Treatment of Burkitt Lymphoma in Adults

Lymphoma Tumor Board

November 3, 2017

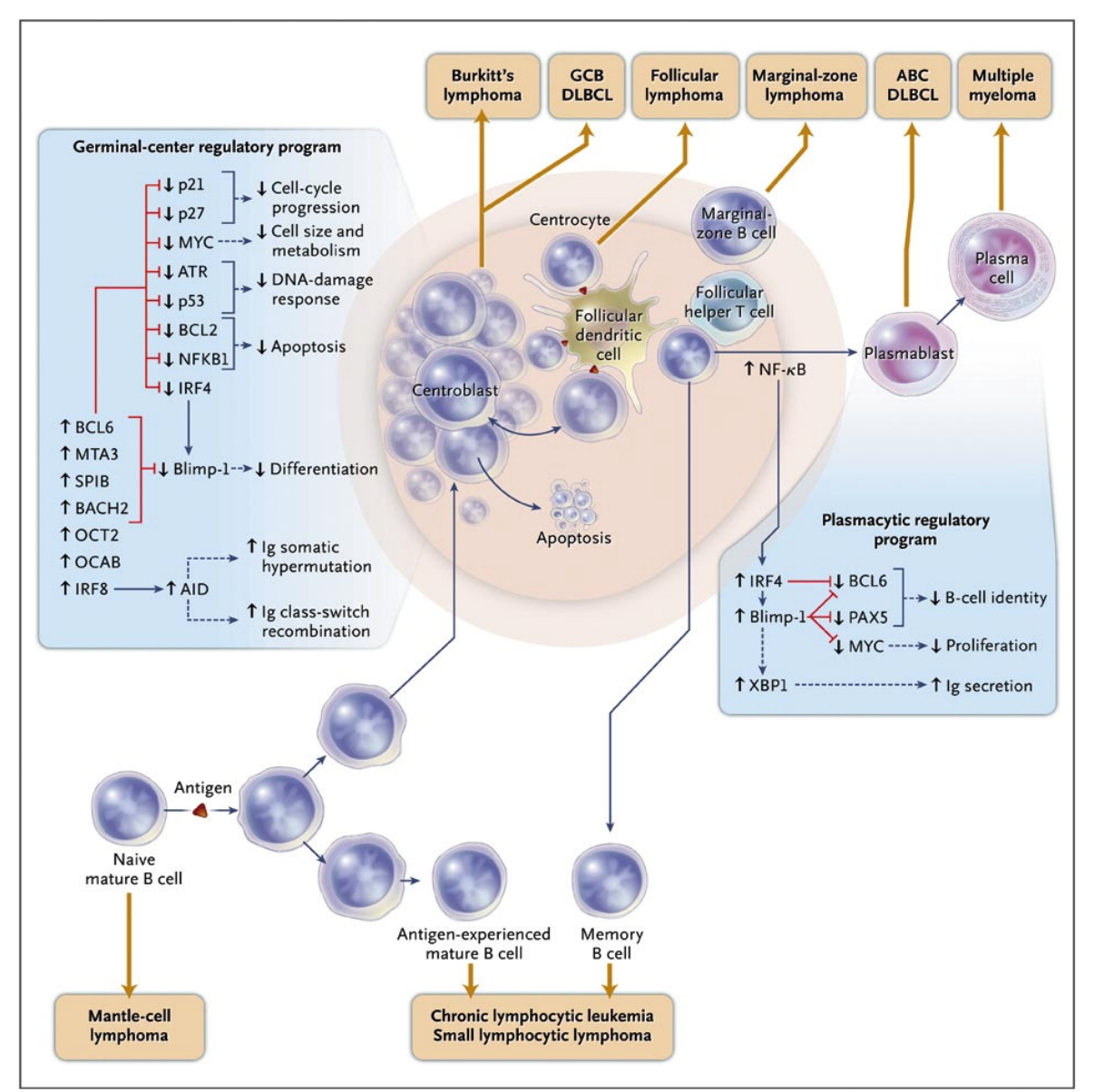
Burkitt lymphoma (BL) is an aggressive B cell non-Hodgkin lymphoma classified into three subtypes

African (Endemic)	2.9 - 4.6 per 100,000 Ugandan children (<15 years) 50-74% of childhood malignancies Foci of ↑ incidence: 21.5 per 100,000 (NW Cameroon)
Sporadic	0.15 - 0.29 per 100,000 U.S. children (<15 years) 1% of childhood malignancies 1% of adult non-Hodgkin lymphoma
HIV-associated	24-35% of HIV-associated non-Hodgkin lymphoma

Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis Arvin A, Campadelli-Fiume G, Mocarski E, et al., Cambridge University Press, 2007

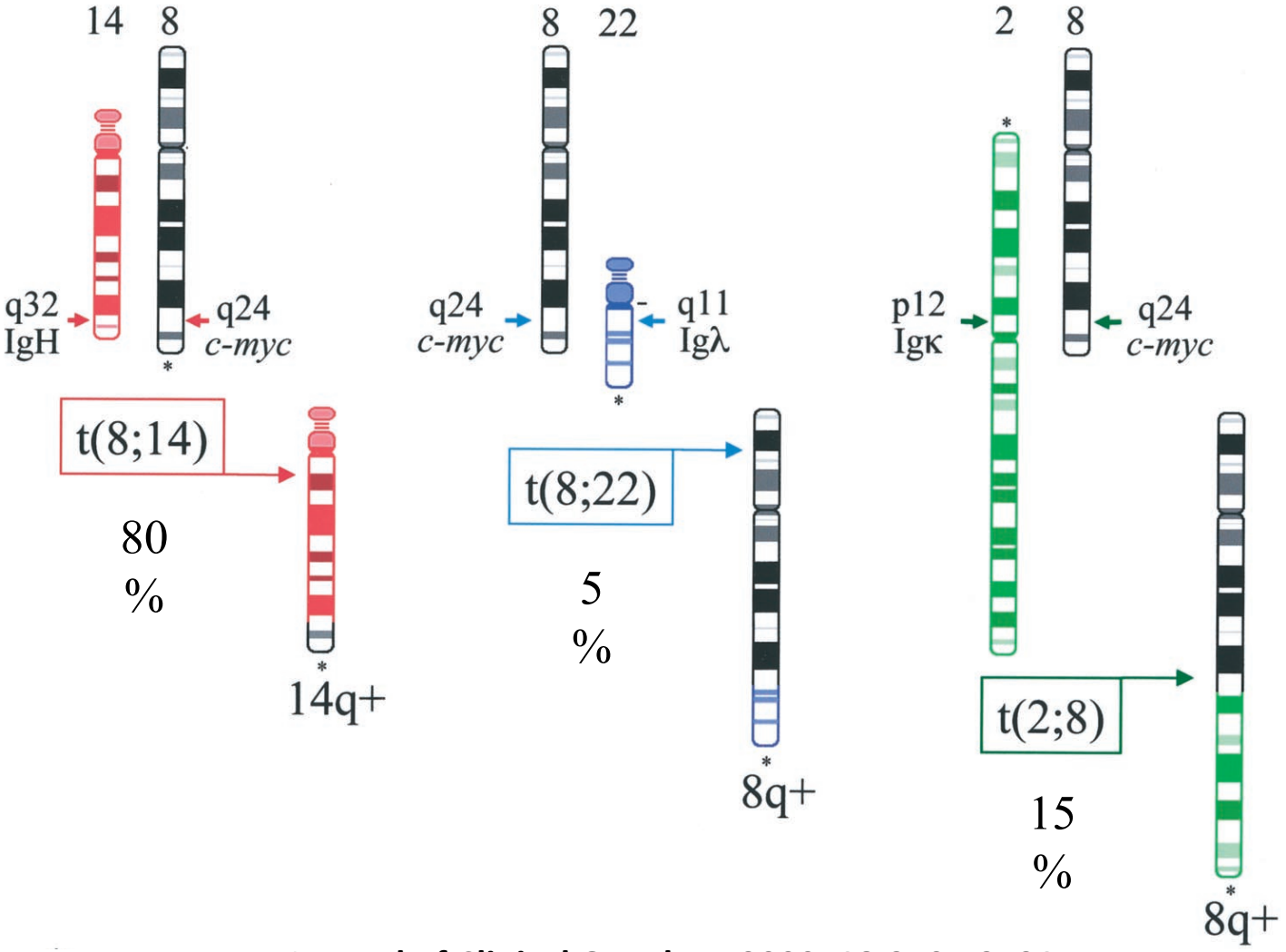
JCO 2000; 18(21):3707-3721.

