# Yüksek doz ARA-C endikasyonları, uygulama yöntemi, yan etki yönetimi

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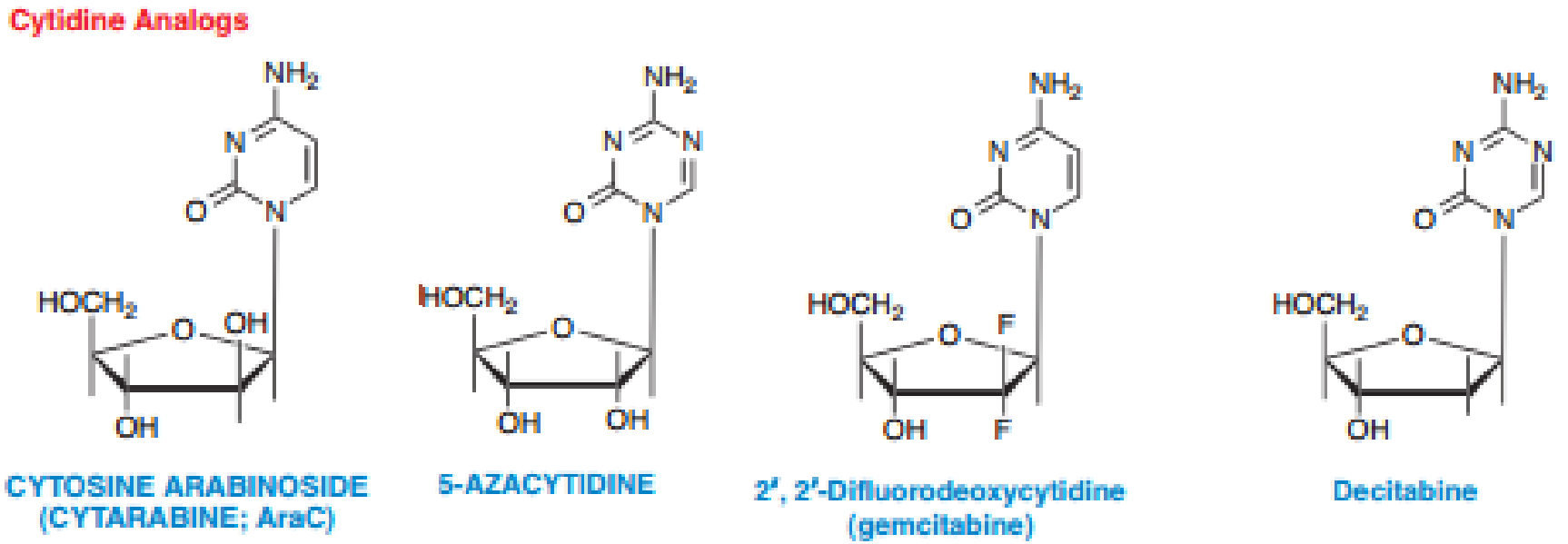
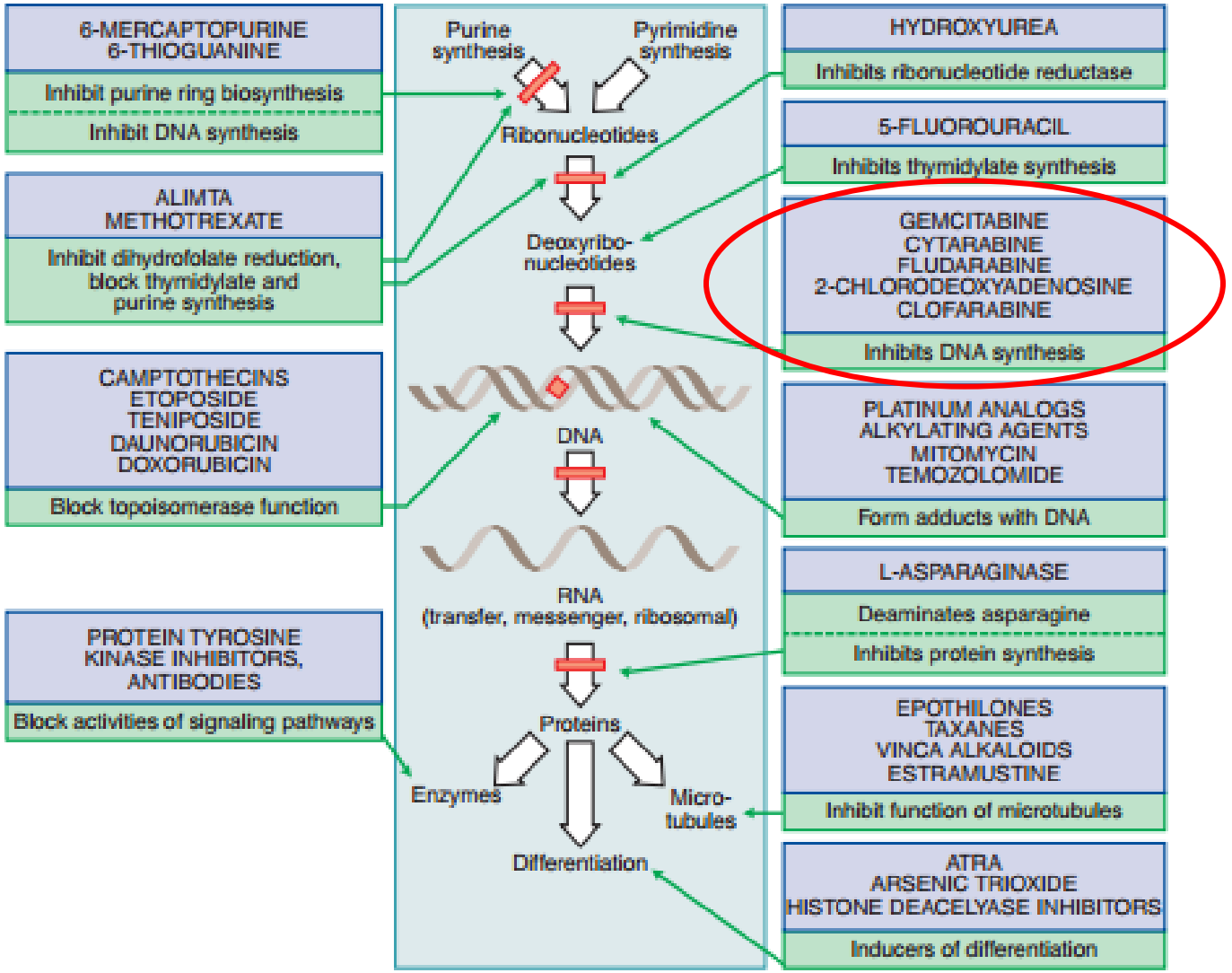
Koç Üniversitesi Hastanesi

