# Hematolojide İmmünosüpresyon Yapan Hastalıklar & İlaçlar (HBV Reaktivasyon Riski)

*İmmünosüpressif hastalarda HBV profilaksisi ve HBVizyon*

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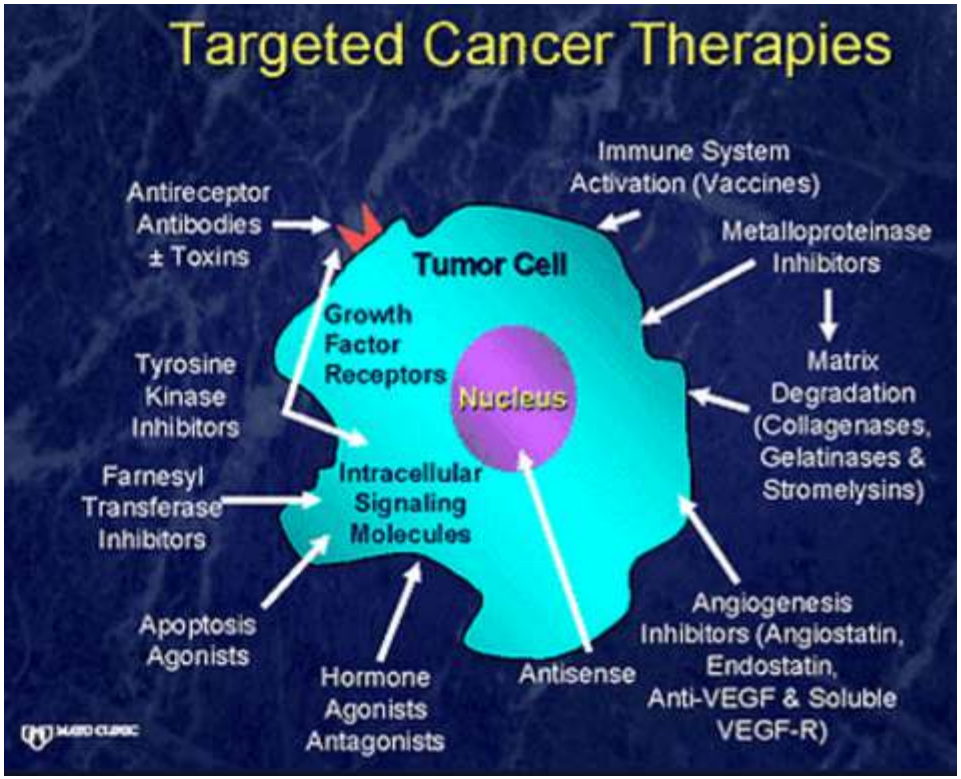
06.04.2017, Antalya




**Kemoterapi**

- **Genellikle hızlı çoğalan hücrelere etki eder**
- **Sitotoksiktir**
- **Seçici değildir**
- **Genellikle IV, çok daha az po**

KÜÇÜK MOLEKÜLLER

MONOKLONAL ANTİKORLAR

AŞILAR

**Hedefe Yönelik Tedavi**

- **Hücre içinde çok daha spesifik bir hedefi inhibe etme özelliğindedir**
- **Sitotoksik ve sitostatiktir**
- **Tümör proliferasyonunu engeller**
- **Genellikle po**

# Son 20 yılda FDA'in onayladığı hematolojik ilaçlar (malign hastalıklar)

Rituxan; Biogen IDEC, Genentech; Treatment for non-hodgkin's lymphoma, Approved November 1997

Bexxar; Corixa; For the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma following chemotherapy relapse, Approved June 2003

Vidaza (azacitidine); Pharmion Corporation; For the treatment of several myelodysplastic syndrome subtypes including refractory and chronic myelomonocytic leukemias, Approved May 2004

Revlimid (lenalidomide); Celgene; For the treatment of low- and intermediate-1-risk myelodysplastic syndromes, Approved December 2005

Dacogen (decitabine); MGI Pharma; For the treatment of both treatment-naïve and -experienced Myelodysplastic Syndromes, Approved May 2006

Arzerra (ofatumumab); GlaxoSmithKline; For the treatment of chronic lymphocytic leukemia, Approved October 2009

Jakafi (ruxolitinib); Incyte; For the treatment of myelofibrosis, Approved November 2011

Adcetris (brentuximab vedotin); Seattle Genetics; For the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma, Approved August 2011

Synribo (omacetaxine mepesuccinate); Teva Pharmaceutical; For the treatment of chronic or accelerated phase chronic myeloid leukemia, Approved October 2012

# Son 20 yılda FDA'in onayladığı hematolojik ilaçlar (malign hastalıklar)

Marqibo (vinCRIStine sulfate LIPOSOME injection); Talon Therapeutics; For the treatment of Ph- acute lymphoblastic leukemia, Approved August 2012

Kyprolis (carfilzomib); Onyx Pharmaceuticals; For the treatment of multiple myeloma, Approved July 2012

Iclusig (ponatinib); Ariad Pharmaceuticals; For the treatment of chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia, Approved December 2012

Bosulif (bosutinib); Pfizer; For the treatment of Ph+ chronic myelogenous leukemia, Approved September 2012

Revlimid (lenalidomide); Celgene; For the treatment of mantle cell lymphoma, Approved June 2013

Pomalyst (pomalidomide); Celgene; For the treatment of relapsed and refractory multiple myeloma, Approved February 2013

Imbruvica (ibrutinib); Pharmacyclics; For the treatment of mantle cell lymphoma, Approved November of 2013

Gazyva (obinutuzumab); Genentech; For the treatment of previously untreated chronic lymphocytic leukemia, Approved October of 2013

Zydelig (idelalisib); Gilead; For the treatment of relapsed CLL, follicular B-cell NHL and small lymphocytic lymphoma, Approved July 2014

# Son 20 yılda FDA'in onayladığı hematolojik ilaçlar (malign hastalıklar)

Sylvant (siltuximab); Janssen Biotech; For the treatment of multicentric Castleman's disease, Approved April 2014

Imbruvica (ibrutinib); Pharmacyclics; For the treatment of chronic lymphocytic leukemia, Approved February 2014

Blincyto (blinatumomab); Amgen; For the treatment of Philadelphia chromosome-negative relapsed / refractory B cell precursor acute lymphoblastic leukemia, Approved December 2014

Beleodaq (belinostat); Spectrum Pharmaceuticals; For the treatment of relapsed or refractory peripheral T-cell lymphoma, Approved July 2014

Farydak (panobinostat); Novartis; For the treatment of multiple myeloma, Approved February 2015

Darzalex (daratumumab); Janssen Biotech; For the treatment of multiple myeloma, Approved November 2015

Venclexta (venetoclax); AbbVie; For the treatment of chronic lymphocytic leukemia with 17p deletion, Approved April 2016

Opdivo (nivolumab); Bristol-Myers Squibb; For the treatment of classical Hodgkin lymphoma, Approved May 2016

**SON 20 YILDA ONAYLANAN 26 İLACIN SADECE 1 TANESİ KLASİK KEMOTERAPÖTİK**

# TheramAbs*



**> 50 approved mAbs, Fabs, Fc-fusions, ADCs, RadioICs, Bispecs [28 years]**
(INN= International Non-proprietary Names, WHO)

2015? MAA secukinumab(IL17a) dinutuximab(GD2) evolocumab[IgG2λ](PSK9) blinatumomab(CD19/CD3) necitumumab(EGFR)

2014 ramucirumab(VEGFR-2) siltuximab(IL6) vedolizumab(α4β7) nivolumab[IgG4s](PD1)[Jpn] pembrolizumab[IgG4s](PD1)

2013 itolizumab(CD6)[Ind] ado trastuzumab emtansine(HER2) obinutuzumab[low fuc](CD20) [Remsima/infliximab, EMA]

2012 mogamulizumab[low fuc](CCR4)[Jpn] pertuzumab(HER2) ziv-aflibercept[PrFc](VEGF) raxibacumab(antrax)

2011 brentuximab vedotin[IgG1-vcMMAE](CD30) belatacept[PrFc](CD80/86) aflibercept[PrFc](VEGF)
belimumab(BLyS) ipilimumab(CTLA-4)

2010 denosumab[IgG2](RANK-L)

2009 golimumab(TNFα) catumaxomab(EpCAM/CD3) ustekinumab(IL12/23) canakinumab(IL1) ofatumumab(CD20)

2008 rinolacept[PrFc](IL1) certolizumab[Fab-PEG](TNFα) romiplostim[FcPe](TPO) [Clotinab/abciximab So-Ko]

2007 eculizumab[IgG2/4](C5) [Reditux/rituximab Ind]

2006 ranibizumab[Fab](VEGFA) panitumumab[IgG2](EGFR)

2005 nimotuzumab(EGFR)[Chi] abatacept[PrFc](CD80/86) tocilizumab(IL6R)[Jpn]

2004 cetuximab(EGFR) bevacizumab(VEGFA) natalizumab[IgG4](α4 integr)

2003 $^{131}$I-tositumomab[mIgG2a](CD20) [withdrawn 2014] omalizumab(IgE-Fc) efalizumab(CD11a)[withdrawn, 2009] alefacept[PrFc](CD2)

2002 $^{111}$In/$^{90}$Y-ibritumomab tiuxetan[mIgG1](CD20) adalimumab(TNFα)

2001 alemtuzumab(CD52)

2000 gemtuzumab ozogamicin[IgG4s-calicheamycin](CD33)[withdrawn 2010]

1999

1998 basiliximab(CD25) palivizumab(RSV-F) infliximab(TNFα) trastuzumab(HER2) etanercept[PrFc](TNFα)

1997 rituximab(CD20) daclizumab(CD25)

1996

1995 edrecolomab[mIgG2a](EpCAM)[Ger, withdrawn]

1994 abciximab[Fab](GPIIb)

1993

1986 muromomab[mIgG2a](CD3)

1984 Nobel Prize for mAbs

**Technologies**

**Transgenic mice (10Y)**

**Phage display (9Y)**

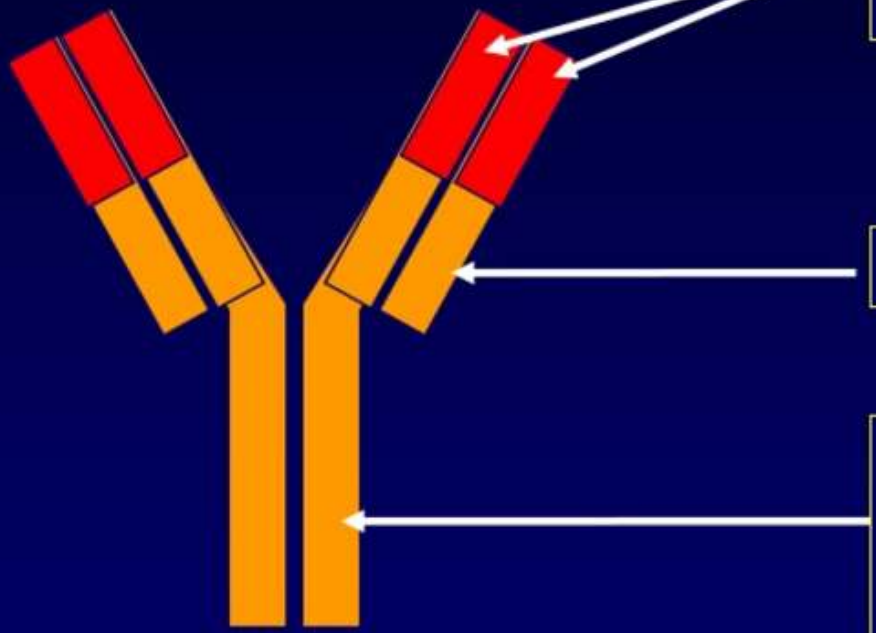
**Humanization (11Y)**

Chimerization (10 Y)

* FDA, EMA, SFDA and /or DCGI
(SFDA = China FDA;
DCGI = Drugs Controller General of India)

**[Biosimilars mAbs]**

# Rituximab (mabthera®) : a mouse/ human chimeric anti- CD20 monoclonal antibody

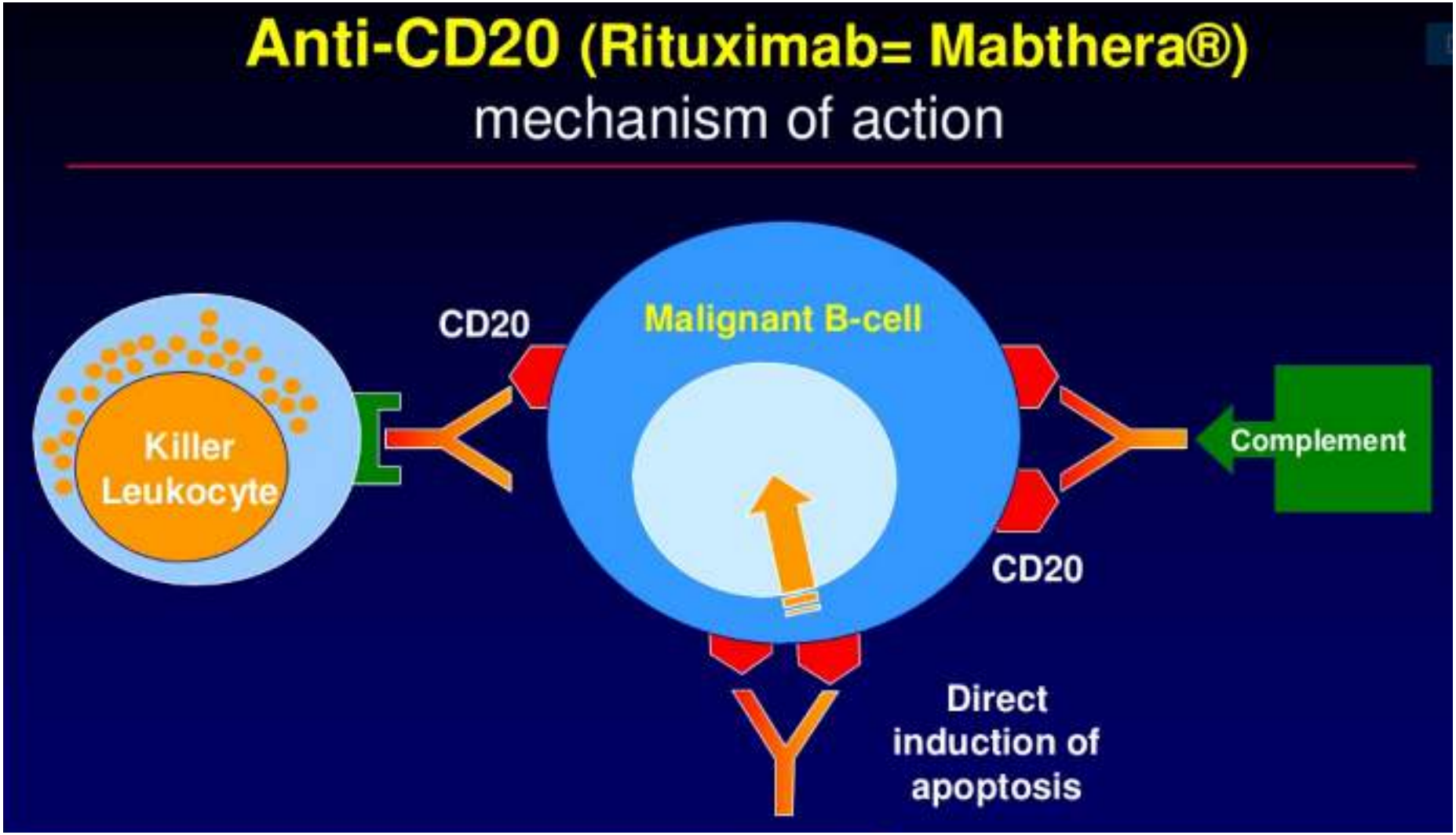


Murine variable regions bind specifically to CD20 on normal/ malignant B-cells

Human K constant regions

Human IgG1 Fc domain

- interacts with human effector mechanisms (ADCC, CDC)
- low immunogenicity



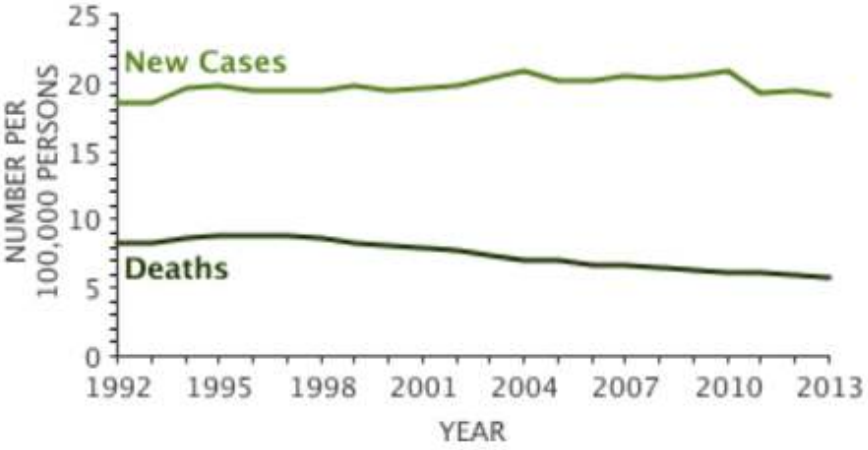

There are three postulated mechanisms of action of rituximab for B-cell depletion. These are **complement-mediated cytotoxicity**, **antibody-dependent cell-mediated cytotoxicity** and **induction of apoptosis**. In vivo, most likely the first mechanisms are dominant and the primary mechanism might depend on the specific anatomic location of the cell.

| | Common Types of Cancer | Estimated New Cases 2016 | Estimated Deaths 2016 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 246,660 | 40,450 |
| 2. | Lung and Bronchus Cancer | 224,390 | 158,080 |
| 3. | Prostate Cancer | 180,890 | 26,120 |
| 4. | Colon and Rectum Cancer | 134,490 | 49,190 |
| 5. | Bladder Cancer | 76,960 | 16,390 |
| 6. | Melanoma of the Skin | 76,380 | 10,130 |
| **7.** | **Non-Hodgkin Lymphoma** | **72,580** | **20,150** |
| 8. | Thyroid Cancer | 64,300 | 1,980 |
| 9. | Kidney and Renal Pelvis Cancer | 62,700 | 14,240 |
| 10. | Leukemia | 60,140 | 24,400 |

Non-Hodgkin lymphoma represents 4.3% of all new cancer cases in the U.S.


https://seer.cancer.gov/statfacts/html/ (Nisan 2017)

| | |
|---|---|
| Estimated New Cases in 2016 | 72,580 |
| % of All New Cancer Cases | 4.3% |
| Estimated Deaths in 2016 | 20,150 |
| % of All Cancer Deaths | 3.4% |




**Percent Surviving 5 Years**

70.7%

2006–2012

**Number of New Cases and Deaths per 100,000**: The number of new cases of non-Hodgkin lymphoma was 19.5 per 100,000 men and women per year. The number of deaths was 6.0 per 100,000 men and women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths.

**Lifetime Risk of Developing Cancer**: Approximately 2.1 percent of men and women will be diagnosed with non-Hodgkin lymphoma at some point during their lifetime, based on 2011–2013 data.

**Prevalence of This Cancer**: In 2013, there were an estimated 569,536 people living with non-Hodgkin lymphoma in the United States.

https://seer.cancer.gov/statfacts/html/ (Nisan 2017)

| Sıra | Ülke (veya bağımlı bölge) | Nüfus | Tarih | % dünya nüfusuna oranı | Kaynak |
|---|---|---|---|---|---|
| | Dünya | 7.428.725.440 | 31 Aralık 2015 | 100,00% | worldometers dünya nüfusu sayacı |
| 1 | Çin Halk Cumhuriyeti[1] | 1.374.390.000 | 19 Ocak 2016 | %18,8 | Resmi nüfus sayacı |
| 2 | Hindistan | 1.284.552.330 | 06 Şubat 2016 | %17,6 | Nüfus sayacı |
| 3 | Amerika Birleşik Devletleri | 322.856.495 | 19 Ocak 2016 | %4,43 | Resmi nüfus sayacı |
| 4 | Endonezya | 255.993.674 | 26 Nisan 2015 | %3,47 | Resmi tahmin |
| 5 | Brezilya | 205.506.000 | 19 Ocak 2016 | %2,82 | Resmi nüf |
| 6 | Pakistan | 192.540.254 | 19 Ocak 2016 | | |
| 7 | Nijerya | 181.562.056 | | | BM tahmini[2] |
| 8 | Bangladeş | | | %2,19 | Resmi nüfus sayacı |
| 9 | Rusya | | 26 Nisan 2015 | %1,91 | Resmi tahmin |
| 10 | J | 126.919.659 | 26 Nisan 2015 | %1,72 | Aylık Resmi nüfus tahmini |
| 11 | Meksika | 121.736.809 | 26 Nisan 2015 | %1,65 | Resmi nüfus sayımı |
| 12 | Filipinler | 109.615.913 | 26 Nisan 2015 | %1,48 | Resmi nüfus sayacı |
| 13 | Etiyopya | 99.465.819 | 26 Nisan 2015 | %1,35 | Resmi nüfus sayacı |
| 14 | Vietnam | 91.348.835 | 26 Nisan 2015 | %1,24 | [1] |
| 15 | Mısır | 90.375.892 | 19 ocak 2016 | %1,24 | Resmi nüfus sayacı |
| 16 | Kongo DC | 85.026.000 | 1 Temmuz 2015 | %1,05 | Resmi nüfus sayacı |
| 17 | Almanya | 81.459.000 | 30 Haziran 2015 | %1.05 | Üç aylık Resmi nüfus sayımı |
| 18 | Türkiye | 78.941.054 | 28 Ocak 2016 | %1.06 | 2016 TÜİK Verileri |
| 19 | İran | 77.176.930 | 31 Ocak 2016 | %1,11 | Resmi nüfus sayacı |
| 20 | Tayland | 67.367.943 | 1 Temmuz 2014 | %0,91 | Resmi tahmin |
| 21 | Fransa[3] | 65.107.000 | 1 Temmuz 2013 | %0,88 | Aylık Resmi nüfus sayımı |

**2016 için Türkiye' de yaklaşık 18.000 yeni NHL olgusu beklenmektedir.**

**Table 1.** Relative frequencies of B-cell lymphoma subtypes in adults[1]

| Mature B-cell neoplasms | Percentage of total cases* |
|---|---|
| Diffuse large B-cell lymphoma | 37 |
| Follicular lymphoma | 29 |
| Chronic lymphocytic leukemia/small lymphocyctic lymphoma | 12 |
| Extranodal marginal zone B-cell lymphoma of MALT (MALT lymphoma) | 9 |
| Mantle cell lymphoma | 7 |
| Primary mediastinal large B-cell lymphoma | 3 |
| Nodal marginal zone lymphoma | 2 |
| Lymphoplasmacytic lymphoma | 1.4 |
| Splenic marginal zone lymphoma | 0.9 |
| Burkitt lymphoma/leukemia | 0.8 |

* These figures underestimate the incidence of chronic lymphocytic leukemia/small lymphocytic lymphoma, as only patients presenting clinically with lymphoma were included.

The MEDIAN AGE at diagnosis is **66** YEARS[2]

5-YEAR OVERALL SURVIVAL RATE

Although significant strides have been made in the treatment of DLBCL, the current 5-year overall survival rate is approximately 60%[3]

DLBCL is the most common aggressive non-Hodgkin's lymphoma (NHL), comprising approximately 37% of all NHLs (Table 1).[1]


1) Jaffe ES, et al. Introduction and overview of the classification of the lymphoid neoplasms. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* 4th ed. Lyon, France: International Agency for Research on Cancer; 2008:158-166.

2) Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2011. National Cancer Institute website. http://seer.cancer.gov/csr/1975_2011/results_single/sect_19_table.29_2pgs.pdf. Updated December 17, 2014. Accessed February 01 2016.

**Günümüzde tedavi kararı için ilk gözetilen kriter klinik evredir.** **1**

National Comprehensive Cancer Network®

## NCCN Guidelines Version 1.2016
## Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
NHL Table of Contents
Discussion

**STAGE** | **FIRST-LINE THERAPY[m]**

**Consider prophylaxis for tumor lysis syndrome (See NHODG-B)**

**See monoclonal antibody and viral reactivation (NHODG-B)**

**Stage I, II[i,j]**

- **Nonbulky (<7.5 cm)** → **RCHOP[n] x 3 cycles + RT[o] (category 1) or RCHOP[n] x 6 cycles ± RT[o,p]** → See Pre RT Evaluation (BCEL-4)
- **Bulky (≥7.5 cm)** → **RCHOP[n] x 6 cycles ± RT[o,p]** → See Pre RT Evaluation (BCEL-4)

**Stage III, IV[i,k,l]** → **Clinical trial[q] or RCHOP[n,r] (category 1)[s]** → **Interim restaging after 2–4 cycles** → See BCEL-5

**2**

ease at presentation. The definition of bulky disease has varied from 5 to 10 cm in different reports. Some physicians believe that a patient who achieves a complete remission with a rituximab-containing regimen, particularly if defined by negative results on a positron emission tomographic (PET) scan, does not require consolidative radiotherapy to sites of bulky disease. However, a recent report from MD Anderson Cancer Center found that radiotherapy after CHOP-R chemotherapy improved 5-year progression-free survival (90% vs 75%) and overall survival (91% vs 83%) in patients with all stages of disease.[27]

**3**

I still offer radiotherapy to most patients with sites of bulky disease (ie, ≥10 cm) regardless of the initial stage of disease. An equivocal PET scan result at the completion of treatment would make me more likely to administer the radiotherapy.[30]

**TABLE 1. Predicting Treatment Outcome in Diffuse Large B-Cell Lymphoma[a]**

| IPI adverse risk factors (APLES) | |
|---|---|
| **A**ge >60 y | |
| **P**erformance status ≤ECOG grade 2 | |
| **L**actate dehydrogenase >maximum normal | |
| **E**xtranodal sites ≥2 | |
| **S**tage III or IV | |

| Outcome by risk group with or without rituximab | | |
|---|---|---|
| Adverse IPI risk factors | 4-year event-free survival (%)[b] Without rituximab | With rituximab |
| 1 | 68 | 80 |
| 2 | 48 | 62 |
| 3 | 39 | 50 |
| 4-5 | 20 | 47 |

[a] ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index.
[b] Estimates from Ziepert et al.[6]

Armitage, JO. My treatment approach to patients with diffuse large B-cell lymphoma. Mayo Clin Proc. 2012 ;87(2):161-71.

# Erken Evre

# R eklemenin yararı?

J Clin Oncol. 2008 May 10;26(14):2258-63. doi: 10.1200/JCO.2007.13.6929. Epub 2008 Apr 14.

## Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014.

Persky DO[1], Unger JM, Spier CM, Stea B, LeBlanc M, McCarty MJ, Rimsza LM, Fisher RI, Miller TP; Southwest Oncology Group.

⊕ Author information

**Abstract**

**PURPOSE:** To evaluate the effect of rituximab in limited-stage diffuse large B-cell lymphoma (DLBCL), we conducted a multicenter phase II trial combining rituximab with three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) followed by involved-field radiation therapy (IFRT).

**PATIENTS AND METHODS:** Southwest Oncology Group (SWOG) study S0014 enrolled patients with newly diagnosed, aggressive, CD20-expressing non-Hodgkin's lymphoma (NHL). Patients had limited-stage disease and at least one adverse risk factor as defined by the stage-modified International Prognostic Index (nonbulky stage II disease, age > 60 years, WHO performance status of 2, or elevated serum lactate dehydrogenase). Four doses of rituximab were infused on days -7, 1, 22, and 43, and CHOP was administered on days 3, 24, and 45, followed 3 weeks later by 40 to 46 Gy of IFRT.

**RESULTS:** Sixty patients with aggressive NHL were eligible. With the median follow-up of 5.3 years, treatment resulted in a progression-free survival (PFS) of 93% at 2 years and 88% at 4 years. Overall survival (OS) was 95% at 2 years and 92% at 4 years. These results were compared with those from a historic group of patients treated without rituximab on S8736, demonstrating PFS of 78% and OS of 88% at 4 years.

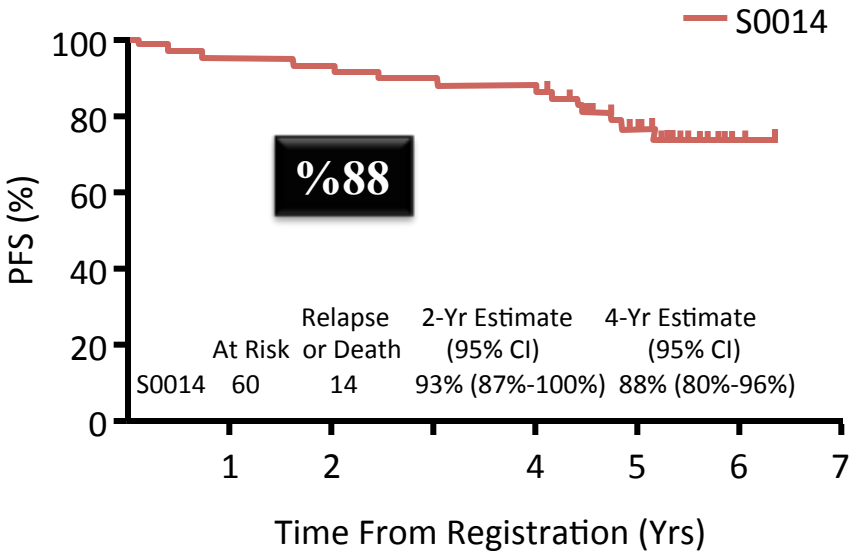
**CONCLUSION:** In limited-stage DLBCL, the addition of rituximab to three cycles of CHOP plus IFRT met prespecified study criteria of efficacy, with 2-year PFS of at least 84%, meriting further investigation. There is a pattern of continuing relapse with modest survival gains. We hypothesize that such a pattern may be the result of biologic differences between limited- and advanced-stage lymphoma.

- Hasta (n=60, yeni tanı agressif NHL)
  - DLBCL (n = 56)
  - Burkitt-like (n = 3)
  - High grade B (n = 1)
- Tedavi
  - Rituximab: Days -7, 1, 22, and 43
  - CHOP: Days 3, 24, 45
  - 40-46 Gy IFRT given 3 wks following end of CHOP therapy

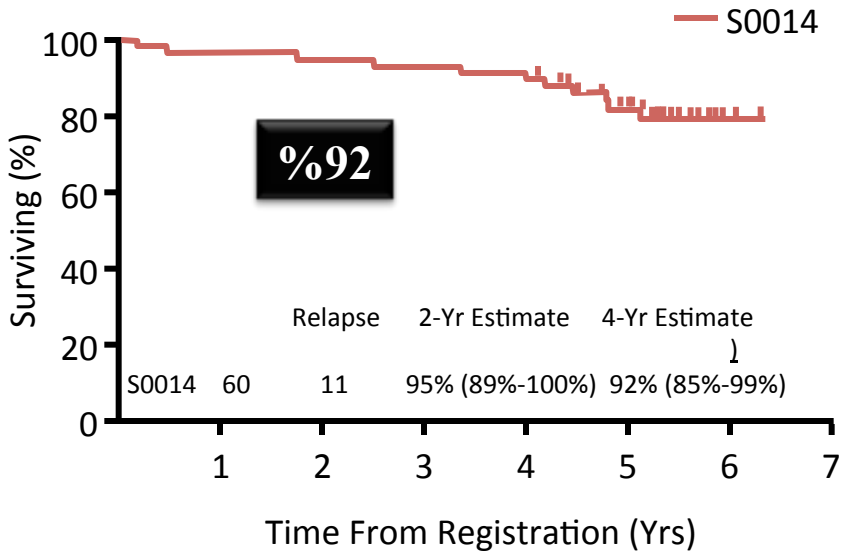
# SWOG 0014: R-CHOP + IFRT
# Sonuç

**Tarihsel kontrollere göre R eklemek PFS ve OS avantajı sağlamakta**

- Median follow-up: 5.3 yrs




**Önceki çalışmada PFS %78**



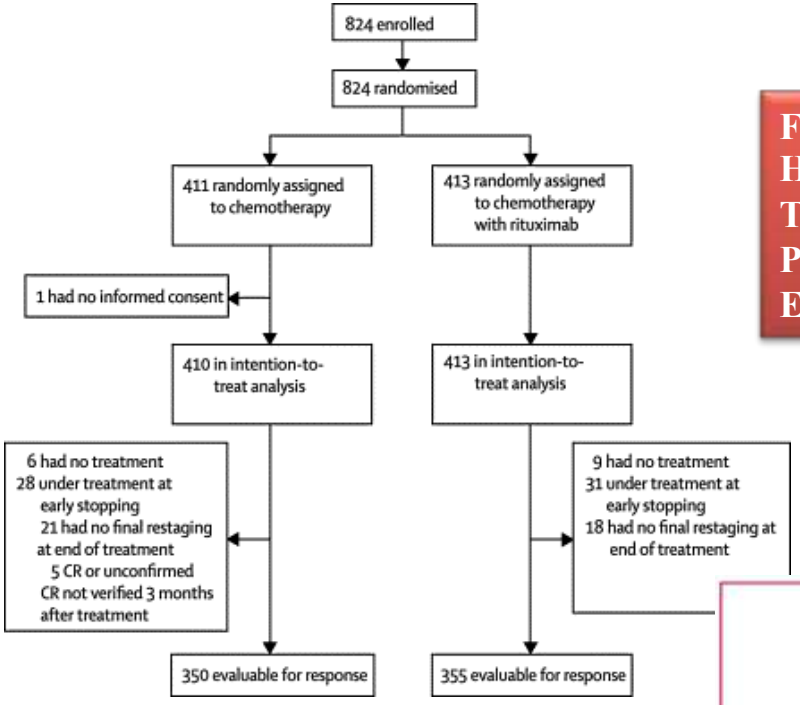

**Önceki çalışmada OS %88**

Persky DO, et al. J Clin Oncol. 2008;26:2258-2263.

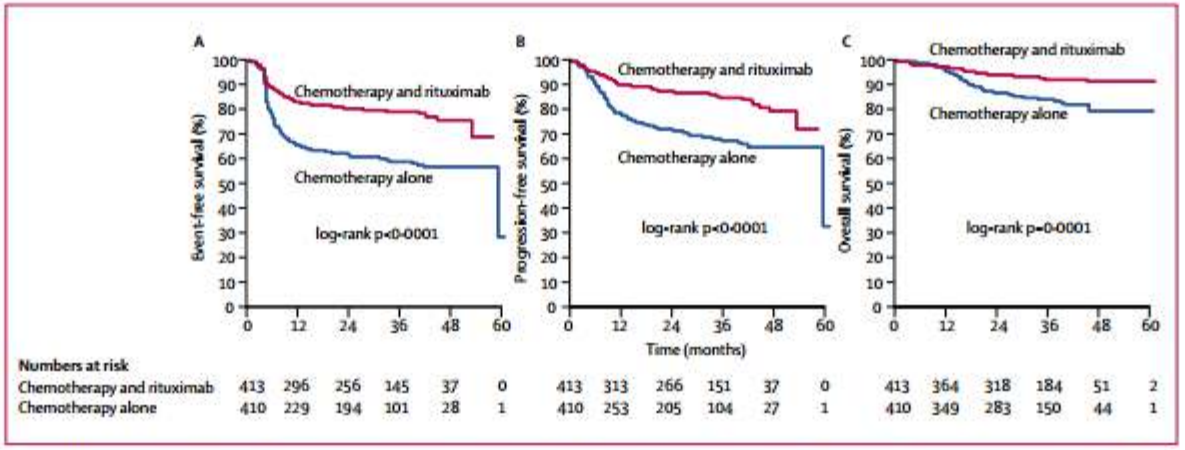
Lancet Oncol. 2006 May;7(5):379-91.

# CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group.

Pfreundschuh M[1], Trümper L, Osterborg A, Pettengell R, Trneny M, Imrie K, Ma D, Gill D, Walewski J, Zinzani PL, Stahel R, Kvaloy S, Shpilberg O, Jaeger U, Hansen M, Lehtinen T, López-Guillermo A, Corrado C, Scheliga A, Milpied N, Mendila M, Rashford M, Kuhnt E, Loeffler M; MabThera International Trial Group.



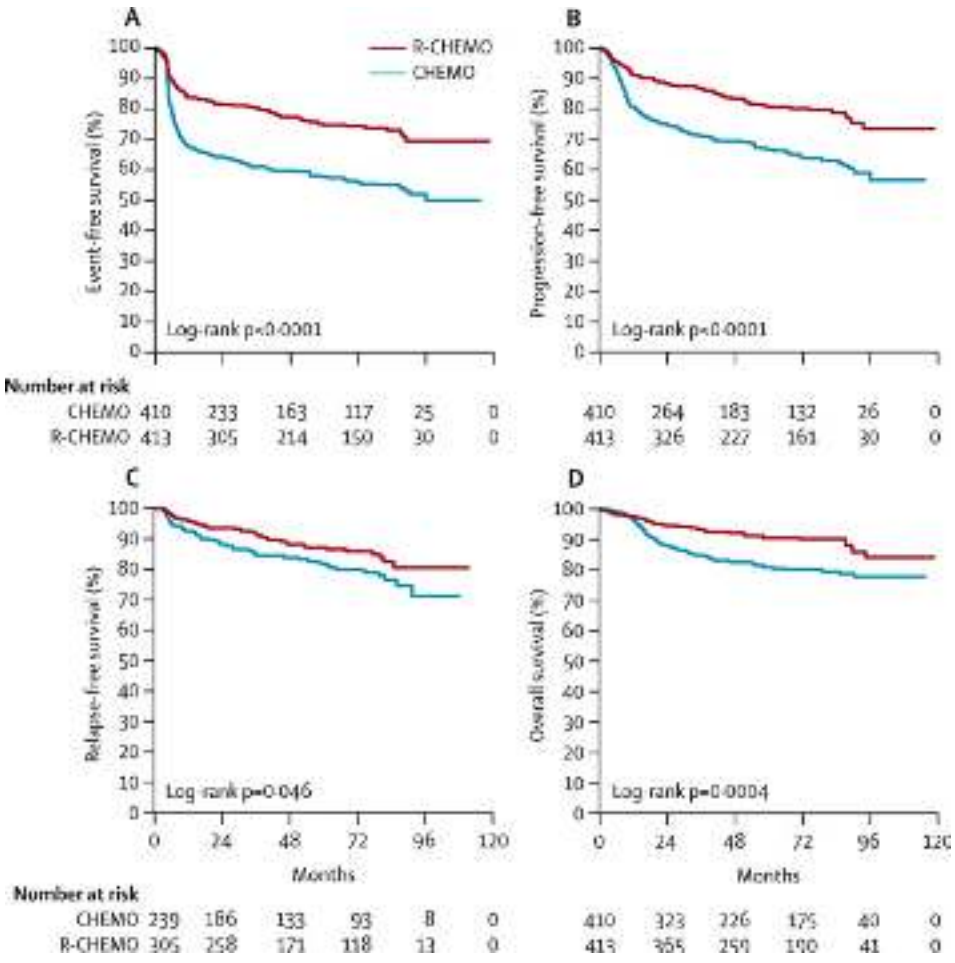

**Faz 3 çalışma**
**Hastalar < 60 yaş**
**Tüm evreler dahil**
**Performans statusu görece iyi olgular (0 ve 1)**
**Ekstranodal tutulum ya da 7,5 cm.den büyük kitleler için RT eklendi**



Lancet Oncol. 2011 Oct;12(11):1013-22. doi: 10.1016/S1470-2045(11)70235-2. Epub 2011 Sep 21.

# CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group.

Pfreundschuh M, Kuhnt E, Trümper L, Osterborg A, Trneny M, Shepherd L, Gill DS, Walewski J, Pettengell R, Jaeger U, Zinzani PL, Shpilberg O, Kvaloy S, de Nully Brown P, Stahel R, Milpied N, López-Guillermo A, Poeschel V, Grass S, Loeffler M, Murawski N; MabThera International Trial (MInT) Group.




Faz 3 çalışma
Hastalar < 60 yaş
Tüm evreler dahil
Performans statusu görece iyi olgular (0 ve 1)
Ekstranodal tutulum ya da 7,5 cm.den büyük kitleler için RT eklendi

| | Kemo (%) | R-Kemo (%) | p |
|---|---|---|---|
| 6 yıl OS | 80 | 90,1 | =0,0004 |
| 6 yıl EFS | 55,8 | 74,3 | <0,0001 |
| 6 yıl PFS | 63,9 | 80,2 | <0,0001 |

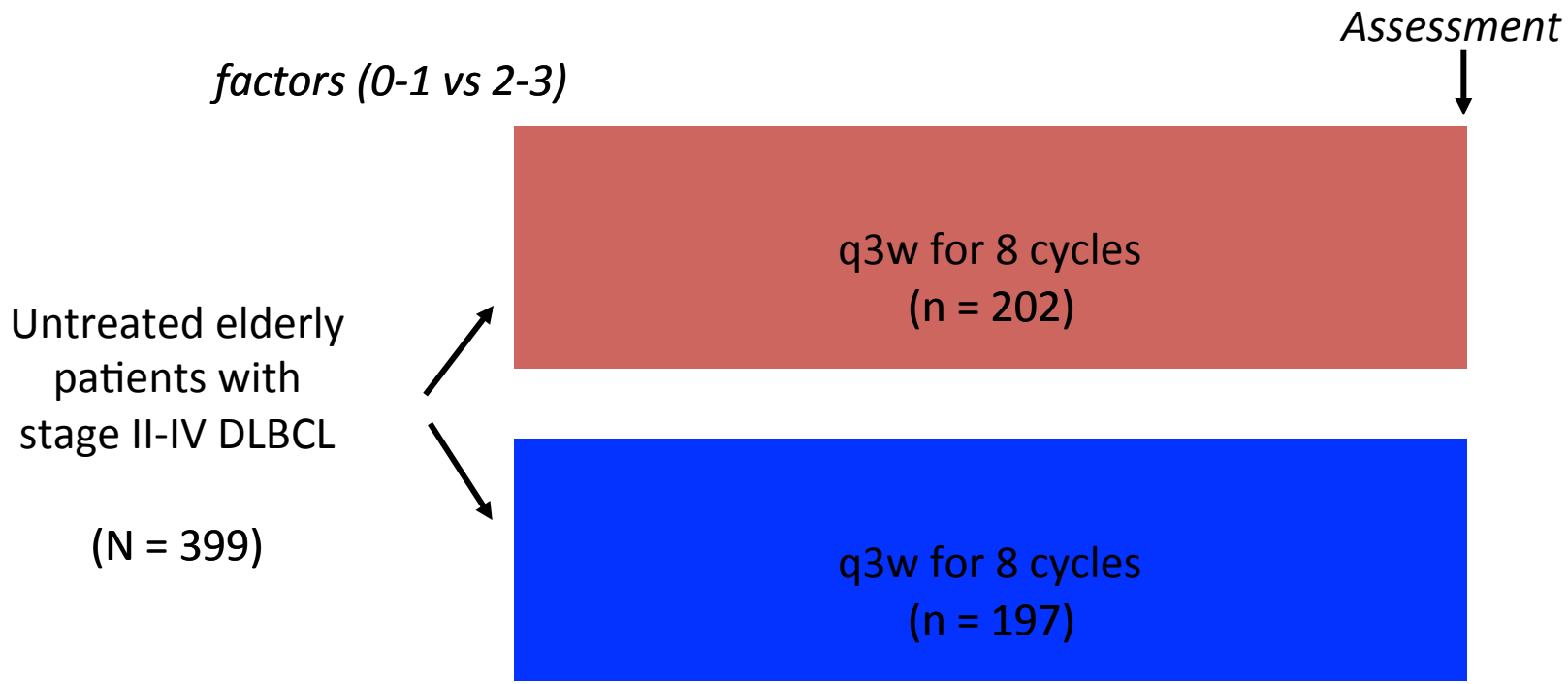
# İleri Evre

N Engl J Med. 2002 Jan 24;346(4):235-42.

**CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.**

Coiffier B[1], Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C.

**CHOP ± Rituximab in Advanced-Stage DLBCL: GELA LNH-98.5 Phase III Study**




- Primary endpoint: EFS
- Secondary endpoints: OS, RR

N Engl J Med. 2002 Jan 24;346(4):235-42.

# CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

Coiffier B[1], Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C.

**TABLE 1.** CHARACTERISTICS OF THE 399 PATIENTS.*

| CHARACTERISTIC | CHOP PLUS RITUXIMAB (N=202) | CHOP (N=197) |
|---|---|---|
| | no. (%) | |
| Age | | |
| <65 yr | 44 (22) | 48 (24) |
| 65–69 yr | 57 (28) | 62 (31) |
| 70–74 yr | 52 (26) | 56 (28) |
| ≥75 yr | 49 (24) | 31 (16) |
| Male sex | 92 (46) | 107 (54) |
| Performance status† | | |
| 0 | 67 (33) | 70 (36) |
| 1 | 90 (45) | 94 (48) |
| >1 | 45 (22) | 33 (17) |
| Stage | | |
| I | 0 | 1 (1) |
| II | 41 (20) | 39 (20) |
| III | 33 (16) | 29 (15) |
| IV | 128 (63) | 128 (65) |
| B symptoms‡ | 78 (39) | 70 (36) |
| No. of extranodal sites | | |
| 0 | 46 (23) | 44 (22) |
| 1 | 95 (47) | 102 (52) |
| >2 | 61 (30) | 51 (26) |
| Bulky tumor (>10 cm) | 60 (30) | 64 (32) |
| Bone marrow involvement | 56 (28) | 55 (28) |
| Elevated lactate dehydrogenase | 131 (65) | 132 (67) |
| Histologic findings | | |
| Not reviewed | 6 (3) | 8 (4) |
| Reviewed | 196 (97) | 189 (96) |
| Diffuse large-B-cell lymphoma | 176 (87) | 160 (81) |
| Not diffuse large-B-cell lymphoma | 20 (10) | 29 (15) |
| Burkitt's lymphoma | 2 | 2 |
| Mantle-cell lymphoma | 4 | 4 |
| Marginal-zone lymphoma | 2 | 1 |
| Follicular lymphoma | 5 | 10 |
| Small lymphocytic lymphoma | 1 | 6 |
| B-cell lymphoma, unspecified | | 2 |
| T-cell lymphoma | 4 | 3 |
| Hodgkin's lymphoma | 2 | 1 |
| Age-adjusted International Prognostic Index score§ | 20 (10) | 21 (11) |
| 0 | 61 (30) | 56 (28) |
| 1 | 87 (43) | 94 (48) |
| 2 | 34 (17) | 26 (13) |
| 3 | | |
| Standard International Prognostic Index score§ | 29 (14) | 23 (12) |
| 0–1 | 64 (32) | 69 (35) |
| 2 | 78 (39) | 82 (42) |
| 3 | 31 (15) | 23 (12) |
| 4–5 | | |

*CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone. None of the differences between treatment groups were significant (i.e., $P<0.05$).

†Performance status was defined according to the criteria of the Eastern Clinical Oncology Group (with an increasing score indicating declining performance).

‡B symptoms were defined as weight loss, fever, and night sweats.

§Higher scores indicate a higher risk of death.

