO'nun geçici olarak kesilmesi ve doz modifikasyonuyla tedavi edilir

2.Hidroksiüre 500 mg x3/gün (WBC < 50.000) ve 1 g x3/gün (>50.000)

Lo Coco et al. NEJM, 2013

APL 0406 ÇALIŞMASI: GENEL SAĞKALIM



Lo Coco et al. NEJM,2013

İNDÜKSİYON

- Varsa klinik çalışma
- ATRA + Ida (veya dauno + ara-C)
- ATRA + ATO (yüksek riskte + ida)
- Yüksek riskte SSS profilaksisi (her konsolidasyonla IT x 6 veya iki kez)

Tallman and Altman Blood, 2009; Lo Coco et al. NEJM, 2013; Iland et al. Blood 2012

KONSOLİDASYON

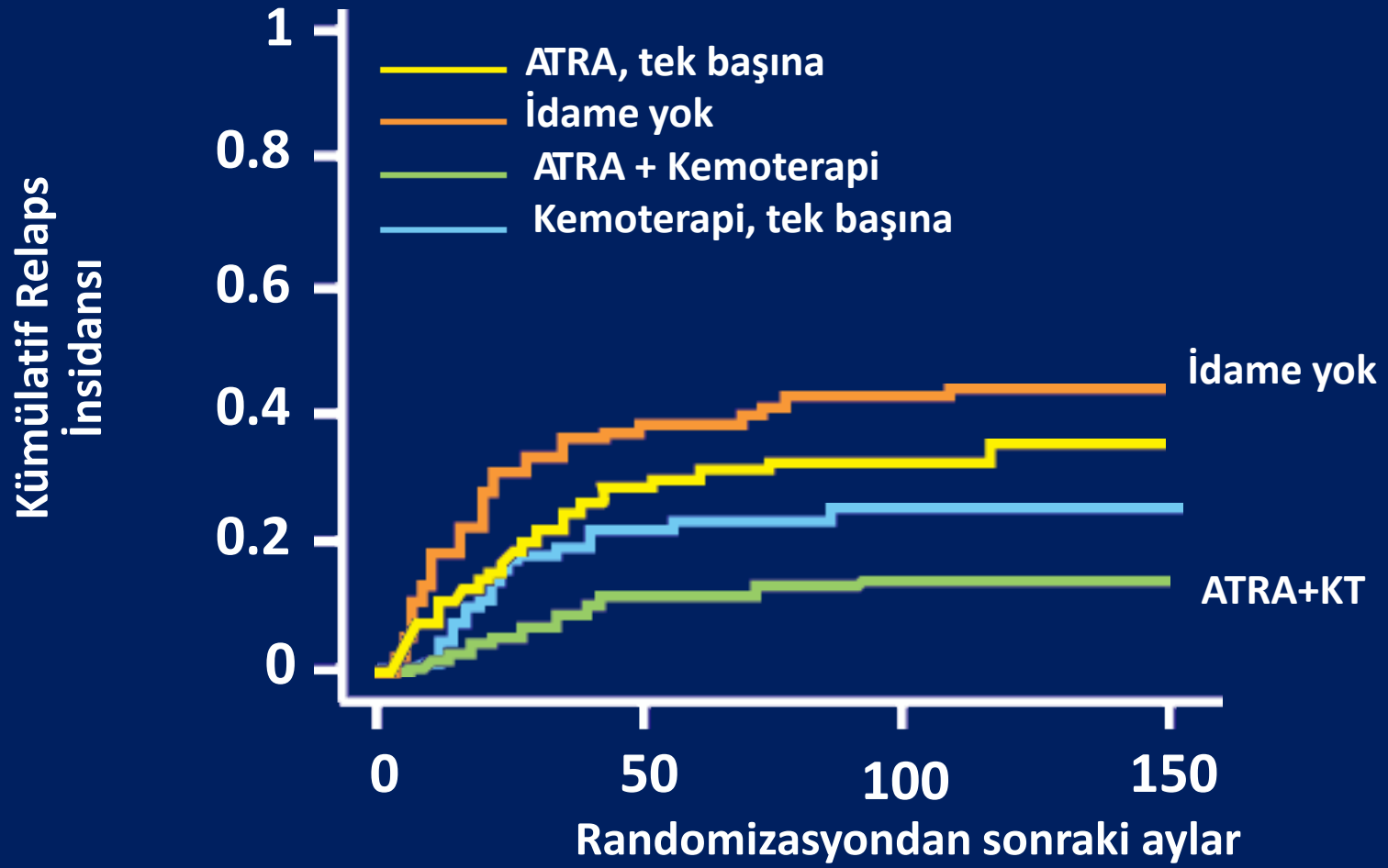
- 2-3 kür antrasiklin-tabanlı KT (%95'inde moleküler TR'e yol açar)

- Geçmişte yapılan ardışık seri karşılaştırmalarına dayanarak her döngüde 1-2 hafta süreyle ATRA

- Yüksek risk grubundaki hastalara
  - konsolidasyonda IDAC veya
  - konsolidasyonda ATO

Mandelli et al. Blood, 1997; Diverio et al. Blood, 1999; Sanz et al. Blood, 2009; Powell et al. Blood, 2010

KÜMÜLATİF RELAPS İNSİDANSI



Ades et al. Blood, 2010

İntergrup C9710: ATO konsolidasyon çalışması

- North american intergroup protokol C9710; 5 grup; CALGB, ECOG, SWOG, COG,NCIC-CTG, Randomize Faz-III çalışma
- Amaç:
  - Yeni tanı APL olgularında ilk post-remisyon tedavisi olarak İki 25 günlük (5 gün/hafta, 5 hafta) arsenik trioksit kürünün fayda ve toksisitelerinin değerlendirilmesi

Powell BL, et al. Blood 2010;116:3751-3757.

