ANTİMİKROBİYAL
YÖNETİM SİMPOZYUMU
ANTIMICROBIAL STEWARDSHIP

6-8 EKİM 2016
Wyndham Grand
İstanbul Kalamış Marina Hotel

LENFOMA VE HIV

Doç. Dr. Uluhan Sili
Marmara Üniversitesi
Pendik Eğitim ve Araştırma Hastanesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

6-10-2016

ÖĞRENİM HEDEFLERİ

- HIV ile enfekte hastalarda lenfoma insidansı
- Etkin ART'in lenfoma insidansı üzerine etkileri
- Lenfoma tanı ve tedavisi
- Kemoterapi sırasında ART yönetimi

HIV ve Maligniteler

- Daha sık görülür
- Daha erken yaşta ortaya çıkar
- Yüksek derecelidir
- Tanı anında ileri evrededir
- Nüksler sıktır
- Prognoz daha kötüdür

British HIV Association guidelines for HIV-associated malignancies 2014

HIV ve Maligniteler

	Malignite	RR (relatif risk)
AIDS-tanımlayıcı	Kaposi sarkomu	73,000
	Non-Hodgkin lenfoma	165
	Skuamoz hücreli servikal karsinom	32
AIDS-tanımlayıcı olmayan	Skuamoz hücreli ano-genital karsinom	30 – 40
	Prostat kanseri	12 – 20
	Hodgkin lenfoma	8 – 18
	Skuamoz hücreli baş/boyun karsinomu	5 – 13
	Multipıl miyelom	5 – 7
	Lösemi (AML, ALL)	5 – 7
	Akciğer kanseri	4 – 5
	Beyin maligniteleri (lenfoma dışı)	4 – 5
	Testiküler kanser (seminom dışı)	4 – 5
	Hepatoselüler karsinom	3 – 4

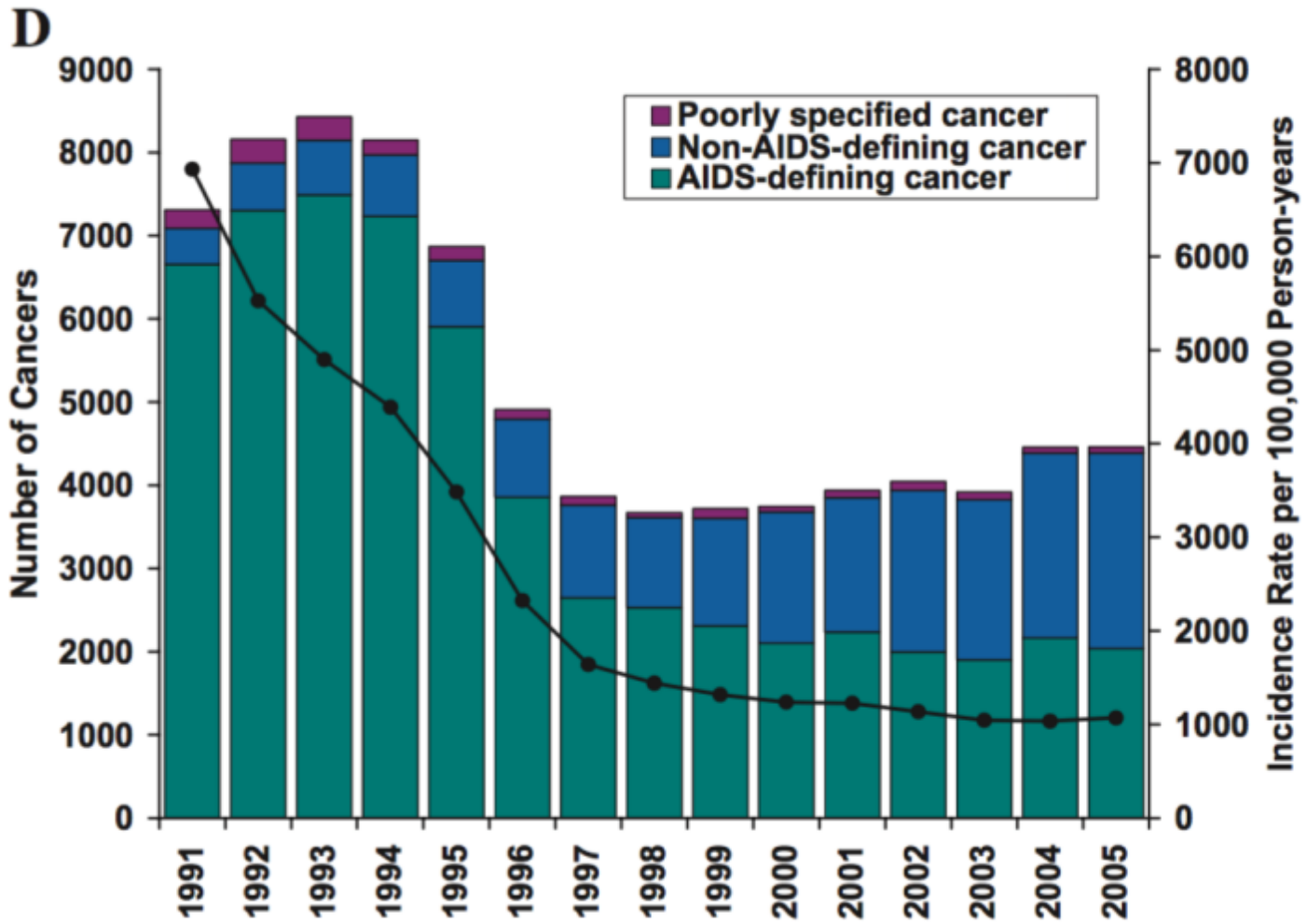
Albany Medical College
DIVISION OF HIV MEDICINE

Caring for the HIV-Infected Inmate: *Malignancies and HIV Infection*
http://www.cumc.columbia.edu/dept/aetc/pdf/Resource_Prescribing_Physicians4.pdf

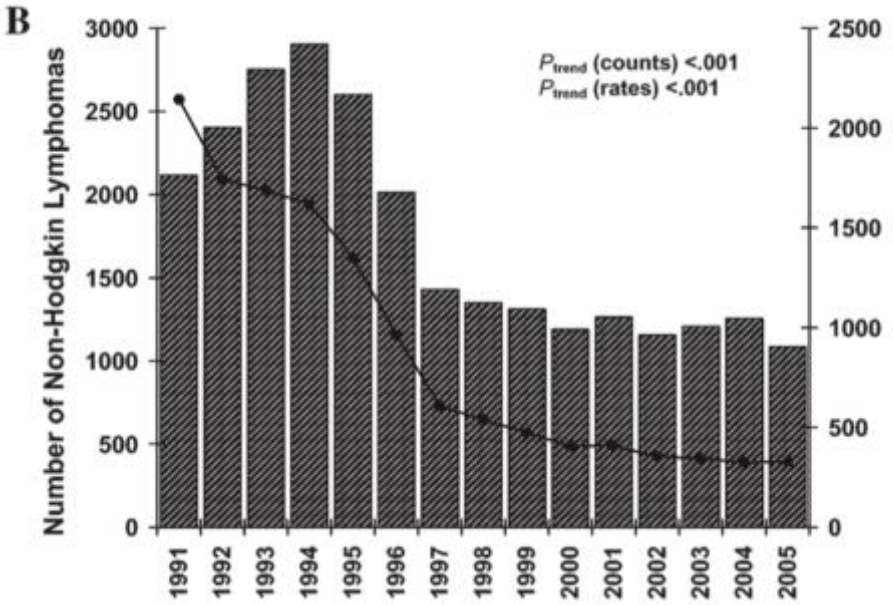
Cancer Burden in the HIV-Infected Population in the United States

Meredith S. Shiels, Ruth M. Pfeiffer, Mitchell H. Gail, H. Irene Hall, Jianmin Li, Anil K. Chaturvedi, Kishor Bhatia, Thomas S. Uldrick, Robert Yarchoan, James J. Goedert, Eric A. Engels