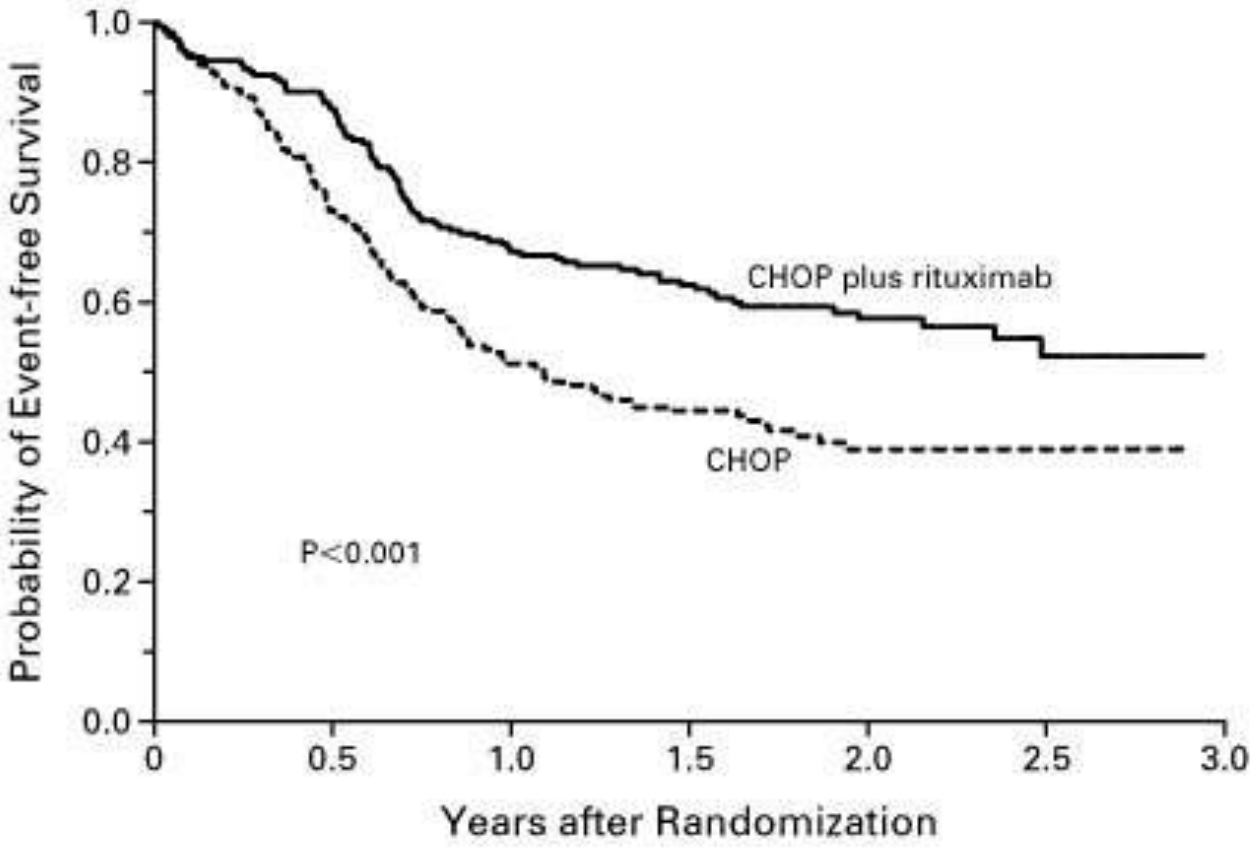
**TABLE 3.** RESPONSE TO TREATMENT WITH CHOP OR CHOP PLUS RITUXIMAB.*

| RESPONSE | CHOP PLUS RITUXIMAB (N=202) | CHOP (N=197) |
|---|---|---|
| | no. (%) | |
| Complete response | 106 (52) | 72 (37) |
| Unconfirmed complete response | 46 (23) | 52 (26) |
| Partial response | 15 (7) | 11 (6) |
| Stable disease | 2 (1) | 1 (1) |
| Progressive disease | 19 (9) | 43 (22) |
| Death without progression | 12 (6) | 11 (6) |
| Could not be assessed† | 2 (1) | 7 (4) |

N Engl J Med. 2002 Jan 24;346(4):235-42.

# CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

Coiffier B[1], Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C.

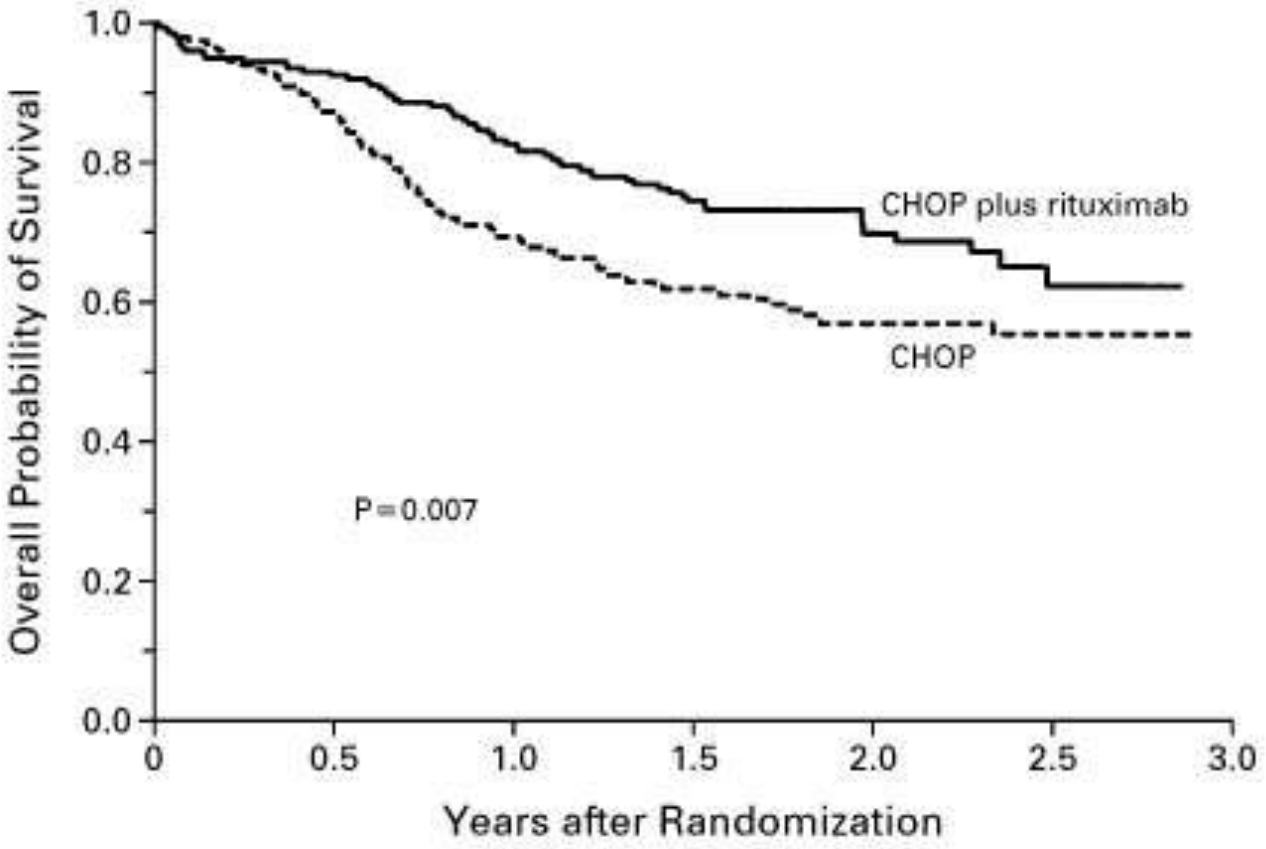



| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| CHOP plus rituximab | 202 | 177 | 137 | 108 | 63 | 19 |
| CHOP | 197 | 144 | 101 | 72 | 42 | 17 |

N Engl J Med. 2002 Jan 24;346(4):235-42.

# CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

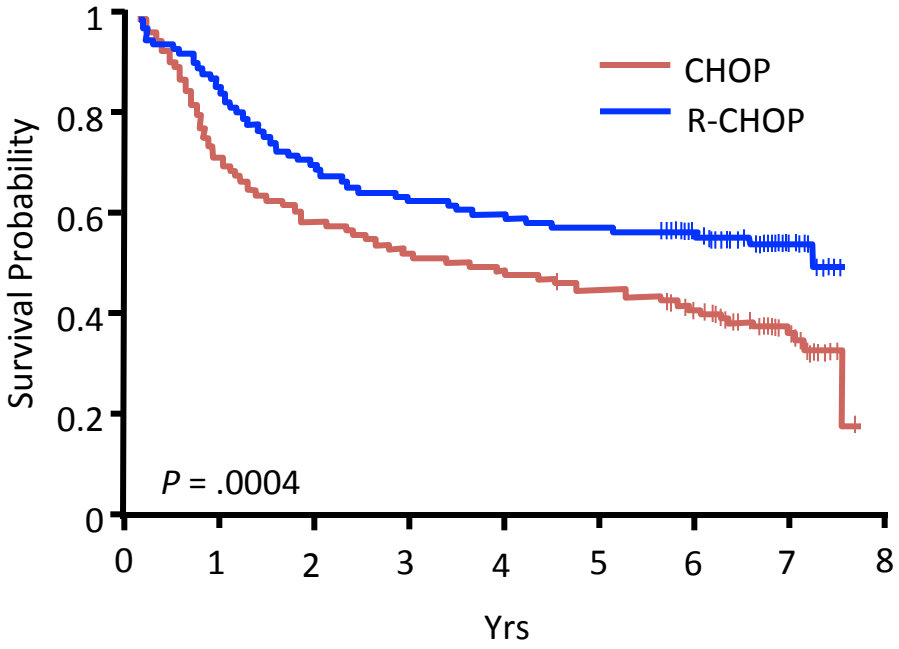
Coiffier B[1], Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C.




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| CHOP plus rituximab | 202 | 187 | 167 | 118 | 64 | 21 |
| CHOP | 197 | 171 | 136 | 96 | 58 | 16 |

# Results (GELA LNH-98.5 Study)

Coiffier B, et al. ASCO 2007. Abstract 8009.

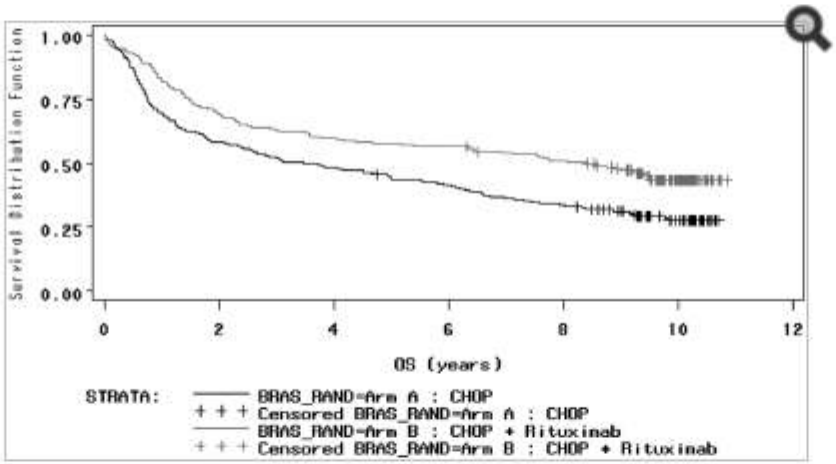



| Parameter, % | Low Risk | High Risk |
|---|---|---|
| Age, < 70 vs ≥ 70 yrs | 58.0 | 49.0 |
| LDH, NI vs > NI | LDH, NI | vs > NI |
| Stage, I/II vs III/IV | 67.0 | 50.0 |
| | 60.0 | |
| | 60.0 | |
| $\beta_2$-microglobulin, NI vs > NI | | 39.0* |
| Serum albumin, ≥ 35 vs < 35 g/L | 60.0 | 40.0 |

*$P$ < .05 (multivariate analysis).

Coiffier B, et al. ASCO 2007. Abstract 8009.

## Figure 2

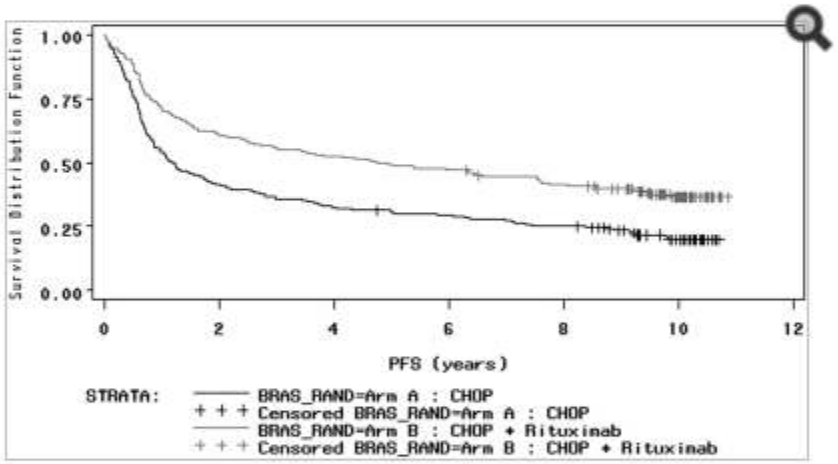



10 yıllık takip sonucu

| | CHOP (%) | R-CHOP (%) | p |
|---|---|---|---|
| PFS | 20 | 36,5 | <0,0001 |
| DFS | 43 | 64 | <0,0001 |
| OS | 28 | 43,5 | <0,0001 |

**Overall survival in patients treated with CHOP and R-CHOP**. Median overall survival (OS) was 3.5 years (95% CI: 2.2-5.5) in the CHOP arm and 8.4 years (95% CI: 5.4-not reached) in the R-CHOP arm ($P < .0001$).

## Figure 1




**Progression-free survival in patients treated with CHOP and R-CHOP**. Median progression-free survival (PFS) was 1.2 years (95% CI: .9-1.8) in the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) arm and 4.8 years (95% CI: 2.7-7.6) in the CHOP plus rituximab (R-CHOP) arm ($P < .0001$).

# Doz yoğun KT? → Pekiyi R-CHOP-14

Leuk Lymphoma. 2005 Apr;46(4):541-7.

## R-CHOP-14 in patients with diffuse large B-cell lymphoma: feasibility and preliminary efficacy.

Halaas JL[1], Moskowitz CH, Horwitz S, Portlock C, Noy A, Straus D, O'Connor OA, Yahalom J, Zelenetz AD.

⊕ Author information

**Abstract**

Treatment of diffuse large B-cell lymphoma (DLBCL) with CHOP-21 (cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m2, prednisone 100 mg for 5 days every 21 days) results in long-term remission in approximately 45% of patients. Recent phase III trials have demonstrated improved survival by modifying CHOP either through adding rituximab or shortening the time between cycles to 14 days. These studies prompted our institution to treat newly diagnosed patients with DLBCL refusing or not eligible for protocol-based therapy with R-CHOP-14. In this single-institution retrospective analysis, we report our results with this regimen. Forty-nine patients with newly diagnosed DLBCL and ineligible or refusing protocol-based therapy were retrospectively identified. Patients were treated with 6-8 cycles of R-CHOP-14 given with filgrastim and prophylactic antibiotics. The main toxicities with R-CHOP-14 were hematological and neurological and were not unexpected. There were no treatment-related deaths. Patients received 90% of planned cytotoxic drug density. The complete remission/complete remission uncertain (CR/CRu) rate was 82.2%. At a median follow-up of 24 months, the event-free survival was 80% and overall survival 90%. These results demonstrate R-CHOP-14 can be given to patients safely and short-term results regarding survival are promising. Whether adding rituximab and increasing dose intensity improves survival over either alone will require randomized studies.

Table I. Characteristics of the 49 patients treated with R-CHOP-14.

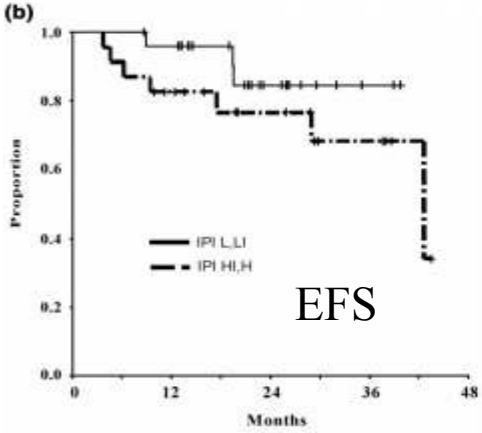
| | *n* | % |
|---|---|---|
| *n* | 49 | 100.0 |
| Sex | | |
| Male | 23 | 46.9 |
| Female | 26 | 53.1 |
| Median age (years) | 52 | |
| < 60 years | 35 | 71.4 |
| > 60 years | 14 | 28.6 |
| Karnofsky performance status | | |
| > 70 | 29 | 59.2 |
| ⩽ 70 | 20 | 40.8 |
| Extranodal sites | | |
| 0–1 | 31 | 63.3 |
| ⩾ 2 | 18 | 36.7 |
| Stage | | |
| 1 | 3 | 6.1 |
| 2 | 11 | 22.4 |
| 3 | 8 | 16.3 |
| 4 | 27 | 55.1 |
| International Prognostic Index (risk factors) | | |
| Low risk (0,1) | 15 | 30.6 |
| Low–intermediate risk (2) | 11 | 22.4 |
| High–intermediate risk (3) | 14 | 28.6 |
| High risk (4,5) | 9 | 18.4 |
| Bulky disease | 11 | 22.4 |
| B symptoms | 7 | 14.3 |
| Intrathecal prophylaxis | 19 | 38.8 |
| Involved-field radiation therapy | 16 | 32.7 |

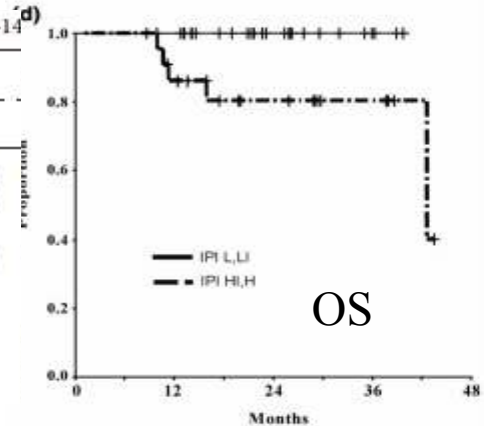
Table IV. End of treatment response of 45 evaluable patients to R-CHOP-14.

| Response | *n* | % |
|---|---|---|
| Complete remission | 19 | 42.2 |
| Complete remission uncertain | 18 | 40.0 |
| Partial response | 7 | 15.6 |
| Stable disease | 0 | 0 |
| Progressive disease | 1 | 2.2 |
| Total | 45 | 100 |

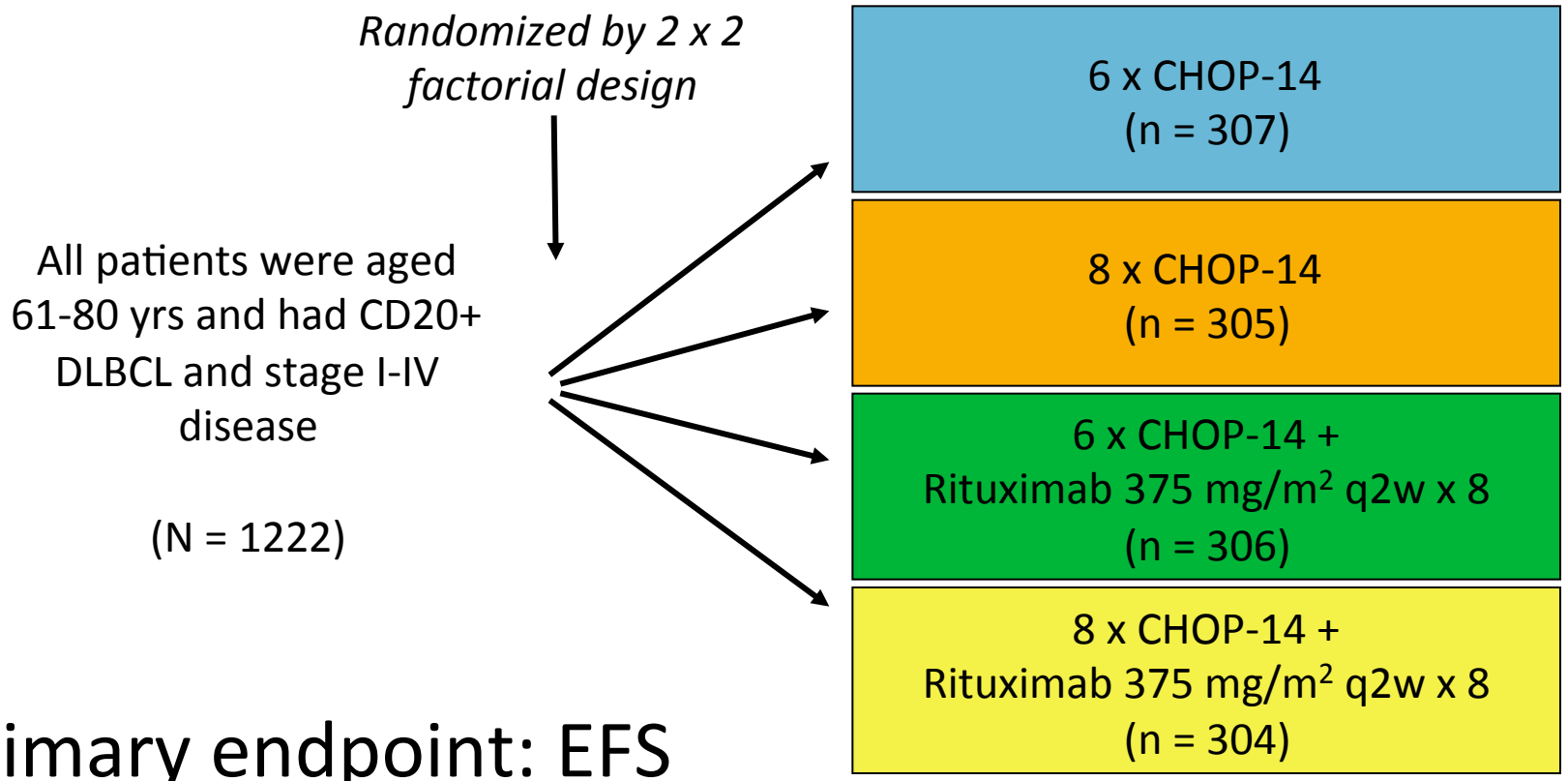
Table III. Toxicity of R-CHOP-14

| | Cycles | | All Patients (*n* = 49) | |
|---|---|---|---|---|
| Grade | 1/2 | 3/4 | 1/2 | 3/4 |
| White blood cells ( × $10^3$/μl) | 48 (16%) | 31 (11%) | 21 (43%) | 14 (29%) |
| Absolute neutrophil count ( × $10^3$/μl) | 5 (1.7%) | 25 (8.5%) | 1 (2.0%) | 12 (25%) |
| Hemoglobin (mg/dl) | 193 (66%) | 16 (6.4%) | 34 (69%) | 10 (20%) |
| Platelets | 10 (3.4%) | 2 (0.7%) | 3 (6%) | 2 (4%) |
| Sensory peripheral neuropathy | | | | |
| All patients | 165 (56%) | 0 (0%) | 43 (88%) | 0 (0%) |
| Capped | 81 (61%) | 0 (0%) | 19 (86%) | 0 (0%) |
| Uncapped | 84 (52%) | 0 (0%) | 24 (89%) | 0 (0%) |



# CHOP-14 vs R-CHOP-14 RICOVER-60 Trial: Patients Aged 61-80 Yrs




- Primary endpoint: EFS

*Radiotherapy (36 Gy) was planned for patients with initial bulky disease or extranodal involvement.