B-Cell differentiation and lymphomagenesis



Lenz G, Staudt LM. N Engl J Med 2010;362:1417-1429.

c-MYC translocation into immunoglobulin loci is the molecular hallmark of BL

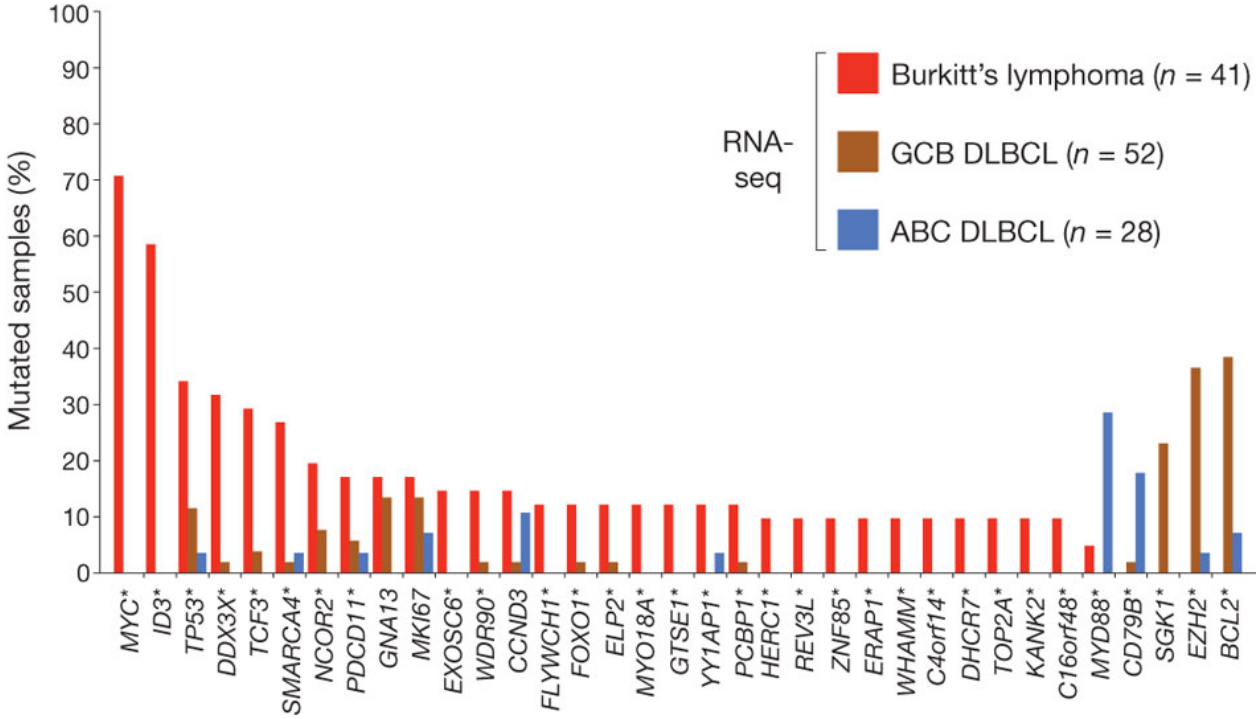


Journal of Clinical Oncology 2000; 18:3707-3721

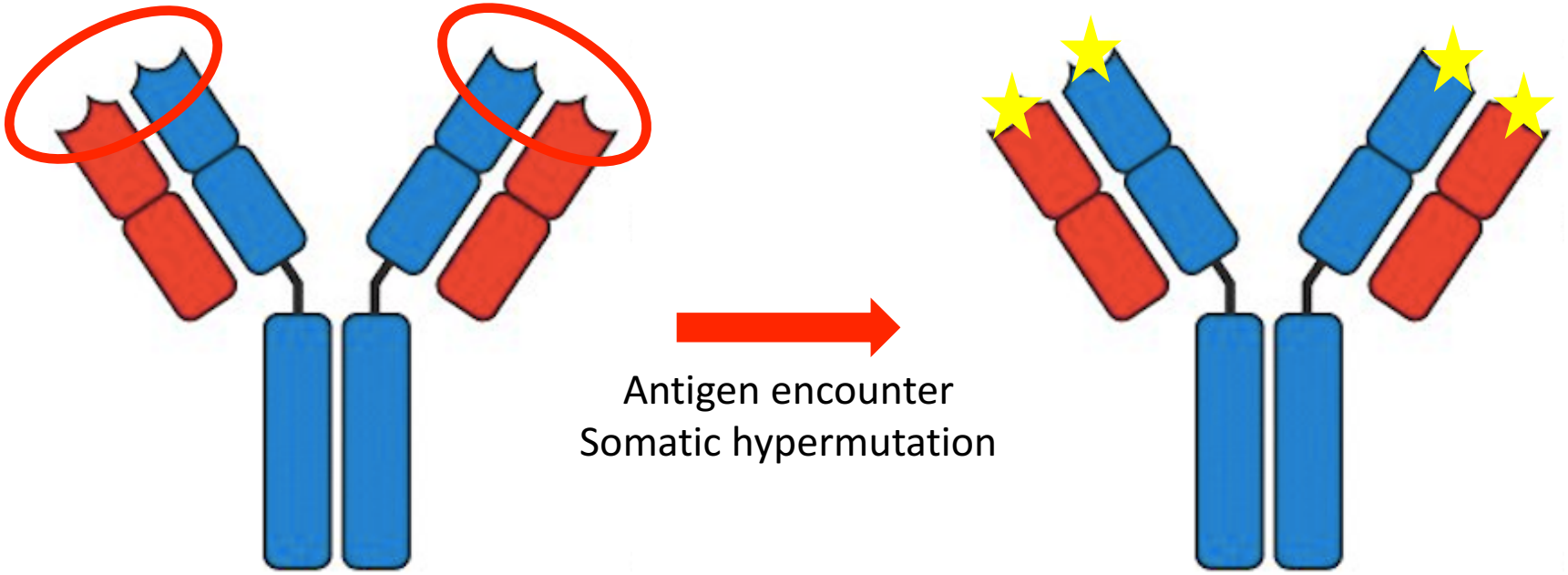
BL development requires *additional* mutations in key genes

MYC
TP53
ID3
TCF3
DDX3X
ARID1A
SMARCA4
others…

Schmitz *et al*., Nature 2012
Richter *et al*., Nat Genetics 2012
Love *et al*., Nat Genetics 2012
Giulino-Roth *et al*., Blood 2012
Abate *et al*., PLoS Pathogens 2015



BL is a malignancy of antigen-experienced B cells that carry *extensively* mutated BCRs



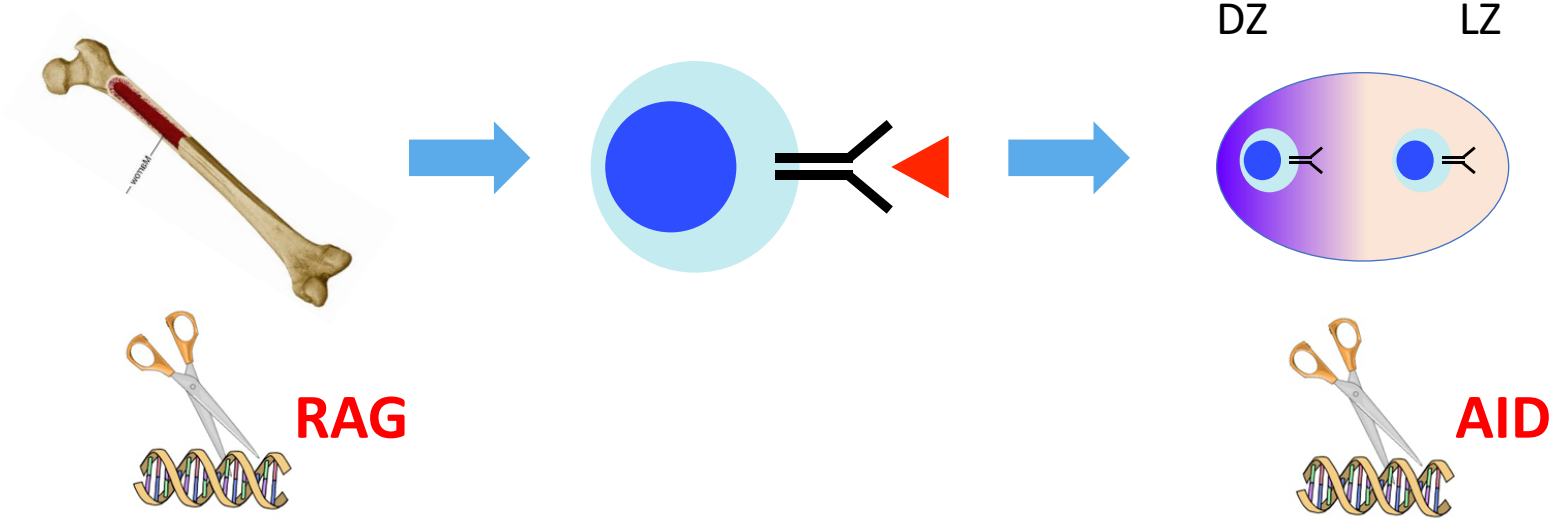
BCR: B cell antigen receptor

Normal B cell development involves cutting and splicing DNA at multiple stages

B cell development in bone marrow

Antigen encounter in periphery

Germinal center of lymph node



Immunoglobulin gene rearrangement

Somatic hypermutation; class switch recombination

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Burkitt Lymphoma

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NHL Table of Contents
Discussion

DIAGNOSIS[a,b]

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (immunohistochemistry, flow cytometry, PCR for IgH and TCR gene rearrangements, and FISH for major translocations) may be sufficient for diagnosis.
- Adequate immunophenotyping to establish diagnosis[c,d,e]
  - IHC panel: CD45, CD20, CD3, CD10, Ki-67, BLC2, BCL6, TdT with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD20, CD3, CD5, CD19, CD10, TdT
- Cytogenetics ± FISH: t(8;14) or variants; *MYC*

USEFUL UNDER CERTAIN CIRCUMSTANCES
- FISH: *BCL2*; *BCL6* rearrangements
- EBER-ISH

→

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
- Chest/abdominal/pelvic CT with contrast of diagnostic quality
- Lumbar puncture
- Flow cytometry of cerebrospinal fluid
- Unilateral or bilateral bone marrow biopsy ± aspirate
- HIV testing (if positive, see AIDS-1)
- Hepatitis B testing[f]
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- Neck CT
- Discussion of fertility issues and sperm banking
- Brain MRI
- PET-CT scan[g]

→ See Risk Assessment and Induction Therapy (BURK-2)

[a]WHO 2008 classification recognizes that it may not always be possible to distinguish between DLBCL and Burkitt lymphoma. In the setting where it is not possible to distinguish, aggressive therapy per this guideline is appropriate in selected cases. Treatment of double or triple hit tumors is controversial. Optimum regimen has not been identified.