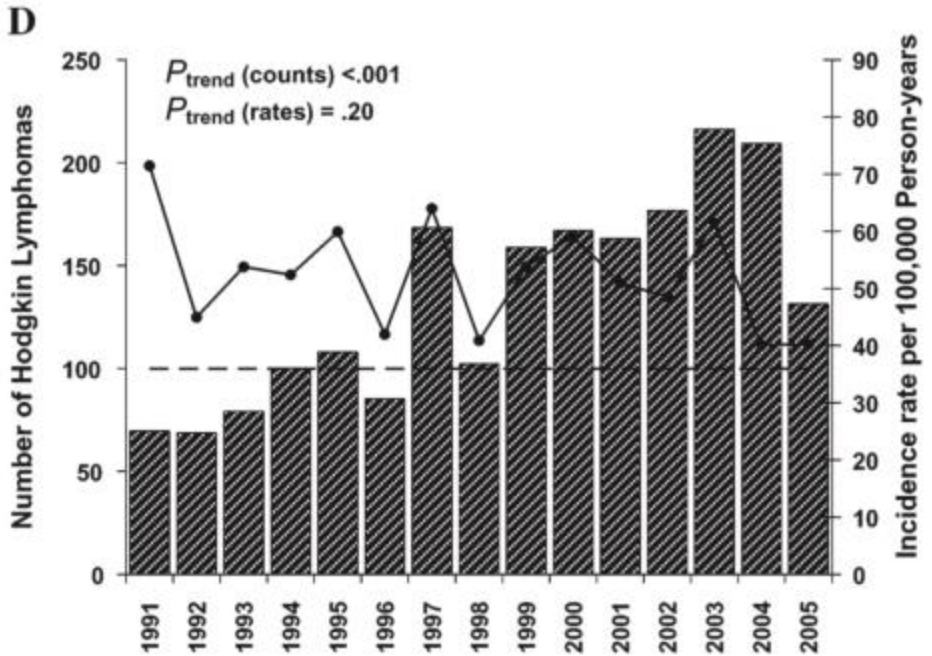
J Natl Cancer Inst 2011;103:753–762



Non-Hodgkin lenfoma



Hodgkin lenfoma



Shiels MS et al. 2011

Annals of Internal Medicine ORIGINAL RESEARCH

Cumulative Incidence of Cancer Among Persons With HIV in North America

A Cohort Study

Michael J. Silverberg, PhD, MPH*; Bryan Lau, PhD, MHS*; Chad J. Achenbach, MD, MPH; Yuezhou Jing, MS; Keri N. Althoff, PhD, MPH; Gypsyamber D'Souza, PhD; Eric A. Engels, MD, MPH; Nancy A. Hessol, MSPH; John T. Brooks, MD; Ann N. Burchell, PhD, MSc; M. John Gill, MB ChB, MSc; James J. Goedert, MD; Robert Hogg, PhD; Michael A. Horberg, MD, MAS; Gregory D. Kirk, MD, PhD, MPH; Mari M. Kitahata, MD, MPH; Philip T. Korthuis, MD, MPH; William C. Mathews, MD, MSPH; Angel Mayor, MD, MSc; Sharada P. Modur, PhD; Sonia Napravnik, PhD; Richard M. Novak, MD; Pragna Patel, MD, MPH; Anita R. Rachlis, MD, MEd; Timothy R. Sterling, MD; James H. Willig, MD, MSPH; Amy C. Justice, MD, PhD; Richard D. Moore, MD, MHS; and Robert Dubrow, MD, PhD, for the North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS†

Ann Intern Med. 2015;163:507-518.

Table 2. Crude Cancer Type–Specific Incidence Rates and All-Cause Death Rates, by HIV Infection Status, NA-ACCORD, 1996–2009

Event	Persons With HIV		Uninfected Persons	
	Persons, *n*	Incidence Rate per 100 000 Person-Years	Persons, *n*	Incidence Rate per 100 000 Person-Years
Kaposi sarcoma	612	130.4	3	0.2
Non-Hodgkin lymphoma	725	153.5	233	12.6
Lung cancer	614	129.3	839	45.4
Anal cancer	285	60.1	22	1.2
Colorectal cancer	173	36.4	510	27.7
Liver cancer	220	46.3	201	10.9
Hodgkin lymphoma	159	33.5	36	1.9
Melanoma	78	16.4	268	14.5
Oral cavity/pharyngeal cancer	163	34.3	340	18.4
Death	17 534	3686.0	15 400	833.0

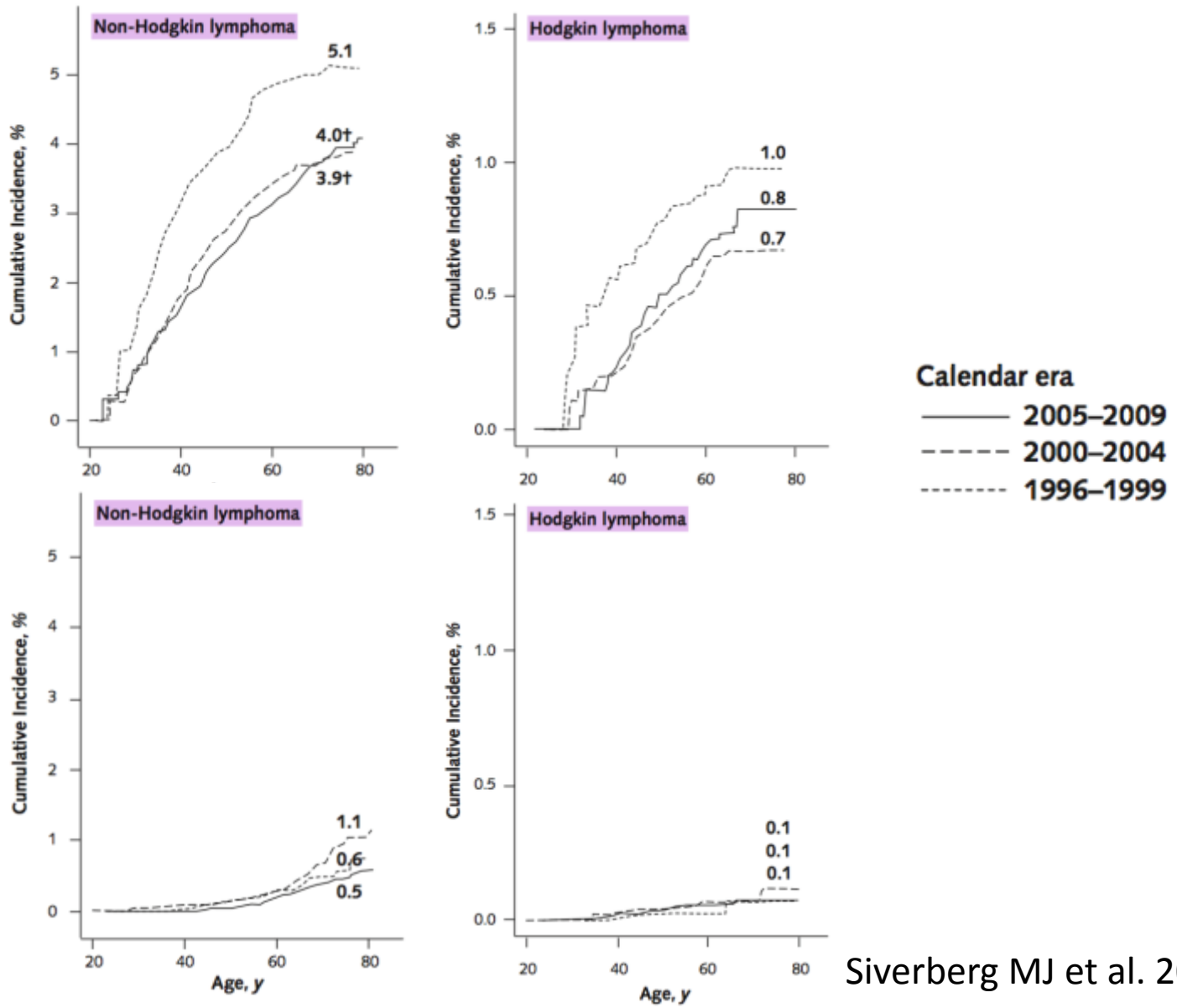
NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design.

Figure 1. Cumulative cancer incidence for persons with HIV, by calendar era and cancer type with age as the time scale, NA-ACCORD, 1996–2009.

NHL **HL**

HIV

enfekte olmayan



Siverberg MJ et al. 2015

PLOS | ONE

Cancer-Related Causes of Death among HIV-Infected Patients in France in 2010: Evolution since 2000

Marie-Anne Vandenhende[1,2,3]*, Caroline Roussillon[1,2], Sandrine Henard[4], Philippe Morlat[1,2,3], Eric Oksenhendler[5], Hugues Aumaitre[6], Aurore Georget[1,2], Thierry May[4], Eric Rosenthal[7,8], Dominique Salmon[9,10], Patrice Cacoub[11,12], Dominique Costagliola[13,14], Geneviève Chêne[1,2], Fabrice Bonnet[1,2,3], the ANRS EN20 Mortalité 2010 study group[¶]

PLOS ONE | DOI:10.1371/journal.pone.0129550 June 17, 2015

Table 1. Cancer-related causes of death.

	Mortalité 2000	Mortalité 2005	Mortalité 2010	p-value[a]
Reported deaths	**964**	**1042**	**728**	
Cancer-related causes of death, n (%)	**269 (27.9%)**	**344 (33.0%)**	**262 (36.0%)**	**0.003**
AIDS-related, n (%)	**149 (15.5%)**	**134 (12.9%)**	**68 (9.3%)**	**0.024**
Non Hodgkin lymphoma	105 (10.9%)	103 (9.9%)	53 (7.3%) [b]	0.122
Kaposi sarcoma	40 (4.1%)	25 (2.4%)	11 (1.5%)	0.084
Cervical cancer	4 (0.4%)	6 (0.6%)	4 (0.5%)	0.848
Hepatitis-related, n (%)	**17 (1.8%)**	**37 (3.6%)**	**31 (4.3%)**	**0.028**
Hepatitis C	8 (0.8%)	27 (2.6%)	19 (2.6%)	0.021
Hepatitis B	7 (0.7%)	6 (0.6%)	10 (1.4%)	0.279
Hepatitis B and C	2 (0.2%)	4 (0.4%)	2 (0.3%)	0.732
Non AIDS/non hepatitis related, n (%)	**103 (10.7%)**	**173 (16.6%)**	**163 (22.4%)**	**<0.001**
Respiratory	50 (5.2%)	65 (6.2%)	78 (10.7%)	0.004
Lung	44 (4.6%)	53 (5.1%)	61 (8.4%)	0.040
Ear, nose and throat	6 (0.6%)	12 (1.2%)	17 (2.3%)	0.056
Digestive	6 (0.6%)	13 (1.2%)	10 (1.4%)	0.342
Pancreas	3 (0.3%)	11 (1.1%)	7 (1.0%)	0.282
Anal	6 (0.6%)	11 (1.1%)	13 (1.8%)	0.073
Skin	2 (0.2%)	10 (1.0%)	3 (0.4%)	0.065
Hodgkin's lymphoma	12 (1.2%)	9 (0.9%)	8 (1.1%)	0.473
Other hemopathies	5 (0.5%)	8 (0.8%)	7 (1.0%)	0.602
Breast	3 (0.3%)	7 (0.7%)	5 (0.7%)	0.647
Central nervous system	4 (0.4%)	6 (0.6%)	2 (0.3%)	0.530
Other and unknown[c]	12 (1.2%)	33 (3.2%)	27(3.7%)	0.029
Multiple[d]	-	-	3 (0.4%)	-

The Mortalité 2000, Mortalité 2005 and Mortalité 2010 surveys, France.