İntergrup C9710: ATO konsolidasyon çalışması

- N= 518, Yaş= 15-79 yaş, Median takip= 29 ay
- TR=
  - TR oranı %89 olup her 2 kolda fark yok
- Ölüm=
  - İlk 60 günde %8 ölüm (n=41)
  - Toplam olarak hastaların %84'ü canlı
- EFS= (%20 fark var)
  - ATO kolunda 3-yıllık EFS = %77
  - Standart kolda 3-yıllık EFS = %59 (p=0.0013)
- OS= (%10 fark var)
  - Arsenik kolunda 3-yıllık OS = %86
  - Standart kolda 3-yıllık OS = %77 (p=0.029)
- Sonuç:
  - Remisyon indüksiyonu takiben 2 kür arsenik trioksit konsolidasyonunun eklenmesi erişkinlerde EFS ve OS düzeltmekte

Powell BL, et al. Blood 2010;116:3751-3757.

İdame Tedavi

- Konsolidasyondan idameye geçiş için ardışık 2 ay PCR ile t(15;17) negatif olmalı
  - Hastalar 3 aylık dönemler halinde PCR ile t(15;17) yönünden araştırılmalı
- İdame tedavi randomize çalışmalarda test edilmemiştir.
- İdame tedavi alan çalışmalarda remisyon süresi daha uzun gözükmekte
- İdame tedavide ATRA ile birlikte oral kullanılabilen ajanlar Mtx ve 6-MP/6TG 2-3 yıl süre ile kullanılmaktadır.
- ATRA idame tedavisi alan hastaların %70'inde 2.5 yıl süren remisyon görülmekte
  - ATRA almayan hastalarda ise bu oran %20

İDAME

- İdamenin indüksiyon ve konsolidasyonun yoğunluğuna bağlı olması olasıdır
- Şu an için, idameyi kullanılan protokole göre verin;
- ATRA+ATO ilk tedavi olarak verildiği takdirde idame verilmeyebilir, ancak açık değildir (APL0406 sadece 2 yıllık takiple yayınlanmıştır)

Relasp APL

- Relaps sonrası Konvansiyonel KT rejimleri etkili
  - ATRA ve KT tekrar kullanılabilir
- Arsenik ve gemtuzumab ozogamisin (CD33-directed immünkonjugat) çok etkili
  - >%80 remisyon oranları
  - Konsolidasyonu takiben aynı oranlarda RT-PCR negatifliği bildirilmekte
    - Bu durum Oto-KHT kapısını açmakta
- Oto-KHT; PCR negatif hastalarda yapılabilir
- PCR pozitif hastalarda Allo-KHT yapılabilir

Arsenik trioksid

- Trisenox 10 mg/mL ampul (100-250 cc %5dekstroz veya SF ile sulandırılır)
- 1-2 saat IV infüze edilir (vazomotor reaksiyon gözlenirse 4 saate uzatılır)
- Dilusyondan sonra buzdolabında 48 saat (oda ısısında 24 saat) saklanabilir.
- 0.15 mg/kg/gün IV Kİ remisyona girene kadar devam edilir. Total doz 60 dozu aşmamalıdır (2 ay)
- Konsolidasyon tedavisi indüksiyon tedavisi tamamlandıktan 3-6 hafta sonra başlanmalı ve 0.15 mg/kg/gün, 25 doz (5gün/hafta, 5 hafta üzerinde) verilmeli

ATO Güvenli uygulaması için FDA önerileri

Before Starting Arsenic Trioxide Therapy

Obtain electrolyte abnormalities

Correct preexisting electrolyte abnormalities

If Q-Tc interval is >500 msec:

- Institute corrective measures
- Reassess Q-Tc before starting therapy
- Discontinue (whenever possible) concurrent medications known to prolong the Q-Tc interval

During Arsenic Trioxide Therapy

Maintain:

- Potassium concentration above 4 mEq/dL
- Magnesium concentration above 1.8 mg/dL

Obtain serial ECGs

Hospitalize patient and place on cardiac telemetry if:

- Absolute Q-T interval >500 msec *or*
- Patient has any symptoms such as syncope or palpitations

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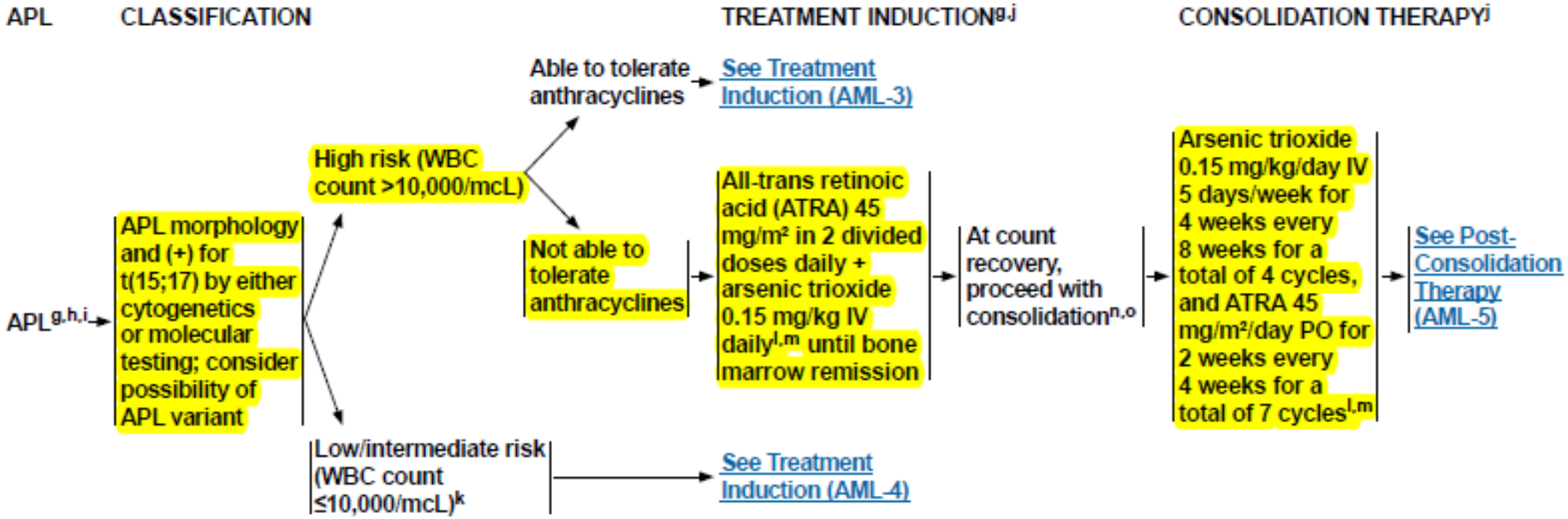