[b]This disease is complex and curable; it is preferred that treatment occur at centers with expertise in the management of the disease.

[c]Typical immunophenotype: sIg+, CD10+, Cd20+, TdT-, Ki-67+ (≥95%), BCL2-, BCL6+, simple karyotype with *MYC* rearrangement as sole abnormality.

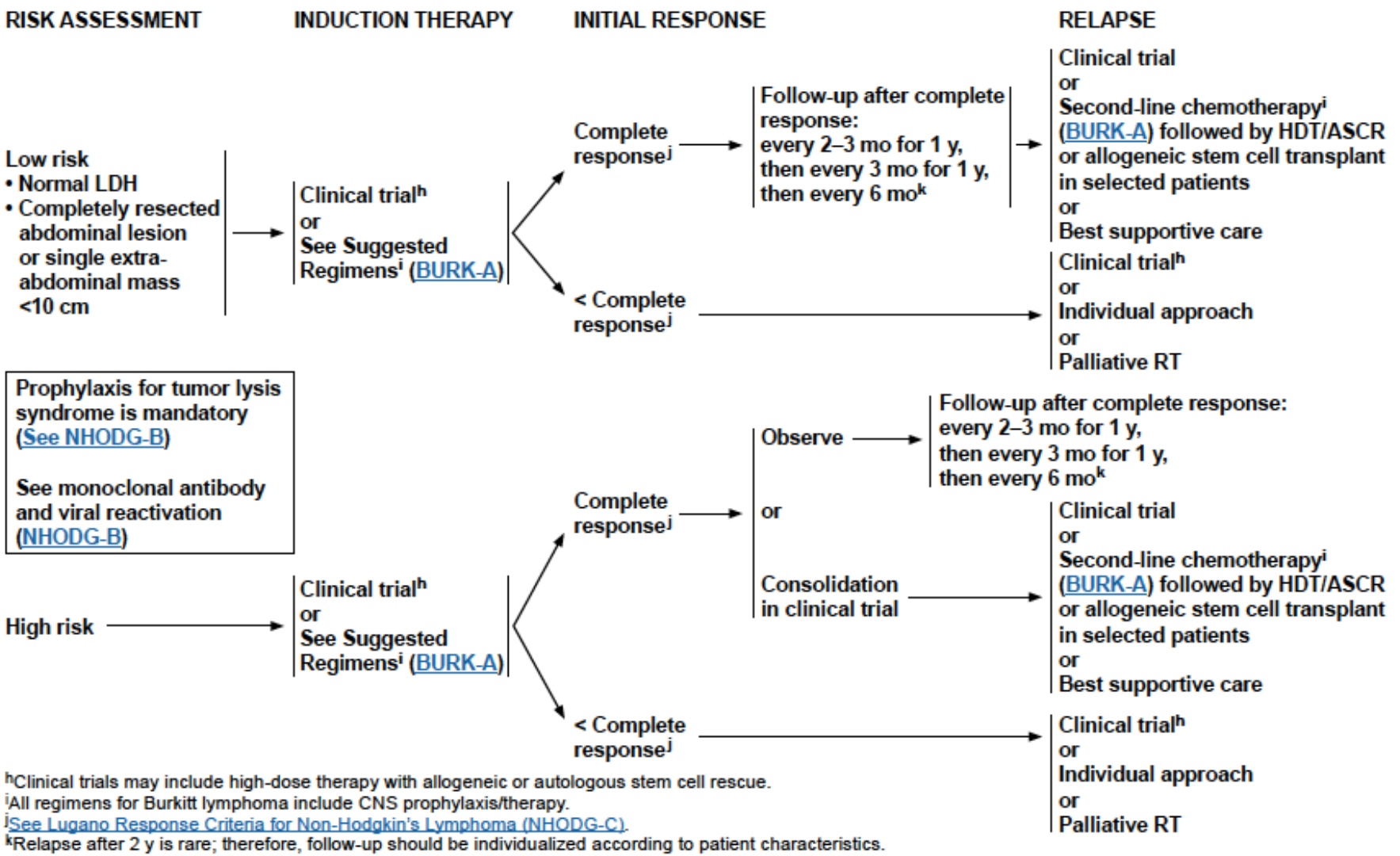
[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).

[e]If flow cytometry initially performed, IHC for selected markers (BCL2 and Ki-67) can supplement the flow results.

[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.

[g]Initiation of therapy should not be delayed in order to obtain a PET-CT scan.

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



[h]Clinical trials may include high-dose therapy with allogeneic or autologous stem cell rescue.
[i]All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.
[j]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[k]Relapse after 2 y is rare; therefore, follow-up should be individualized according to patient characteristics.

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SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

Prophylaxis for tumor lysis syndrome is mandatory (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

CHOP is not adequate therapy.

Induction Therapy

Low Risk- Combination Regimens

- CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine, and hydrocortisone]) + rituximab.
- CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) ± rituximab (3 cycles)
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

High Risk- Combination Regimens

- CALGB 10002 regimen (cyclophosphamide and prednisone followed by cycles containing either ifosfamide or cyclophosphamide; high-dose methotrexate, leucovorin, vincristine, dexamethasone, and either doxorubicin or etoposide or cytarabine; or intrathecal triple therapy [methotrexate, cytarabine, and hydrocortisone] with prophylactic CNS irradiation in select patients) + rituximab
- CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) ± rituximab
- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (for high-risk patients not able to tolerate aggressive treatments) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab (regimen includes intrathecal therapy)

Second-line Therapy (select patients with reasonable remission)

While no definitive second-line therapies exist, there are limited data for the following regimens:

- Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (minimum 3 cycles with one additional cycle beyond CR) (regimen includes intrathecal methotrexate) (Data are for patients without CNS disease.)
- RICE (rituximab, ifosfamide, carboplatin, etoposide); intrathecal methotrexate if have not received previously
- RIVAC (rituximab, ifosfamide, cytarabine, etoposide); intrathecal methotrexate if have not received previously
- RGDP (rituximab, gemcitabine, dexamethasone, cisplatin)
- High-dose cytarabine + rituximab

[a]See references for regimens BURK-A 2 of 2.
[b]All regimens for Burkitt lymphoma include CNS prophylaxis/therapy.

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

SUGGESTED TREATMENT REGIMENS
References

Low- and High-Risk Combination Regimens

CALGB 10002

Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Br J Haematol 2014;165:102-111.

CODOX-M (original or modified) (cyclophosphamide, doxorubicin, vincristine with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) with (for high-risk) or without (for low-risk) alternating IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate ± rituximab)

LaCasce A, Howard O, Lib S, et al. Modified magrath regimens for adults with Burkitt and Burkitt-like lymphoma: preserved efficacy with decreased toxicity. Leuk Lymphoma 2004;45:761-767.

Mead GM, Sydes MR, Walewski J, et al. An international evaluation of CODOX-M and CODOX-M alternating with IVAC in adult Burkitt's lymphoma: results of United Kingdom Lymphoma Group LY06 study. Ann Oncol 2002;13:1264-1274.

Barnes JA, Lacasce AS, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 2011;22:1859-1864.

Evens AM, Carson KR, Kolesar J, et al. A multicenter phase II study incorporating high-dose rituximab and liposomal doxorubicin into the CODOX-M/IVAC regimen for untreated Burkitt's lymphoma. Ann Oncol 2013;24:3076-3081.

Dose-adjusted EPOCH plus rituximab (regimen includes IT methotrexate)

Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 2013;369:1915-1925.

HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab

Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-1580.

Thomas DA, Kantarjian HM, Cortes J, et al. Long-term outcome after hyper-CVAD and rituximab chemoimmunotherapy for Burkitt (BL) or Burkitt-like (BLL) leukemia/lymphoma and mature B-cell acute lymphocytic leukemia (ALL) [abstract]. Blood 2008;112:Abstract 1929.

Second-line Therapy

RICE (rituximab, ifosfamide, carboplatin, etoposide)

Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatr Blood Cancer 2009;52:177-181.