# ARA-C




Hc içi aktif form 5’-monofosfat ribonükleotid

# ARA-C Etki Mekanizması




Goodman&Gilmen's 2011

# Uygulama

- Oda ısısında 24 saat, buz dolabında 72 saat stabil. Koruyuculu formları izotonik ile dilüe ve ışıktan korunarak oda ısısnda 6 güne kadar saklanabilir.

- %5 Dextroz
- Laktatlı ringerde verilebilir.
- %0,9 NaCl ile uygulanması öneriliyor.

- Sentezi 1951 yılı
- 1972 yılında HiDAC araştırmaları başlıyor.

- Eliminasyon Deoksisitidin deaminaz ile
- Yarılanma ömrü kısa 10 dk

- Konvansiyonel doz 100-200 mg/m2
- İntermediate doz 500-1000 mg/m2
- Yüksek doz 2000-3000 mg/m2

Kline et all, Cancer Chemother Rep 1972

# Uygulama

- Tümör hücrelerinin S fazını yakalamak için 24 saatlik infüzyon.
- Düşük doz 24 saatlik uygulama.
- Yüksek doz kısa t 1/2, intraselüler ilaç terapötik düzeyinin oluşturulması nedeniyle 8-12 saatlik aralıklarla hızlı infüzyon (3 gr/m2 3 saatlik infüzyon)