[g]Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one trial with consolidation from another.

[h]Therapy-related APL is treated the same as de novo APL.

[i]In patients with clinical and pathologic features of APL, start ATRA upon first suspicion of APL without waiting for genetic confirmation of the diagnosis. Early initiation of ATRA may prevent the lethal complication of bleeding. If cytogenetic and molecular testing do not confirm APL, discontinue ATRA and continue treatment as for AML.

[j]Monitor for APL differentiation syndrome and coagulopathy; see Supportive Care (AML-C 2 of 2).

[k]New data suggest similar outcomes in patients with low or intermediate risk. These risk groups are combined into one category in most treatment protocols.

[l]Shen ZX, Shi ZZ, Fang J, et al. All-trans retinoic acid/As2O3 combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia. Proc Natl Acad Sci USA 2004;101(15):5328-35.
Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol 2009;27:504-510.

[m]See Arsenic trioxide monitoring, Supportive Care (AML-C 2 of 2).

[n]Premature morphologic and molecular assessment (day 10–14 marrow) can be misleading; a nadir marrow is not recommended. Patients often remain molecularly positive at the end of induction, even when the marrow shows morphologic remission. The first assessment of molecular remission should be made after consolidation.

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TREATMENT INDUCTION (HIGH RISK)[g,j,p]

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r]

→ At count recovery,[n,v] LP and proceed with consolidation[o]

→ Arsenic trioxide[m] 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r,x]

→ See Post-Consolidation Therapy (AML-5)

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s]

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→ Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 2 g/m² (age <50) or 1.5 g/m² (age 50–60) every 12 h x 5 days[y,z] + daunorubicin 45 mg/m² x 3 days x 1 cycle 5 doses of IT chemotherapy[s] (category 1)

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or

ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t]

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→ ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[t,x]

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or

ATRA 45 mg/m² (days 1–36, divided) + age-adjusted idarubicin 6–12 mg/m² on days 2, 4, 6, 8 + arsenic trioxide 0.15 mg/kg (days 9–26 as 2 h IV infusion)[u]

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→ ATRA 45 mg/m² x 28 days + arsenic trioxide[m] 0.15 mg/kg/day x 28 days for 5 wks x 1 cycle, then ATRA 45 mg/m² x 7 d every 2 wks x 3 + arsenic trioxide 0.15 mg/kg/day x 5 d for 5 wks x 1 cycle[u]

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[s] Ades LA, et al. Treatment of newly diagnosed acute promyelocytic leukemia (APL): A comparison of French-Belgian-Swiss and PETHEMA results. Blood 2008;111:1078-1086.

[t] Sanz MA, et al. Risk-adapted treatment of acute promyelocytic leukemia based on all trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high risk patients: further improvements in treatment outcomes. Blood 2010;115:5137-5146.

[u] Iland HJ, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-1580. Prophylaxis with prednisone 1mg/kg/d for at least 10 d is needed for differentiation syndrome regardless of WBC at presentation.

[v] Breccia M, et al. Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. Br J Haematol 2003;120:266-270.

[w] All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.

[x] Consider 4–6 doses of IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis.

[y] Although the original regimen included high-dose cytarabine as second consolidation, some investigators recommend using high-dose cytarabine early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.

[z] Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

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[v] Breccia M, et al. Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. Br J Haematol 2003;120:266-270.

[w] All regimens include high cumulative doses of cardiotoxic agents. Cardiac function should be assessed prior to each anthracycline/mitoxantrone-containing course.

[x] Consider 4–6 doses of IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis.

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[z] Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

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TREATMENT INDUCTION (HIGH RISK)[g,j,p]

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r]
→ At count recovery,[n,v] LP and proceed with consolidation[o]
→ **Arsenic trioxide[m] 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r,x]**
→ See Post-Consolidation Therapy (AML-5)

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s]
→ At count recovery,[n,v] LP and proceed with consolidation[o]
→ **Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 2 g/m² (age <50) or 1.5 g/m² (age 50–60) every 12 h x 5 days[y,z] + daunorubicin 45 mg/m² x 3 days x 1 cycle 5 doses of IT chemotherapy[s] (category 1)**
→ See Post-Consolidation Therapy (AML-5)

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t]
→ At count recovery,[n,v] LP and proceed with consolidation[o]
→ **ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[t,x]**
→ See Post-Consolidation Therapy (AML-5)

or

ATRA 45 mg/m² (days 1–36, divided) + age-adjusted idarubicin 6–12 mg/m² on days 2, 4, 6, 8 + arsenic trioxide 0.15 mg/kg (days 9–26 as 2 h IV infusion)[u]
→ At count recovery,[n,v] LP and proceed with consolidation[o]
→ **ATRA 45 mg/m² x 28 days + arsenic trioxide[m] 0.15 mg/kg/day x 28 days for 5 wks x 1 cycle, then ATRA 45 mg/m² x 7 d every 2 wks x 3 + arsenic trioxide 0.15 mg/kg/day x 5 d for 5 wks x 1 cycle[u]**
→ See Post-Consolidation Therapy (AML-5)

or

Clinical trial

CONSOLIDATION THERAPY[w]

[g] Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one trial with consolidation from another.