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

Modified Hyperfractionated Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone (Hyper-CVAD) regimen for acute lymphoblastic leukemia (ALL) in adults[1]

Dose intensive phase:			
The dose intensive phase consists of 8 courses of therapy administered at 21-day intervals. The drugs used in each course alternate such that Hyper-CVAD is used for courses 1, 3, 5, and 7 while high-dose methotrexate plus cytarabine is given for courses 2, 4, 6, and 8.			
Hyper-CVAD (courses 1, 3, 5, and 7)			
Cyclophosphamide	IV	300 mg/m^2 over 2 to 3 hours every 12 hours for 6 doses	Days 1 to 3
Mesna	IV	600 mg/m^2/day administered as a continuous infusion starting with cyclophosphamide and ending 6 hours after last dose of cyclophosphamide	Days 1 to 3
Vincristine	IV	2 mg per day	Days 4 and 11
Doxorubicin	IV	if LVEF ≥50 percent: 50 mg/m^2 over 24 hours if LVEF <50 percent: 50 mg/m^2 over 48 hours[1,2]	Day 4
Dexamethasone	PO or IV	40 mg per day	Days 1 to 4 and days 11 to 14
High dose methotrexate plus cytarabine (courses 2, 4, 6, and 8)			
Methotrexate	IV	200 mg/m^2 administered over first 2 hours then 800 mg/m^2 administered over 24 hours (total dose per cycle of 1 gram/m^2)	Day 1
Leucovorin	IV	50 mg IV 12 hours after end of methotrexate; then 15 mg IV every 6 hours for 8 doses or until methotrexate level ≤0.1 micromol/L. Dose modifications made based upon methotrexate levels.	Day 2
Cytarabine	IV	for patients <60 years old: 3 g/m^2 administered over 2 hours every 12 hours for 4 doses for patients ≥60 years old: 1 g/m^2 administered over 2 hours every 12 hours for 4 doses	Days 2 and 3
Methylprednisolone	IV	50 mg twice daily	Days 1 to 3

Rituximab for CD20+ ALL (courses 1, 2, 3, 4)			
Rituximab	IV	Give only if ≥20 percent of lymphoblasts are CD20 positive: 375 mg/m^2	Days 1 and 11 of Hyper-CVAD and Days 1 and 8 of high dose methotrexate plus cytarabine
CNS prophylaxis: total number of intrathecal treatments varies based upon risk factors*			
Methotrexate	IT	12 mg (6 mg if through Ommaya)[3,4]	Day 2 of each cycle
Cytarabine	IT	100 mg	Day 8 of each cycle

Maintenance phase:

Therapy after the intensive phase varies depending upon ALL subtype:			
• Patients with Burkitt leukemia (mature B-cell ALL) are not given maintenance			
• Patients with Philadelphia chromosome positive ALL undergo allogeneic hematopoietic cell transplantation if they are candidates for this procedure and have a donor			
• All other patients receive maintenance chemotherapy with POMP intensification plus intensification cycles of Hyper-CVAD and methotrexate plus L-asparaginase			
Maintenance POMP: administered months 1 through 5, 8 through 17, 20 through 30			
Mercaptopurine	PO	50 mg three times a day on an empty stomach	Days 1 to 28
Methotrexate	PO	20 mg/m^2	Days 1, 8, 15, and 22
Vincristine	IV	2 mg	Day 1
Prednisone	PO	200 mg per day	Days 1 to 5
Intensification Hyper-CVAD: administered months 6 and 18, plus rituximab on days 1 and 11 if CD20+			
Intensification methotrexate and L-asparaginase: administered months 7 and 19			
Methotrexate	IV	100 mg/m^2	Day 1 weekly x 4
L-asparaginase	IV	20,000 units	Day 2 weekly x 4

Details on dose modification, prophylactic antibiotics, growth factor support, and mediastinal irradiation can be found in the original articles. In addition, it is now standard practice to include a tyrosine kinase inhibitor for patients with Philadelphia chromosome positive ALL.

LVEF: left ventricular ejection fraction.

* Patients were given central nervous system (CNS) prophylaxis based upon risk factors as follows: Patients with a lactate dehydrogenase level >600 u/liter or with a proliferative index of 14 percent or above were considered "High risk" and received 8 intrathecal (IT) treatments. Patients with neither of these features were considered "Low risk" and received 6 IT treatments. Patients with unknown risk received 8 IT treatments[1]. Patients with cranial neuropathies or CNS involvement are given whole brain radiation therapy (24 to 30 Gy) at the time of diagnosis and receive even more frequent IT

therapy.

References:

1. *Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol 2010; 28:3880.*
2. *Thomas DA, O'Brien S, Cortes J, et al. Outcome with the hyper-CVAD regimens in lymphoblastic lymphoma. Blood 2004; 104:1624.*
3. *Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000; 18:547.*
4. *Kantarjian HM, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004; 101:2788.*

Graphic 50617 Version 5.0

bjh research paper

Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002

David A. Rizzieri,[1] Jeffrey L. Johnson,[2] John C. Byrd,[3] Gerard Lozanski,[4] Kristie A. Blum,[3] Bayard L. Powell,[5] Thomas C. Shea,[6] Sreenivasa Nattam,[7] Eva Hoke,[2] Bruce D. Cheson[8] and Richard A. Larson[9] for the Alliance for Clinical Trials In Oncology (ACTION)

Summary

To improve long-term outcomes for Burkitt leukaemia/lymphoma (BL) or aggressive lymphomas in adults, we assessed the benefit of adding rituximab and filgrastim support to a dose-dense modified chemotherapy regimen from the Cancer and Leukemia Group B (CALGB) 9251 trial. One hundred and five patients (aged 19–79 years) were enrolled; 27% were

Table I. CALGB 10 002 treatment schema.

Cycle 1	Dose-Schedule based on actual weight	Days given
Cyclophosphamide	200 mg/m^2/d	1–5
Prednisone	60 mg/m^2/d oral	1–7
Allopurinol	300 mg/d oral	1–14
Cycles 2, 4, and 6		**Cycle length 21 d**
Ifosfamide	800 mg/m^2/d over 1 h with Mesna	1–5
Dexamethasone	10 mg/m^2/d	1–5
Methotrexate§	150 mg/m^2 load, then 1·35 g/m^2 over 23·5 h	1
Leucovorin*	25 mg/m^2 36 h after initiation of methotrexate, then 10 mg/m^2 every 6 h until level <0·05 μmol/l	2
Vincristine	2 mg push	1
Cytarabine	1000 mg/m^2/d over 2 h	4–5
Etoposide	80 mg/m^2/d over 1 h	4–5
Filgrastim	5 μg/kg/d	Seven, until ANC > 0·5 × 10^9/l
Rituximab	†	Eight, 10 and 12 of cycle 2 only
Rituximab	†	Eight of cycle 4 and 6
Intrathecal therapy	‡	1
Cycles 3, 5 and 7		**Cycle length 21 d**
Cyclophosphamide	200 mg/m^2/d	1–5
Dexamethasone*	10 mg/m^2/d	1–5
Methotrexate§	150 mg/m^2 load, then 1·35 g/m^2 over 23·5 h	1
Leucovorin†	50 mg/m^2 36 h after initiation of methotrexate, then 10 mg/m^2 every 6 h until level <0·05 μmol/l	2
Vincristine	2 mg push	1
Doxorubicin	25 mg/m^2/d	4–5
Filgrastim	5 μg/kg/d	7, until ANC> 0·5 × 10^9/l
Rituximab	†	8
Intrathecal therapy	‡	1

CALGB, Cancer and Leukemia Group B; ANC, absolute neutrophil count.

*Intravenous or oral.

†Rituximab administered in cycle 2 at a dose of 50 mg/m^2 on day 8 and 375 mg/m^2/d on days 10 and 12. For cycles 3–7, rituximab was given at 375 mg/m^2 only on day 8 of each cycle.

‡Intrathecal therapy Methotrexate 15 mg, Cytarabine 40 mg, Hydrocortisone 50 mg; Patients with central nervous system disease received additional intrathecal therapy twice weekly until clear of malignant cells, then once weekly for 4 weeks, then radiotherapy was initiated.

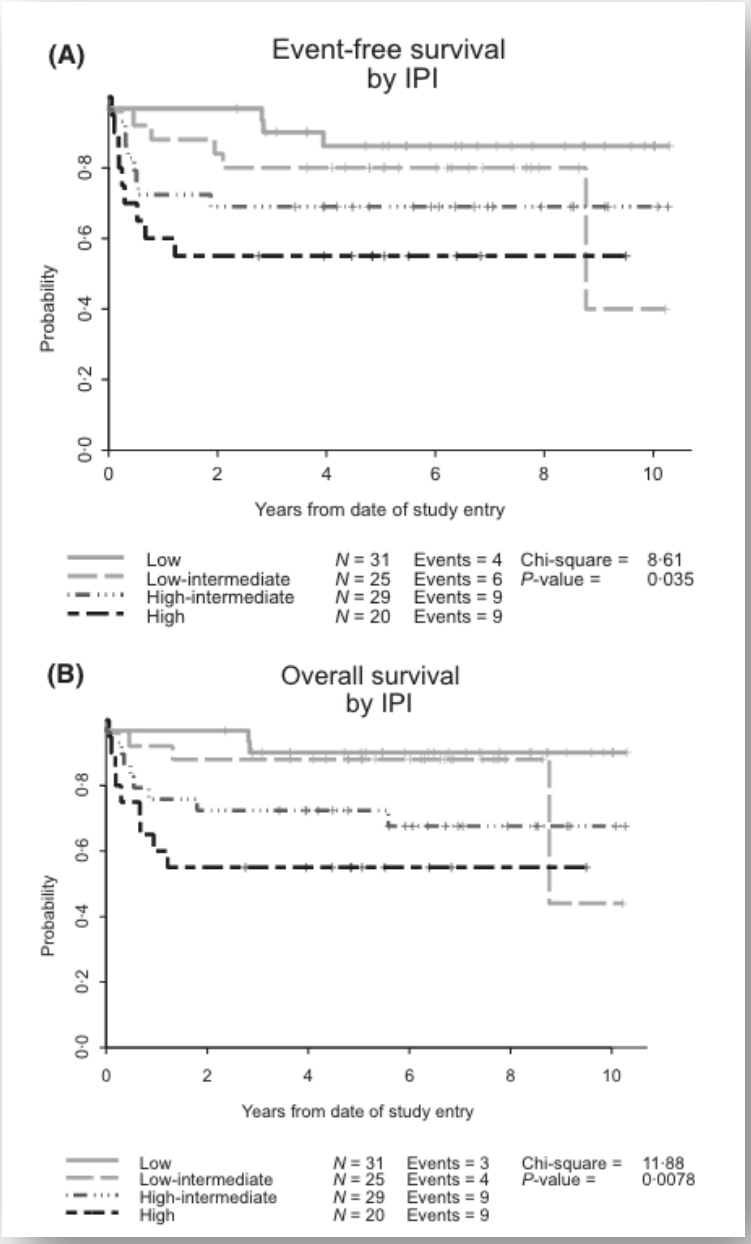
§Methotrexate dose held for creatinine clearance <50 ml/min.