[a]Comparisons between 2000, 2005 and 2010 adjusted on age and gender

[b]including 3 patients with both non Hodgkin lymphoma and Kaposi sarcoma

[c]See Appendix for details

[d]Multiple: anus+prostate, anus+lung, lung+breast

doi:10.1371/journal.pone.0129550.t001

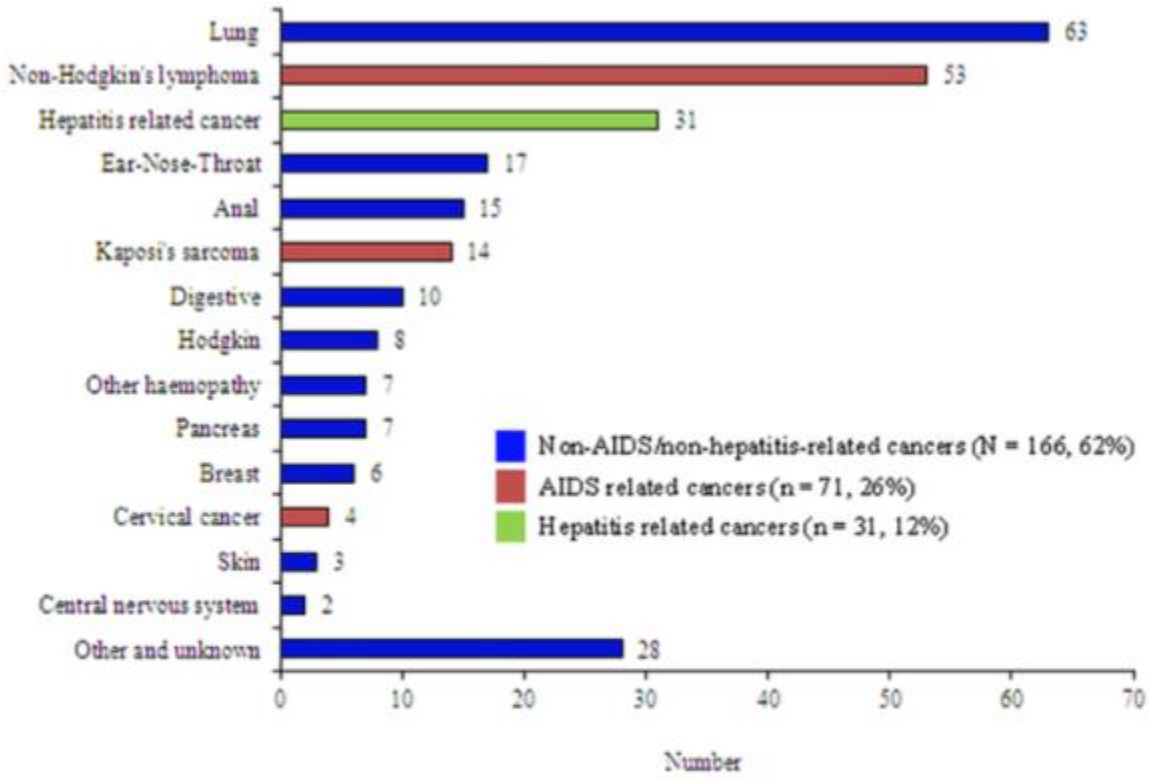


Fig 1. Location of cancers (N = 268) among HIV-infected adults with underlying cause of death being cancer (N = 262), Mortalité 2010 survey, France.

doi:10.1371/journal.pone.0129550.g001

Değişen Epidemiyoloji

- NHL maligneteler arasında sıklıkta 1. sırada
- NHL ölüm nedeni olarak akciğer kanserinden sonra 2. sırada

- Erken ve kararlı ART kullanımı artırılmalı
  - KS ve NHL gibi immün baskılanma veya kronik enflamasyon sonucu oluşan kanserlerden korunmanın en iyi çaresi

Silverberg MJ et al. 2015

Cancer: Screening Methods[i]

Problem	Persons	Procedure	Evidence of benefit	Screening interval	Additional comments
Anal cancer	MSM	Digital rectal exam ± anal cytology	Unknown; advocated by some experts	1-3 years	If anal cytology abnormal, anoscopy
Breast cancer	Women 50-70 years	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	Sexually active women	Liquid based cervical cytology test	↓ Cervical cancer mortality	1-3 years	Target age group should include the 25 to 64 years at least. HPV testing may aid screening
Colorectal cancer	Persons 50-75 years	Faecal occult blood test	↓ Colorectal cancer mortality	1-3 years	Flexible sigmoidscopy at 55-years is an alternative
Hepatocellular carcinoma	Persons with cirrhosis & Persons with HBV irrespective of fibrosis stage	Ultrasound and alpha-foetoprotein	Earlier diagnosis allowing for improved ability for surgical eradication	Every 6 months	
Prostate cancer	Men > 50 years	Digital rectal exam ± prostate specific antigen (PSA)	Use of PSA is controversial	1-3 years	Pros: ↑ early diagnosis. Cons: overtreatment; ambiguity about size of ↓ cancer-related mortality

i Screening recommendations derived from the general population. These screenings should preferably be done as part of national general population-screening programmes. Although non-Hodgkin's lymphoma has a higher incidence in HIV-positive persons than in the general population, it is currently unknown whether it can be screened. Careful examination of skin should be performed regularly to detect cancers such as Kaposi's sarcoma, basal cell carcinoma and malignant melanoma.

EACS European AIDS Clinical Society

EACS Guidelines 8.0

AIDS ile ilişkili NHL

- Sistemik NHL (>%80)
  - Diffüz büyük B hücreli lenfoma (**DLBCL**, ≈%75) ↓
  - **Burkitt** ve Burkitt benzeri lenfoma (≈%25) →
- Primer MSS lenfoması (**PCNSL**, ≈%15) ↓
- Primer effüzyon (veya vücut kavite) lenfoması (**PEL**, <%5) ↓

- Çoğu yüksek dereceli, B lenfosit kökenli

To be or not to be HIV+, that is no longer the question

Stefan K. Barta FOX CHASE CANCER CENTER/TEMPLE UNIVERSITY HEALTH SYSTEM

BLOOD, 9 JULY 2015 • VOLUME 126, NUMBER 2

CLINICAL TRIALS AND OBSERVATIONS

AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma

Ariela Noy,[1] Jeannette Y. Lee,[2] Ethel Cesarman,[3] Richard Ambinder,[4] Robert Baiocchi,[5] Erin Reid,[6] Lee Ratner,[7] Nina Wagner-Johnston,[7] and Lawrence Kaplan,[8] for the AIDS Malignancy Consortium

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical Center, New York, NY; [2]University of Arkansas Medical Center, Little Rock, AR; [3]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY; [4]Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD; [5]Division of Hematology, Ohio State Medical Center, Columbus, OH; [6]University of California San Diego, Moores Cancer Center, La Jolla, CA; [7]Division of Oncology, Washington University School of Medicine, St. Louis, MO; and [8]Department of Medicine, University of California San Francisco, San Francisco, CA

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BLOOD, 9 JULY 2015 • VOLUME 126, NUMBER 2

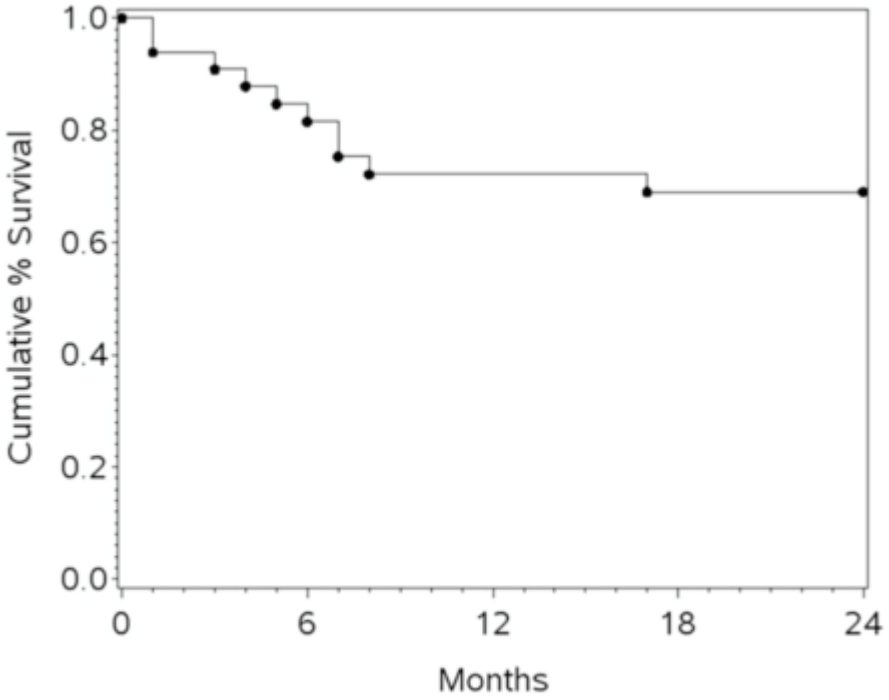


Figure 1. Cumulative survival for all enrolled patients.