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[m] See Arsenic trioxide monitoring, see Supportive Care (AML-C 2 of 2).

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ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r]	→ At count recovery,[n,v] LP and proceed with consolidation[o]	→ Arsenic trioxide[m] 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r,x]	→ See Post-Consolidation Therapy (AML-5)
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ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s]	→ At count recovery,[n,v] LP and proceed with consolidation[o]	→ Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 2 g/m² (age <50) or 1.5 g/m² (age 50–60) every 12 h x 5 days[y,z] + daunorubicin 45 mg/m² x 3 days x 1 cycle 5 doses of IT chemotherapy[s] (category 1)	→ See Post-Consolidation Therapy (AML-5)
or			
ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t]	→ At count recovery,[n,v] LP and proceed with consolidation[o]	→ ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[t,x]	→ See Post-Consolidation Therapy (AML-5)
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TREATMENT INDUCTION (LOW/INTERMEDIATE RISK)[g,j,p]

ATRA 45 mg/m² in divided doses until clinical remission daily + arsenic trioxide[m] 0.15 mg/kg IV daily until bone marrow remission[aa] (category 1)

→ At count recovery,[n,o] proceed with consolidation

→ Arsenic trioxide[m] 0.15 mg/kg/day IV 5 days/week for 4 weeks every 8 weeks for a total of 4 cycles, and ATRA 45 mg/m²/day for 2 weeks every 4 weeks for a total of 7 cycles[aa] (category 1)

→ See Post-Consolidation Therapy (AML-5)

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 50 mg/m² x 4 days + cytarabine 200 mg/m² x 7 days[r,bb] (category 1)

→ At count recovery,[n,o] proceed with consolidation

→ Arsenic trioxide[m] 0.15 mg/kg/day x 5 days for 5 wks x 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[r] (category 1)

→ See Post-Consolidation Therapy (AML-5)

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[s,bb] (category 1)

→ At count recovery,[n,o] proceed with consolidation

→ Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 1 g/m² every 12 h x 4 days + daunorubicin 45 mg/m² x 3 days x 1 cycles (category 1)

→ See Post-Consolidation Therapy (AML-5)

or

ATRA[q] 45 mg/m² in divided doses until clinical remission + idarubicin 12 mg/m² on days 2, 4, 6, 8[t,bb] (category 1)

→ At count recovery,[n,o] proceed with consolidation

→ ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/day x 5 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 dose x 1 cycle (category 1)[cc]

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Clinical trial

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→ See Post-Consolidation Therapy (AML-5)

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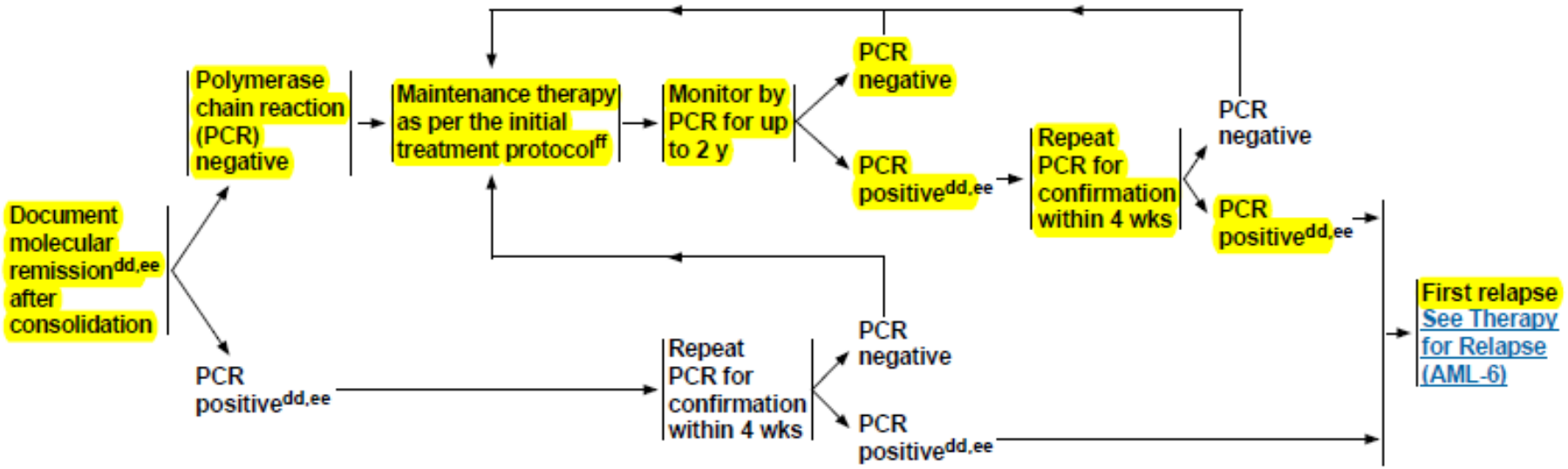
POST-CONSOLIDATION THERAPY

MONITORING



[dd]PCR should be performed on a marrow sample at completion of consolidation to document molecular remission. Subsequent monitoring by PCR can be done with peripheral blood, although marrow is a more sensitive monitoring technique and may give earlier signs of relapse. Prior practice guidelines have recommended monitoring marrow by PCR every 3 mo for 2 y to detect molecular relapse. We continue to endorse this for high-risk patients, those >age 60 y or who had long interruptions during consolidation, or patients on regimens that use maintenance and are not able to tolerate maintenance. Clinical experience indicates that risk of relapse in patients with low-risk disease who are in molecular remission at completion of consolidation is low and monitoring may not be necessary outside the setting of a clinical trial.