Table IV. Response evaluation by age group and for all patients on CALGB studies 10 002 and 9251; and by IPI category.

	<60 years	≥60 years	CALGB 10 002	CALGB 9251
Patients (*n*)	77	28	105	133
Complete response (95% CI)	86% (76, 93)	75% (55, 89)	83% (74, 90)	69% (61, 77)
Current status of all patients				
Continuous remission	62 (80%)	15 (54%)	77 (73%)	58 (44%)
Treatment-related death	2 (3%)	5 (18%)	7 (7%)	15 (11%)
Died from progressive disease	9 (12%)	7 (25%)	16 (15%)	54 (41%)
Died from another cause	4 (5%)	1 (3%)	5 (5%)	6 (5%)
2-year probability EFS (95% CI)	0·87 (0·77, 0·93)	0·54 (0·34, 0·70)	0·78 (0·69, 0·85)	0·49 (0·40, 0·57)
4-year probability EFS (95% CI)	0·82 (0·71, 0·89)	0·54 (0·34, 0·70)	0·74 (0·65, 0·81)	0·46 (0·38, 0·55)
2-year probability OS (95% CI)	0·87 (0·77, 0·93)	0·61 (0·40, 0·76)	0·80 (0·71, 0·86)	0·57 (0·48, 0·65)
4-year probability OS (95% CI)	0·84 (0·74, 0·91)	0·61 (0·40, 0·76)	0·78 (0·69, 0·85)	0·52 (0·43, 0·60)
Hazard Ratio		3·0 (1·4, 6·3)		

	CALGB 10 002		CALGB 9251	
IPI Category	4-year probability EFS (95% CI)	4-year probability OS (95% CI)	4-year probability EFS (95% CI)	4-year probability OS (95% CI)
Low	0·86 (0·67, 0·95)	0·90 (0·72, 0·97)	0·67 (0·38, 0·85)	0·73 (0·44, 0·89)
Low-intermediate	0·80 (0·58, 0·91)	0·88 (0·67, 0·96)	0·56 (0·41, 0·69)	0·65 (0·49, 0·77)
High-intermediate	0·69 (0·49, 0·82)	0·72 (0·52, 0·85)	0·36 (0·22, 0·50)	0·39 (0·24, 0·52)
High IPI	0·55 (0·31, 0·73)	0·55 (0·31, 0·73)	0·35 (0·19, 0·53)	0·39 (0·22, 0·57)

CALGB, Cancer and Leukemia Group B; IPI, International Prognostic Index; EFS, event-free survival; OS, overall survival; 95% CI, 95% confidence interval.



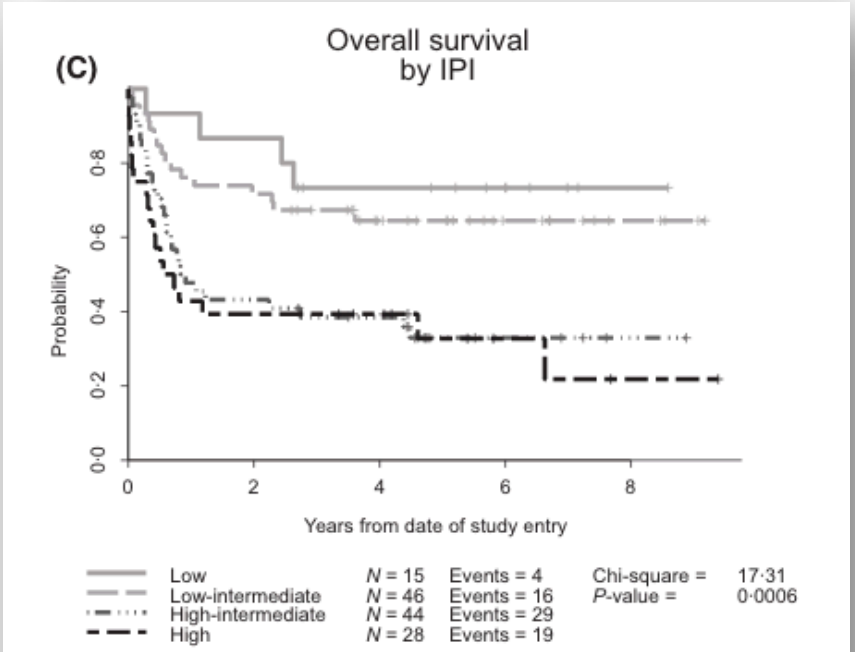


Fig 1. Event-free (A) and overall survival (B) for all patients stratified by IPI criteria in CALGB 10 002 and overall survival for all patients stratified by IPI criteria in CALGB 9251 (C). Though developed for diffuse large B-cell lymphoma, the IPI was found to predict outcomes for our patients with BL as well. The addition of rituximab appears to improve outcomes compared to the prior regimen (CALGB 9251) without. CALGB, Cancer and Leukemia Group B; IPI, International Prognostic Index.

Chemoimmunotherapy with Hyper-CVAD plus Rituximab for the Treatment of Adult Burkitt and Burkitt-Type Lymphoma or Acute Lymphoblastic Leukemia

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BACKGROUND. Adult Burkitt-type lymphoma (BL) and acute lymphoblastic leukemia (B-ALL) are rare entities composing 1% to 5% of non-Hodgkin lymphomas NHL) or ALL. Prognosis of BL and B-ALL has been poor with conventional NHL or ALL regimens, but has improved with dose-intensive regimens.

METHODS. To evaluate the addition of rituximab, a CD20 monoclonal antibody, to intensive chemotherapy in adults with BL or B-ALL, 31 patients with newly diagnosed BL or B-ALL received the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen with rituximab. Their median age was 46 years; 29% were 60 years or older. Rituximab 375 mg/m^2 was given on Days 1 and 11 of hyper-CVAD courses and on Days 1 and 8 of methotrexate and cytarabine courses.

RESULTS. Complete remission (complete response [CR]) was achieved in 24 of 28 (86%) evaluable patients; 3 had a partial response, and 1 had resistant disease. There were no induction deaths. The 3-year overall survival (OS), event-free survival, and disease-free survival rates were 89%, 80%, and 88%, respectively. Nine elderly patients achieved CR with all of them in continuous CR (except 1 death in CR from infection), with a 3-year OS rate of 89%. Multivariate analysis of current and historical (those treated with hyper-CVAD alone) groups identified age and treatment with rituximab as favorable factors.

CONCLUSIONS. The addition of rituximab to hyper-CVAD may improve outcome in adult BL or B-ALL, particularly in elderly patients. ***Cancer* 2006;106:1569–80.**

KEYWORDS: adult Burkitt lymphoma, BL, acute lymphoblastic leukemia, B-ALL, chemoimmunotherapy, hyper-CVAD, rituximab.

TABLE 1
Short-Term Dose-Intensive Regimens in Adult BL and B-ALL

Study	Therapy	No. Pts	Age		% CR	% CR (X yrs)	% Survival (X yrs)
			Median	% ≥ 60 y			
Hoelzer[16]	B-NHL83	24	33	0	63	50 (8)	49 (8)
	B-NHL86	35	36	≍ 10	74	71 (4)	51 (4)
Hoelzer[23]	B-NHL90	45	NR	All > 55	71	NR	39 (6)
Magrath[10]	89-C-41 (CODOX-M/IVAC)	20	25	0	89	89 (2)	74 (4)
Soussain[18]	LMB 81, 84, 86, 89	65	26	≍ 2	89	NR	72 (3)
		22	NR	0	77	NR	57 (3)
Mead[21]	CODOX-M/IMVAC	52	35	NR*	75	NR	73 (2)
Rizzieri[20]	CALGB 9251						
	Cohort 1	52	44	19	79	66 (3)	54 (3)
	Cohort 2	40	50	23	68	67 (3)	50 (3)
Di Nicola[22]	CMVP-16/Ara-C/CDDP	22	36	NR†	77	68 (2)	77 (2)
Thomas[17]	Hyper-CVAD	26	58	46	81	61 (3)	49 (3)
	Age < 60	14	38	—	93	83 (3)	77 (3)
	≥ 60	12	NR	—	—	—	17 (3)
Current	Hyper-CVAD	48	48	33	85	60 (3)	53 (3)
	Hyper-CVAD + rituximab	31	46	29	86	88 (3)	89 (3)

BL: Burkitt lymphoma; B-ALL: Burkitt-type acute lymphoblastic leukemia; CR: complete remission; X yrs: year reported; NR: not reported; CODOX-M/IMVAC: cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine; CDDP: cisplatin; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine.

* None older than 60 years.

† 31% aged ≥ 50.