Pfreundschuh M, et al. Lancet Oncol. 2008;9:105-116.

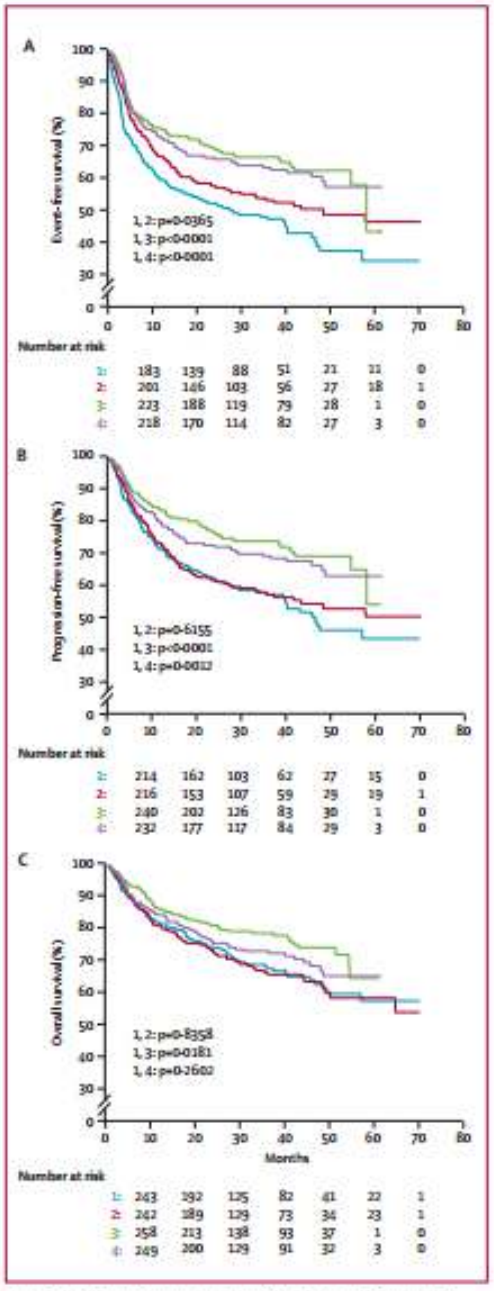



*Figure 2:* Event-free (A), progression-free (B), and overall (C) survival of 1222 elderly patients with aggressive CD20+ B-cell lymphoma treated in the RICOVER-60 trial

Patients were assigned to six or eight cycles of CHOP-14 with or without eight cycles of rituximab. 1=6×CHOP-14; 2=8×CHOP-14; 3=6×R-CHOP-14; 4=8×R-CHOP-14.

| | 6×CHOP-14 (n=307) | 8×CHOP-14 (n=305) | 6x8-CHOP-14 (n=306) | 8×R-CHOP-14 (n=304) |
|---|---|---|---|---|
| Complete response, n (%); 95% CI | 209 (68); 63–73 | 219 (72); 66–77 | 238 (78); 73–82 | 230 (76); 70–80 |
| p | .. | p=0·3150 | p=0·0069 | p=0·0372 |
| Complete response after additional therapy, n (%); 95% CI | 2 (0·7); 0·1–2·3 | 3 (1); 0·2–2·9 | 5 (2); 0·5–3·8 | 5 (2); 0·5–3·8 |
| p | .. | p=0·6854 | p=0·2858 | p=0·2842 |
| Partial response, n (%); 95% CI | 20 (7); 4–10 | 13 (4); 2–7 | 11 (4); 2–6 | 8 (3); 1–5 |
| p | .. | p=0·2176 | p=0·0990 | p=0·0217 |
| Stable disease, n (%); 95% CI | 2 (0·7); 0·1–2·3 | 2 (0·7); 0·1–2·4 | 0; 0–1 | 4 (1); 0·4–3·3 |
| p | .. | p=1·0000 | p=0·4992 | p=0·4489 |
| Progressive disease, n (%); 95% CI | 25 (8); 5–12 | 29 (10); 7–13 | 20 (7); 4–10 | 19 (6); 4–10 |
| p | .. | p=0·5517 | p=0·4455 | p=0·3654 |
| Treatment-associated deaths, n (%); 95% CI | 25 (8); 5–12 | 25 (8); 5–12 | 17 (6); 3–9 | 25 (8); 5–12 |
| p | .. | p=0·9808 | p=0·2048 | p=0·9711 |
| Unknown, n (%); 95% CI | 24 (8); 5–11 | 14 (5); 3–8 | 15 (5); 3–8 | 13 (4); 2–7 |
| p | .. | p=0·0981 | p=0·1392 | p=0·0665 |
| 3-year EFS, 95% CI | 47·2%; 41·3–53·3 | 53·0%; 47·0–59·1 | 66·5%; 60·9–72·0 | 63·1%; 57·4–68·8 |
| p | .. | p=0·0365 | p<0·0001 | p<0·0001 |
| 3-year PFS, 95% CI | 56·9%; 50·8–63·0 | 56·9%; 50·8–63·0 | 73·4%; 68·1–78·7 | 68·8%; 63·2–74·5 |
| p | .. | p=0·6155 | p<0·0001 | p=0·0012 |
| 3-year OS, 95% CI | 67·7%; 62·0–73·5) | 66·0%; 60·1–71·9 | 78·1%; 73·2–83·0 | 72·5%; 67·1–77·9 |
| p | .. | p=0·8358 | p=0·0181 | p=0·2602 |

EFS=event-free survival. PFS=progression-free survival. OS=overall survival. p values were derived from comparisons with 6×CHOP-14 treatment.

Table 2: Treatment findings

CHOP-14, six cycles of R-CHOP-14, and eight cycles of R-CHOP-14) by use of three indicator variables in all multivariate models. All tests for significance were two-sided and were adjusted for multiple comparisons of treatment regimens. Characteristics of patients, toxic effects, acco... inter... were exact... with inten... descr... SPSS Canc... EU-20243.

7 YILLIK TAKİP SONUCU

OS avantajı:

6 siklus R-CHOP-14 > 6 siklus CHOP-14

8 siklus R-CHOP-14 > 6 siklus CHOP-14 (yeni sonuç)

Ancak 8 R-CHOP-14 , 6 R-CHOP-14'den üstün değil.

Toksisitesi fazla

Nihayetinde:

6 R-CHOP-14

2 R daha önerilmekte

*JCO 2011:29:Abstract 8029.*

8 siklus R-CHOP-14,
6 siklus R-CHOP-14'e üstün değil

SONUÇ:

6 siklus R-CHOP-14 tercih edilen tedavi şekli

| | EFS (%) | PFS (%) | OS (%) | p |
|---|---|---|---|---|
| 6 R-CHOP 14 | 66,5 | 73,4 | 78,1 | <0,005 |
| 6 CHOP-14 | 47,2 | 56,9 | 67,7 | <0,005 |

# R-Kemoterapi > Kemoterapi: Pekiyi idame R?

J Clin Oncol. 2006 Jul 1;24(19):3121-7. Epub 2006 Jun 5.

## Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma.

Habermann TM[1], Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB, Dakhil SR, Woda B, Fisher RI, Peterson BA, Horning SJ.

⊕ Author information

**Abstract**

**PURPOSE:** To address early and late treatment failures in older patients with diffuse large B-cell lymphoma (DLBCL), we designed a two-stage randomized trial of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) versus rituximab plus CHOP (R-CHOP), with a second random assignment to maintenance rituximab (MR) or observation in responding patients.

**PATIENTS AND METHODS:** Untreated DLBCL patients who were 60 years or older were randomly assigned to R-CHOP (n = 318) or CHOP (n = 314); 415 responders were randomly assigned to MR (n = 207) or observation (n = 208). The primary end point was failure-free survival (FFS). All P values were two sided.

**RESULTS:** Three-year FFS rate was 53% for R-CHOP patients and 46% for CHOP patients (P = .04) at a median follow-up time of 3.5 years. Two-year FFS rate from second random assignment was 76% for MR compared with 61% for observation (P = .009). No significant differences in survival were seen according to induction or maintenance therapy. FFS was prolonged with MR after CHOP (P = .0004) but not after R-CHOP (P = .81) with 2-year FFS rates from second random assignment of 77%, 79%, 74%, and 45% for R-CHOP, R-CHOP + MR, CHOP + MR, and CHOP, respectively. In a secondary analysis excluding MR patients, R-CHOP alone reduced the risks of treatment failure (P = .003) and death (P = .05) compared with CHOP alone.

**CONCLUSION:** Rituximab administered as induction or maintenance with CHOP chemotherapy significantly prolonged FFS in older DLBCL patients. After R-CHOP, no benefit was provided by MR. These results, which are consistent with an additive effect of rituximab, suggest that future studies could focus on maintenance strategies with novel agents as well as new induction therapies.

Comparison of R-CHOP Alone Versus CHOP Alone

| Outcome | 3-Year Rate (%) | | *P* | HR | 95% CI |
|---|---|---|---|---|---|
| | R-CHOP | CHOP | | | |
| FFS | 52 | 39 | .003 | 0.64 | 0.47 to 0.85 |
| OS | 67 | 57 | .05 | 0.72 | 0.52 to 1.0 |

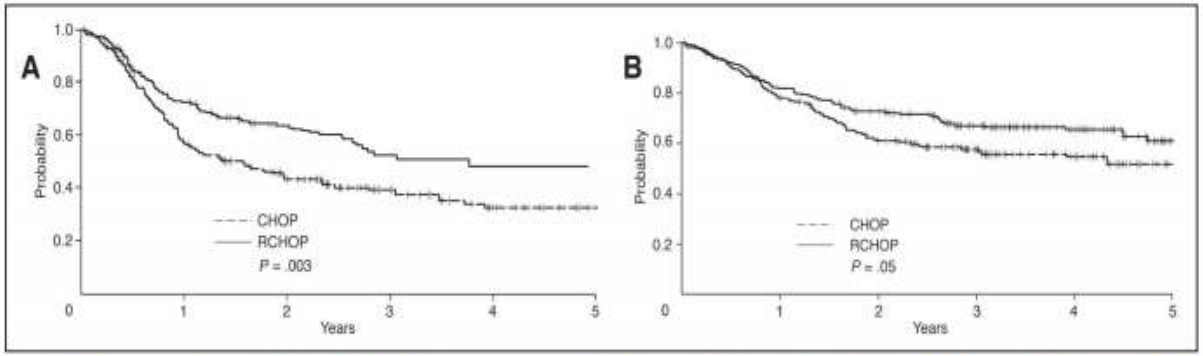


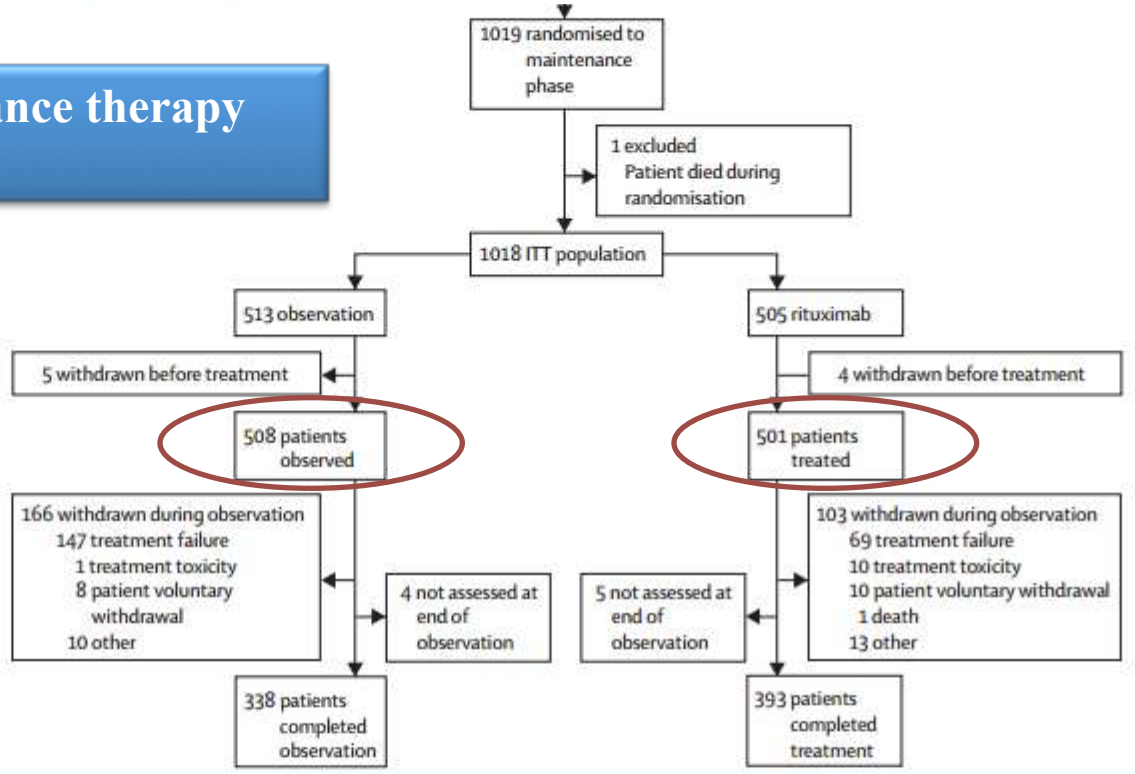

**Fig 3.** Failure-free survival (FFS) and overall survival (OS) after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab with CHOP (RCHOP), excluding maintenance rituximab (MR) patients. (A) FFS according to induction without MR; RCHOP decreased the risk of treatment failure compared with CHOP (hazard ratio [HR] = 0.64; 95% CI, 0.47 to 0.85; *P* = .003). (B) OS according to induction without MR; RCHOP improved survival compared with CHOP (HR = 0.72; 95% CI, 0.52 to 1.00; *P* = .05).

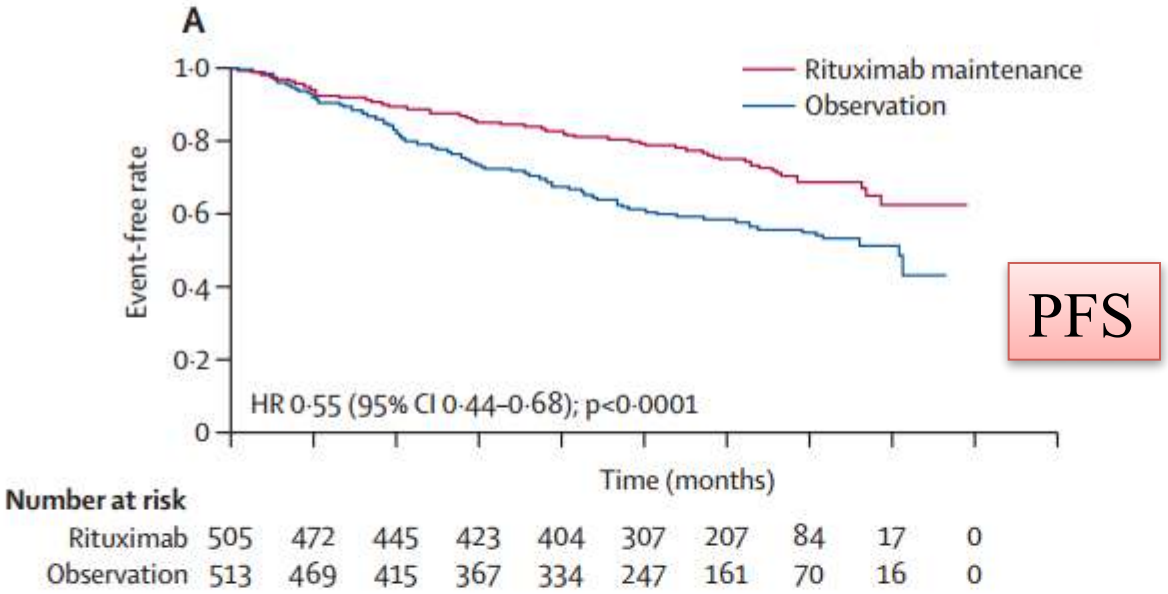
THE LANCET
Volume 377, Issue 9759, 1–7 January 2011, Pages 42–51

# Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial

*Gilles Salles, John Francis Seymour, Fritz Offner, Armando López-Guillermo, David Belada, Luc Xerri, Pierre Feugier, Réda Bouabdallah, John Vincent Catalano, Pauline Brice, Dolores Caballero, Corinne Haioun, Lars Moller Pedersen, Alain Delmer, David Simpson, Sirpa Leppa, Pierre Soubeyran, Anton Hagenbeek, Olivier Casasnovas, Tanin Intragumtornchai, Christophe Fermé, Maria Gomes da Silva, Catherine Sebban, Andrew Lister, Jane A Estell, Gustavo Milone, Anne Sonet, Myriam Mendila, Bertrand Coiffier, Hervé Tilly*

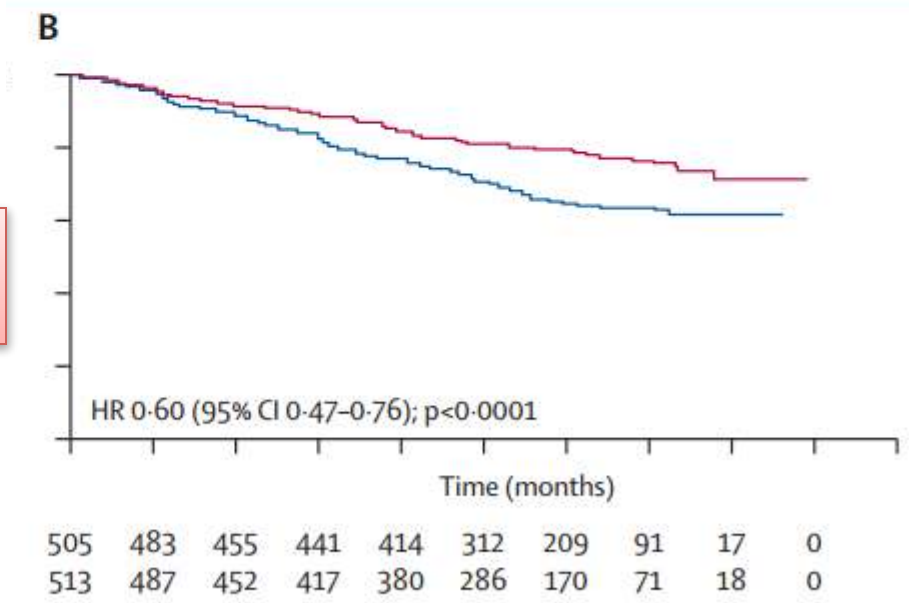
**2 years of rituximab maintenance therapy (375 mg/m² every 8 weeks)**






PFS

Sonraki antilenfoma tedaviye kadar geçen süre



# Folliküler Lenfoma'da ilk sıra R



**TABLO 6:** İlk sıra Folliküler Lenfoma tedavisinde sadece kemoterapi ile rituximab+kemoterapinin karşılaştırıldığı randomize çalışmalardan bazılarının sonuçları.[1]

| Çalışma | Tedavi, n | İzlem (ortanca ay) | Toplam yanıt (%) | Tam yanıt (%) | TTP, TTF, EFS (ortanca ay) | Toplam Sağkalım (%) |
|---|---|---|---|---|---|---|
| Marcus | CVP, 159 | 53 | 57 | 10 | 15 | 77 |
| R | -CVP, 162 | | 81 | 41 | 34 (p<0,0001) | 83 (p=0,029) |
| Hiddemann | CHOP, 205 | 18 | 90 | 17 | 29 | 74 |
| | R-CHOP, 223 | | 96 | 20 | NR (p<0,001) | 87 (p=0,016) |
| Herold | MCP, 96 | 47 | 75 | 25 | 26 | 74 |
| | R-MCP, 105 | | 92 | 50 | NR (p<0,0001) | 87 (p=0,009) |

TTP: Progresyona kadar geçen süre; TTF: Tedavi yetersizliğine kadar geçen süre; EFS: Olaysız sağkalım; CVP: Siklofosfamid, vinkristin, prednizon; R: Rituximab; CHOP: Siklofosfamid, doksorubisin, vinkristin, prednizon; NR: Belirtilmemiş; MCP: Mitoksantron, klorambusil, prednizon.

## 4.1 Terapötik endikasyonlar

Hodgkin-dışı Lenfoma (NHL)
MABTHERA'nın,

- Nükseden veya kemorezistan CD20 pozitif foliküler lenfoma, difüz büyük B hücreli lenfoma, mantle hücreli lenfoma tanılı hastaların tedavisinde
- Daha önce tedavi edilmemiş evre III-IV foliküler lenfomalı hastalarda kemoterapi ile kombinasyon halinde
- İndüksiyon tedavisine yanıt veren foliküler lenfomalı hastalarda idame tedavisi olarak (en fazla 2 yıl süreyle ve en fazla 8 siklus olarak)
- CD20 pozitif, difüz büyük B hücreli lenfomada CHOP kemoterapi şemasına ek olarak kullanımı endikedir.

Kronik Lenfositik Lösemi (KLL)
*Birinci basamak:*
MABTHERA, tedavi endikasyonu olan, performans durumu iyi olan (ECOG 0-1), 17 p delesyonu bulunmayan KLL hastalarının birinci basamak tedavisinde fludarabin ve siklofosfamid ile kombine olarak kullanılır.

*Relaps/Refrakter (Nükseden/Dirençli):*
Relaps/refrakter, tedavi endikasyonu olan, daha önce fludarabin ve alkilleyici ajanlarla tedavi sonrası progresyon gelişmiş, 65 yaş ve altı, ECOG performans statüsü 0-1 olan, 17p delesyonu bulunmayan, kronik lenfositer lösemi hastalarında, fludarabin ve siklofosfamid ile kombine olarak 4 kür rituksimab kullanılması uygundur.
İlk kürde 375 $mg/m^2$, diğer kürlerde 500 $mg/m^2$ kullanılabilir; 4 kür sonunda en az kısmi yanıt alınması halinde, 2 kür daha verilerek tedavi 6 küre tamamlanabilir.

JOURNAL OF CLINICAL ONCOLOGY
Official Journal of the American Society of Clinical Oncology

J Clin Oncol. 2010;28(10):1756-65.

# Rituximab Plus Fludarabine and Cyclophosphamide Prolongs Progression-Free Survival Compared With Fludarabine and Cyclophosphamide Alone in Previously Treated Chronic Lymphocytic Leukemia

*Tadeusz Robak, Anna Dmoszynska, Philippe Solal-Céligny, Krzysztof Warzocha, Javier Loscertales, John Catalano, Boris V. Afanasiev, Loree Larratt, Christian H. Geisler, Marco Montillo, Ilya Zyuzgin, Peter S. Ganly, Caroline Dartigeas, András Rosta, Jörg Maurer, Myriam Mendila, M. Wayne Saville, Nancy Valente, Michael K. Wenger, and Sergey I. Moiseev*

Faz 3, REACH trial 6 FC vs 6 FCR

| | FC (n=276) | FCR (n=276) | p |
|---|---|---|---|
| CR (%) | 13 | 24 | < 0,001 |
| PR (%) | 45 | 46 | |
| ORR (%) | 58 | 70 | 0,003 |
| PFS (ay), ort | 20,6 | 30,6 | <0,001 |

blood®

Blood. 2011;117(11):3016-24.