[ee]To confirm PCR positivity, a second marrow sample should be done in 2–4 weeks in a reliable laboratory. If molecular relapse is confirmed by a second positive test, treat as first relapse (AML-6). If the second test was negative, frequent monitoring (every 3 mo for 2 y) is strongly recommended to confirm that the patient remains negative. The PCR testing lab should indicate level of sensitivity of assay for positivity (most clinical labs have a sensitivity level of 10^{-4}), and testing should be done in the same lab to maintain the same level of sensitivity. Consider consultation with a physician experienced in molecular diagnostics if results are equivocal.

[ff]The majority of studies showing benefit with maintenance occurred prior to the use of ATRA and/or arsenic trioxide and/or cytarabine for consolidation. The role of maintenance chemotherapy remains unclear, particularly for patients with low-risk disease who achieve a molecular remission at the end of consolidation. Avvisati G, Lo-Coco F, Paoloni FP, et al. AIDA 0493 protocol for newly diagnosed acute promyelocytic leukemia: very long-term results and role of maintenance. Blood 2011;117:4716-4725.

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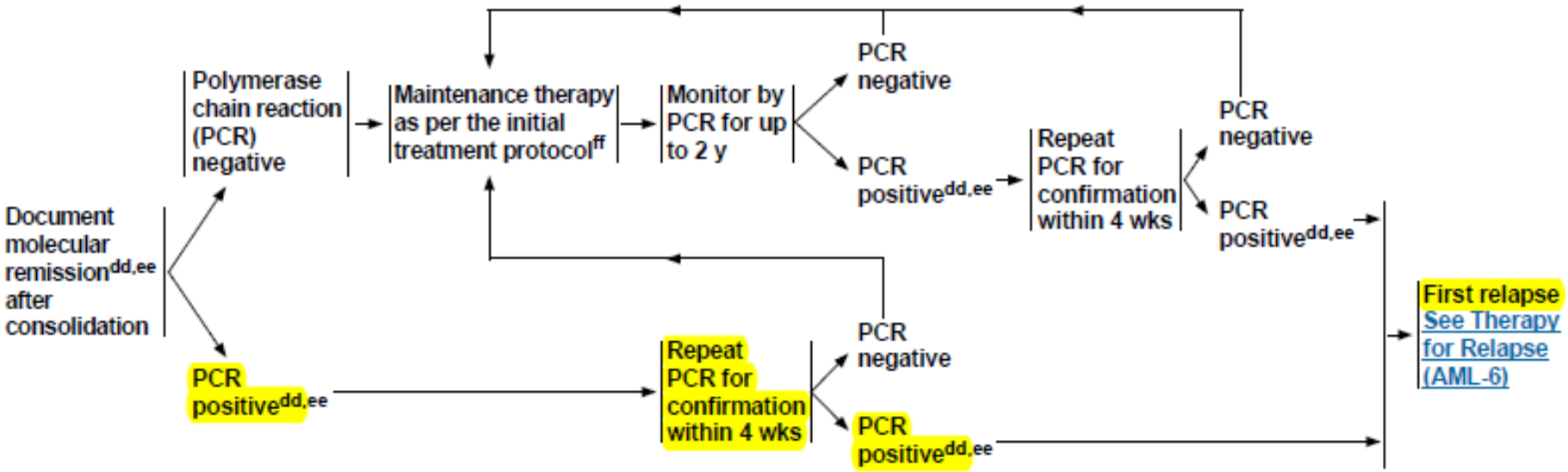
MONITORING



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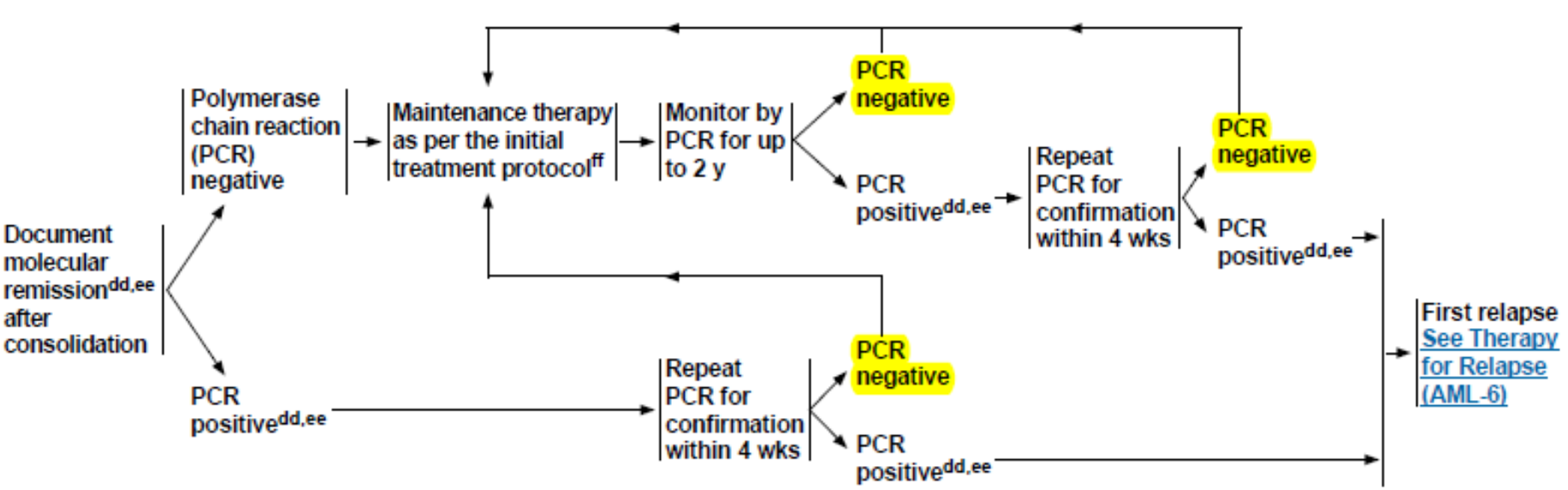