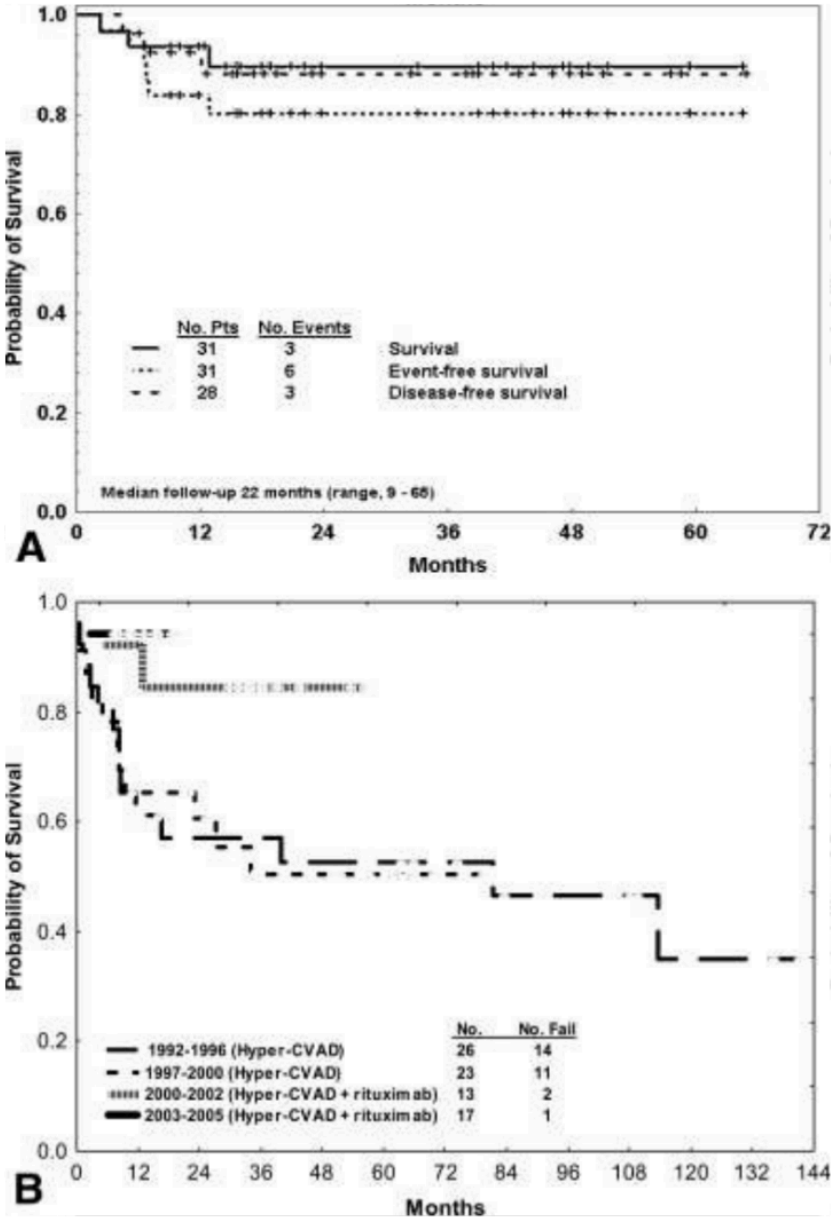
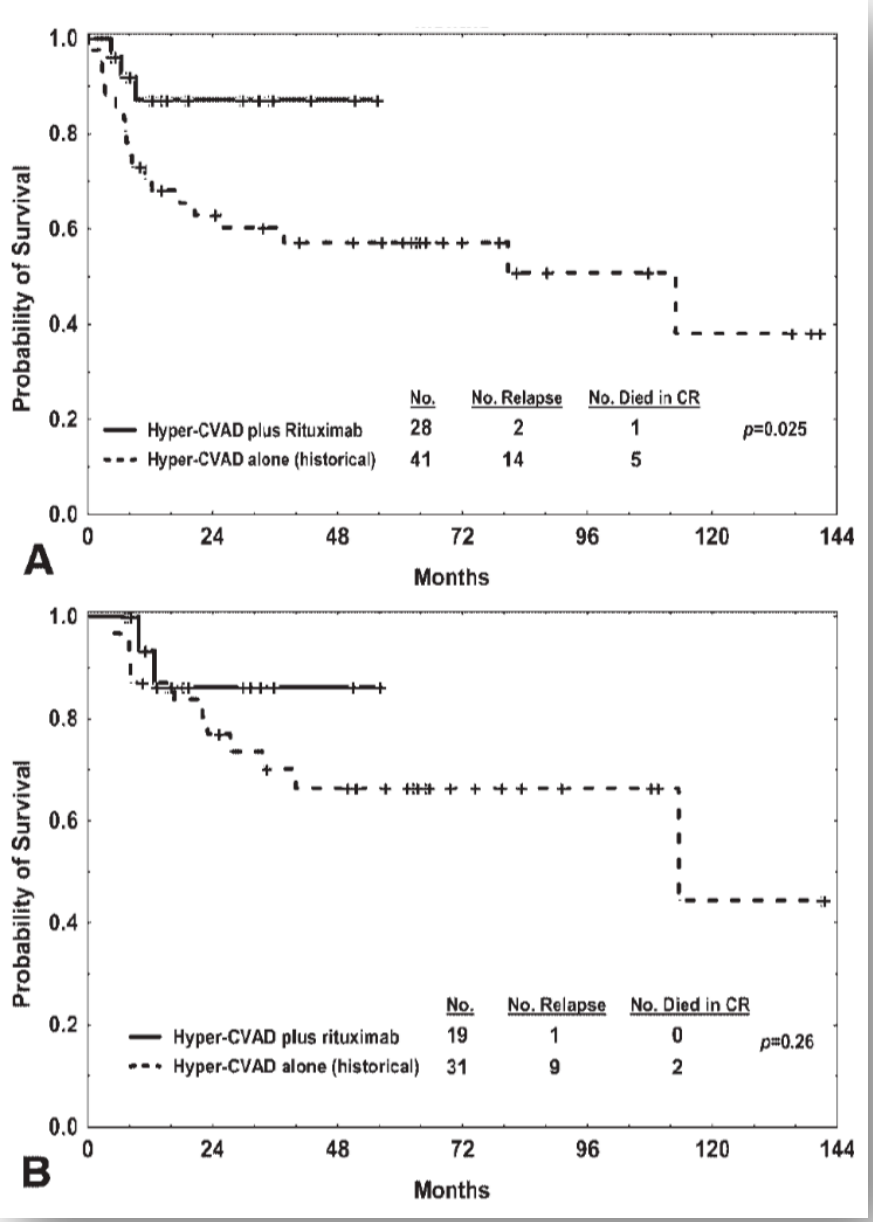


FIGURE 1. (A) Overall, event-free and disease-free survival (DFS) in BL or B-ALL after hyper-CVAD plus rituximab; (B) Survival by time period for BL or B-ALL after treatment with hyper-CVAD and rituximab or hyper-CVAD.



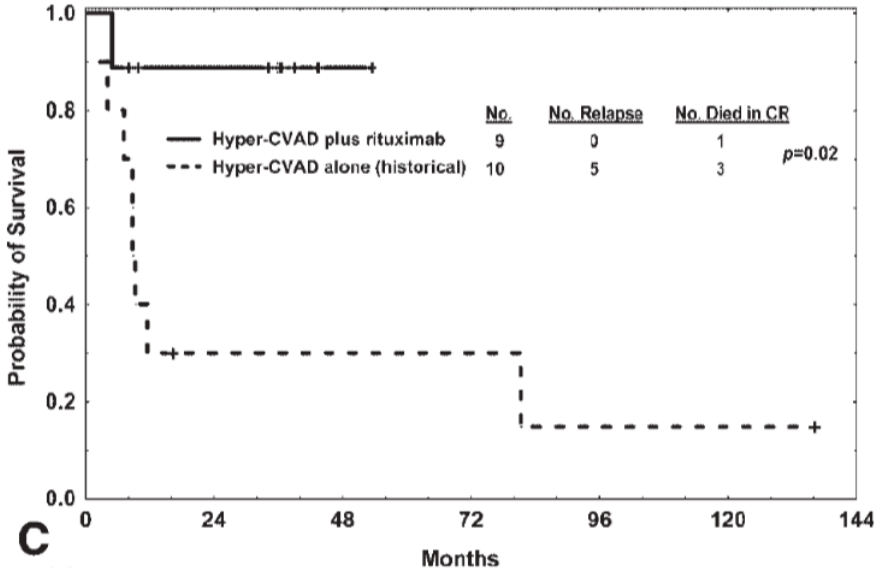


FIGURE 3. Disease-free survival (DFS) with hyper-CVAD plus rituximab compared with hyper-CVAD, (A) overall, (B) age $<$ 60 years, (C) age $\geq$ 60 years.

A multicenter phase II study incorporating high-dose rituximab and liposomal doxorubicin into the CODOX-M/IVAC regimen for untreated Burkitt's lymphoma

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Background: Despite improvement with intensive multi-agent chemotherapy, 2-year progression-free survival (PFS) rates for adults with high-risk Burkitt's lymphoma (BL) remains <55%.