- HIV ile ilişkili BL'da yapılan ilk faz 2 çalışma
- mukozit, hematolojik ve nörolojik toksisiteler açısından geliştirilmiş rejim
- 2 senelik sağ kalım %69
  - HIV negatiflerinkine yaklaşık oran (%72.8)
- %84 etkin ART'a devam etmiş
- HIV pozitiflere de yoğun KT rejimleri verilebilir
- Problem HIV pozitiflerin negatiflere göre KT önerilme oranlarının düşük olması

A new standard for HIV-associated lymphoma

Andrew R. Rezvani STANFORD UNIVERSITY

BLOOD, 25 AUGUST 2016 • VOLUME 128, NUMBER 8

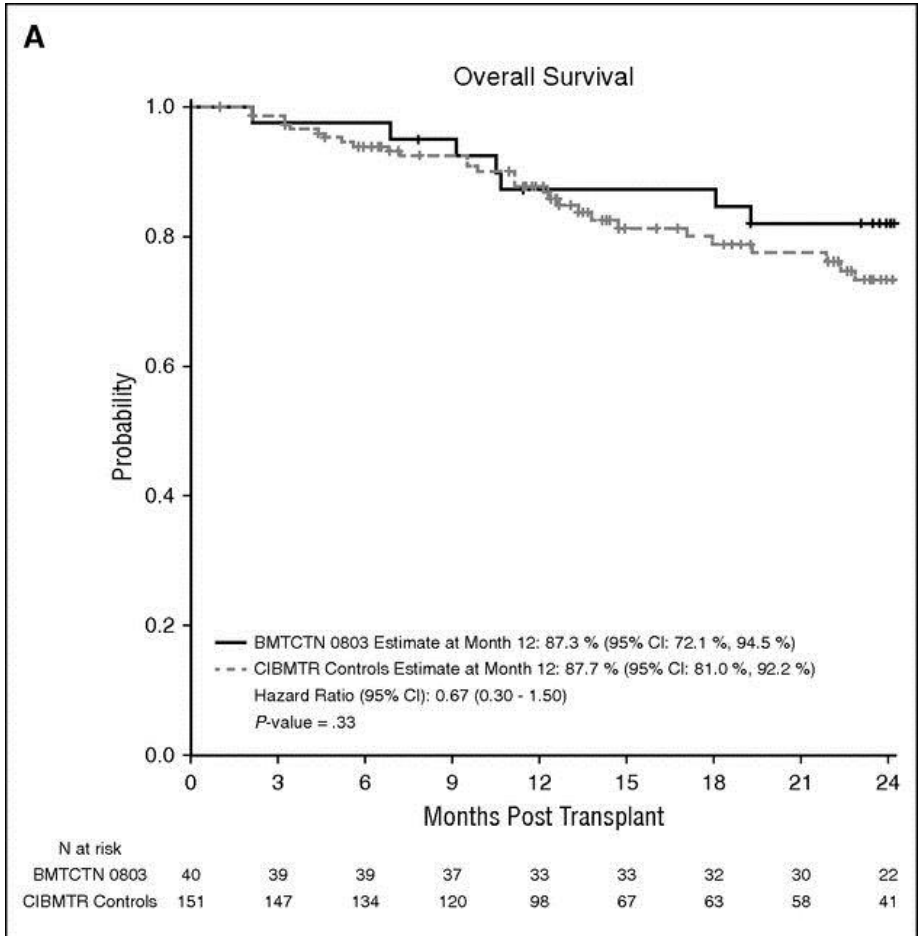
CLINICAL TRIALS AND OBSERVATIONS

Autologous hematopoietic cell transplantation for HIV-related lymphoma: results of the BMT CTN 0803/AMC 071 trial

Joseph C. Alvarnas,[1] Jennifer Le Rademacher,[2] Yanli Wang,[3] Richard F. Little,[4] Gorgun Akpek,[5] Ernesto Ayala,[6] Steven Devine,[7] Robert Baiocchi,[7] Gerard Lozanski,[7] Lawrence Kaplan,[8] Ariela Noy,[9] Uday Popat,[10] Jack Hsu,[11] Lawrence E. Morris Jr,[12] Jason Thompson,[3] Mary M. Horowitz,[2] Adam Mendizabal,[3] Alexandra Levine,[13] Amrita Krishnan,[1] Stephen J. Forman,[1] Willis H. Navarro,[14] and Richard Ambinder[15]

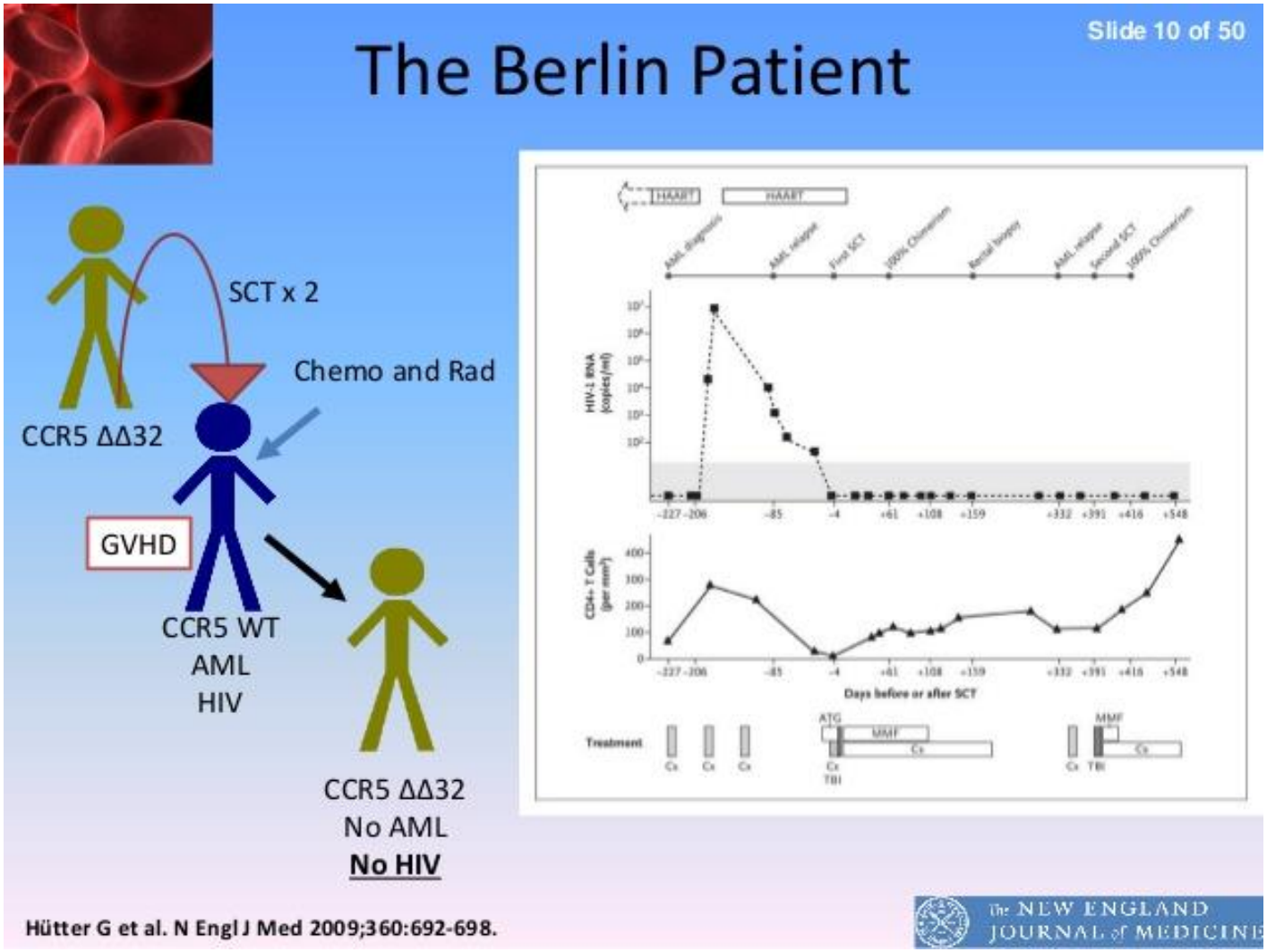
[1]Department of Hematology/Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; [2]Center for International Blood & Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI; [3]The Emmes Corporation, Rockville, MD; [4]Cancer Therapy Evaluation Program, National Cancer Institute, Rockville, MD; [5]Greenebaum Cancer Center, University of Maryland Medical Systems, Baltimore, MD; [6]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center, Tampa, FL; [7]Department of Hematology, The Ohio State University–Arthur G. James Cancer Center Hospital, Columbus, OH; [8]Division of Hematology/Oncology, University of California, San Francisco, CA; [9]Division of Hematological Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; [10]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX; [11]Bone Marrow Transplant Program, University of Florida Health Cancer Center, Gainesville, FL; [12]The Blood and Marrow Transplant Group of Georgia, Northside Hospital Cancer Institute, Atlanta, GA; [13]City of Hope National Medical Center, Duarte, CA; [14]National Marrow Donor Program, Minneapolis, MN; and [15]Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD

OS and PFS for HIV-infected and noninfected patients.



Joseph C. Alvarnas et al. Blood 2016;128:1050-1058

KÜR



Davey Smith, MD, MAS, of UC San Diego AntiViral Research Center, presents "The Lastest on HIV Cure Strategies," at AIDS Clinical Rounds

Project activity overview

Observational study
Altogether we study allogeneic SCT recipients with HIV-1 infection, collecting complete information on underlying malignancy, chemotherapy, transplant procedure, donor selection, HIV-tropism, cART, and a variety of samples taken before and after the transplant.