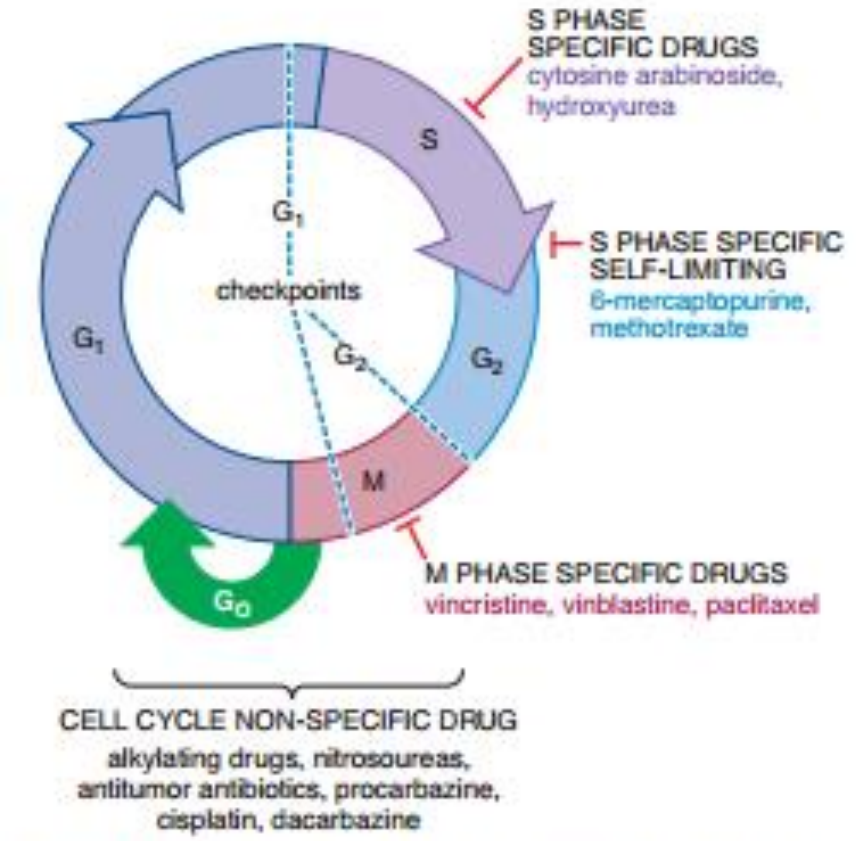



Figure 60–2. *Cell cycle specificity of antineoplastic agents.*

# Yüksek Doz ARA-C Endikasyonları

- AML indüksiyon
- AML konsolidasyon
- AML salvage tedavisi
- ALL tedavisi
- Lenfoma tedavisi (Mantle)
- Lenfoma salvage tedavi
- Kök hücre mobilizasyonu
- MSS lenfoması

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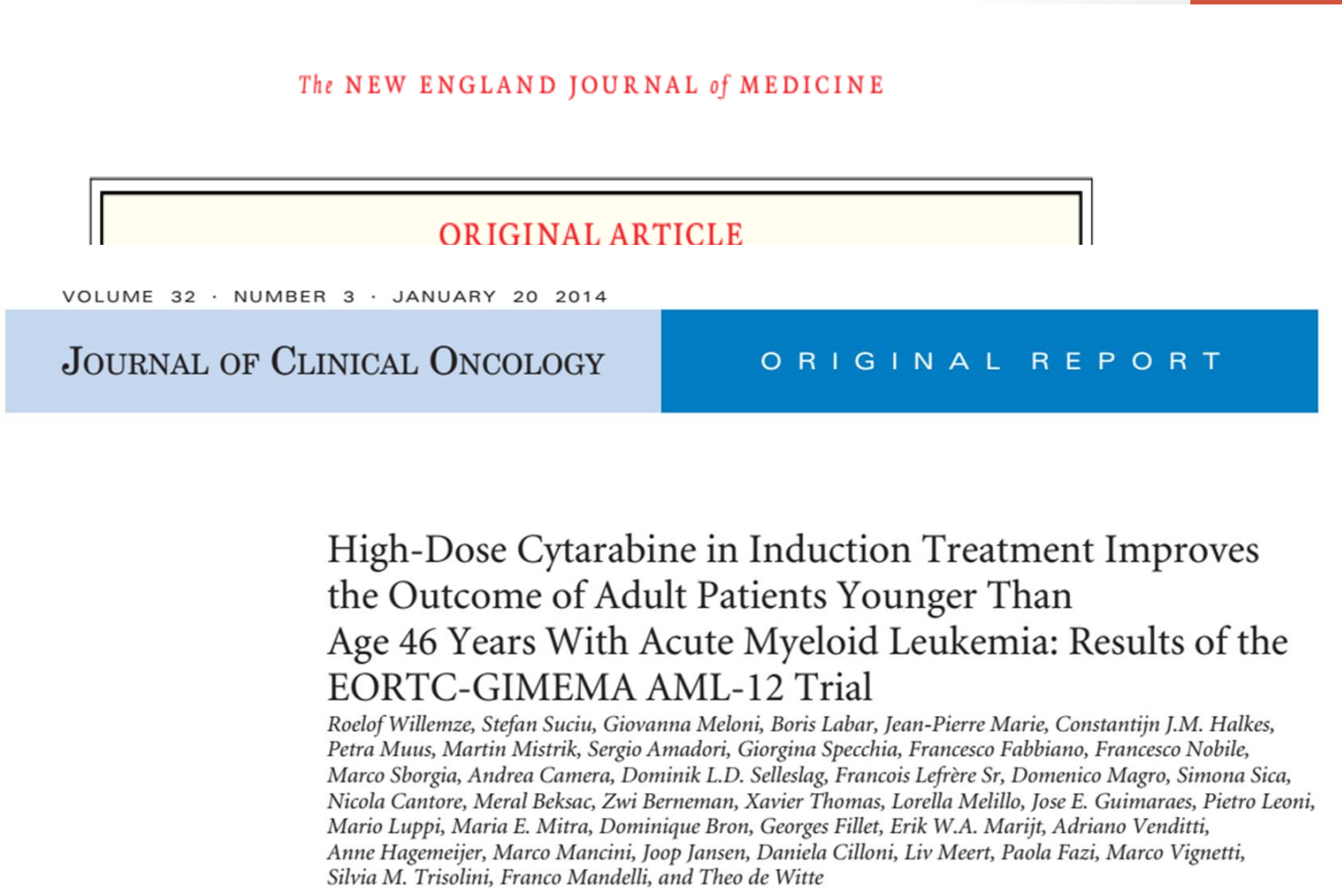

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

VOLUME 32 · NUMBER 3 · JANUARY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High-Dose Cytarabine in Induction Treatment Improves the Outcome of Adult Patients Younger Than Age 46 Years With Acute Myeloid Leukemia: Results of the EORTC-GIMEMA AML-12 Trial