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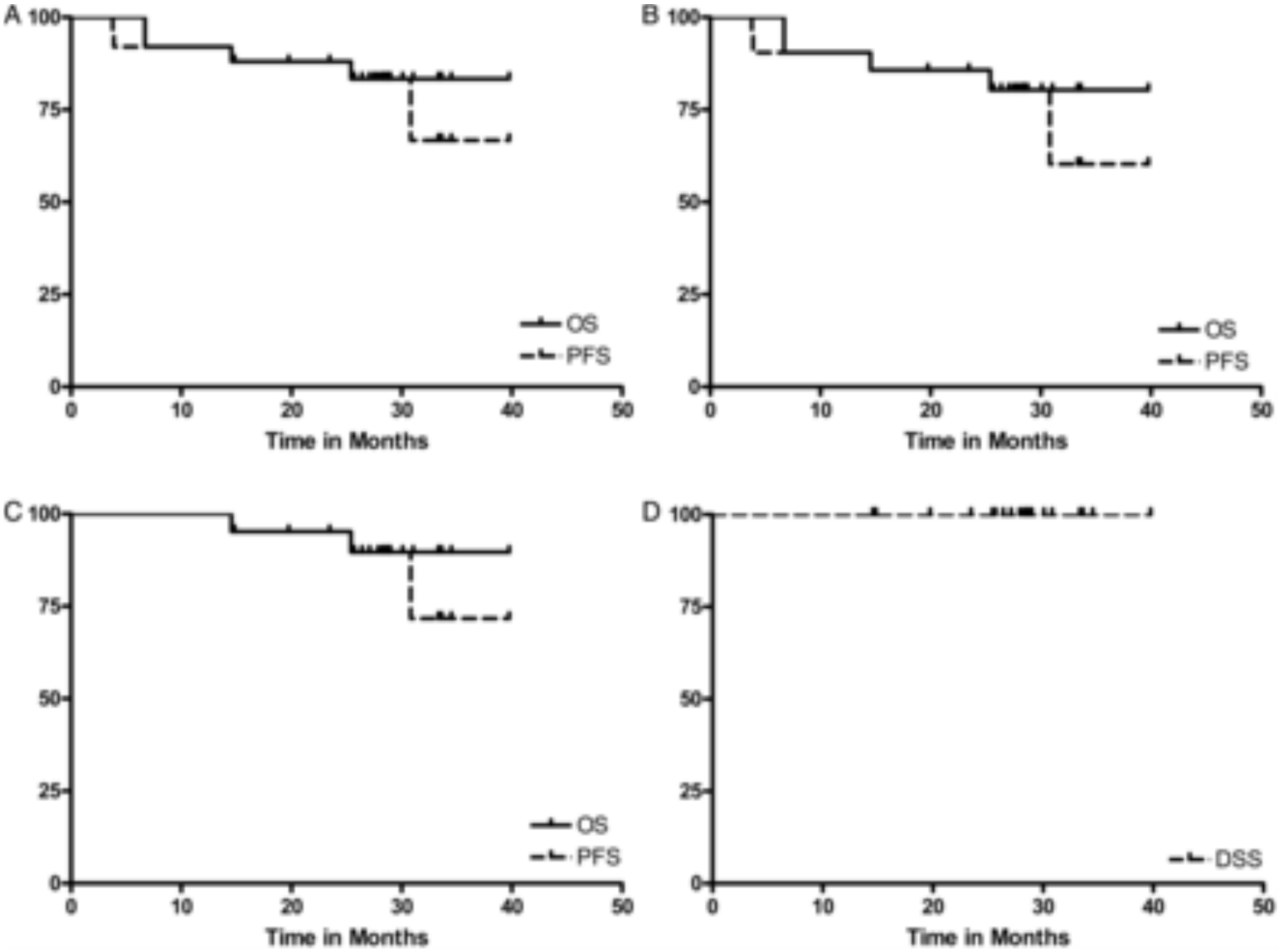
Table 3.

Serum and CSF rituximab levels for patients with and without early progression

Chemotherapy cycle and hours after rituximab infusion	Mean serum rituximab level (μg/ml) for patients w/o relapse	Serum rituximab levels (μg/ml) for two patients with early progression		Mean CSF rituximab level (μg/ml) for patients w/o relapse	CSF rituximab levels (μg/ml) for two patients with early progression	
		Pt #1	Pt #2		Pt #1	Pt #2
C1/24 h	258*	171	91	0.104	0.27	0.23
C1/72 h	139*	60	29	0.253	0.22	0.12
C3/24 h	306*	162	224	0.246	0.27	N/A
C3/72 h	219	149	135	0.196	0.38	0.50

Abbreviations: CSF, cerebrospinal fluid; Pt, patient; C, cycle; w/o, without; N/A, not available.

*$P < 0.005$ when compared with the mean serum levels of the two patients with early progression.



From: A multicenter phase II study incorporating high-dose rituximab and liposomal doxorubicin into the CODOX-M/IVAC regimen for untreated Burkitt's lymphoma

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Published online 21 February 2011

Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis

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Received 26 August 2010; revised 19 October 2010; accepted 21 October 2010

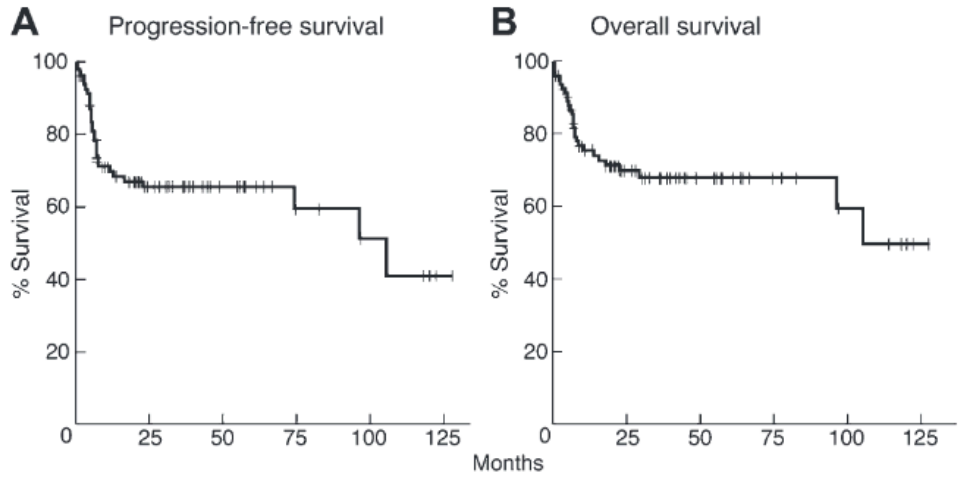


Figure 1. (A) Progression-free survival and (B) overall survival for the entire cohort.

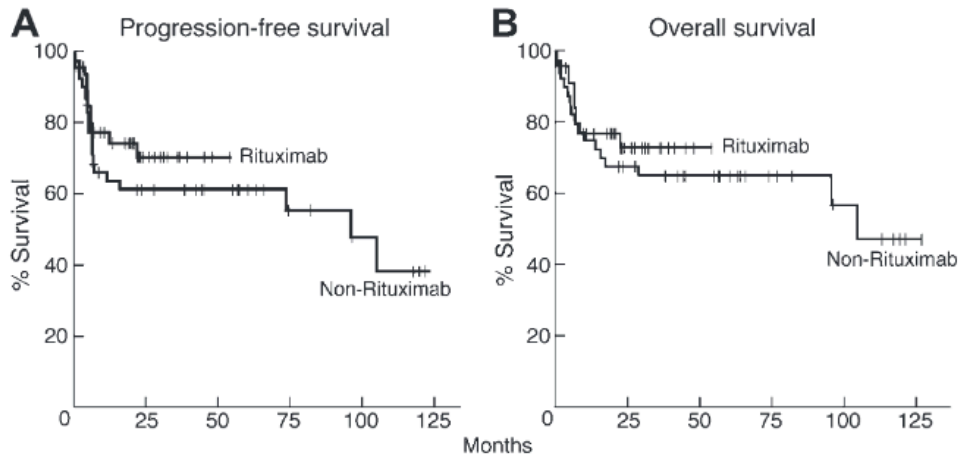


Figure 2. Progression-free survival (PFS) and overall survival (OS) by inclusion of rituximab. No statistical difference is observed in (A) PFS ($P = 0.44$ by log-rank, $P = 0.53$ by Wilcoxon) or (B) OS ($P = 0.61$ by log-rank, $P = 0.76$ by Wilcoxon).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Low-Intensity Therapy in Adults with Burkitt's Lymphoma

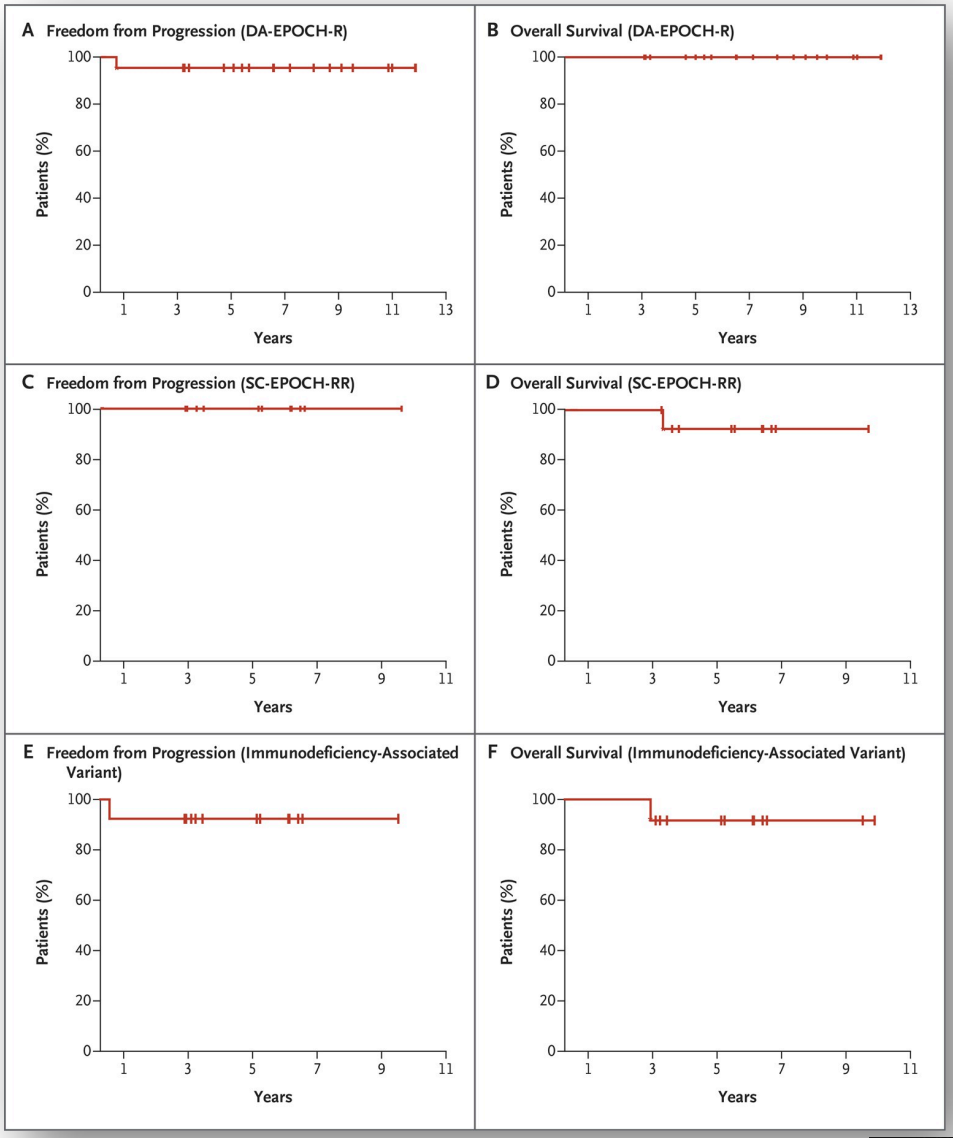
Kieron Dunleavy, M.D., Stefania Pittaluga, M.D., Ph.D., Margaret Shovlin, R.N., Seth M. Steinberg, Ph.D., Diane Cole, M.S., Cliona Grant, M.D., Brigitte Widemann, M.D., Louis M. Staudt, M.D., Ph.D., Elaine S. Jaffe, M.D., Richard F. Little, M.D., and Wyndham H. Wilson, M.D., Ph.D.