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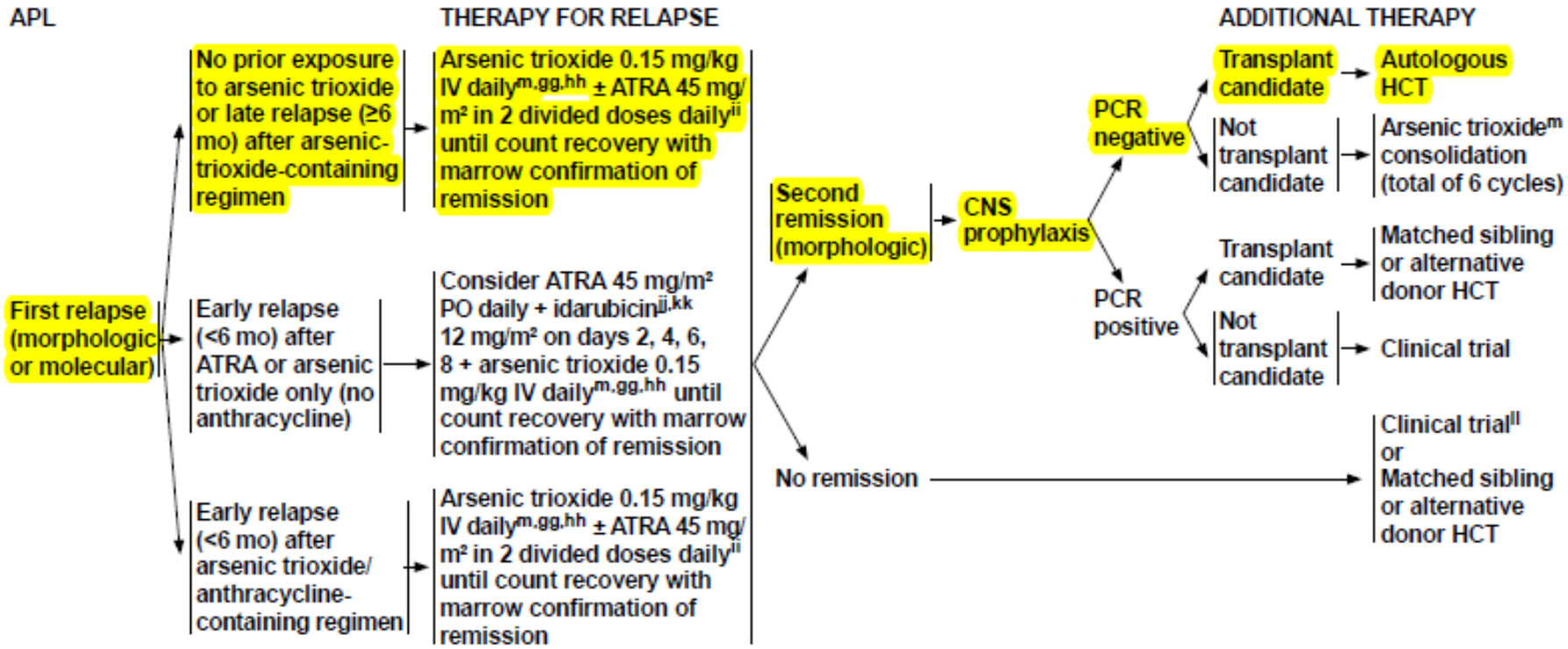

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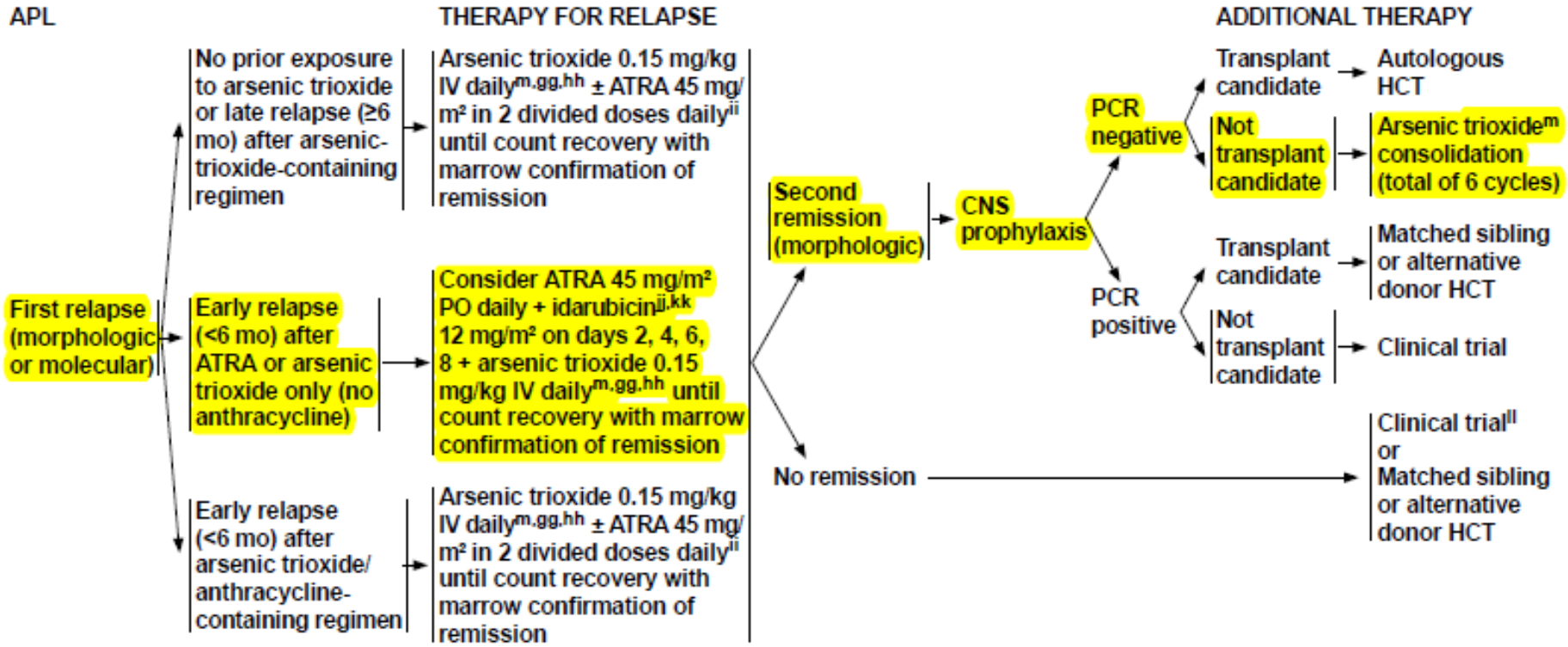