*Roelof Willemze, Stefan Suciu, Giovanna Meloni, Boris Labar, Jean-Pierre Marie, Constantijn J.M. Halkes, Petra Muus, Martin Mistrik, Sergio Amadori, Giorgina Specchia, Francesco Fabbiano, Francesco Nobile, Marco Sborgia, Andrea Camera, Dominik L.D. Selleslag, Francois Lefrère Sr, Domenico Magro, Simona Sica, Nicola Cantore, Meral Beksac, Zwi Berneman, Xavier Thomas, Lorella Melillo, Jose E. Guimaraes, Pietro Leoni, Mario Luppi, Maria E. Mitra, Dominique Bron, Georges Fillet, Erik W.A. Marijt, Adriano Venditti, Anne Hagemeijer, Marco Mancini, Joop Jansen, Daniela Cilloni, Liv Meert, Paola Fazi, Marco Vignetti, Silvia M. Trisolini, Franco Mandelli, and Theo de Witte*

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**INTENSIVE POSTREMISSION CHEMOTHERAPY IN ADULTS WITH ACUTE MYELOID LEUKEMIA**

Robert J. Mayer, M.D., Roger B. Davis, Sc.D., Charles A. Schiffer, M.D., Deborah T. Berg, R.N., Bayard L. Powell, M.D., Philip Schulman, M.D., George A. Omura, M.D., Joseph O. Moore, M.D.,

[CANCER RESEARCH 58, 4173–4179, September 15, 1998]

**Frequency of Prolonged Remission Duration after High-Dose Cytarabine Intensification in Acute Myeloid Leukemia Varies by Cytogenetic Subtype[1]**

**Clara D. Bloomfield, David Lawrence, John C. Byrd,[2] Andrew Carroll, Mark J. Pettenati, Ramana Tantravahi, Shivanand R. Patil, Frederick R. Davey, Deborah T. Berg, Charles A. Schiffer, Diane C. Arthur, and Robert J. Mayer**

*The Ohio State University, Columbus, Ohio 43210 [C. D. B.]; Roswell Park Cancer Institute, Buffalo, New York 14263 [D. L.]; Walter Reed Army Medical Center, Washington, D.C. 20307 [J. C. B.]; University of Alabama at Birmingham, Birmingham, Alabama 35229 [A. C.]; Bowman Gray School of Medicine, Winston-Salem, North Carolina 27157 [M. J. P.]; Dana-Farber Cancer Institute, Boston, Massachusetts 02115 [R. T., D. T. B., R. J. M.]; University of Iowa, Iowa City, Iowa 52242 [S. R. P.]; State University of New York Health Science Center at Syracuse, Syracuse, New York 13210 [F. R. D.]; University of Maryland Cancer Center, Baltimore, Maryland 21201 [C. A. S.]; and University of Minnesota, Minneapolis, Minnesota 55455 [D. C. A.]*

**ABSTRACT**

**Advances in the treatment of acute myeloid leukemia (AML) have occurred with the introduction of new therapies including high-dose cytarabine and the identification of powerful prognostic factors such as cytogenetics that predict for long-term outcome. To date, the prognostic impact of cytarabine dose escalation within various cytogenetic groups of AML has not been assessed. We describe 285 newly diagnosed patients with primary AML who had adequate karyotypes and were enrolled on a prospective Cancer and Leukemia Group B cytogenetic study. All patients were randomly assigned to postremission treatment with standard-, in-**

**order of importance were cytogenetic group (CBF > normal > other abnormality; $P = 0.00001$), cytarabine dose (3 g/m$^2$ > 400 mg/m$^2$ > 100 mg/m$^2$; $P = 0.00001$), logarithm of leukocyte count at the time of diagnosis ($P = 0.0005$), and histological subtype of AML ($P = 0.005$). This study demonstrates that the curative impact of cytarabine intensification varies significantly among cytogenetic groups and results in a substantial prolongation of CR among patients with CBF and normal karyotypes, but not in those with other karyotypic abnormalities. These findings support the use of pretreatment cytogenetics in risk stratification of postremission AML therapy.**

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## High-Dose Cytosine Arabinoside Therapy for Refractory Leukemia

By Roger H. Herzig, Steven N. Wolff, Hillard M. Lazarus, Gordon L. Phillips, C. Karanes, and Geoffrey P. Herzig