Faz 2

Leading the way in experimental and clinical research in hematology

# Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL

Xavier C. Badoux,[1] Michael J. Keating,[1] Xuemei Wang,[2] Susan M. O'Brien,[1] Alessandra Ferrajoli,[1] Stefan Faderl,[1] Jan Burger,[1] Charles Koller,[1] Susan Lerner,[1] Hagop Kantarjian,[1] and William G. Wierda[1]

Departments of [1]Leukemia and [2]Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

**Table 1. Outcomes after FCR by patient pretreatment characteristics**

| Pretreatment characteristics | No. of patients | NCI-WG response, % | | | Median | |
|---|---|---|---|---|---|---|
| | | CR | nPR | OR | PFS, mo | OS, mo |
| All patients | 284 | 30 | 14 | 74 | 21 | 46.5 |
| **Age, y*** | | | | | | |
| 0-60 | 154 | 39 | 12 | 74 | 28 | 60 |
| 61-70 | 90 | 23‡ | 19 | 78 | 22 | 48 |
| > 70 | 40 | 13‡ | 13 | 68 | 13‡ | 22§ |

**Table 2. Outcome after FCR by most-intensive prior therapy**

Önceki tedavi sayısı, ortanca 2 (1-10)

| Prior therapy hierarchy | No. of patients | Median no. of prior | F/Alk refractory, % | NCI-WG Response (%) | | Median, mo | |
|---|---|---|---|---|---|---|---|
| | | | | CR + nPR | OR | PFS | OS |
| Antibody only | 25 | 1 (1-2) | –/– | 64 | 92 | 49 | 69 |
| Fludarabine only | 61 | 1 (1-5) | 11/– | 61 | 80 | 39 | 88 |
| Alkylating agent only | 36 | 1 (1-4) | –/47 | 39 | 78 | 20 | 48 |
| F and alkylating agent, nonconcurrent | 57 | 3 (2-9) | 35/51 | 43 | 74 | 17 | 44 |
| FC, FCR, FCM, FND | 78 | 2 (1-10) | 13/9 | 42 | 73 | 19 | 41 |
| Multiagent (CHOP, ESHAP, DHAP) or SCT | 27 | 3 (1-10) | 63/52 | 11 | 44 | 6 | 20 |

Studies exploring chemoimmunotherapy with rituximab in treatment-naïve chronic lymphocytic leukemia

| Reference | Phase | N | Regimen(s) | OR (%) | CR (%) | Median survival (months) |
|---|---|---|---|---|---|---|
| **Single-arm studies** | | | | | | |
| Keating et al33 and Tam et al34 | II | 300 | Fludarabine + Cyclophosphamide + Rituximab (FCR) | 95 | 72 | NR |
| O'Brien et al36 | II | 65 | Fludarabine + Cyclophosphamide + Rituximab × 3 days (FCR3) | 94 | 65 | NR |
| Foon et al37 | II | 50 | Fludarabine (↓20%) + Cyclophosphamide (↓40%) + Rituximab × 2 days (FCR-Lite) | 100 | 77 | NR |
| Kay et al38 | II | 64 | Pentostatin + Cyclophosphamide + Rituximab (PCR) | 91 | 41 | PFS:33 |
| Kay et al39 | II | 33 | Pentostatin + Rituximab (PR) | 76 | 27 | TFS:16 |
| Bosch et al40 | II | 67 | Fludarabine + Cyclophosphamide + Mitoxantrone + Rituximab (FCMR) | 93 | 82 | NR |
| Faderl et al47 | II | 30 | Fludarabine + Cyclophosphamide + Mitoxantrone + Rituximab (FCMR) | 96 | 83 | NR |
| Fischer et al52 | II | 117 | Bendamustine + Rituximab (BR) | 91 | 33 | NR |
| **Randomized Studies** | | | | | | |
| Byrd et al27 and Woyach et al28 | II | 104 | Fludarabine + Rituximab (FR) (Concurrent) | 90 | 47 | OS:84; PFS:32 |
| | | | Fludarabine + Rituximab (FR) (Sequential) | 77 | 28 | OS:91; PFS:40 |
| Hallek et al35 | III | 817 | Fludarabine + Cyclophosphamide + Rituximab (FCR) | 95 | 44 | PFS:52; OS:NR |
| | | | Fludarabine + Cyclophosphamide (FC) | 88 | 22 | PFS:33; OS:NR |

**Abbreviations:** N, evaluable patients; OR, overall response; CR, complete remission; OS, overall survival; PFS, progression-free survival; FFS, failure-free survival; TFS, treatment-free survival; NR, not reported or reached

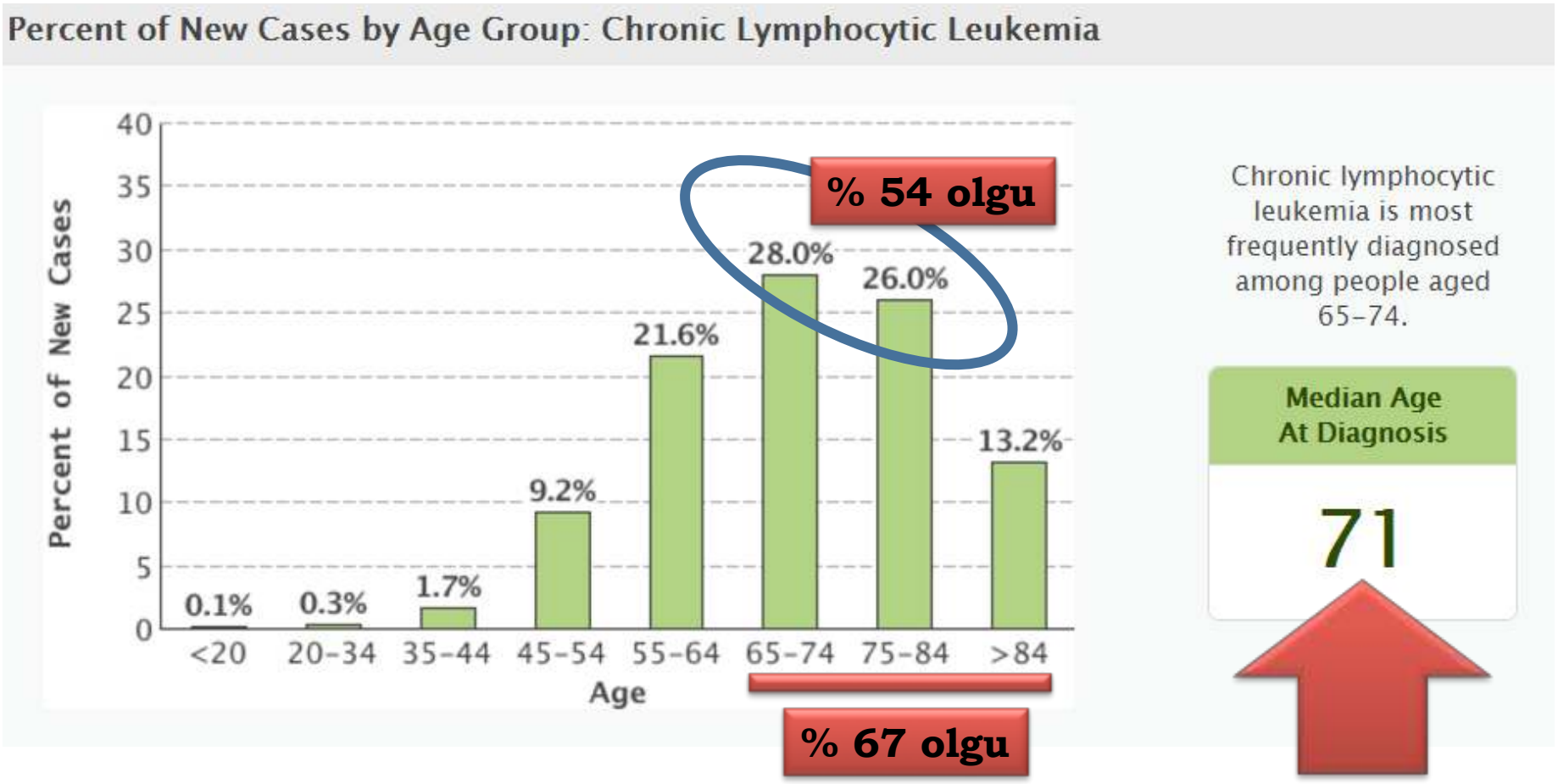
# Relaps KLL' de del 17p varlığı: Tedaviye Yanıtlar

| TEDAVİ | n | ORR (%) | CR (%) | PR (%) |
|---|---|---|---|---|
| Kemoimmünoterapi | 59 | 36 | 5 | 31 |
| FCR | 13 | 38 | 8 | 31 |
| CFAR | 13 | 38 | 15 | 23 |
| OFAR | 13 | 33 | 0 | 33 |
| mAb | 27 | 33 | 7 | 26 |
| Rituksimab | 12 | 17 | 0 | 17 |
| Alemtuzumab | 5 | 40 | 20 | 20 |
| A+R | 10 | 50 | 10 | 40 |
| IMİD | 10 | 50 | 10 | 40 |

OFAR: Oxaliplatin, flu, ARA-C, R

CFAR: Siklofosfamid, flu, alemtuzumab, R

Veliz M, et al. Cancer Control. 2012;19:37-53.




https://seer.cancer.gov/statfacts/html/clyl.html

# Dolayısıyla

- İlk sıra tedavide başarılı ve fakat relaps/ refrakterde
  - Özellikle “poor” prognostik grupta belirgin başarısız

Ve

  - Toksisiteleri (ve enfeksiyöz yan etkileri) nedeniyle neredeyse çoğunlukla ancak **fit ve genç hastalara** uygun olabilecek

kemoimmünoterapilerin kullanımı sınırlı kalmaktadır.

# KLL'de Yeni tedavi seçenekleri

| İlaç | Hedef |
| --- | --- |
| İbrutinib | BTK |
| İdelalisib | PI3K-delta |
| Venetoclax | Bcl-2 |
| Obinutuzumab | CD20 |

HEDEFE YÖNELİK TEDAVİLER

# HEDEFE YÖNELİK TEDAVİLER' in **en sık görülen** YANETKİLERİ

- Diyare
- Hepatit
- Cilt problemleri (döküntü, vb)
- Pıhtılşmaya/kanamaya yatkınlık
- Yara iyileşmesinde bozukluk
- Kan basıncı yüksekliği
- Gastrointestinal sistem bozuklukları
- İmmunosüpresyon

**Table 1. Novel agents and HBV reactivation status**

| [a]Agent | Target | Indication | HBV reactivation Status | Data source | References |
|---|---|---|---|---|---|
| **Monoclonal antibodies** | | | | | |
| Rituximab* | CD20 | Relapsed or refractory indolent lymphoma maintenance therapy in B-cell NHL | FDA boxed warning | FDA AERS | 13–15,30,31,37 |
| Ofatumumab* | CD20 | Relapsed/refractory CLL | FDA boxed warning | FDA AERS | 37,38 |
| Obinutumumab* | CD20 | Rituximab-refractory patients | FDA boxed warning | FDA AERS | 39–41 |
| Alemtuzumab§ | CD52 | Refractory B-CLL | +HBVr but no FDA warning yet | Case reports | 27,43 |
| Mogamulizumab§ | CC chemokine receptor | Aggressive adult T-cell leukemia-lymphoma (ATL) and peripheral T-cell lymphoma | +HBVr but no FDA warning yet | Case reports | 44,45 |
| **Small molecule inhibitors** | | | | | |
| Ibrutinib§ | BTK inhibitors | Low-grade NHL | Immune hepatitis | Clinical trials | 46,47 |
| Idelalisib§ | PI3Kδ inhibitors | Relapsed/Refractory low-grade NHL | Immune hepatitis/ Transaminitis | Clinical trials | 46,47 |

[a] Agent – Confirmed* and suspected§ agents with HBV reactivation sequela

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; BTK, Bruton's kinase; FDA, Food and Drug Administration; FDA AERS, FDA Adverse Event Reporting System; HBV, hepatitis B virus; NHL, non-Hodgkin lymphoma; PI3Kδ, phosphatidylinositol 3-kinase delta inhibitor.

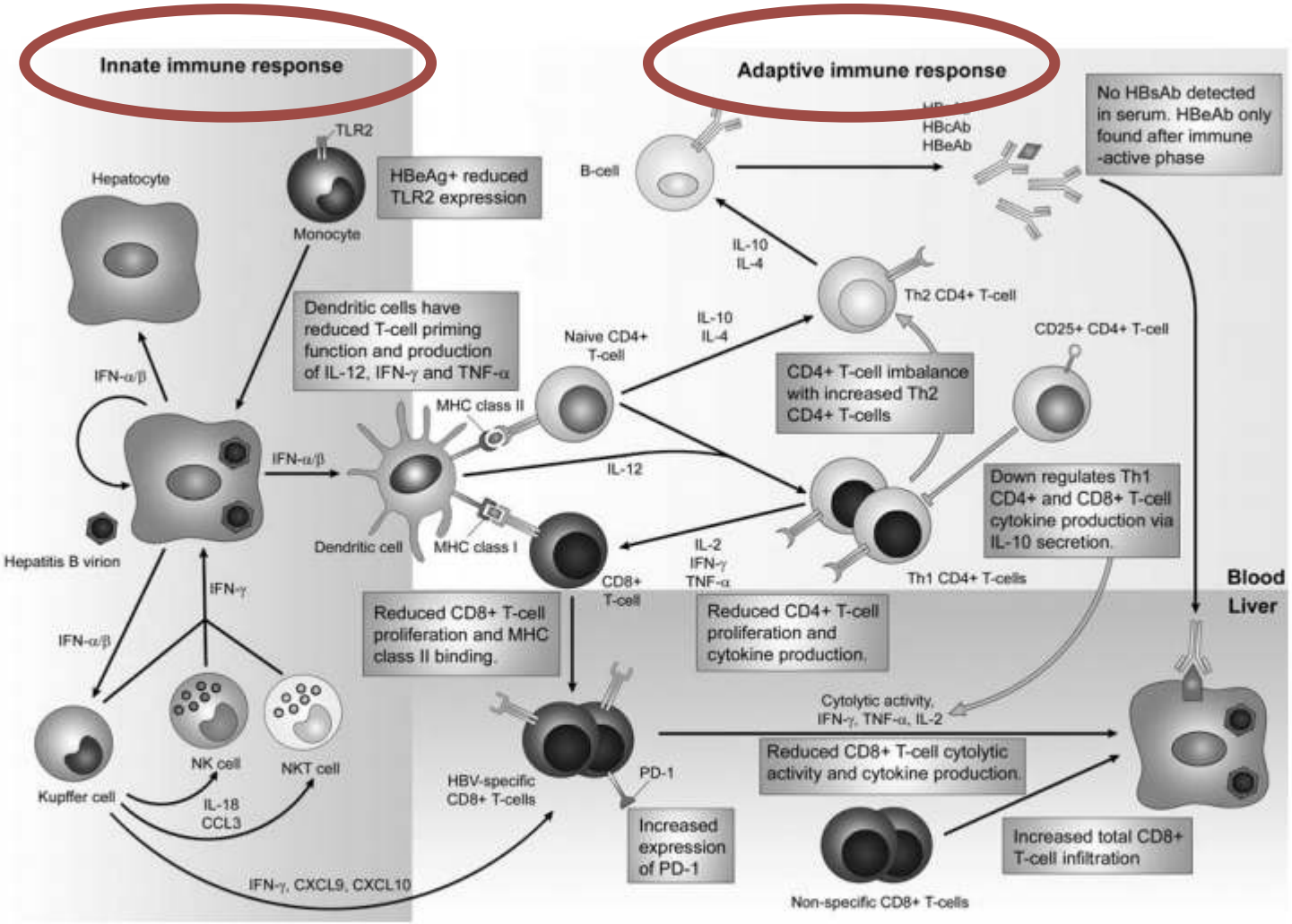
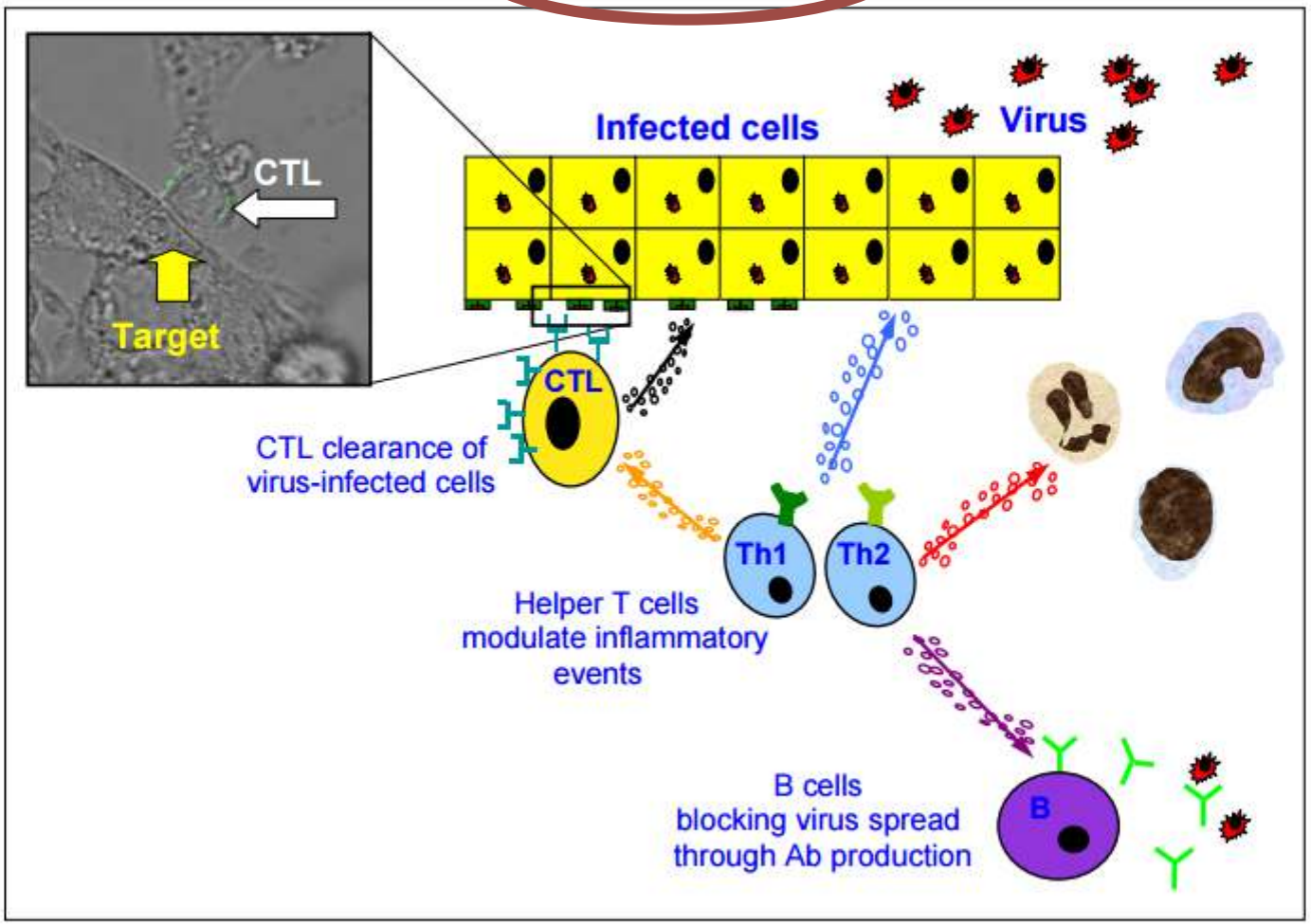



**Figure 1** Immune responses against HBV and effects of chronic HBV infection. Control of HBV infection requires the combined action of both the innate immune response and the humoral and cellular arms of the adaptive immune response (summarized in text). There are several mechanisms that have been associated with persistent or chronic HBV infection (shown in text boxes in figure). Chronic HBV infection is associated with reduced ability of DCs to prime T-cells and produce cytokines as well as reduced expression of TLR2 on peripheral monocytes.[47–50,54,56,88] $CD4^+$ T-cells are skewed toward a Th2 $CD4^+$ T-cells phenotype.[88] In addition, an increase in activity of regulatory T-cells, or $CD25^+$ $CD4^+$ T-cells further increase production of IL-10.[44–46] The remaining Th1 $CD4^+$ T-cells have reduced proliferative capacity and impaired production of antiviral cytokines.[27,31,69,70,89] Reduced function of Th1 $CD4^+$ T-cells and reduced priming from DCs both impair the function and number of HBV-specific $CD8^+$ T-cells. These anergic HBV-specific $CD8^+$ T-cells may have elevated PD-1 expression.[39] Liver damage may still occur in the liver and is largely mediated by infiltration of HBV-nonspecific $CD8^+$ T-cells.[26,33]

Chang JJ, et al. Immunol Cell Biol. 2007 Jan;85(1):16-23.

**Figure 1.** Anti-viral adaptive immune response during HBV infection.




Bertoletti A, et al. Viruses 2009, 1, 91-103.

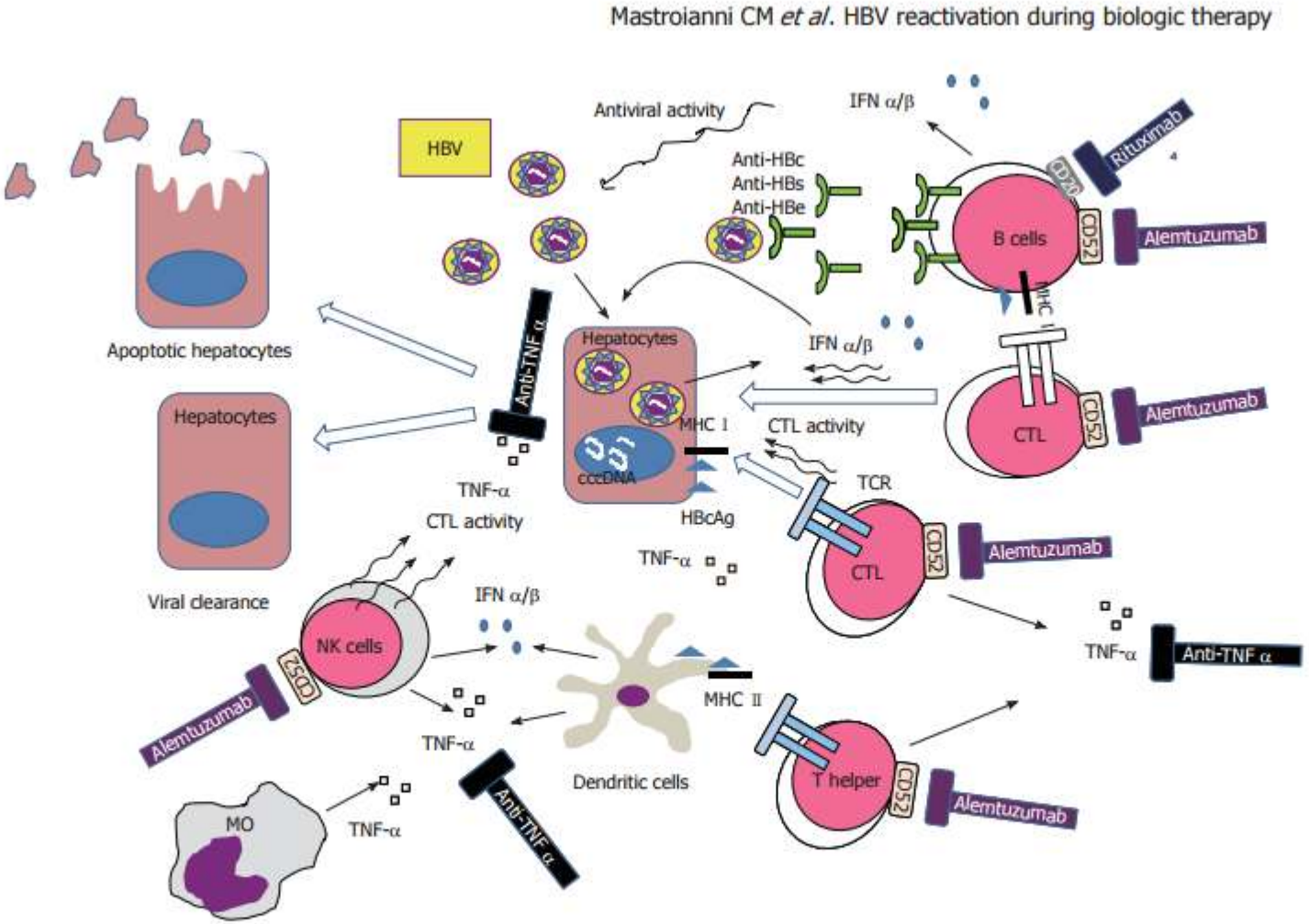



**Figure 1 Pathogenetic hypothesis of hepatitis B virus reactivation following monoclonal antibody treatment.** IFN: Interferon; TNF: Tumor necrosis factor; MHC: Major histocompatibility complex; NK: Natural killer; MO: Monocytes; TCR: T-cell receptor; CTL: Cytotoxic T lymphocyte; HBV: Hepatitis B virus; HBcAg: HBV core antigen.