To systematically study recipient samples for:

1. multiple complementary quantifications of the viral reservoirs
2. molecular and functional characterization of infecting virus
3. immunological determinations during the multiple phases of an allogeneic SCT, which might help to understand the biological bases of a potential new case of HIV-1 cure.

Clinicial Guidance
In addition, hematologist or infectious disease specialists who would like to receive clinical guidance on an allogeneic SCT procedure can contact the clinical consultation team of the EPISTEM project via the EPISTEM coordination center.

Members of the team are:
Hematology:
J. Diez-Martin, Department of Hematology and Hematopoietic transplantation, Hospital General Universitario Gregorio Marañón, Madrid, Spain.
G. Hütter, CellexGmbH, Dresden, Germany.
J. Kuball, Department of Hematology, University Medical Center Utrecht, Utrecht, the Netherlands.
V. Rocha, Department of Clinical Hematology, Oxford University Hospitals NHS Trust, Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, United Kingdom.

Infectious Disease:
J. Schulze zur Wiesch, Infectious Diseases Unit, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

Clinical Virology:
A. Wensing, Department Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands.

Clinical Pharmacology:
E. van Maarseveen, Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands.

Clinical work group

Eva Steel, MD
Hematologist
Ghent University
Belgium

Linos Vandekerckhove, MD, PhD
Infectious Disease Specialist
Ghent University
Belgium

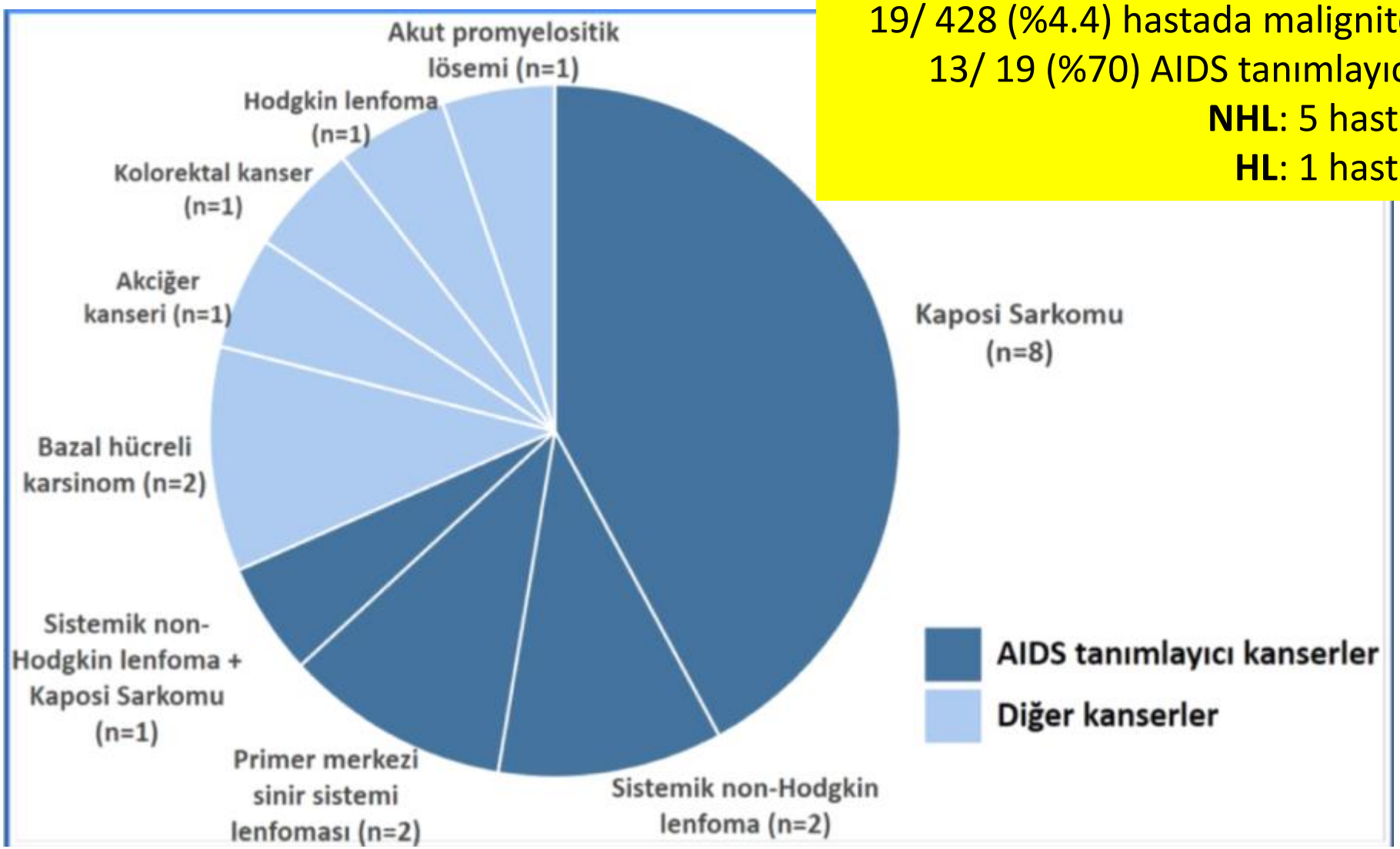
Pauline Ellerbroek, MD, PhD
Infectious Disease Specialist
University Medical Center Utrecht
the Netherlands

KLİNİĞİMİZDE HIV ENFEKSİYONU İLE TAKİP EDİLEN HASTALARDA SAPTANAN MALİGNİTELERİN RETROSPEKTİF DEĞERLENDİRİLMESİ

Aysun Tekin, Uluhan Sili, Volkan Korten
Marmara Üniversitesi Tıp Fakültesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

KLİMİK 2016
30. YIL KURULTAYI

19/ 428 (%4.4) hastada malignite
13/ 19 (%70) AIDS tanımlayıcı
NHL: 5 hasta
HL: 1 hasta



	Malignite	HIV tanı süresi	ART kullanım süresi	CD4 (hücre/mm³)	Kemoterapi	Eksitus*	Eksitusa kadar geçen süre
M.A, 34e	Hodgkin lenfoma	15 ay	15 ay	331	var	var	10 ay
C.C, 28e	NHL - Burkitt lenfoma	15 ay	15 ay	1131	var	var	8 ay
H.Ö, 63e	NHL - *Double hit* lenfoma	14 ay	14 ay	193	var	var	6 ay
H.U.S, 33e	NHL - primer effüzyon lenfoması + Kaposi sarkomu	42 ay	12 ay	65	yok	var	postmortem tanı
H.Ç, 40e	NHL - primer CNS DLBCL	Eş zamanlı	Yeni tanı	84	var	var	4 ay
E.K, 24e	NHL - primer CNS DLBCL	Eş zamanlı	Yeni tanı	170	var	yok	

* Hastaların tümünde eksitus nedeni malignite progresyonu olarak değerlendirildi.

Tekin A et al. KLİMİK 2015

AIDS ile ilişkili NHL -Patogenez-

1. CD4 yıkımı ile oluşan immün baskılama sonucu onkojenik virüslerin kontrol edilemeyişi

2. Kronik immün aktivasyon → B lenfositlerde hipermutasyon

3. HIV'in bir retrovirüs olarak genoma entegre oluşu

Deeken JF et al. 2012, Braoudaki M et al. 2011, Carbone A et al. 2005, Knowles DM et al. 2003, Bende RJ et al. 2009

HIV, onkojenik virüsler ve lenfoma

Maligniteler	İlişkili virüsler
Kaposi sarkomu	HHV-8
Diffüz büyük B hücreli lenfoma	**EBV**
Primer effüzyon lenfoması	**HHV-8**
Multisentrik Castleman hastalığı	HHV-8
Primer beyin lenfoması	**EBV**
Hodgkin lenfoma	**EBV**
Merkel hücreli karsinom	Merkel hücre polyoma virüsü
Anogenital kanser	HPV
Hepatoselüler karsinom	HBV ve HCV
Baş ve boyun kanserleri	HPV
Leiomyosarkoma	EBV

AIDS ile ilişkili NHL
-Klinik Özellikler-

Öykü

- **Sistemik NHL**
  - boyunda şişlik
    - LAP (sert, immobil veya az mobil, ağrısız)
  - organ tutulumu: akciğer, kemik iliği, GİS, KC, dalak
  - midede şişkinlik, erken doygunluk, karında şişlik, karın ağrısı, sağ üst kadran ağrısı ve sarılık
  - B semptomları (%60 - %80): ateş, %10'un üzerinde kilo kaybı, gece terlemeleri
- **Primer MSS lenfoması**
  - baş ağrısı, bulanık görme, kas güçsüzlüğü, duyu kaybı, kişilik değişikliği, depresyon, apati, konfüzyon, hafıza problemleri, kranyal sinir tutulumları, nöbet

AIDS ile ilişkili NHL
-Ayırıcı Tanı-

Sistemik NHL

- enfeksiyoz mononükleoz
- tüberküloz
- dissemine fungal enfeksiyonlar
- sarkoidoz
- toksoplazmoz
- kedi tırmığı hastalığı
- multisentrik Castleman hastalığı
- Kaposi sarkomu

Primer MSS lenfoması

- serebral toksoplazmozis
- sistemik lenfomanın serebral tutulumu
- primer MSS lenfomatoid granülomatoz (EBV)

- Anti-toksoplazma-IgG pozitif hastada toksoplazmoz tedavisi ver, yanıtsızsa sterotaktik beyin biyopsisi