Fifty-seven patients with refractory acute leukemia were treated with high-dose cytosine arabinoside to establish the maximum tolerated dose and duration and to determine the antileukemic activity. The maximum tolerated regimen was found to be 3 g/sq m every 12 hr for 6 days. At this dose, nonhematologic toxicity was limited to conjunctivitis in approximately half of the patients, and liver toxicity (transient elevations in transaminase, alkaline phosphatase, or bilirubin) was frequently observed, but neither was dose-limiting. Extending the duration of treatment to 8 days resulted in excessive diarrhea and skin toxicity (painful erythema with bullae), while increasing the dose to 4.5 g/sq m q. 12 hr for 6 days resulted in severe cerebellar toxicity. Myelosuppression was severe, but was not related to the intensity of treatment; granulocyte recovery occurred a median of 28 days (range 22–40 days) after initiating therapy, and platelet recovery occurred after a median of 25 days (range 16–41 days). Antileukemic activity was evaluable in the 46 patients who survived at least 3 wk. Complete remissions were obtained in 1 of 6 patients with chronic myelogenous leukemia (CML) in accelerated phase and 1 of 3 acute lymphoblastic leukemia (ALL) patients. A more detailed analysis of response was possible for the 37 evaluable patients with acute nonlymphoblastic leukemia: 70% of these patients responded, with 51% complete remissions. The median unmaintained response was 4 mo (range 2–26+ mo). The complete response rate was higher in patients who received at least 12 doses of high-dose cytosine arabinoside compared to shorter regimens [17/28 (61%) versus 2/9 (22%), $p < 0.05$]. Resistance to cytosine arabinoside in conventional doses was documented in 11 patients, 5 of whom responded (2 complete remissions) to high-dose regimens. We conclude that high-dose cytosine arabinoside in the maximally tolerated regimen of 3 g/sq m every 12 hr for 6 days has substantial antileukemic activity in patients refractory to standard therapy. Durable unmaintained remissions can be achieved, even in patients who fail to respond to cytosine arabinoside in conventional doses.

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Cancer. 2004 Dec 15;101(12):2788-801.

**Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia.**

Kantarjian H[1], Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, Bueso-Ramos CE, Pierce S, Shan J, Koller C, Beran M, Keating M, Freireich EJ.

Author information

**Abstract**

**BACKGROUND:** Modern intensive chemotherapy regimens have improved the prognosis for patients with adult acute lymphocytic leukemia (ALL). With these regimens, the complete response rates are now reported to be > 80%, and the long-term survival rates range from 30% to 45%. The current analysis updated the long-term results with the original hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) program, with a median follow-up time of 63 months.

**METHODS:** Between 1992 and 2000, 288 patients were treated with Hyper-CVAD. The median age of the patients was 40 years, and 59 patients (20%) were > or = age 60 years. The incidence of Philadelphia chromosome (Ph)-positive ALL was 17%, and the incidence of of T-cell ALL was 13%.

**RESULTS:** A complete response (CR) was achieved in 92% of patients. The induction mortality rate was 5% (2% if the patient's age was < 60 years, and 15% if the patient's age was > or = 60 years). With a median follow-up time of 63 months, the 5-year survival rate was 38% and the 5-year CR duration rate was 38%. Multivariate analysis of prognostic factors for CR duration identified the following adverse factors: age > or = 45 years, leukocytosis > or = 50 x 10(9)/L, poor performance status (an Eastern Cooperative Oncology Group score of 3-4), Ph-positive disease, French-American-British L2 morphology, > 1 course to achieve CR, and Day 14 bone marrow blasts > 5%. Patients were divided into low-risk (risk score 0-1; 37%), intermediate risk (risk score 2-3; 36%), and poor-risk groups (risk score > or = 4; 27%) with 5-year CR duration rates of 52%, 37%, and 10%, respectively.

**CONCLUSIONS:** Compared with the previous VAD regimens, Hyper-CVAD was associated with significantly better CR rates, CR duration, and survival. The long-term follow-up results of Hyper-CVAD were favorable. Comparison of Hyper-CVAD with other established adult ALL regimens is warranted.

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CLINICAL TRIALS AND OBSERVATIONS

## Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo–purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group

Christian H. Geisler,[1] Arne Kolstad,[2] Anna Laurell,[3] Niels S. Andersen,[1] Lone B. Pedersen,[1] Mats Jerkeman,[4] Mikael Eriksson,[4] Marie Nordström,[5] Eva Kimby,[5] Anne Marie Boesen,[6] Outi Kuittinen,[7] Grete F. Lauritzsen,[2] Herman Nilsson-Ehle,[8] Elisabeth Ralfkiær,[1] Måns Åkerman,[4] Mats Ehinger,[4] Christer Sundström,[3] Ruth Langholm,[2] Jan Delabie,[2] Marja-Liisa Karjalainen-Lindsberg,[9] Peter Brown,[1] and Erkki Elonen[9] for the Nordic Lymphoma Group

[1]Rigshospitalet, Copenhagen, Denmark; [2]Norwegian Radium Hospital, Oslo, Norway; [3]Uppsala University Hospital, Uppsala, Sweden; [4]Lund University Hospital, Lund, Sweden; [5]Karolinska Institute, Stockholm, Sweden; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Oulu University Hospital, Oulu, Finland; [8]Sahlgrenska Hospital, Gothenburg, Sweden; and [9]Helsinki University Central Hospital, Helsinki, Finland