Mastroianni CM, et al. World J Gastroenterol. 2011 Sep 14;17(34):3881-7.

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World J Gastroenterol 2011 September 14; 17(34): 3881-3887
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REVIEW

# Current trends in management of hepatitis B virus reactivation in the biologic therapy era

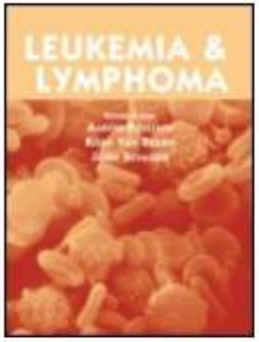
Claudio M Mastroianni, Miriam Lichtner, Rita Citton, Cosmo Del Borgo, Angela Rago, Helene Martini, Giuseppe Cimino, Vincenzo Vullo

Özellikle monoklonal ab ile etkilenen B hücrelerin uzun süreli ve derin hasarlanması, hasta immünitesindeki en belirgin sorunu oluşturmaktadır.

Bu da viral replikasyon ve reaktivasyon için zemin hazırlamaktadır.

Her ne kadar HBV enfeksiyonunun asıl kontrolü HBV-spesifik sitotoksik T lenfositleri ile yapılıyor olsa da, B lenfositler halihazırda antijen prezentasyonu için olmazsa olmazdırlar.

Rituximab tedavisi nedeniyle B hücre hasarlanması neticesinde gelişen antijen prezentasyonundaki sorun da HBV'nin sitotoksik T lenfosit denetiminden kaçması-kurtulmasına yol açmakta ve böylece viral hepatit reaktivasyonu gelişebilmektedir.

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Leukemia & Lymphoma

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# Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis

Sercan Aksoy, Ömer Dizdar, Mutlu Hayran & Hakan Harputluoğlu

**To cite this article:** Sercan Aksoy, Ömer Dizdar, Mutlu Hayran & Hakan Harputluoğlu (2009) Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis, Leukemia & Lymphoma, 50:3, 357-365, DOI: 10.1080/10428190902730219

Table I. Summary of the randomised rituximab maintenance therapy studies.

| References | Study type | Diagnosis | Induction | | Maintenance protocol | No. of patients (maintenance) | | Median follow-up | Infections | | Specific infections in maintenance arm | Neutropenia | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Regimen 1 | Regimen 2 | | R | O | | R | O | | R | O |
| [4] | RCT phase III | Newly diagnosed or relapsed/resistant FL | Rituximab 375 mg/m$^2$ × 4 weekly | NA | Rituximab 375 mg/m$^2$ at months 3, 5, 7 and 9 | 78 | 78 | 35 months | 8% (Any G)* | 1% (any G) | – | 1%† | – |
| [5] | RCT, phase III | MCL | Rituximab 375 mg/m$^2$ × 4 weekly | NA | Rituximab 375 mg/m$^2$ every 8 weeks for four times | 56 | 27 | 29 months | 9% (Any G)* | 4% (any G) | One patient experienced three episodes of pneumonia, one case of hepatitis, one case of septic shock | NR | NR |
| [6] | RCT phase III | Relapse/Resistant FL or MCL | R-FCM | FCM | Rituximab 375 mg/m$^2$ × 4 weekly at months 3 and 9 after completion of salvage therapy | 80 | 82 | 26 months | 24% (G1/2)*; 4% (G 3/4)* | 16% (G 1/2); 3% (G 3/4) | | 18% (G 1/2)*; 13% (G $\frac{3}{4}$)* | 14% (G 1/2); 6% (G 3/4) |
| [7] | RCT Phase III | Relapsed/ resistant FL | R-CHOP | CHOP | Rituximab 375 mg/m$^2$ once every 3 months until relapse or for a maximum of 2 years | 167 | 167 | 39.4 months | 9% (G 3/ 4)‡ | 2.4% (G 3/4) | Most of the infections in the ear-nose-throat area | 10.8% (any G)* | 5.4% (any G) |
| [8] | RCT phase III | Untreated DLBCL | R-CHOP | CHOP | Four courses at 6-month intervals, with each course consisting of 375 mg/m$^2$ Weekly, four times | 174 | 170 | 42 months | – | – | – | 12% (G 3/4)‡ | 4% (G 3/4) |

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL, diffuse large B-cell lymphoma; FCM, fludarabine, cyclophosphamide and mitoxantrone; FL, follicular lymphoma; G, grade; MCL, mantle cell lymphoma; NA, not applicable; NR, not reported; O, observation; RCT, randomised controlled trial; R, rituximab; R-FCM, rituximab, fludarabine, cyclophosphamide and mitoxantrone.

*$p > 0.05$.

†Agranulocytosis.

‡$p \leq 0.05$.

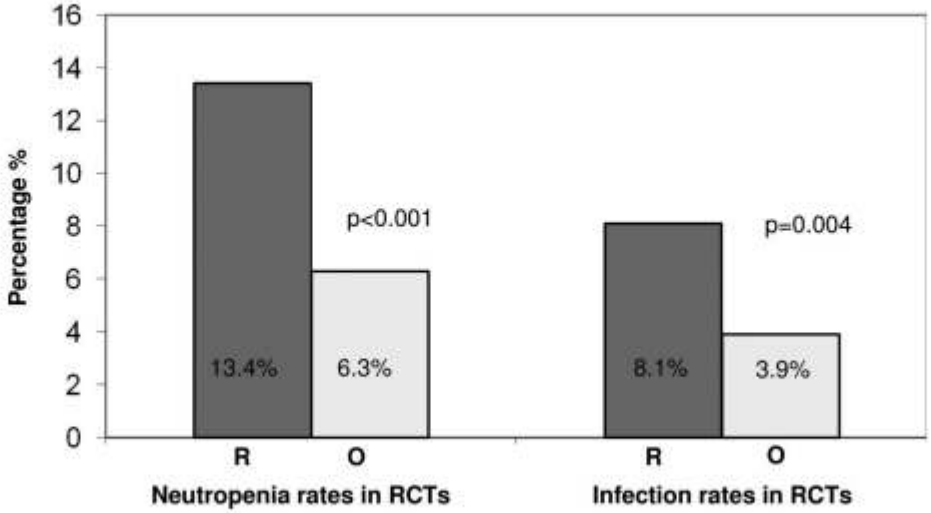


Figure 2. Infection and neutropenia rates in pooled analysis of randomized studies. R, rituximab; O, observation.

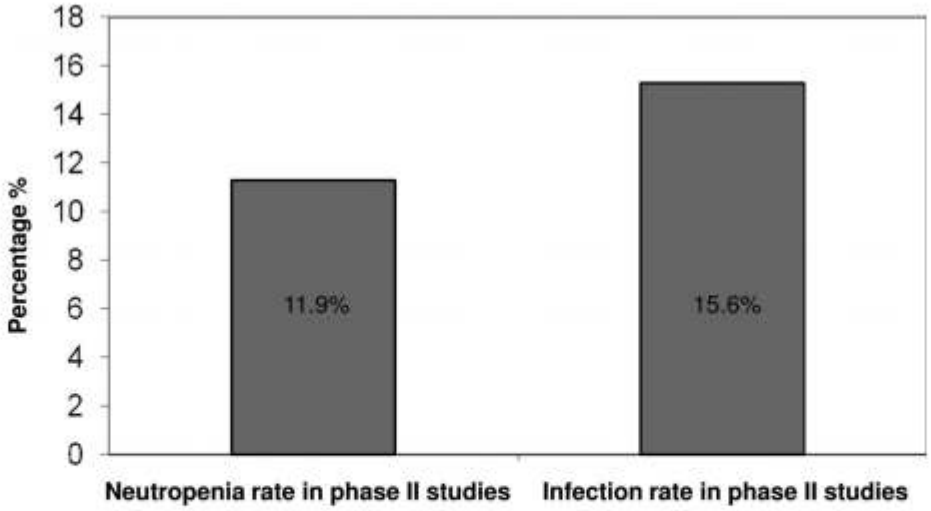


Figure 3. Infection and neutropenia rates in pooled analysis of phase II studies.

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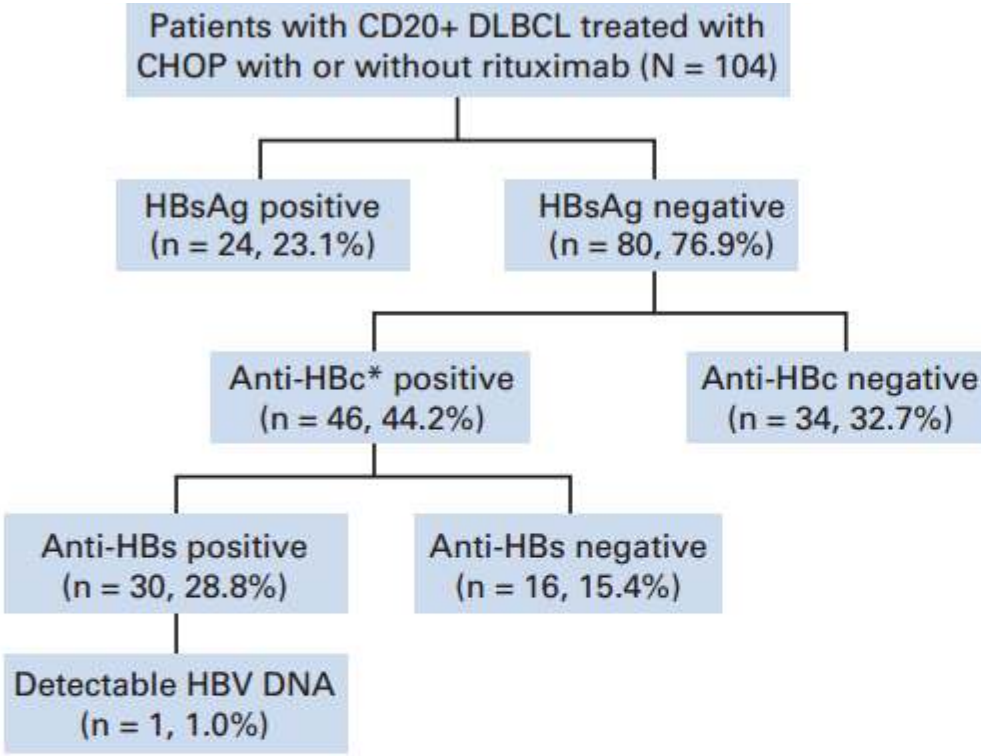
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Hepatitis B Virus Reactivation in Lymphoma Patients With Prior Resolved Hepatitis B Undergoing Anticancer Therapy With or Without Rituximab

*Winnie Yeo, Tung C. Chan, Nancy W.Y. Leung, Wai Y. Lam, Frankie K.F. Mo, Miu Ting Chu, Henry L.Y. Chan, Edwin P. Hui, Kenny I.K. Lei, Tony S.K. Mok, and Paul K.S. Chan*




* All IgG anti-HBc positive and IgM anti-HBc negative

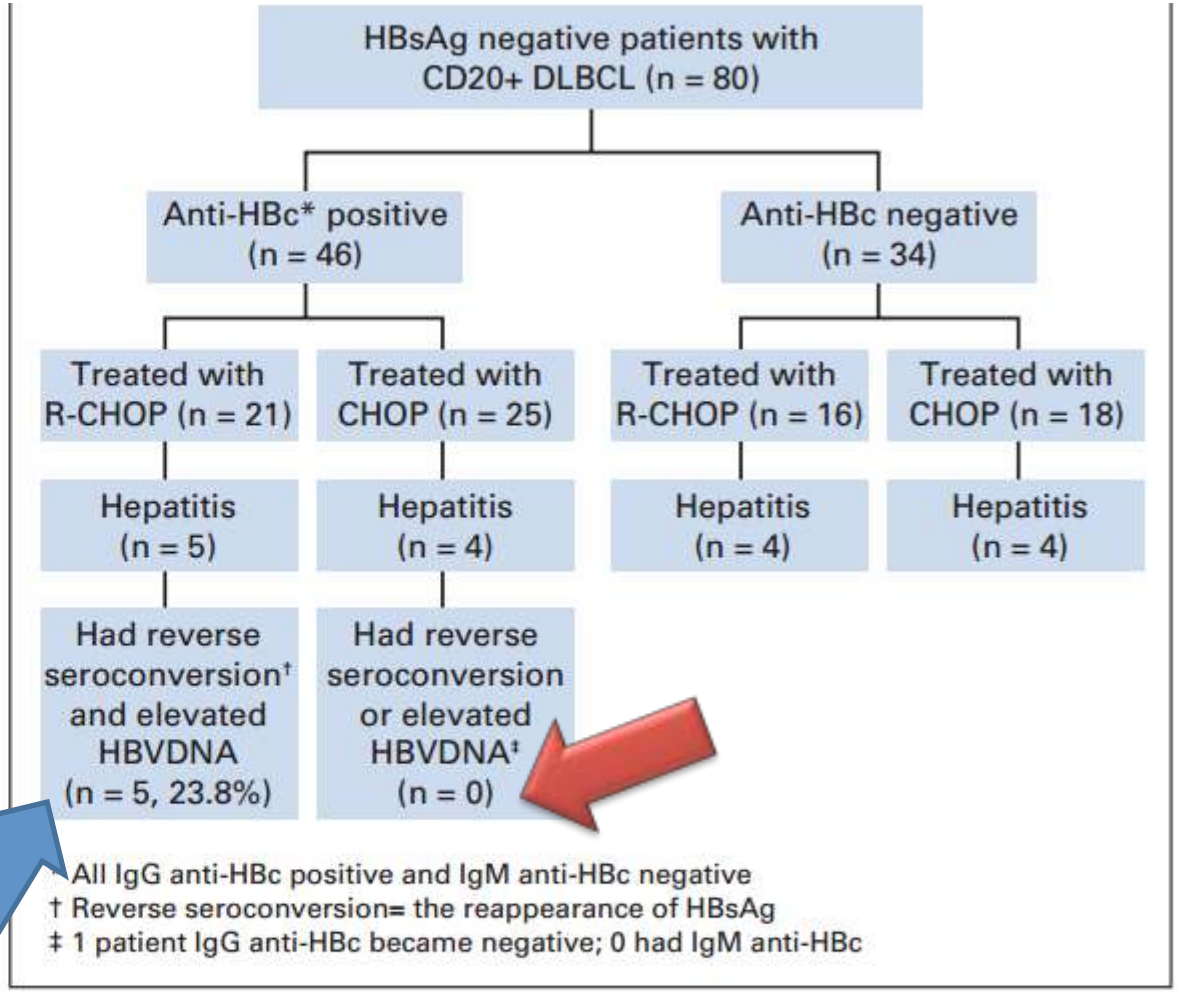



**Fig 2.** Hepatitis outcomes of 80 hepatitis B surface antigen (HBsAg)–negative patients studied. DLBCL, diffuse large B-cell lymphoma; anti-HBc, antibody to hepatitis B core antigen; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

Among HBsAg-negative/anti-HBc–positive DLBCL patients treated with R-CHOP, 25% developed HBV reactivation.

**Table 1.** Details and Outcome of the Five CD20+ DLBCL Patients Who Were HBsAg Negative/Anti-HBc Positive and Who Developed HBV Reactivation After R-CHOP

| | | | | Baseline | | | At Diagnosis of HBV Reactivation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient No. | Age (years) | Sex | Stage of Lymphoma | Anti-HBs | HBV DNA (copies/μL) | ALT (U/L) | No. of Cycles of R-CHOP Received Before Reactivation | No. of Days Between Last R-CHOP and Reactivation | HBV DNA (copies/μL) | Peak ALT (U/L) | Peak Total Bilirubin (μmol/L) | Treatment With Lamivudine | Outcome |
| 1 | 77 | M | II | — | 0 | 21 | 6 | 85 | 71,118.4 | 2,110 | 249 | Yes | Died of HBV reactivation |
| 2 | 58 | M | III | — | 0 | 27 | 5 | 19 | 4,840 | 362 | 65 | Yes | Alive and well |
| 3 | 60 | M | IV | — | 0 | 35 | 8 | 110 | 111,726.4 | 3,499 | 192 | No | Alive with lymphoma |
| 4 | 63 | M | I | — | 0 | 24 | 6 | 78 | 66,267.1 | 649 | 19 | Yes | Alive and well |
| 5 | 46 | M | II | — | 0 | 13 | 6 | 170 | 231,597.6 | 809 | 29 | Yes | Died of lymphoma |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; HBV, hepatitis B virus; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; anti-HBs, antibody to hepatitis B surface antigen; M, male.

**Table 3.** HBV Reactivation in HBsAg-Negative Patients in Association With Rituximab in the Absence of Prophylactic Antiviral Therapy

| Study | Age (years) | Sex | Disease | Anticancer Therapy | Other Pretreatment HBV Markers | Time of HBV Reactivation in Relation to Anticancer Therapy | Peak ALT (U/L) | Treatment of HBV Reactivation | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Tsutsumi et al[13] | 80 | M | DLC | R + O | Anti-HBs positive, anti-HBe positive | After approximately 3 cycles of R + O | 101 | Supportive | Resolved |
| Tsutsumi et al[13] | 55 | M | DLC | R + C + Ara-C + VP16 + Dex | Anti-HBs positive, anti-HBe positive | After 2 cycles of R + C + Ara-C + VP16 + Dex | 84 | Supportive | Resolved |
| Dervite et al[14] | 73 | M | FL | CHOP + IFN + Ara-C + R | Anti-HBs positive | 6 months after stopping R | 1,230 | Supportive | Persistent HBsAg positive, anti-HBs negative |
| Westhoff et al[15] | 73 | M | DLC | R | Anti-HBs positive (S mutant), anti-HBc positive | After 3 months of starting R | NR | Lamivudine | Died of hepatic failure |
| Sarrecchia et al[26] | 53 | M | CLL | R | Anti-HBs positive, anti-HBc positive | After 3 months of starting R | 2,120 | Lamivudine | Died of hepatic failure |
| Law et al[27] | 67 | M | NHL | R-CHOP | Anti-HBs weakly positive; anti-HBc positive | After 8 cycles of R-CHOP | 2,240 | Lamivudine | Died of hepatic failure |
| Niscola et al[28] | 51 | M | CLL | R | Anti-HBs negative, anti-HBc positive | After 7 months of R | NR | Lamivudine | Died of hepatic failure |
| Sera et al[29] | 59 | M | NHL | R + VP16 + P + Dex | Anti-HBs positive, anti-HBc positive | 2 months after stopping R | 359 | Lamivudine | Died of hepatic failure |
| Ozgönenel et al[30] | 21 | M | DLC | R-CHOP | Not stated | After 3 cycles of R-CHOP | NR | Lamivudine | Died of hepatic failure |
| Yamagata et al[31] | 54 | M | DLC | R-CHOP | Anti-HBc positive | After 7 cycles of R-CHOP | 531 | Lamivudine | Died of hepatic failure |

Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; M, male; DLC, diffuse large-cell lymphoma; R, rituximab; O, vincristine; anti-HBs, antibody to hepatitis B surface antigen; anti-HBe, antibody to hepatitis B e antigen; C, cyclophosphamide; Ara-C, cytarabine; VP16, etoposide; Dex, dexamethasone; FL, follicular lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; IFN, interferon; anti-HBc, antibody to hepatitis B core antigen; NR, not reported; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin's lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; P, prednisone.

Yeo W, et al. J Clin Oncol. 2009 Feb 1;27(4):605-11.

original article

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doi:10.1093/annonc/mdq583
Published online 29 November 2010

# Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports

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**Table 1.** HBV core antibody-positive (surface antigen negative) rituximab-associated HBV reactivation: case reports

| Author | NHL type | Age/ gender | Co-morbidity | Prior immunosuppressive therapy | Concurrent immune suppressants | Time to reactivate from first rituximab | Doses of rituximab | Time to reactivate from last rituximab | Liver outcome | Treatment of reactivation | Death |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dervite et al. [18] | FL | 69/M | None | 7 cycles CHEP and IFN, then 6 cycles HDAC (1 year prior) | Steroids for 6 months immediately prior | 7 months | 4 | 6 months | Hepatitis | NR | No |
| Westhoff et al. [16] | DLBCL | 73/M | None | CHOP 3 months prior | None | 3 months | NR | 1 month | Liver failure | Lamivudine | Yes |
| Niscola et al. [30] | CLL | 51/M | None | Fludarabine 34 months prior | None | 26 months | 10 | 1 month | Liver failure | Lamivudine | Yes |
| Sarrecchia et al.[31] | CLL | 53/M | HTN | Fludarabine 2 years prior | None | 4 months | 3 | 1 month | Liver failure | Lamivudine | Yes |
| Law et al [32] | DLBCL | 67/M | None | None | CHOP | 5 months | 8 | 1 month | Liver failure | Lamivudine | Yes |
| Sera et al. [33] | Indolent NHL | 59/M | None | CHOP 3 years prior, Dex and VCR 1 year prior | Etoposide, prednisone | 2 months | 3 | 0 month | Liver failure | Lamivudine | Yes |
| Ozgonenel et al. [34] | DLBCL | 21/M | Evans syndrome | None in 6 years prior | CHOP | 2 months | 3 | 0 month | Liver failure | Lamivudine | Yes |
| Yamagata et al. [35] | DLBCL | 55/M | None | None | CHOP | 6 months | 7 | 1 month | Liver failure | Lamivudine | Yes |
| Colson et al. [36] | DLBCL | 48/M | None | None | CHOP | 4 months | 4 | 1 month | Hepatitis | Entecavir | No |
| Garcia-Rodriguez et al. [21] | FL | 53/F | None | Yes (not stated-third-line therapy) | CHOP | 11 months | 3 | 9 months | Hepatitis | Lamivudine | No |
| Garcia-Rodriguez et al. [21] | DLBCL | 68/F | None | None | CHOP | 17 months | 6 | 12 months | Liver failure | Lamivudine | Yes |
| Miyagawa et al. [37] | DLBCL | 75/M | None | None | CHOP | 10 months | 6 | 6 months | Hepatitis | Lamivudine | No |
| Koo et al. [38] | MCL | 71/M | None | None | CHOP | 15 months | 9 | 0 | Liver failure | NR | NR |
| Northwestern active surveillance, 2007 | DLBCL | 61/M | Prior GIST | None | CHOP and radiation | 5 months | 6 | 1 month | Liver failure (warranting liver transplant) | Adefovir | No |
| Northwestern active surveillance, 2009 | DLCBL | 47/F | None | None | CHOP | 10 months | 6 | 0 months | Hepatitis | Tenofovir | No |
| Taiwan active surveillance, 2009 | DLBCL | 79/F | None | None | CHOP | 6 months | 6 | 2 months | Hepatitis | Telbivudine | No |

NHL, non-Hodgkin's lymphoma; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; FSGN, focal segmental glomerulonephritis; M, male; F, female; pts, patients; HBV, hepatitis B virus; DLBCL, diffuse large B-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHEP, cyclophosphamide doxorubicin, etoposide, prednisone; CP, cyclophosphamide, prednisone; AZA, azathioprine; IFN, interferon; HDAC, high-dose cytarabine; GIST, gastrointestinal stromal tumor; SLL, small lymphocytic lymphoma; NR, not reported; VCR, vincristine; Dex, dexamethasone.