AIDS ile ilişkili NHL
-Klinik Özellikler-

Laboratuvar

- tüm LN biyopsisi, tutulan organlardan biyopsi
- immün fenotipleme, akış sitometresi
- LDH, beta-2 mikroglobulin
- HBV ve HCV ko-enfeksiyonları

AIDS ile ilişkili NHL
-Klinik Özellikler-

Görüntüleme

- toraks BT
  - hilar ve/veya mediastinal lenfadenopati
  - plevral effüzyon
  - kitle, lobar konsolidasyon
  - plevral kalınlaşma
- gastrointestinal BT
- MSS için kontrastlı kranyal MRI
- FDG-PET

Kemik iliği aspirasyon ve biyopsisi

Lomber ponksiyon

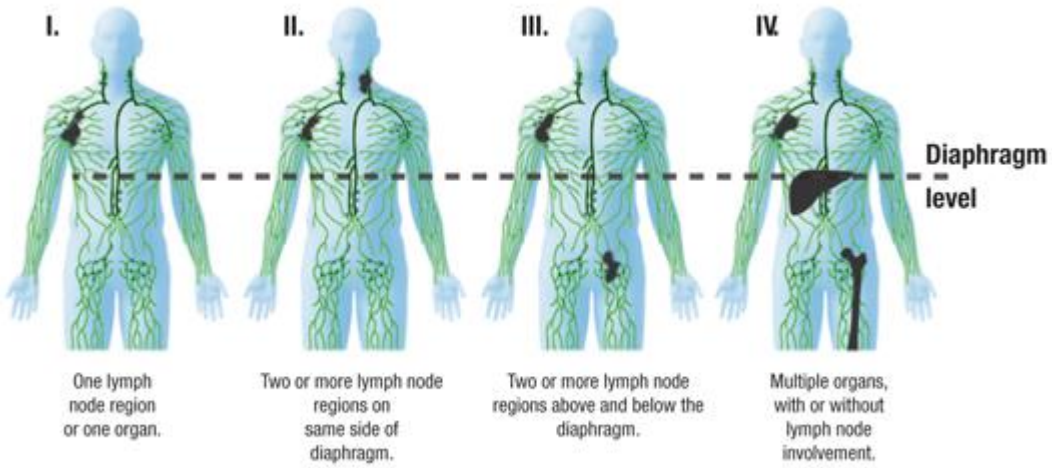
MSS tutulumu riski

- ileri evre
- artmış LDH
- ekstranodal hastalık
- MSS hastalığı belirtileri
- Paranazal sinüs, meme, renal, epidural, kemik veya testiküler tutulum varsa

AIDS ile ilişkili NHL
-Klinik Özellikler-

Evreleme

- Ann-Arbor
- Ekstra-nodal tutulum sıktır; genelde Ann Arbor evre III-IV
- HIV enfeksiyonunun neden olduğu LAP tümör evresini olduğundan daha ileri gösterebilir



AIDS ile ilişkili NHL
-Tedavi ve Prognoz-

- HIV ile enfekte olmayanlarla aynı esasları içerir
- Küratif olmak hedeflenmelidir
  - gecikilmemelidir (gerekli testler 1 haftada tamamlanmalı)

- Kemoterapinin amacı:
  - remisyon indüksiyonu
  - morbiditeyi azaltmak
  - lenfoma ile ilişkili komplikasyonları önlemek

- İlerlemiş AIDS hastalarında ko-morbiditeler ve fırsatçı enfeksiyonlar prognozu kötü şekilde etkiler
- Prognoz HIV ile enfekte olmayanlara göre daha kötü

Table 4.2 International prognostic index for aggressive non-Hodgkin lymphoma [30]

Score 1 for each factor present:
Age >60 years
Serum LDH > normal
Performance status >1
Stage III/IV
Extranodal site >1
Final IPI risk group
0 or 1, low risk;
2, low intermediate risk;
3, high intermediate risk;
4 or 5, high risk

Table 4.4 Outcome of DLBCL according to IPI score in HIV-positive patients (adapted from [32])

IPI risk group (no. of patients)	Complete responses to chemotherapy (%)	3-year survival (%)
Low (42)	63	64
Low intermediate (35)	64	64
High intermediate (13)	28	50
High (11)	13	13

HIV Medicine (2014), **15** (Suppl. 2), 1–92

British HIV Association guidelines for HIV-associated malignancies 2014

NHL	İlk basamak	2. basamak		Prognoz
DLBCL	cART/ frstç. prflks.* CHOP veya EPOCH CD20 (+) ise R-mab	DHAP veya ICE HDT→ oto KİT	SSS nüksü riski varsa profilaksi	2-yr survival: %64 - %75
BL	cART/ frstç. prflks. CODOX-M/IVAC veya DA-EPOCH CD20 (+) ise R-mab	DHAP veya ICE HDT → oto KİT	Hepsine SSS profilaksisi	2-yr survival: %52 - %88
PCNSL	cART yüksek doz MTX'li KT kranyal RT			Ortanca sağkalım: 9 ay
PEL	cART CHOP-benzeri KT			Ortanca sağkalım: 6 ay

- CD4<200 hc/mm^3 ise PCP, CD4<50 hc/mm^3 ise MAC, azol ile fungi, rutin FQ önerilmiyor, HSV profilaksisi
- TMP-SMX 960 mg haftada 3 kez, CD4 düzeyinden bağımsız, KT bitişi +1 ay (Hoffmann C. HIV Medicine 2015-2016)

CLINICAL TRIALS AND OBSERVATIONS

AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma

Ariela Noy,[1] Jeannette Y. Lee,[2] Ethel Cesarman,[3] Richard Ambinder,[4] Robert Baiocchi,[5] Erin Reid,[6] Lee Ratner,[7] Nina Wagner-Johnston,[7] and Lawrence Kaplan,[8] for the AIDS Malignancy Consortium

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical Center, New York, NY; [2]University of Arkansas Medical Center, Little Rock, AR; [3]Department of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York, NY; [4]Department of Oncology, Johns Hopkins School of Medicine, Baltimore, MD; [5]Division of Hematology, Ohio State Medical Center, Columbus, OH; [6]University of California San Diego, Moores Cancer Center, La Jolla, CA; [7]Division of Oncology, Washington University School of Medicine, St. Louis, MO; and [8]Department of Medicine, University of California San Francisco, San Francisco, CA

BLOOD, 9 JULY 2015 • VOLUME 126, NUMBER 2

- PCP: Ayda bir pentamidine 300 mg aerosolize
  - TMP/ SMX olabilir ama nötropeni riski var
- HSV: Famsiklovir 250 mg PO BID
  - Asiklovir veya valsiklovir olabilir ama nötropeni riski var
- MAC profilaksisi
  - tüm CD4 <50/mm^3 olanlar: azitromisin 1200 mg haftada bir
- Kinolon profilaksisi
  - nötropeninin derinlik ve öngörülen süresine, rituksimab kullanımına ve başlangıçtaki immünkompromizasyon düzeyine göre
  - Ör: KT'nin 8. gününde başla, 8 gün devam et, nötropenik ise uzatılabilir
- Febril nötropeni
  - aminoglikozidleri nefrotoksisite riski nedeniyle kullanma
  - yüksek doz metotreksattan sonra 7 gün süre AG kullanma

Hangi ART, ne zaman?

- ART ile NHL prognozu ciddi oranlarda iyileşmiştir
- Sağkalım, hastalıksız sağkalım, KT'ye yanıt oranları, KT'ye katlanılabilirlik ↑
- İmmün derlenmenin kansere toleransı tersine çevirmesi
  - Sadece ART ile gerileyen NHL
- ART başlandıktan sonra ortaya çıkan NHL
  - İnsidans hızı ART'nin ilk 6 ayında en yüksek (Yanik EL et al. 2013)

Hoffmann C. HIV 2015/16 *www.hivbook.com*

Hangi ART, ne zaman?

- Lenfomalı tüm hastalara ART başlanmalı, mümkünse kesilmemeli
  - **İstisnalar** olabilir
    - otolog KİT öncesi
    - CD4 sayısı iyiyse EPOCH'un ilk 2 döngüsünde
    - ciddi mukozit, bulantı, kusma → emilim sorunu varsa

The Rising Challenge of Non–AIDS-Defining Cancers in HIV-Infected Patients

John F. Deeken,[1] Angelique Tjen-A-Looi,[2] Michelle A. Rudek,[4] Catherine Okuliar,[3] Mary Young,[2] Richard F. Little,[5] and Bruce J. Dezube[6]

Divisions of [1]Hematology/Oncology, [2]Infectious Disease, and [3]Internal Medicine, Georgetown University Medical Center, Washington, DC; [4]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, and [5]Clinical Investigations Branch/CTEP, National Cancer Institute, Bethesda, Maryland; and [6]Department of Medicine (Hematology/Oncology), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Table 2. Highly Active Combination Antiretroviral Therapy Agents That Cause Common Chemotherapy-Related Side Effects [81]

Adverse Reaction	Human Immunodeficiency Virus Antiretroviral Agents
Myelosuppression	Zidovudine
Neuropathy	Didanosine, stavudine
Nephrotoxicity	Tenofovir, indinavir
Nausea/Emesis	All protease inhibitors, zidovudine, didanosine
Diarrhea	Nelfinavir, lopinavir
Hepatoxicity	All nonnucleoside reverse transcriptase inhibitors, all protease inhibitors, and all nucleoside reverse transcriptase inhibitors

Table 3. Select Metabolizing Enzymes and Transporters, Highly Active Combination Antiretroviral Therapy, and Chemotherapy [80, 81]

Enzyme	HAART Inhibitor	HAART Inducer	Chemotherapy
CYP3A4	Delavirdine, ritonavir, amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir	Nevirapine, efavirenz	Paclitaxel, docetaxel, erlotinib, sunitinib, sorafenib, etoposide, vincristine, vinblastine, vinorelbine, cyclophosphamide
CYP2C9	Efavirenz, ritonavir		Cyclophosphamide
CYP2C19	Efavirenz, amprenavir		Cyclophosphamide, ifosfamide, thalidomide
CYP2D6	Ritonavir		Tamoxifen
CYP2B6	Efavirenz, nelfanivir, ritonavir	Nevirapine	Cyclophosphamide, ifosfamide
CYP2E1	Ritonavir		Etoposide, dacarbazine
UGT1A1	Atazanavir		Irinotecan

Abbreviation: HAART, highly active combination antiretroviral therapy.