**Mantle cell lymphoma (MCL) is considered incurable. Intensive immunochemotherapy with stem cell support has not been tested in large, prospective series. In the 2nd Nordic MCL trial, we treated 160 consecutive, untreated patients younger than 66 years in a phase 2 protocol with dose-intensified induction immunochemotherapy with rituximab (R) + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP), alternating with R + high-dose cytarabine. Responders received high-dose chemotherapy with BEAM or BEAC (carmustine, etoposide, cytarabine, and melphalan/cyclophosphamide) with R-in vivo purged autologous stem cell support. Overall and complete response was achieved in 96% and 54%, respectively. The 6-year overall, event-free, and progression-free survival were 70%, 56%, and 66%, respectively, with no relapses occurring after 5 years. Multivariate analysis showed Ki-67 to be the sole independent predictor of event-free survival. The nonrelapse mortality was 5%. The majority of stem cell products and patients assessed with polymerase chain reaction (PCR) after transplantation were negative. Compared with our historical control, the Nordic MCL-1 trial, the event-free, overall, and progression-free survival, the duration of molecular remission, and the proportion of PCR-negative stem cell products were significantly increased ($P < .001$). Intensive immunochemotherapy with in vivo purged stem cell support can lead to long-term progression-free survival of MCL and perhaps cure. Registered at www.isrctn.org as #ISRCTN 87866680.**
**(Blood. 2008;112:2687-2693)**

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VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

*Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz*

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Biol Blood Marrow Transplant 20 (2014) 295–308

Review

## Optimizing Autologous Stem Cell Mobilization Strategies to Improve Patient Outcomes: Consensus Guidelines and Recommendations

Sergio Giralt [1,*], Luciano Costa [2], Jeffrey Schriber [3], John DiPersio [4], Richard Maziarz [5], John McCarty [6], Paul Shaughnessy [7], Edward Snyder [8], William Bensinger [9], Edward Copelan [10], Chitra Hosing [11], Robert Negrin [12], Finn Bo Petersen [13], Damiano Rondelli [14], Robert Soiffer [15], Helen Leather [16], Amy Pazzalia [17], Steven Devine [18]

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[2] *Department of Medicine, Medical University of South Carolina, Charleston, South Carolina*
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[5] *Oregon Health and Science University, Portland, Oregon*
[6] *Adult Bone Marrow Transplant, Virginia Commonwealth University, Richmond, Virginia*
[7] *Adult Bone Marrow Transplant, Texas Transplant Institute, San Antonio, Texas*
[8] *Yale University Medical School, New Haven, Connecticut*
[9] *Fred Hutchinson Cancer Research Institute, Seattle, Washington*
[10] *Levine Cancer Institute / Carolinas HealthCare System, Charlotte, North Carolina*

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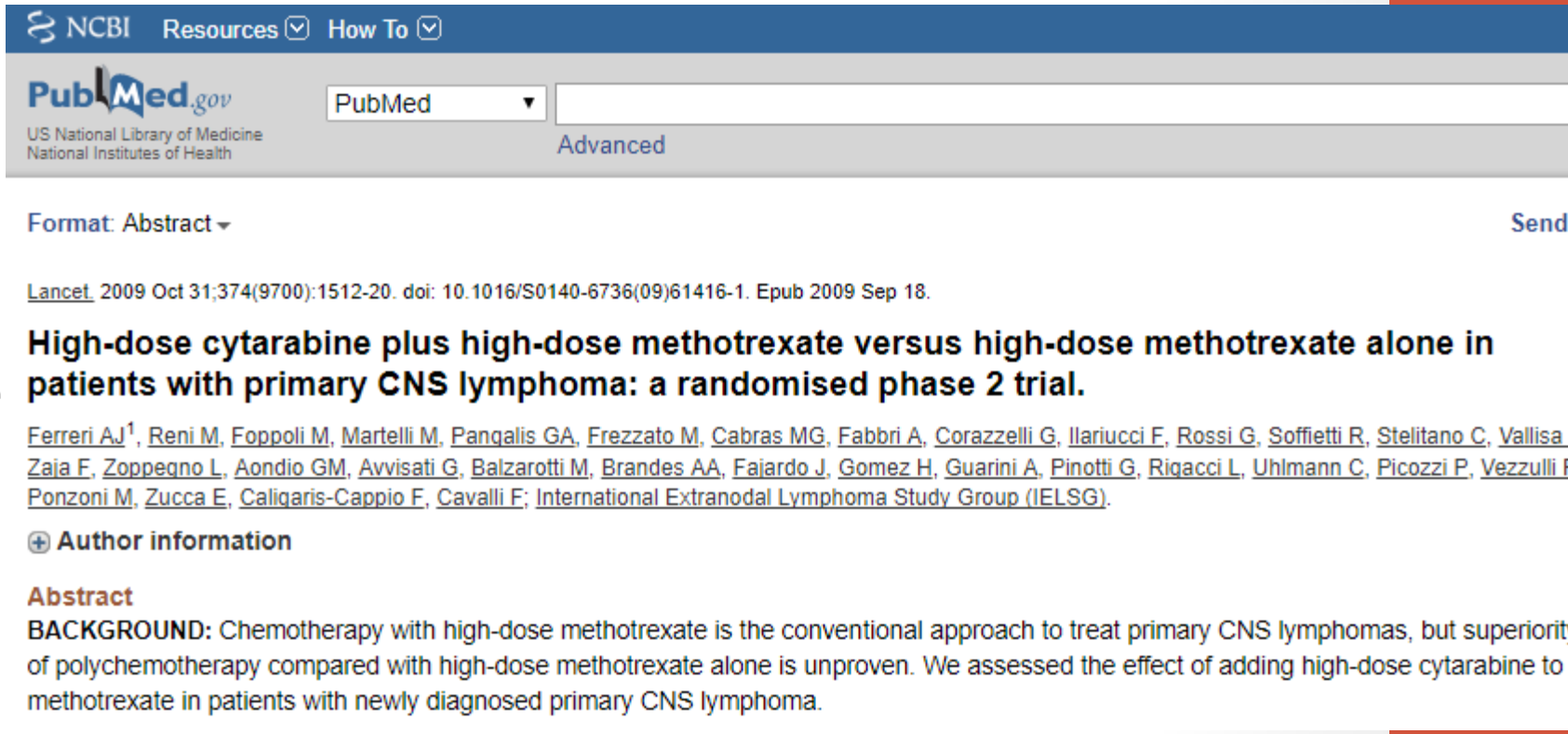