**Table 2.** HBV surface antigen positive rituximab-associated HBV reactivation: case reports

| Author | NHL type | Age/gender | Comorbidity | Received prophylaxis (lamivudine) | Prior immunosuppressive therapy | Concurrent immune suppressants | Time to reactivate from first rituximab | Doses of rituximab | Time to reactivate from last rituximab | Liver outcome | Treatment of reactivation (drug) | Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tsutsumi et al. [39] | DLBCL | 68/F | None | No | None | CHOP | 4 months | 3 | 3 months | Liver failure | Yes (lamivudine) | Yes |
| Dai et al. [20] | DLBCL | 21/M, 33/M, 41/F, 42/M | None | Yes (through 4 weeks after R-CHOP) | None | CHOP (all pts) | 8–12 months | 6 (all pts) | 4, 6, 6, and 8 months | Hepatitis | Yes (lamivudine—all) | None |
| Law et al. [40] | FL | 57/M | None | Yes | None | CHOP | 9 months | 6 | 5 months | Liver failure | Yes (tenofovir; lamivudine resistant) | Yes |
| Perceau et al. [23] | Cutan NHL | 78/F | None | No | CVP 6 years prior, CEP 2 year prior | None | 13 months | 4 | 12 months | Liver failure | Yes (lamivudine) | Yes |
| Kaled et al. [41] | WM | 32/F | None | No | None | Fludarabine | 9 months | 7 | 5 months | Hepatitis | Yes (lamivudine and adefovir) | No |
| Yang et al. [24] | FL | 41/F | None | No | Leukeran 1 year prior | None | 13 months | 4 | 12 months | Hepatitis | Yes (lamivudine) | No |
| Marino et al. [42] | DLBCL | 59/M | None | No | None | CHOP | 9 months | 8 | 3 months | Liver failure | Yes (lamivudine resistant) | Yes |
| Wasmuth et al. [43] | Indolent NHL | 55/M | None | No | None | Fludarabine based | 6 months | 6 | 2 months | Liver failure | Yes (lamivudine) | Yes |
| He et al. [22] | DLBCL | 29/F | None | Yes | None | Chemotherapy | 12 months | NR | 7 months | Hepatitis | Yes (lamivudine) | No |
| Dillon et al. [44] | DLBCL | 21/F | None | No | None | CHOP | 3 months | 4 | 0 months | Liver failure | Yes (lamivudine) | Yes |
| Aomatsu et al. [45] | DLBCL | 57/F | None | No | No | CHOP | 10 months | 6 | 5 months | Liver failure | Yes (lamivudine and plasma exchange) | Yes |
| Taiwan active surveillance, 2009 | SLL | 56/M | None | Yes (lamivudine) | R-CVP × 8 (1 year prior) and rituximab maintenance | No | 14 months | 10 | 1 month | Hepatitis | Yes (adefovir and entecavir; lamivudine resistant) | No |

NHL, non-Hodgkin's lymphoma; FL, follicular lymphoma; WM, Waldenstroms macroglobulinemia; SLL, small lymphocytic lymphoma; M, male; F, female; Cutan, cutaneous; pts, patients; HBV Hepatitis B virus; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide vincristine, prednisone; CEP, cyclophosphamide, etoposide, prednisone; NR, not reported.

Table 4. HBV core antibody positive (surface antigen negative) rituximab-associated HBV reactivation: case series

| Author | NHL type | Concurrent immune suppression | Incidence of rituximab-associated HBV reactivation (versus nonrituximab reactivation, if available) | Time from last rituximab and/or chemotherapy | Mortality rate (rituximab groups)[a] |
|---|---|---|---|---|---|
| Hui et al. [46] | Mixed NHL and HL ($n = 233$) | Rituximab/chemotherapy ($n = 88$); chemotherapy alone ($n = 145$) | 8.0% (7/88) with rituximab/chemotherapy (versus 0.1% (1/145) chemotherapy, $P < 0.001$)[b] | 8–28 weeks conversion to HBsAg(+), but 8–212 weeks HBV DNA (after last therapy)[c] | 43% |
| Li et al. [47] | DLBCL ($n = 11$) | CHOP | 45% (5/11) with HBV reactivation | NR | 40% |
| Targhetta et al. [48] | Mixed ($n = 319$) | Rituximab/chemotherapy ($n = 74$) and chemotherapy alone ($n = 245$) | 2.7% (2/74) with rituximab/chemotherapy (versus 0.8% (2/245) with chemotherapy, $P < 0.05$) | NR | 0 |
| Yeo et al. [49] | DLBCL ($n = 46$) | Rituximab/CHOP ($n = 21$); CHOP ($n = 25$) | 24% (5/21) with R-CHOP (versus 0/25 with CHOP, $P < 0.0148$) | 1–5 months | 20% |
| Hanbali et al. [50] | Mixed ($n = 26$) | Mixed ($n = 26$) | 27% (7/26) acute liver events[d] with rituximab-based therapy; 5/7 with liver failure | Median onset acute liver events[d] 6.2 months after rituximab (2 pts developed acute liver events at 21 and 36 months) | NR |
| Fukushima et al. [51] | Mixed ($n = 48$) | Mixed ($n = 48$) | 6% (2/32) who received rituximab with HBV reactivation (versus 0/16 without rituximab) | 8 months from last rituximab dose | 0 |
| Kusumoto et al. [52] | Mixed ($n = 50$) | None/rituximab alone ($n = 2$), R-CHOP ($n = 40$), R-chemotherapy without steroids ($n = 4$), ASCT ($n = 3$) | NR; 50 total pts with reactivation; 40% of pts with fulminant liver failure | NR | 50% |

# KISA ÜRÜN BİLGİSİ

## 1. BEŞERİ TIBBİ ÜRÜNÜN ADI

MABTHERA 500 mg/50 mL i.v. infüzyon için konsantre solüsyon içeren flakon

## 2. KALİTATİF VE KANTİTATİF BİLEŞİM

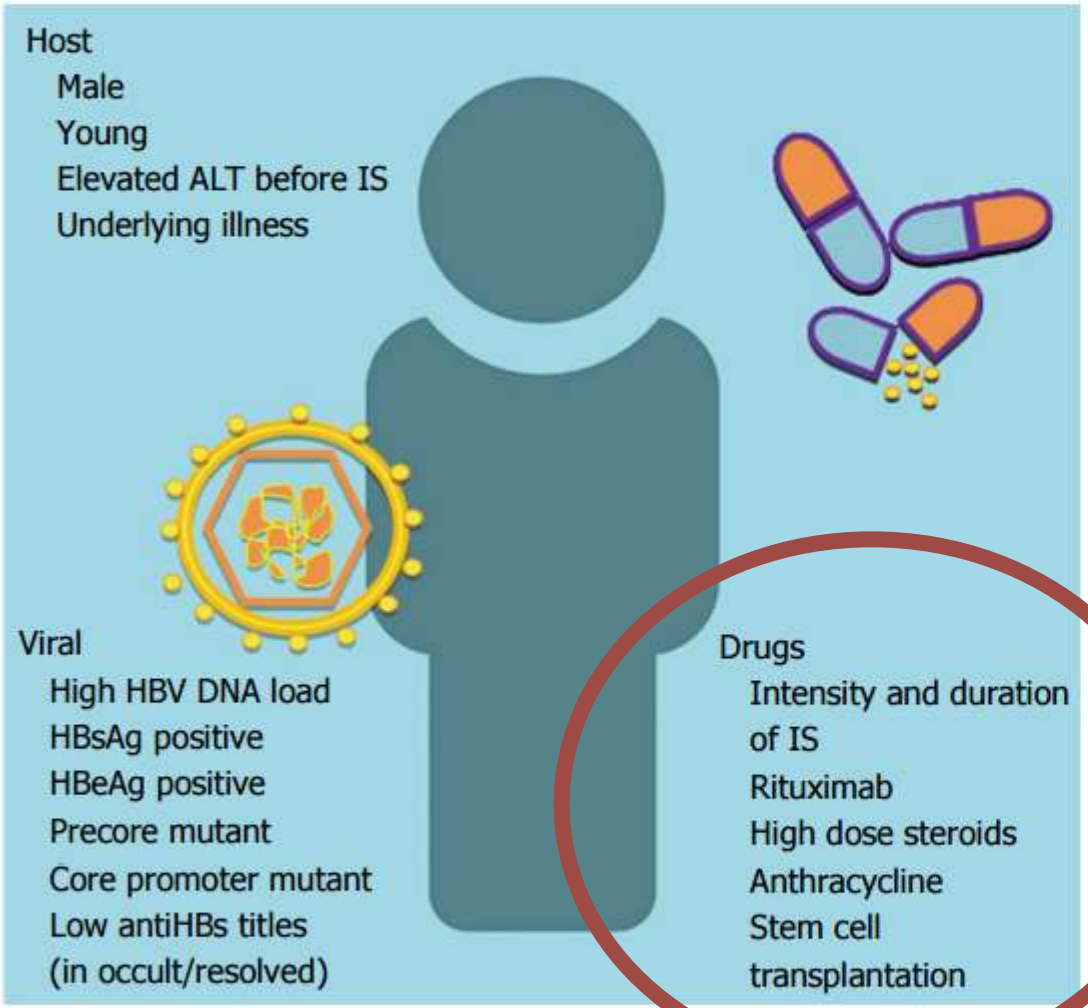
**Etkin madde:**
Her bir flakon 50 mL'lik çözelti içinde 500 mg rituksimab içerir.
Çözeltinin her mL'sinde 10 mg rituksimab bulunur.

Rituksimab insan IgG1 sabit bölgeleri ve sırasıyla değişken mürin hafif zincir ve ağır zincir içeren bir glikozile immünoglobulin sunan, genetik mühendisliği ile üretilen kimerik fare/insan monoklonal antikorudur. Antikor, memelilerin (Çin hamster over hücresi) hücre süspansiyon kültüründe üretilir ve viral aktivasyon ve çıkarma prosedürlerini içerecek şekilde afinite kromotografisi ve iyon değiştirme ile saflaştırılır.

*Hepatit B Enfeksiyonları:*

Fulminan hepatit raporları da dahil olmak üzere, bazı vakalarda ölümcül olabilen hepatit B reaktivasyonu vakaları rapor edilmiştir. Bu vakaların büyük çoğunluğu, sitotoksik kemoterapiye maruz kalmıştır. Raporlarda hem temelde yatan hastalık durumu, hem de sitotoksik kemoterapi birbirine karıştırılmaktadır. Relaps/refrakter KLL hastalarında yapılan bir çalışmadan elde edilen kısıtlı verilere göre, MABTHERA tedavisi primer hepatit B enfeksiyonlarının sonucunu da kötüleştirebilmektedir.
MABTHERA tedavisi başlatılmadan önce, yüksek risk taşıyan hastalarda hepatit B virüs (HBV) taraması göz önünde bulundurulmalıdır. Hepatit B taşıyıcısı olanlar ve geçmişinde hepatit B öyküsü bulunan hastalar, MABTHERA tedavisi sırasında ve tedaviden aylar sonrasına (yedi ay) kadar aktif HBV enfeksiyonunun klinik ve laboratuvar belirtilerine karşı, dikkatlice izlenmelidirler.

# HBV Reaktivasyonu Risk Etkenleri




+ malignite

Bessone F, et al. World J Hepatol 2016 March 18; 8(8): 385-394

# Hastalık bazında
# HBV Reaktivasyon Risk Sınıflaması

- Hematopoietik kök hücre nakli
- Solid organ nakli
- Lösemi
- Lenfoma
- Miyelom
- Solid tümörler
- AIDS
- Otoimmün hastalıklar
- İnflamatuvar barsak hastalıkları


*Ref: Alvarez-Suárez B, et al. Rev Esp Enferm Dig. 2010;102:542-2. ,Roche B, Samuel D. Liver Int. 2011;31(1):104-10.*

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# NCCN Guidelines Version 2.2017
# CLL/SLL

## WORKUP

**ESSENTIAL:**

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- Comprehensive metabolic panel
- Hepatitis B testing[f] if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

**USEFUL UNDER CERTAIN CIRCUMSTANCES:**

- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs' test
- Chest/abdominal/pelvic CT should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes)
- Beta-2-microglobulin
- LDH
- Uric acid
- Unilateral bone marrow biopsy (± aspirate) at initiation of therapy
- Discussion of fertility issues and sperm banking
- PET/CT scan is not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected

→ SLL/Localized (Lugano Stage I) (See CSLL-3)

→ CLL (Rai Stages 0–IV) or SLL (Lugano Stage II–IV) (See CSLL-3)

[f]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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# NCCN Guidelines Version 3.2017
# Diffuse Large B-Cell Lymphoma

**WORKUP**

**ESSENTIAL:**

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Whole-body PET/CT scan ± C/A/P CT with contrast of diagnostic quality
- Adequate bone marrow biopsy (>1.6 cm) ± aspirate; bone marrow may not be needed if PET/CT scan negative unless finding of another lymphoma subtype is important for treatment decision
- Calculation of International Prognostic Index (IPI) (See BCEL-A 1 of 2)
- Hepatitis B testing[i]
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

**USEFUL IN SELECTED CASES:**

- Head CT/MRI with contrast or Neck CT/MRI with contrast
- Discussion of fertility issues and sperm banking
- HIV testing
- Lumbar puncture, consider if have 4–6 factors according to prognostic model (See BCEL-A 2 of 2), HIV lymphoma, testicular, double expressor lymphoma
- Beta-2-microglobulin

→ See Induction Therapy (BCEL-3)

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# NCCN Guidelines Version 3.2017
# Follicular Lymphoma[a] (grade 1-2)

NCCN Gu
Tab

**WORKUP**

**ESSENTIAL:**
- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- LDH
- Beta-2-microglobulin
- Comprehensive metabolic panel
- Hepatitis B testing[h]
- Chest/abdominal/pelvic (C/A/P) CT with contrast of diagnostic quality and/or whole-body PET/CT scan (PET/CT scan essential if RT for stage I, II disease planned)
- Bone marrow biopsy + aspirate to document clinical stage I-II disease[i]
- Pregnancy testing in women of child-bearing age (if chemotherapy or RT planned)

**USEFUL IN SELECTED CASES:**
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Neck CT with contrast
- Uric acid
- Discussion of fertility issues and sperm banking
- SPEP and/or quantitative immunoglobulin levels
- Hepatitis C testing

Stage I, II → See Initial Therapy (FOLL-3)

Stage III, IV → See Initial Management (FOLL-4)

# Risk Faktörleri: HBV Reaktivasyon

- Malignite
  - NHL: 40%-58%  HBsAg positive
  - Meme ca: up to 41% of HBsAg positive

**NHL ile yakın ilişkisi:**

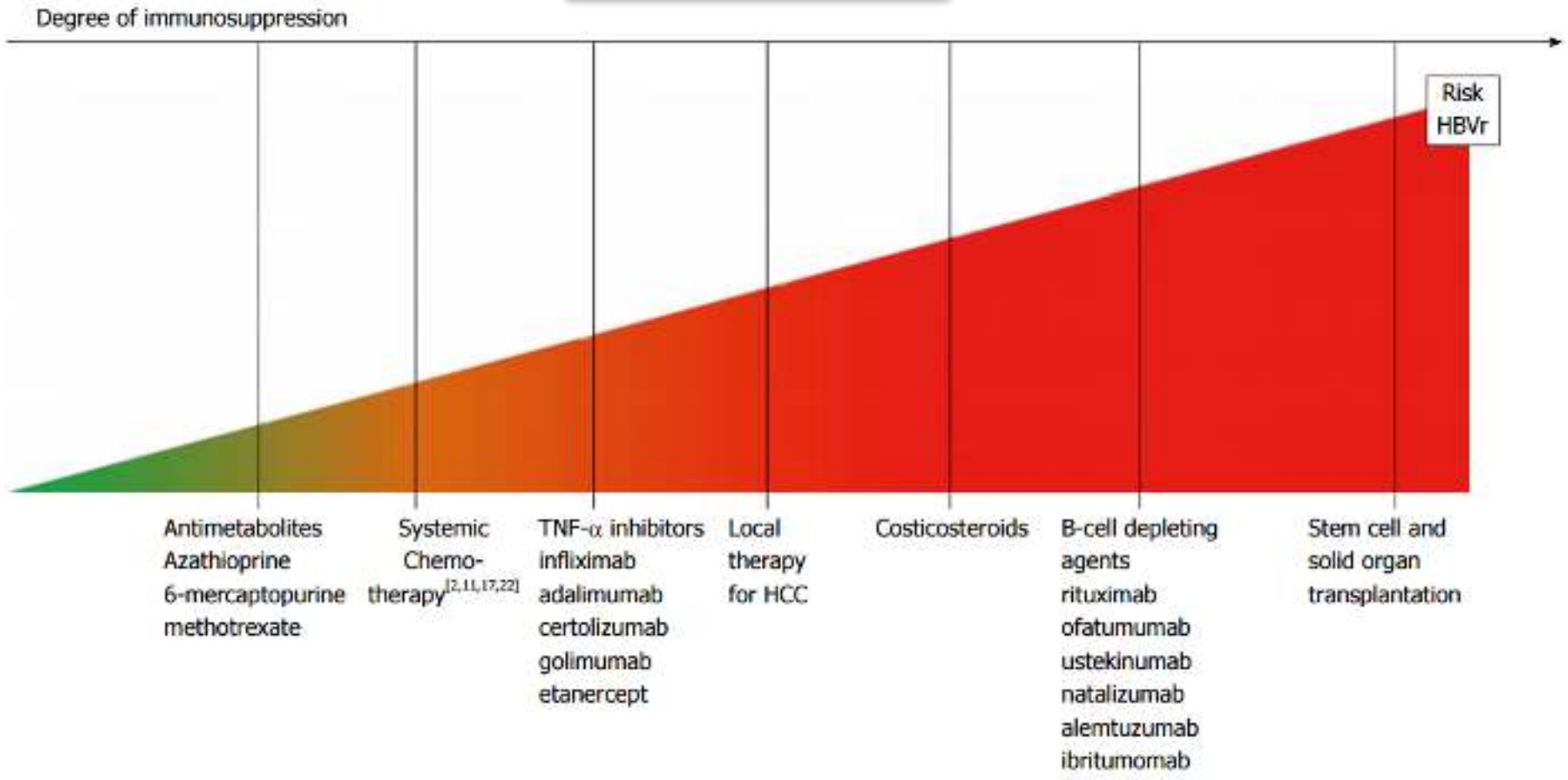
- **Verilen KT rejiminin cinsi, ağırlığı, içeriği alakalı?**
- **Lenfoma gelişimi olan yerlerde HBV prevalansının da yüksek olması?**

**Meme ca ile yakın ilişkisi:**

- **Verilen KT protokllerinde antrasiklin ve steroid olması?**

Yeo W, et al. Hepatology. 2006;43:209-220.

# İlaçların etki derecesi

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# Antimetabolitler

Azotiyoprin
MTX

- Tek başlarına
- Nispeten düşük dozda

HBV reaktivasyonu riski net değildir, düşüktür.

MTX
HBV reaktivasyonu görülmüştür.
Ancak mutlaka eşlik eden başka IS ilaçların da kullanıldığı saptanmıştır.

Düşük riskli ilaçlar <%1

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# Sistemik kemoterapi

Kemoterapinin içeriği
- Antrasiklin
- Steroid
- Monoklonal antikorlarla kombinasyon

İmmunosüpresyonun ağırlığı

CHOP ile reaktivasyon oranları: %48
%24-67

Artmış mortalite riski: %4-41

Orta riskli ilaçlar
%1-10

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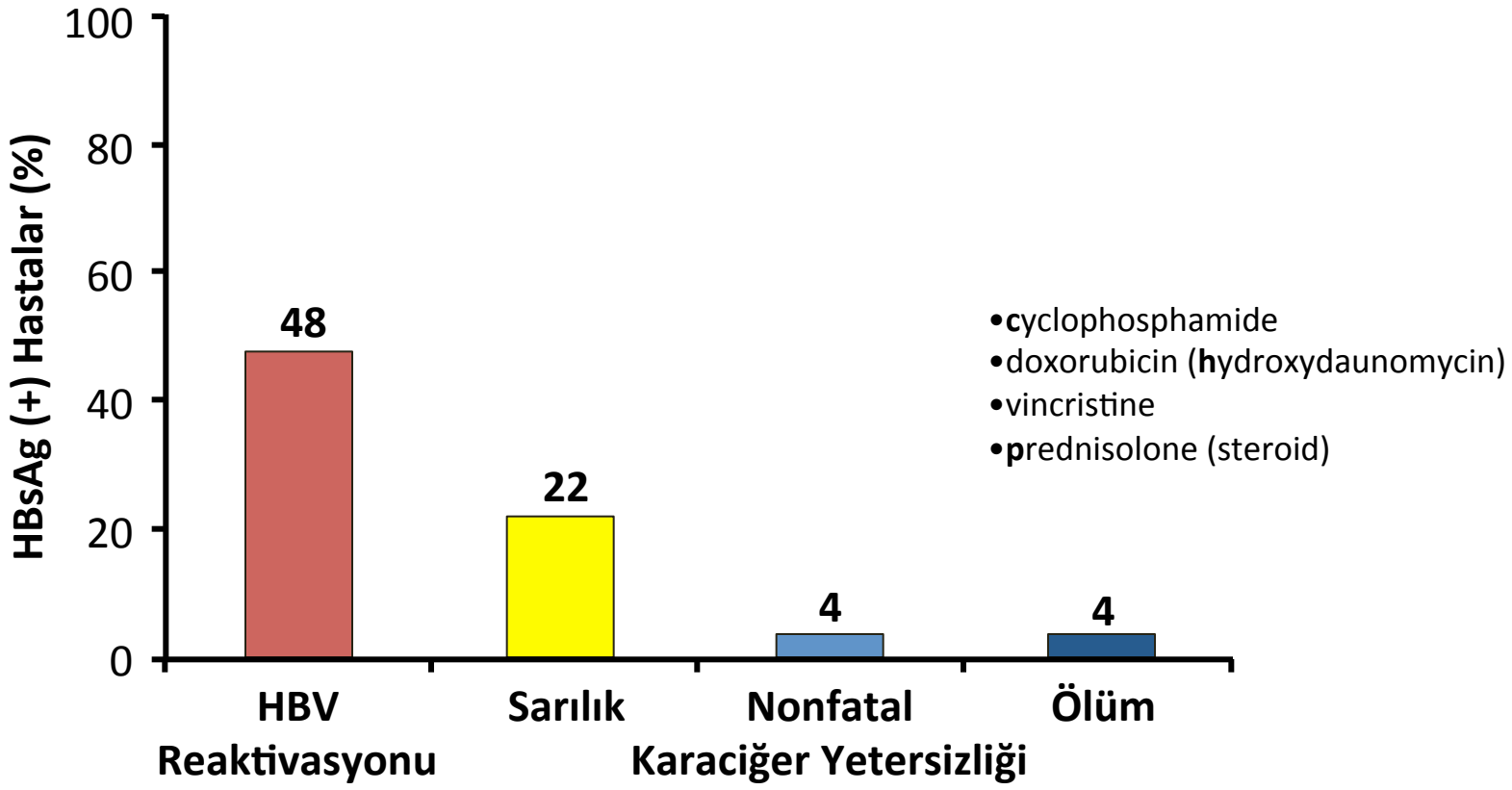
# CHOP alan NHL tanılı 100 hasta; 27 HBsAg (+)




Ref: Lok AS, et al. Gastroenterology. 1991;100:182-188.