- ART KT etkileşimi
  - İntegraz inhibitörleri
  - CCR5 antagonisti (Maraviroc)

OLGU

- 63 yaş, erkek, emekli gemi çalışanı, evli, 2 çocuklu

- Dış merkezde uzamış ateş, yaygın vücut ağrısı, servikal ve aksiller beze nedeniyle tetkik edilirken HIV tanısı konuyor

- Tanı anında kolay kanaması (diş eti ve burundan) var
  - Plt 51700

ART Başlanıyor

- CD4 %16 (193 hc/mm^3)
- HIV-RNA: 62688 kopya/mL
- ART: Truvada 1 × 1 tb po + Kaletra 2 × 2 tb po
- HIV-RNA
  - ART **3**. ay: <261 IU/mL
  - ART **9**. ay: <saptama eşiği
- CD4
  - ART **13**. ay: 785 hc/mm^3 (+ 593 hc/sene)
- Trombosit
  - ART **6**. ay: Plt 145000

Nöropati ve Bel Ağrısı

- ART **14**. ay
  - Çift görme şikayeti ile geliyor
  - 1 aydır yüz sol alt yarısında uyuşma, her iki kulakta uğultu, hafif mide bulantısı, arada gelen baş ağrısı
  - 15 gündür belden her iki uyluk arka yüzüne yayılan şiddetli ağrı
  - Sağ abdusens palsisi, solda silik nazolabial sulkus
- Dış merkez Enfeksiyon Hastalıkları servisine yatırılıyor

Tetkikler

- Na 137 mmol/L K 4.3 mmol/L Ca 10.1 mg/dL
- BK 7250 Ne %62.3 (4520) Lenf. %21.9 (1580)
  Hb 8.9 Htc 26.8 Plt 133000
- **ESR 81 mm/saat CRP ×6**
- ALT 8 U/L AST 17 U/L TB 0.97 mg/dL
- BUN 31 mg/dL kreatinin 1.5 mg/dL
- PT 13.1 INR 0.99
- Protein 6.8 g/dL Albumin 3.6 g/dL
- **LDH 1885 U/L** (N=125–220)

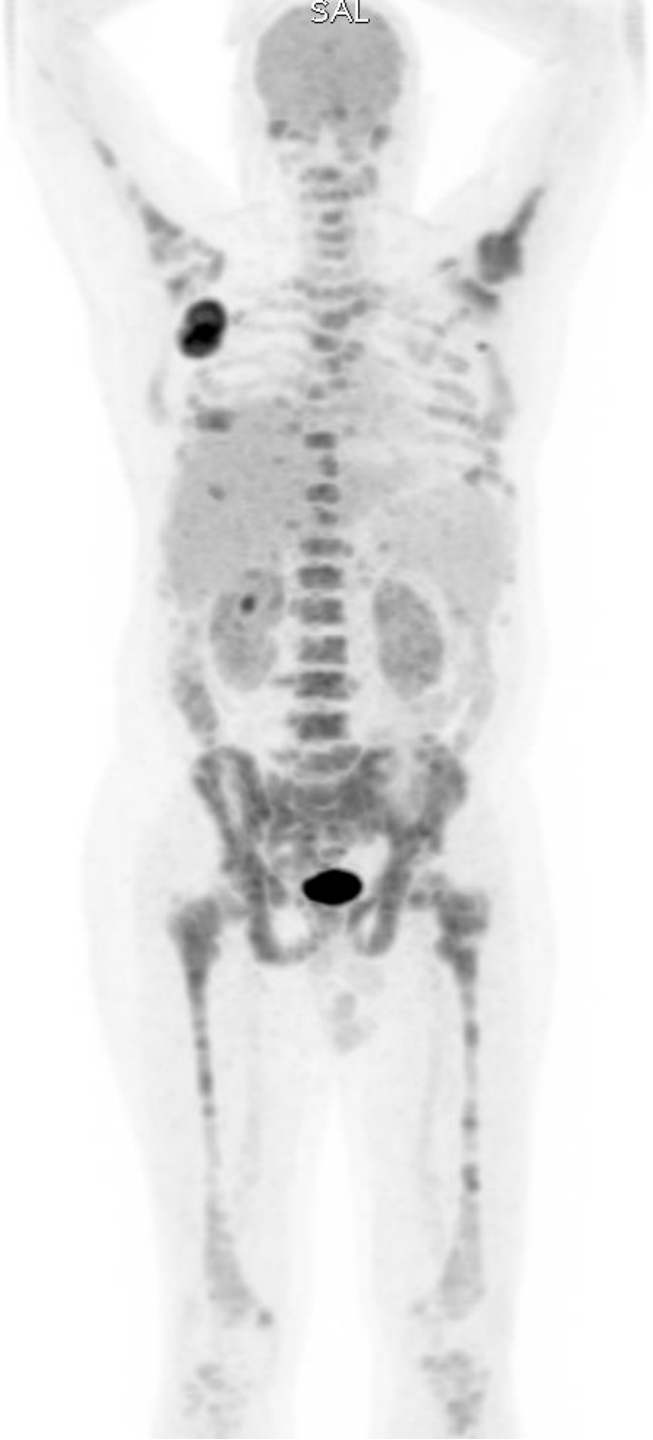
Lomber Tutulum

- Rose Bengal (–) VDRL (–)
- BOS
  - 5 hc/mm^3
  - glukoz 95/194 (%48) mg/dL
  - protein 60 mg/dL
- BOS'ta tüberküloz PZR (–)
- Kranyal MRG: kitle, apse, infarkt yok
- Lomber MRG
  - Tüm lomber vertebralarda **yaygın hipointens** alanlar
  - L4 vertebra spinoz procesini destrükte eden ve spinal kanalı daraltan ≈3 cm boyutunda **tümoral** kitle
  - Öneri: PET-CT

PET-CT

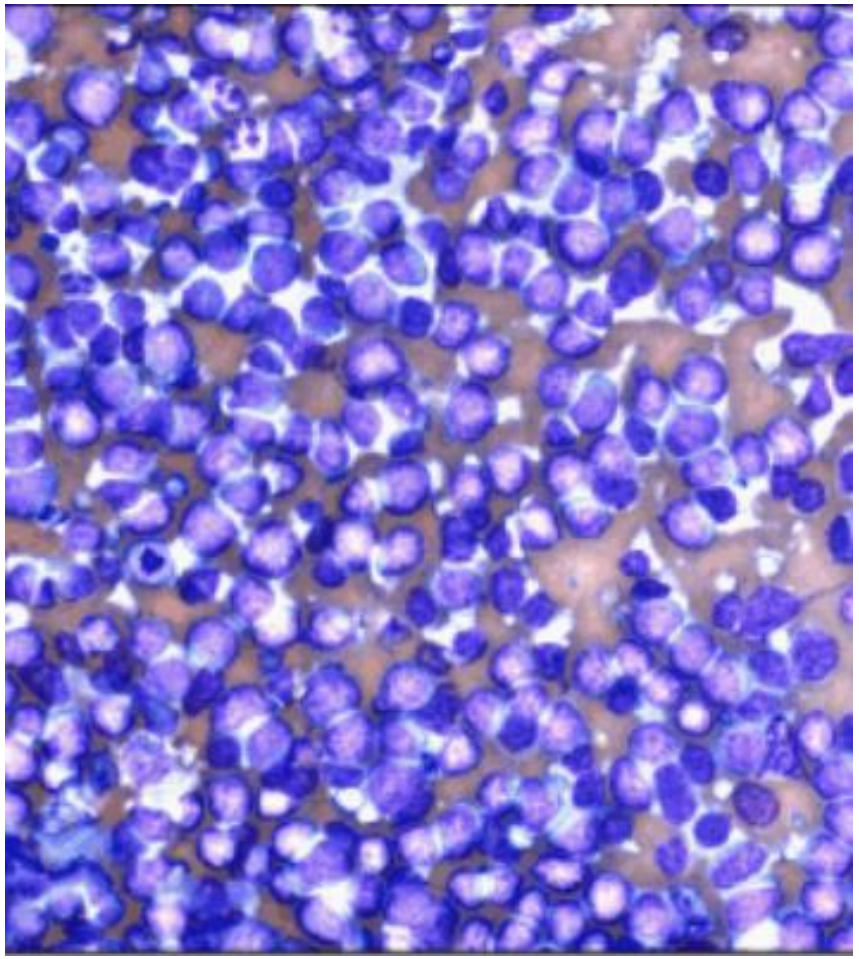
- sağ aksiller 4.5 cm çapında hipermetabolik LAP
- sağ 6. kosta posterolateralinde plevral yerleşimli FDG (+) tümöral lezyon
- karaciğer domu düzeyinde diyafragmatik yüzeyde FDG (+) lezyon
- kemik iliğinde kısmen heterojen karakterde hipermetabolik görünüm

- **LENFOMA?**
  - Öneri: sağ aksilladaki LAP'dan **histopatolojik** inceleme ve kemik iliğinden biyopsi