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Lancet. 2009 Oct 31;374(9700):1512-20. doi: 10.1016/S0140-6736(09)61416-1. Epub 2009 Sep 18.

**High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial.**

Ferreri AJ[1], Reni M, Foppoli M, Martelli M, Pangalis GA, Frezzato M, Cabras MG, Fabbri A, Corazzelli G, Ilariucci F, Rossi G, Soffietti R, Stelitano C, Vallisa
Zaja F, Zoppegno L, Aondio GM, Avvisati G, Balzarotti M, Brandes AA, Fajardo J, Gomez H, Guarini A, Pinotti G, Rigacci L, Uhlmann C, Picozzi P, Vezzulli
Ponzoni M, Zucca E, Caligaris-Cappio F, Cavalli F; International Extranodal Lymphoma Study Group (IELSG).

**Author information**

**Abstract**

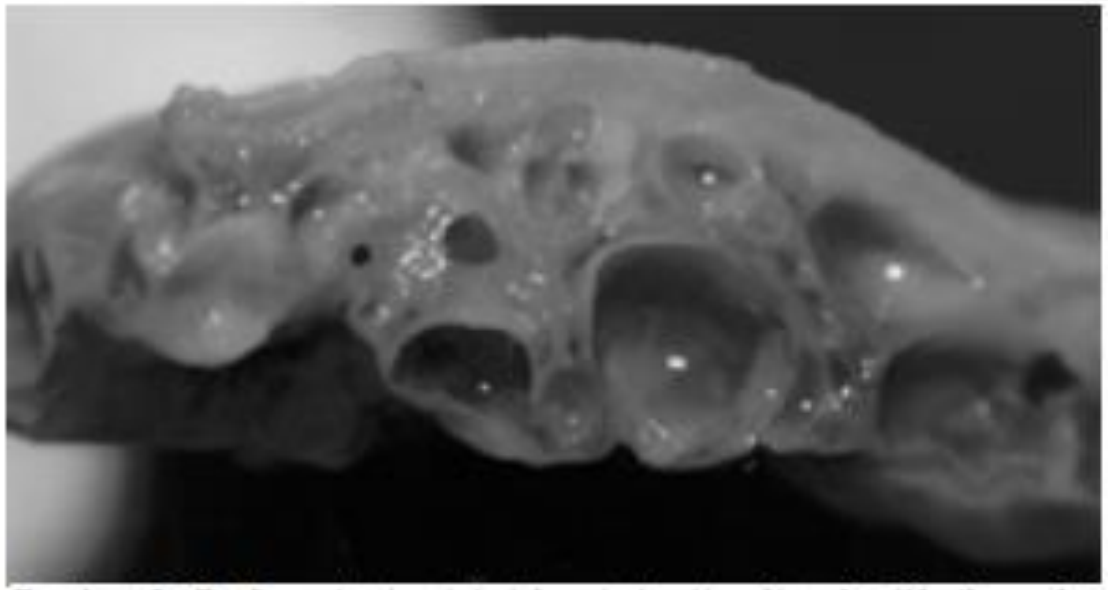
**BACKGROUND:** Chemotherapy with high-dose methotrexate is the conventional approach to treat primary CNS lymphomas, but superiorit
of polychemotherapy compared with high-dose methotrexate alone is unproven. We assessed the effect of adding high-dose cytarabine to
methotrexate in patients with newly diagnosed primary CNS lymphoma.