# Kortikosteroid

Prednizon kullanımı ile:

Glukokortikoid alakalı T hücrelerin baskılanması

HBV genomundaki glucocorticoid-responsive element' in doğrudan uyarılması

Glukokortikoidlerin tek başlarına ya da başka ilaçlarla kombine verilmesi önemli.

Glukokortikoidlerin tek başlarına ya da başka ilaçlarla verildiğinde, süresi önemli.

| | |
|---|---|
| YÜKSEK RİSK: | HBsAg (+) hasta, > 10 mg/gün, 4 hf ve daha üstü sürede kullanırsa |
| ORTA RİSK: | HBsAg (+) hasta, < 10 mg/gün |
| ORTA RİSK: | HBsAg (-), antiHBc (+) hasta, < 20 mg/gün, 4 hf.dan daha az sürede kullanırsa |
| DÜŞÜK RİSK: | antiHBc (+) hasta,< 10 mg/gün, 4 hf.dan daha az sürede kullanırsa |
| DÜŞÜK RİSK: | Lokal tedavi (örn:intraartiküler) |

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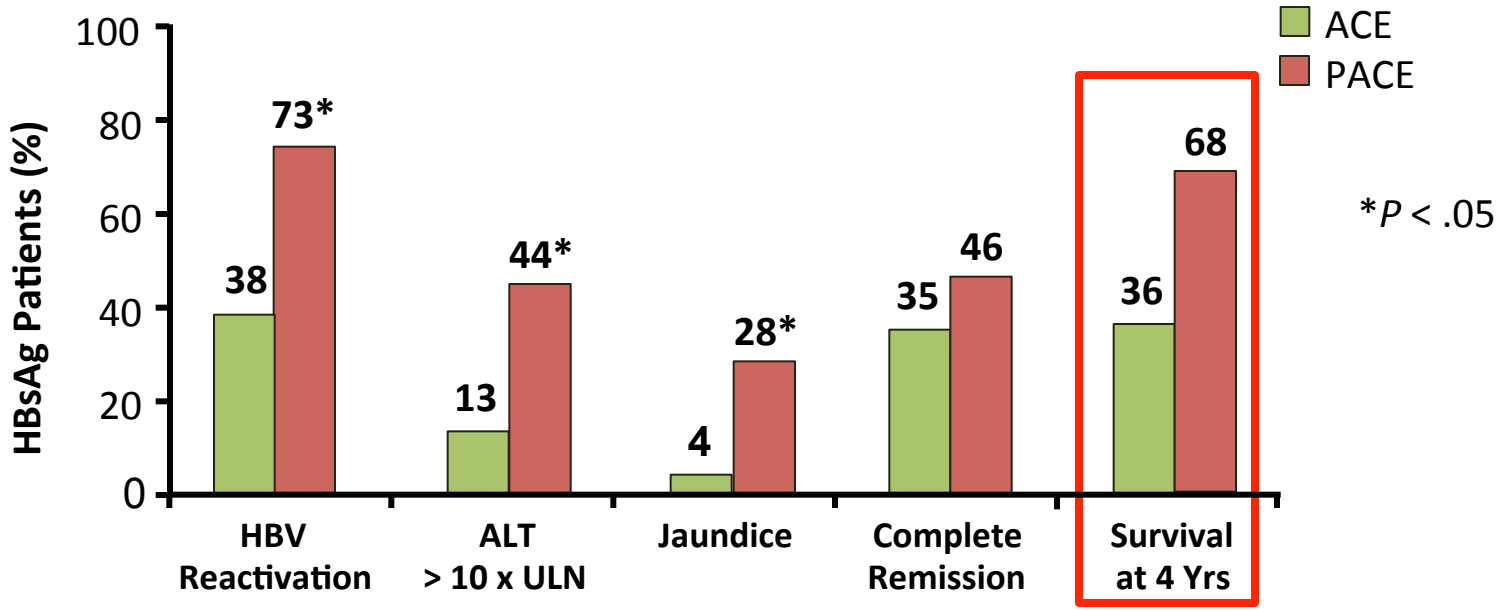
# Steroids Increase Risk of HBV Reactivation

- 50 patients with NHL who were HBsAg positive randomized to epirubicin, cyclophosphamide and etoposide (ACE) ± prednisolone (P)




**Prednisolone increased risk and severity of HBV reactivation but trend toward improved NHL outcome**

Cheng AL, et al. Hepatology. 2003;37:1320-1328.

# Hematopoietik Kök Hücre Nakli

Bone Marrow Transplant. 1997 Aug;20(4):289-96.

**Hepatitis B virus infection in allogeneic bone marrow transplantation.**

Ustün C[1], Koç H, Karayalcin S, Akyol G, Gürman G, Ilhan O, Akan H, Ozcan M, Arslan O, Konuk N, Uysal A, Beksaç M.

**Author information**

1 Department of Haematology/Oncology, Ankara University, Ibn-i Sina Hospital, Turkey.

n=44
alloBMT
HBsAg (+) n=10 (% 22,7)

Bunların 4'ü tx öncesi de (+), 6'sı ise tx sonrası (+)'leşmiş.
Bu 4 taşıyıcıda, tx sonrası IS kesildikten sonra ALT artmaya başlamış
Hepatit tablosu gelişmiş, ancak yetmezlik ve nihayetinde ex yok.

HCT sonrası immün kontrol ile HBV replikasyonu arasındaki denge HBV reaktivasyonu için belirleyici olmaktadır.

# Hematopoietik Kök Hücre Nakli

- Bu hastalar öncesinde mutlaka çoklu sıra KT+IS tedaviler almışlardır
- Nakil sürecinde de hazırlık rejimi olarak IS+KT almaktadırlar

↓

Derin/ağır IS ve daha evvel elde edilmiş olan HBV spesifik immünitenin kaybı

↓

HBV reaktivasyonu: Viral replikasyon

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# Hematopoietik Kök Hücre Nakli

Ayrıca;
Oto ve/veya **allo nakil** sonrası immün iyileşme 2 yıla kadar uzamaktadır

n=137
HBsAg (-) ve antiHBc (+)
HCT
HBV reaktivasyonu: %10
Post tx 9-77 ay aralığında

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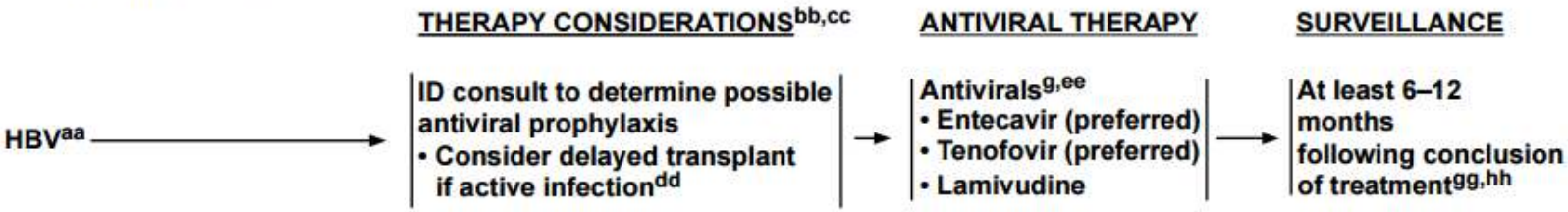
# Bone Marrow Transplantation: Increased Risk of Reactivation

- Markedly high rate of reactivation (HBsAg positive)
  - **Up to 54%[1] → need preemptive antiviral therapy!**
  - Long-term complications: cirrhosis in 10%[2]
- Reverse seroconversion common if anti-HBc positive[3]
  - Up to 50% become HBsAg positive → use preemptive antivirals
  - May occur very late
- HBV status of donor important[1,4]
  - **If natural immunity (anti-HBs, anti-HBc): may clear HBsAg**
  - If vaccinated (anti-HBs): possibly some protection

1. Lau GK, et al. Bone Marrow Transplant. 1997;19:795-799. 2. Hui CK, et al. Blood. 2005;106:464-469.
3. Onozawa M, et al. Transplantation. 2005;79:616-619. 4. Lau GK, et al. J Infect Dis. 1998;178:1585-1591.

## PREVENTION OF HEPATITIS B VIRUS (HBV), HEPATITIS C VIRUS (HCV), AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) REACTIVATION OR DISEASE[z]




[dd] Chronic hepatitis based on biopsy or active viral replication (ie, high levels of HBsAg+ and/or HBeAg+ or increasing HBV viral load). Biopsy should be performed if clinical suspicion of disease. In case of cirrhosis, reconsider decision for transplant.

Eur J Intern Med. 2013 Dec;24(8):e90-2. doi: 10.1016/j.ejim.2013.07.008. Epub 2013 Aug 13.

# Awareness of hepatitis B virus reactivation among physicians authorized to prescribe chemotherapy.

Turker K[1], Oksuzoglu B, Balci E, Uyeturk U, Hascuhadar M.

## Author information

1 Department of Infectious Diseases, Istanbul Bağcılar Training and Research Hospital, Istanbul, Turkey. Electronic address: kamuran.turker@gmail.com.

Hematolog, onkolog, genel cerrah

**Table 1**
Practice and attitudes of physicians (N = 83) regarding hepatitis B infection.

| | n (%) |
|---|---|
| 1–Dou you personally consider hepatitis B infection significant? | |
| Yes | 77 (92.8) |
| No and no idea | 6 (7.2) |
| 2–Are you aware that chemotherapy may cause HBV reactivation? | |
| Yes/No | 67 (80.7)/16 (19.3) |
| 3–Dou you personally perform routine screen for HBV prior to chemotherapy? | |
| Always | 49 (59.0) |
| Sometimes | 15 (18.1) |
| Never | 19 (22.9) |
| 4–Which tests do you use for routine screen for HBV? | |
| HbsAg only | 38 (45.8) |
| HbsAg and AntiHBs | 26 (31.3) |
| HBsAg, AntiHBclgG and AntiHBs | 19 (22.9) |
| 5–What are the indications for the routine screen for HBV prior to chemotherapy?[a] | |
| Universal screening without selection | 49 (59.0) |
| Only some situations | 39 (47) |
| 6–What is your opinion considering prevention of reactivation via administration of prophylactic antiviral medications? | |
| Possible | 50 (60.2) |
| Impossible | 2 (2.4) |
| No idea | 31 (37.3) |
| 7–Have you ever seen reactivation of HBV in your daily practice? | |
| Yes/No | 34 (41.0)/49 (59.0) |
| 8–Which patient should receive prophylaxis?[b] | |
| Chronic HbsAg carriers | 59 (82.0) |
| Patients with active HBV infection | 43 (59.7) |
| Resolved HBV infection with antiHBsAb production | 6 (8.3) |
| Missing data | 11 |

| | |
|---|---|
| 9—Did you personally prescribe prophylactic antiviral therapy? | n (%) |
| Yes/No | 37 (44.6)/46 (55.4) |
| If yes, which antiviral did you give? | |
| Lamivudine monotherapy | 33 (89.2) |
| Lamivudine + Tenofovir + Adefovir | 3 (8.1) |
| Lamivudine + Entekavir | 1 (2.7) |
| 10—What it is the ideal time to start prophylaxis? | |
| Concurrent with chemotherapy | 10 (12.0) |
| One week prior to chemotherapy | 35 (42.2) |
| One month prior to chemotherapy | 38 (45.8) |
| 11—How long should antiviral treatment continue after completing chemotherapy? | |
| One month | 2 (2.4) |
| Two months | 9 (10.8) |
| ≥4 months | 33 (39.8) |
| No idea | 39 (47.0) |
| 12—Is reactivation possible even after the prophylaxis? Yes/Unsure | 58 (69.9)/25 (30.1) |
| 13—How do you monitor HBV reactivation? | |
| Liver function tests | 43 (51.8) |
| Viral serology | 15 (18.1) |
| Quantitative measurement of HBV DNA | 45 (54.2) |
| Clinical symptoms | 2 (2.4) |
| Unsure | 7 (8.4) |
| 14—Would you want a gastroenterologist to follow the patient with you while on chemotherapy? Yes/No | 77 (92.8)/6 (7.2) |
| 15—Would you want an infectious diseases specialist to follow the patient with you while on chemotherapy? Yes/No | 70 (84.3)/13 (15.7) |
| 16—Would you want a gastroenterologist to follow the patient with you after discontinuation of chemotherapy? Yes/No | 76 (91.6)/7 (8.4) |
| 17—Would you want an infectious diseases specialist to follow the patient with you after discontinuation of chemotherapy? Yes/No | 73 (88.0)/10 (12.0) |

[a] N = 64; more than one might be chosen by each physician.
[b] N = 72; more than one might be chosen by each physician.

## SONUÇLAR

n=83
% 92,8'i HBV enfeksiyonunu önemsiyor, dikkate alıyor
% 80,7'si KT ile HBV reaktivasyonu arasında bir ilişki olabileceğini öngörüyor
Buna karşın sadece % 59'u KT öncesi rutin tarama testleri yaparım diyor.

n=83
Hematolog ve onkologların tümü, fakat cerrahların % 76,5'i KT ve HBV reaktivasyonu ilişkisinden haberdar ($p<0,05$).

n=83
Hematolog ve onkologların hepsi biliyor; ancak cerrahların % 67,6'sı antiviral profilaksinin HBV reaktivasyonundaki olumlu yerini bilmiyor ($p<0,05$).

n=83
KT sonrası antiviral profilaksinin süresi hakkında onkologların % 23,5'i ve cerrahların % 64,7'si bilgi sahibi değilken, tüm hematologlar bir öngörüde bulunabiliyorlar ($p<0,05$).

Alimentary Pharmacology & Therapeutics

# Screening for hepatitis B in chemotherapy patients: survey of current oncology practices

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ABD'deki onkologların %20'si KT öncesi hiç tarama yapmıyor

**Table 2.** Practice of hepatitis B (HBV) screening and prophylaxis in chemotherapy patients by surveyed oncologists ($n$ = 265)

| Screening/treatment practice | Number (%) |
|---|---|
| Patients screened for HBV | |
| None | 54 (20) |
| Risk factors or history of hepatitis | 101 (38) |
| Abnormal liver tests | 80 (30) |
| Random patients | 28 (11) |
| All patients | 35 (13) |
| Screening tests ordered | |
| HBsAg | 201 (76) |
| anti-HBs | 169 (64) |
| HBeAg | 59 (22) |
| HBV DNA level | 17 (6) |
| anti-HBc | 123 (46) |
| None | 29 (11) |
| Other | 12 (5) |
| HBV prophylaxis by surveyor | |
| Yes | 18 (7) |
| No, and no referral to specialist | 40 (15) |
| No, but refer to specialist | 205 (15) |
| Missing | 2 (0.7) |

HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; anti-HBc, hepatitis B core antibody.

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# Oncologists and Hepatitis B: A Survey to Determine Current Level of Awareness and Practice of Antiviral Prophylaxis to Prevent Reactivation

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**Table 1.** Questionnaire survey

| | | |
|---|---|---|
| 1 | Are you aware that reactivation of HBV can occur? | |
| | Yes | 78% |
| | No | 22% |
| 2 | Are you aware that prophylactic antiviral therapy is available? | |
| | Yes | 56% |
| | No | 44% |
| 3 | Have you ever seen reactivation of HBV in your practice? | |
| | Yes | 30% |
| | No | 70% |
| 4 | Do you screen for HBV prior to chemotherapy? | |
| | Yes | 38% |
| | No | 62% |
| 4a | If you screen, do you practice universal or selective screening? | |
| | Universal | 14% |
| | Selective | 86% |
| 4b | If selective, which patients do you screen? | |
| | Abnormal LFTs | 70% |
| | HCV co-infection | 70% |
| | Men who have sex with men | 60% |
| | HIV co-infection | 58% |
| | IVDU | 58% |
| | Hx transfusion | 54% |
| | Healthcare workers | 50% |
| | Asian/African descent | 32% |
| 5 | Which patient should receive prophylaxis? | |
| | Chronic HBsAg carrier | 46% |
| | Active HBV | 76% |
| | Resolved HBV infection | 52% |
| 6 | Do you personally prescribe prophylactic antiviral therapy? | |
| | Yes | 28% |
| | No | 72% |
| 7 | Which antiviral would you give? | |
| | Lamivudine | 46% |
| | Adefovir | 14% |
| | Not sure | 40% |
| 8 | Would you start prophylaxis prior to or concurrent with chemotherapy? | |
| | Prior | 90% |
| | Concurrent | 10% |
| 9 | How would you monitor for HBV reactivation? | |
| | LFTs | 46% |
| | Viral serology | 36% |
| | Clinical symptoms | 32% |
| | Not sure | 26% |
| 9a | If you do monitor, how often would monitoring occur? | |
| | Every 2 weeks | 4% |
| | Every 4 weeks | 18% |
| | Every 6 weeks | 14% |
| | Every 8 weeks | 16% |
| | Every 12 weeks | 12% |
| | Not sure | 36% |
| 10 | How long should antiviral treatment continue after completing chemotherapy? | |
| | 1 month | 8% |
| | 2 months | 15% |
| | 3 months | 71% |
| | 4 months or greater | 8% |
| 11 | Would you monitor for reactivation even if you did not give prophylaxis? | |
| | Yes | 66% |
| | No | 6% |
| | Unsure | 28% |
| 12 | Would you want a gastroenterologist/hepatologist to follow the patient with you while on chemotherapy? | |
| | Yes | 88% |
| | No | 12% |
| 13 | Would you want a gastroenterologist/hepatologist to follow the patient with you after chemotherapy? | |
| | Yes | 26% |
| | No | 74% |

HBV = Hepatitis B virus; HCV = hepatitis C virus; IVDU = intravenous drug users; LFT = liver function tests.

%14' ü KT öncesi mutlaka tarama yaparken,
geri kalanı bir şekilde eşlik eden risk faktörü varsa tarama yaptığını söylemiş

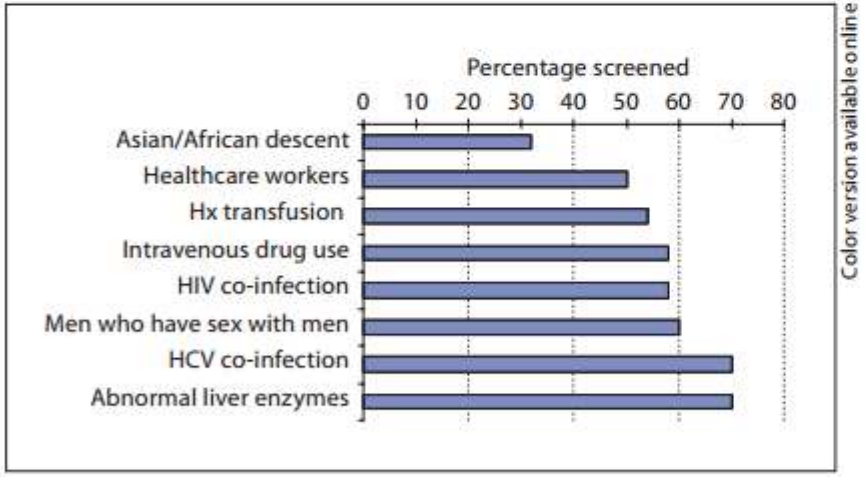


**Fig. 1.** Screening practices of oncologists. HCV = Hepatitis C virus.

n=131 dr

%78' i HBV reaktivasyonunun potansiyel risklerinin farkında
%56' sı profilaktik antiviral uygulamanın var olduğunun farkında

# Low Rates of Hepatitis B Virus Screening at the Onset of Chemotherapy

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The University of Texas MD Anderson Cancer Center; Ingenix Consulting; and Baylor

- Yeni tanı kanser hastaları
- Retrospektif
- 2004-2007 arası
- HBV enfeksiyonu durumunu HBsAg ve antiHBc taraması ile ortaya koyma alışkanlığı

| Characteristic | Total (N = 10,729) No. | % | HBV Screening: Yes (n = 1,787) No. | % | No (n = 8,942) No. | % |
|---|---|---|---|---|---|---|
| Age, years | | | | | | |
| Mean | 54.9 | | 51.5 | | 55.5 | |
| SD | 13.8 | | | | | |
| Sex | | | | | | |
| Male | 4,866 | 45.4 | 1,060 | 21.8 | 3,806 | 78.2 |
| Female | 5,863 | 55.6 | 727 | 12.4 | 5,136 | 87.6 |
| Ethnicity | | | | | | |
| White | 7,810 | 72.8 | 1,310 | 16.8 | 6,500 | 83.2 |
| Hispanic | 1,279 | 11.9 | 230 | 18.0 | 1,049 | 82.0 |
| Black | 1,138 | 10.6 | 139 | 12.2 | 999 | 87.8 |
| Asian | 266 | 2.5 | 45 | 16.9 | 221 | 83.1 |
| Other | 236 | 2.2 | 63 | 26.7 | 173 | 73.3 |
| US residence | 10,428 | 97.2 | 1,716 | 16.5 | 8,712 | 83.5 |
| History of HBV infection* | 95 | 0.9 | 65 | 68.4 | 30 | 31.6 |
| HBV risk factors† | 2,612 | 24.3 | 513 | 19.6 | 2,099 | 80.4 |
| Cancer type | | | | | | |
| Solid tumor | 9,009 | 84.0 | 555 | 6.2 | 8,454 | 93.8 |
| Hematologic malignancy | 1,720 | 16.0 | 1,232 | 71.6 | 488 | 28.4 |
| Chemotherapy type | | | | | | |
| Chemotherapy/ nonimmunotherapy | 8,315 | 77.5 | 887 | 10.7 | 7,428 | 89.3 |
| Immunotherapy, excluding rituximab | 1,293 | 12.1 | 100 | 7.7 | 1,193 | 92.3 |
| Rituximab | 1,121 | 10.4 | 800 | 71.4 | 321 | 28.6 |

| Risk derecesi | HBsAg + Anti-HBc+ | HBsAg – Anti-HBc+ | Tedavi |
|---|---|---|---|
| Yüksek Risk >%10 | B hücre deplesyonu yapan ajanlar (rituximab, ofatumumab)<br>Antrasiklin deriveleri (doxorubicin, epirubicin)<br>Orta (10–20 mg/gün) veya yüksek doz (>20 mg/gün) prednizon 4 hafta | B hücre deplesyonu yapan ajanlar (rituximab, ofatumumab) | Profilaksi |
| Orta Risk %1-10 | TNF-alfa tedavisi (etanercept, adalimumab, certolizumab, infliximab)<br>Sitokin veya integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab)<br>Tirozin kinaz inhibitörleri (imatinib, nilotinib)<br>Düşük doz steroid (<10 mg/gün prednisone), 4 haftalık tedavi | TNF-alfa tedavisi (etanercept, adalimumab, certolizumab, infliximab)<br>Sitokin veya integrin inhibitörleri (abatacept, ustekinumab, natalizumab, vedolizumab)<br>Tirozin kinaz inhibitörleri (imatinib, nilotinib)<br>Orta doz (10–20 mg/gün) veya yüksek doz (>20 mg/gün) prednizon 4 hafta<br>antrasiklin deriveleri (doxorubicin, epirubicin) | Profilaksi veya Pre-emptif |
| Düşük Risk <%1 | İmmunsupresif ajanlar (azathioprine, 6-mercaptopurine, methotrexate)<br>İntra-artiküler kortikosteroidler<br>1 hafta süreli herhangi bir dozda oral steroid tedavisi | İmmunsupresif ajanlar (azathioprine, 6-mercaptopurine, methotrexate)<br>İntra-artiküler kortikosteroidler<br>1 hafta süreli herhangi bir dozda oral steroid tedavisi<br>Düşük doz 4 haftalık steroid (<10 mg prednison) | Profilaksiye gerek yok |