Aksiller LAP Biyopsisi

- **Tanı: diffüz büyük B hücreli lenfoma**
  - Yüksek dereceli non-Hodgkin lenfoma
  - CD20 diffüz pozitif
  - Bcl-2 ve Bcl-6 pozitif
  - Ki-67 proliferasyon indeksi >%95
  - EBV negatif
- Kemik iliği
  - Her üç seride kesintisiz matürasyon gösteren hipersellüler kemik iliği
  - kemik iliğinde lenfoma infiltrasyonu **saptanmamıştır**

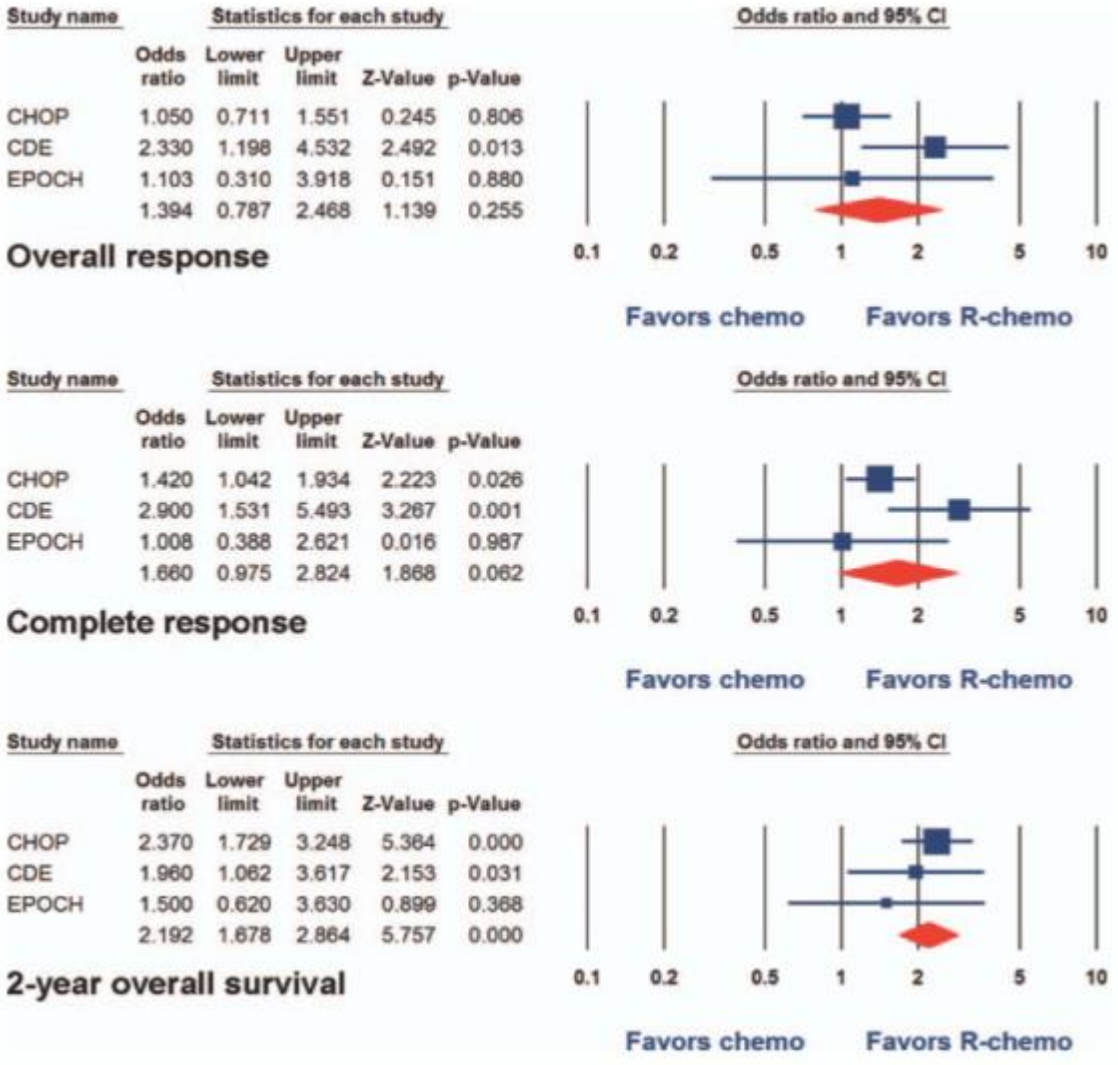


Rituximab in combination with chemotherapy versus chemotherapy alone in HIV-associated non-Hodgkin lymphoma: A pooled analysis of 15 prospective studies

Jorge J. Castillo* and Ignacio A. Echenique

American Journal of Hematology

Volume 87, Issue 3, pages 330–333, March 2012



4. NHL: systemic AIDS-related diffuse large B-cell Lenf.mphoma (DLBL)

- Treatment
  - Start cART, opportunistic infection prophylaxis and chemotherapy (**1B**)
  - First-line chemotherapy as for HIV-negative patients
    - CHOP or EPOCH
  - Add rituximab (**1B**) for CD20+ NHL
    - If CD4 <50 cells/ml, close monitoring advised, OI prophylaxis, G-CSF and prompt OI treatment
  - If high risk of CNS relapse (high LDH, extranodal disease and high-risk sites involved)
    - CNS prophylaxis (intrathecal (IT) and/or IV methotrexate) as for HIV-negative patients (**1C**)

Kemoterapi

- Hematoloji
  - "R-EPOCH"
  - Rituksimab ile birlikte
    - etoposid
    - prednizon
    - vinkristin
    - siklofosfomid
    - doksorubisin
  - intratekal metotreksat ile MSS profilaksi

Tartışma

- Hasta Truvada + Kaletra altında
- ART ???

ART İlaç Etkileşimleri

- Medscape
- UpToDate- Lexicomp
- University of Liverpool

  - R-EPOCH vs Truvada/Stocrin (**efavirenz**)
  - R-EPOCH vs Truvada/Kaletra (**lopinavir/ritonavir**)
  - R-EPOCH vs Truvada/Isentress (**raltegravir**)

Cytotoxics	Emtricitabine (FTC)	Tenofovir
Cyclophosphamide	◇	◇
Doxorubicin	◇	◇
Etoposide	◇	◇
Vincristine	◇	◇
Steroids	**Emtricitabine (FTC)**	**Tenofovir**
Prednisolone	◇	◇

Cytotoxics	Lopinavir	Ritonavir
Cyclophosphamide ↑	□	□
Doxorubicin ↑	□	◇
Etoposide ↑	□	□
Vincristine ↑	□	□
Steroids	**Lopinavir**	**Ritonavir**
Prednisolone ↑	□	□

Cytotoxics	Efavirenz
Cyclophosphamide ↓↑	□
Doxorubicin	◇
Etoposide ↓	□
Vincristine ↓	□
Steroids	**Efavirenz**
Prednisolone ↓	□

⊖ / ⊖	These drugs should not be coadministered
□ / □	Potential interaction – may require close m
◇ / ◇	No clinically significant interaction expected
✦ / ✧	There are no clear data, actual or theoretic
n/a	Data not available

www.hiv-druginteractions.org

Cytotoxics	Raltegravir
Cyclophosphamide	◇
Doxorubicin	◇
Etoposide	◇
Vincristine	◇
Steroids	**Raltegravir**
Prednisolone	◇

Olgu- Özet

HIV 62688
CD4 193

HIV negatif
CD4 785

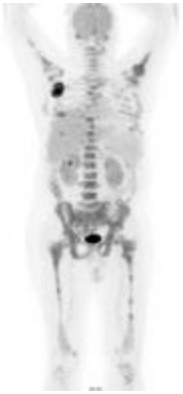
Truvada
Kaletra

Truvada
Isentress

6.2013 — 7.2014 — 26.9.2014 — 17.10.2014 — 8.11.2014

63 yaş, E
uzamış ateş
ağrı
LAP
ITP

NHL



1. kür
R-EPOCH

2. kür
R-EPOCH

3. kür
vinkristinsiz
R-EPOCH

el ve ayaklarda yanma ve karıncalanma
Nöroloji/EMG: *polinöropati*
Hematoloji: *vinkristin toksisitesi*

kontrol
PET

Progrese

Olgu- Özet

HIV <20
CD4 135

HIV <20

HIV 56
CD4 %15 (66)

Truvada
Isentress

25.11.2014 — 11.1.2015 — 26.01.2015 — 07.02.2015 — 02.03.2015 — 17.03.2015

febril nötropeni

pnömoni

seftriakson
klaritromisin

TMP-SMX
metilprednisolon

kat.-kayn. KDYE
ESBL⁺ K. pneumoniae

1. kür
R-IVAC

kat.-kayn. KDYE
ESBL⁺ K. pneumoniae

C. krusei fungemisi

2. kür
R-IVAC

EXITUS
solunum
arresti
(sekresyon
aspirasyonu)

HIV tanısından 2 yıl 3 ay
ART başlanmasından 1 yıl 9 ay
NHL tanısından 6 ay

Lenfoma ve HIV

- ✓ HIV ile enfekte hastalar NHL ve HL açısından risk altındalar
- ✓ NHL artık en sık görülen AIDS tanımlayıcı malignite
- ✓ İleri evre, B semptomları ve ekstranodal tutulum
- ✓ Sağkalım HIV-negatif hastalarınkine yaklaşmakta
- ✓ Tedavide kür hedeflenmeli
- ✓ KT ile etkileşmeyen ART başlanmalı
- ✓ Profilaksilere dikkat edilmeli
- ✓ Literatür yakından takip edilmeli

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uluhan@hotmail.com