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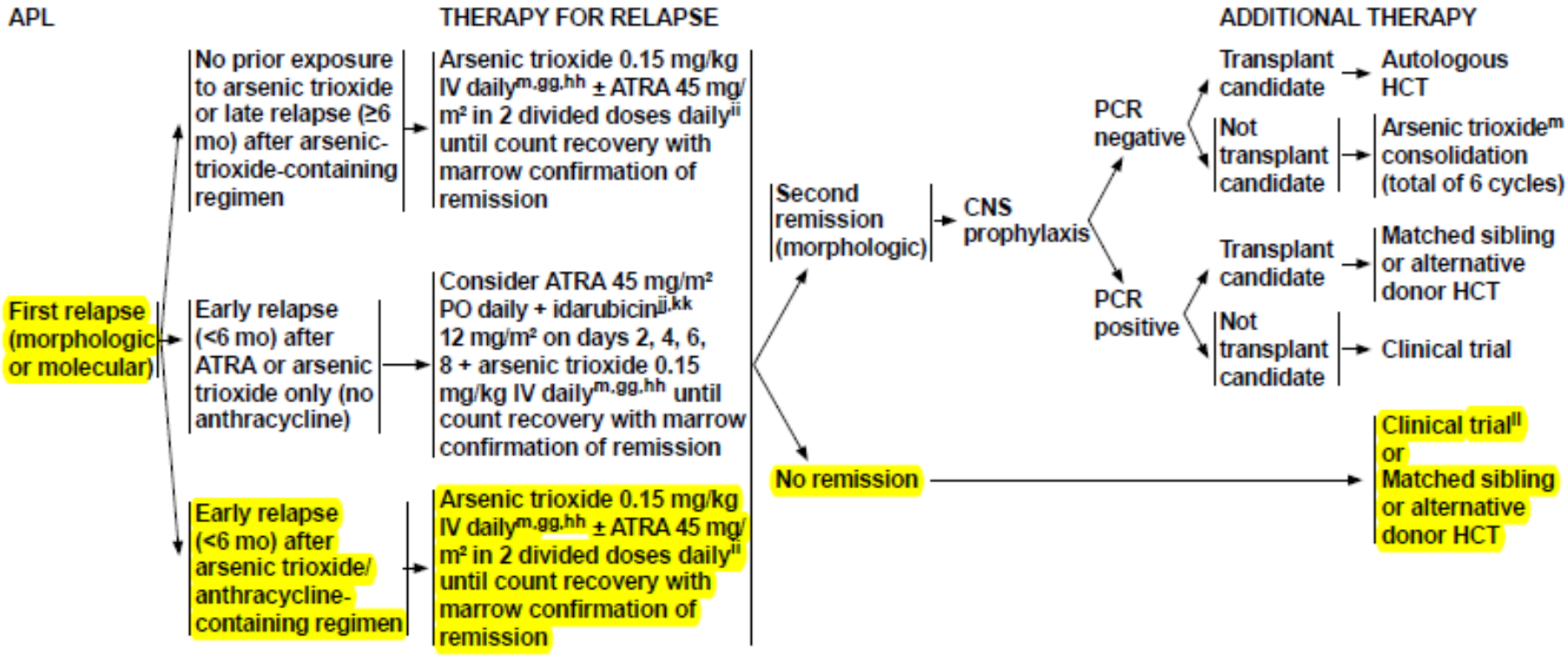