# Yan Etkileri

- Miyelosupresyon
- Bulantı kusma
- Kanama
- Perikardit
- Ateş
- Sarılık
- İnfertilite
- Peritonit, tifilit, pankreatit, KC toksisitesi
- Anafilaksi
- Tümör lizis send
- İmmünsupresyon
- İnfeksiyon
- Nöropati
- MSS toksisitesi
- Göz komp
- Deri döküntüleri
- Pulmoner toksisite

# Yan Etkileri (HiDAC)

- Kardiyomyopati (mortal) sıklık?
- Ciddi ve mortal GI toksisitesi
  - Nekrotizan kolit (%1-10)
  - Gastrointestinal nekroz (?)
  - GIS ülserasyonlar (?)
  - Pnömatosis sisoides intestinalis (?)
  - Peritonit (?)
- Pankreatit
- Karaciğer absesi
- Hiperbilirubinemi



**Resim 2.** Pnömatozis sistoides intestinalise bağlı ileusda barsak kesitinin makroskopik görüntüsü (5)

# Yan Etkileri (HiDAC)

- Solunum sistemi (>%10)
  - Erişkin respiratuar distres send
  - Pulmoner ödem

- Deri yan etkileri (%1-10)
  - Ciddi raş
  - Deskuamasyon
  - Komplet alopesi

- Göz (% 1-10)
  - Hemorajik konjonktivit
  - Korneal ülserasyon

# Sitarabin sendromu

- Ateş
- Miyalji
- Kemik ağrısı
- Göğüs ağrısı
- Makülopapüler raş
- Konjonktivit
- Raş

- Uygulamadan 6-12 saat sonra.
- Kortikosteroid

Castelberry et al, Med Ped Oncol 1981

- MSS toksisitesi ( >60 yaş, KBY, Kr KC hst)
  - Serebral, serebellar disfonksiyon (>36 g/m2) (%1-10)
  - Kişilik değişiklikleri
  - Somnolans
  - Konvülziyon
  - Koma
- Periferal motor nöropati
- Periferal sensoryal nöropati

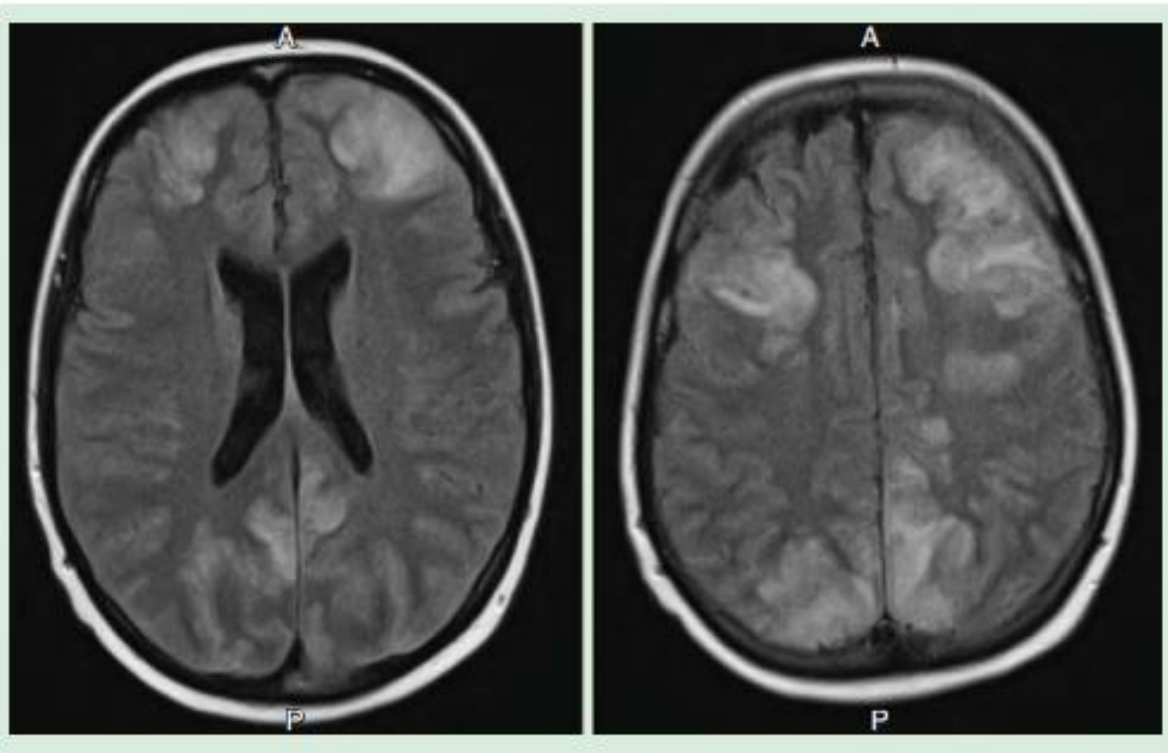



Figure 2. Posterior reversible encephalopathic syndrome seen in MRI fluid attenuated inversion recovery imaging of a patient treated with a cytarabine containing regimen involving both frontal and posterior lobes.

# Yan etki yönetimi

- Nöropati etyolojisinde immün mekanizma?
- Tedavisinde yüksek doz metilprednizolon
- Plazmaferez denenebilir
- Sıklık 2/153 hasta

Cancer

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Original Article

## Acute polyneuropathy after high dose cytosine arabinoside in patients with leukemia

Harry Openshaw M.D., Neal E. Slatkin M.D., Anthony S. Stein M.D., David R. Hinton M.D., Stephen J. Forman M.D.

**First published:** 1 November 1996 Full publication history

**DOI:** 10.1002/(SICI)1097-0142(19961101)78:9<1899::AID-CNCR9>3.0.CO;2-A
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Funding Information




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# Teşekkürler