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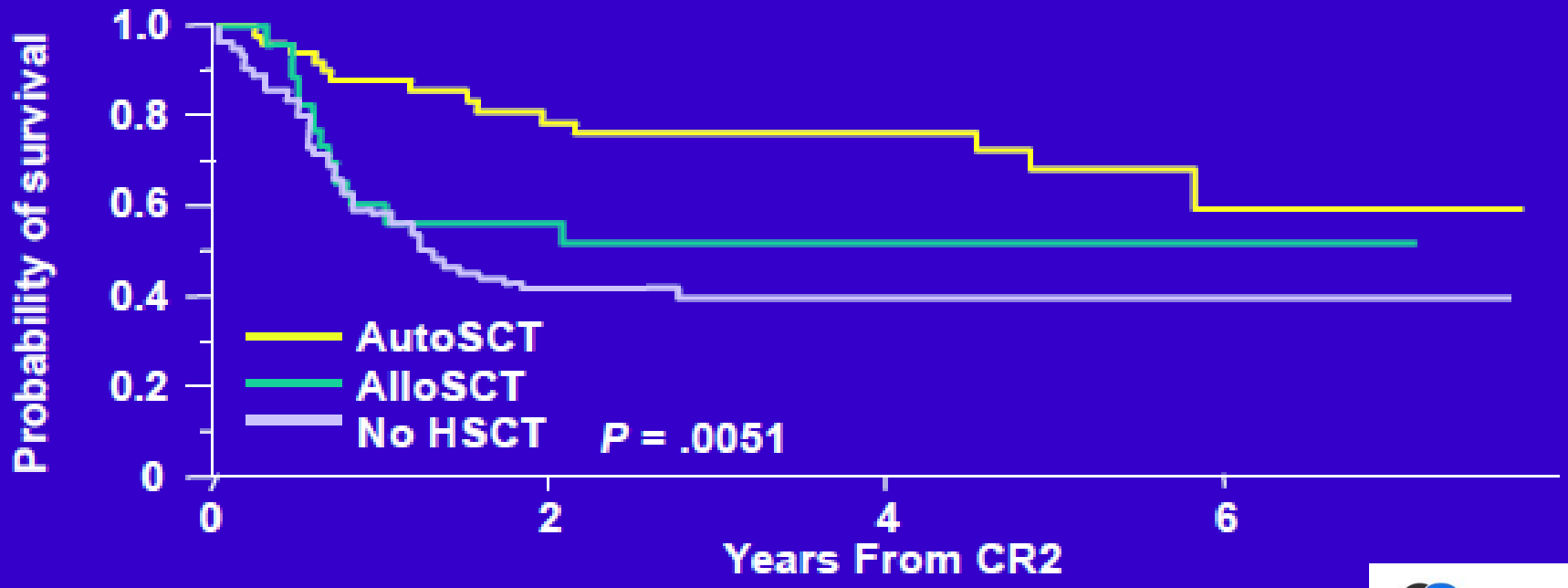
TR2'de APL'de KHN

	Hasta No.	TRM	RFS (7-yıl)	OS (7-yıl)	
Allo KHN	23	%39	%92	%52*	*p=.04
Oto KHN	50	%6	%79	%60*	
KHN Yok	48		%38	%40	



De Botton et al. J Clin Oncol, 2005

SUPPORTIVE CARE (2 of 2)

APL

- Clinical coagulopathy and overt bleeding:
  - Management of clinical coagulopathy and overt bleeding: Aggressive platelet transfusion support to maintain platelets ≥50,000/mcL; fibrinogen replacement with cryoprecipitate and fresh frozen plasma to maintain a level over 150 mg/dL and PT and PTT close to normal values. Monitor daily until coagulopathy resolves.
  - Central venous catheter should not be placed until bleeding is controlled.
- Leukapheresis is not recommended in the routine management of patients with a high WBC count in APL because of the difference in leukemia biology; however, in life-threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.
- APL differentiation syndrome:
  - Maintain a high index of suspicion of APL differentiation syndrome (ie, fever, often associated with increasing WBC count >10,000/mcL, usually at initial diagnosis or relapse; shortness of breath; hypoxemia; pleural or pericardial effusions). Close monitoring of volume overload and pulmonary status is indicated. Initiate dexamethasone at first signs or symptoms of respiratory compromise (ie, hypoxia, pulmonary infiltrates, pericardial or pleural effusions) (10 mg BID for 3–5 days with a taper over 2 weeks). Consider interrupting ATRA therapy until hypoxia resolves.
  - For ATRA + arsenic trioxide regimens, prophylaxis with prednisone 0.5 mg/kg day 1 through completion of induction. If patient develops differentiation syndrome, change prednisone to dexamethasone 10 mg every 12 h until acute differentiation resolves, then return to previous prednisone dose.[4]
- Arsenic trioxide monitoring[5]
  - Prior to initiating therapy
    - Electrocardiogram (ECG) for prolonged QTc interval assessment
    - Serum electrolytes (Ca, K, Mg) and creatinine
  - During therapy
    - Minimize use of drugs that may prolong QT interval
    - Maintain K concentrations above 4 mEq/dL
    - Maintain Mg concentrations above 1.8 mg/dL
    - Reassess patients with absolute QTc interval >500 millisec (weekly during induction therapy and before each course of post-remission therapy)
- Myeloid growth factors should not be used during induction but may be considered during consolidation in selected cases (life-threatening infections, signs/symptoms of sepsis). There are no outcomes data regarding the prophylactic use of growth factors in consolidation.

[4]Package insert for arsenic trioxide (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=22624)
[5]Lo-Coco F, Avvisati G, Vignetti M, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369:111-121

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APL'DE DESTEKLEYİCİ BAKIM

Agresif trombosit transfüzyonu (>50,000/uL) ve fibrinojen replasmanı (>150 mg/dL)

Santral venöz kateter yerleştirilmemelidir

Lökaferez genellikle önerilmez

APL farklılaşma sendromu: yüksek-risk grubunda veya ilk semptom veya belirti görüldüğünde dxm

ATO izlemi: QTc'de EKG, 'lytes'lere devam

Miyeloid GF'leri önerilmez

SONUÇ OLARAK

- **Erken ölümü azaltmak**
- **Yüksek-risk grubundaki hastalarda tedaviyi en uygun hale getirmek/detaylandırmak**
- **Kemoterapiyi minimuma indirgemek veya kaldırmak**
  - **Aktif ajanları birlikte vermek: ATRA, ATO**

- **Yeni stratejiler**
  - **Oral arsenik**
  - **Yeni retinoidler - Tamibaroten**

Lu et al. Blood, 2006; Au et al. Blood, 2008 (abstr); Takeuchi et al, Leuk Lymph, 1998

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