ABSTRACT

BACKGROUND

Burkitt's lymphoma is an aggressive B-cell lymphoma that occurs in children and adults and is largely curable with the use of intensive and toxic chemotherapy. Current treatments are less effective and have more severe side effects in adults and patients with immunodeficiency than in children.

Kaplan–Meier Estimates of Freedom from Disease Progression and Overall Survival



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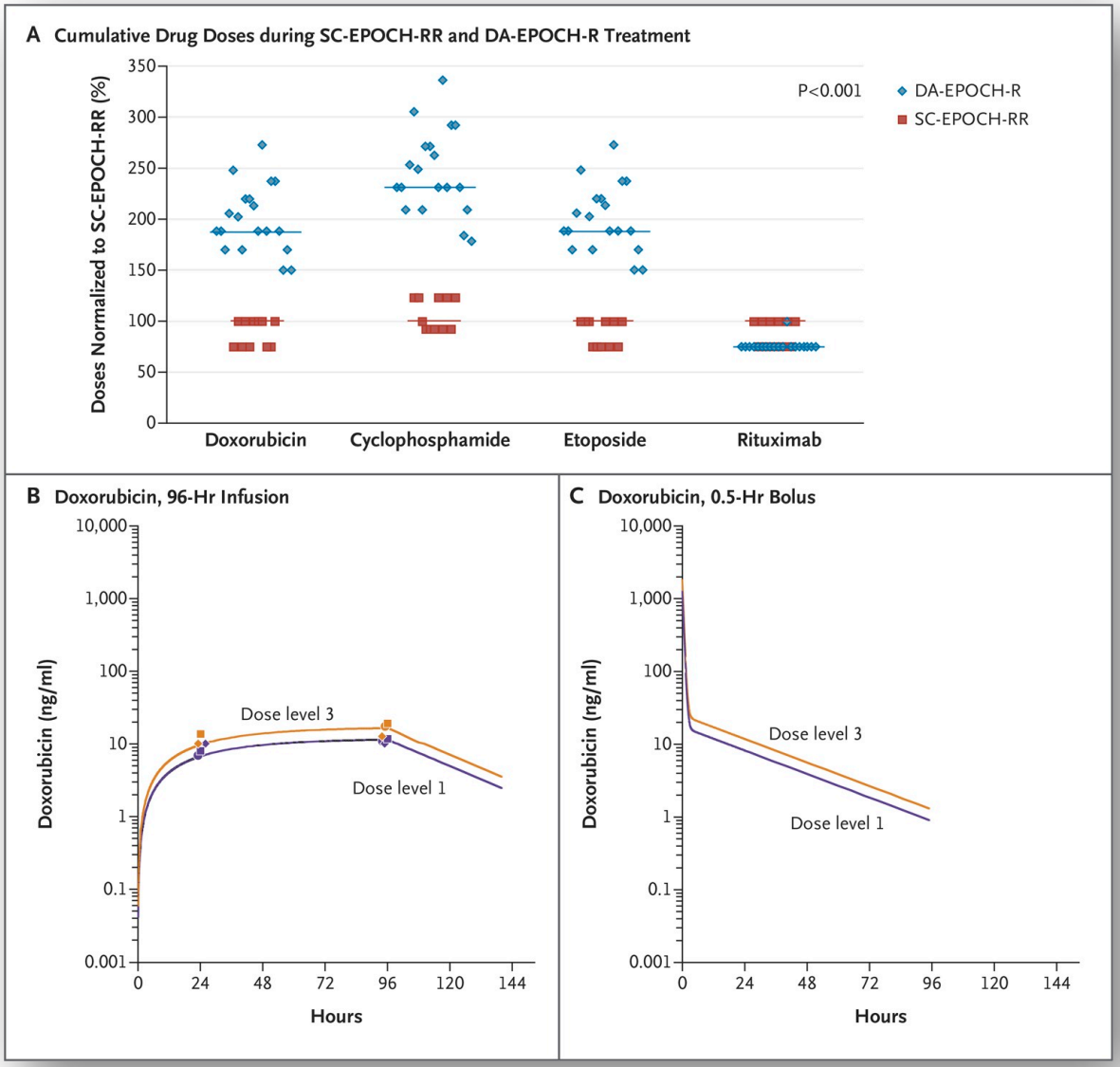
Cumulative Drug Doses and Infusional and Bolus Administrations of Doxorubicin



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Characteristics of the Patients

Table 1. Characteristics of the Patients.*

Characteristic	All Patients (N=30)	DA-EPOCH-R (N=19)	SC-EPOCH-RR (N=11)	P Value
Male sex — no. (%)	22 (73)	13 (68)	9 (82)	0.67
Age — yr				0.03
Median	33	25	44	
Range	15–88	15–88	24–60	
Age ≥40 yr — no. (%)	12 (40)	5 (26)	7 (64)	0.06
Ann Arbor stage III or IV — no. (%)	20 (67)	11 (58)	9 (82)	0.25
ECOG performance-status score ≥2 — no. (%)†	9 (30)	3 (16)	6 (55)	0.04
Serum lactate dehydrogenase >ULN — no. (%)	16 (53)	7 (37)	9 (82)	0.03
Extranodal site — no. (%)‡	19 (63)	10 (53)	9 (82)	0.14
Bowel	15 (50)	9 (47)	6 (55)	1.00
Bone marrow or blood	4 (13)	3 (16)	1 (9)	1.00
Central nervous system	1 (3)	1 (5)	0	1.00
LMB risk group — no. (%)§				
A	5 (17)	5 (26)	0	0.16
B	22 (73)	12 (63)	10 (91)	
C	3 (10)	2 (10)	1 (9)	
Burkitt's lymphoma variant — no. (%)				<0.001
Sporadic	17 (57)	17 (89)	0	
Immunodeficiency-associated¶	13 (43)	2 (11)	11 (100)	
Secondary	11 (37)	0	11 (100)	
Primary	2 (7)	2 (11)	0	
Molecular marker — no./total no. (%)				
MYC rearrangement	22/22 (100)	14/14 (100)	8/8 (100)	1.00
BCL6 protein expression	24/24 (100)	15/15 (100)	9/9 (100)	1.00
BCL2 protein expression	0/26	0/16	0/10	1.00
EBER in situ hybridization	6/21 (29)	4/14 (29)	2/7 (29)	1.00

* DA-EPOCH-R denotes dose-adjusted infusional therapy with etoposide, doxorubicin, vincristine, cyclophosphamide, prednisone, and rituximab; EBER Epstein–Barr virus–encoded RNA; SC-EPOCH-RR short-course infusional therapy with etoposide, doxorubicin, and vincristine with cyclophosphamide, prednisone, and a double dose of rituximab; and ULN upper limit of the normal range.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and full activity and higher scores indicating increasing levels of disability.

‡ Patients may have had more than one extranodal site. In the SC-EPOCH-RR group, three patients had a site not listed in the table (liver, kidney, or other site).

§ Lymphomes malins B (LMB) risk groups are defined as follows: group A includes patients with low-risk disease (resected stage I or abdominal stage II cancer), group B includes those with intermediate-risk disease (patients not in group A or C), and group C includes those with high-risk disease (central nervous system involvement, at least 25% blasts in bone marrow, or both characteristics).[13]

¶ Patients with the immunodeficiency-associated variant may have had HIV infection, the autoimmune lymphoproliferative syndrome, or a deficiency of dedicator of cytokinesis 8.

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Adverse Events

Table 2. Adverse Events.*

Event	All Cycles (N=155)	DA-EPOCH-R Cycles (N=116)	SC-EPOCH-RR Cycles (N=39)	P Value
Tumor lysis syndrome — no. of cycles (%)	1 (1)	0	1 (3)	NA
Absolute neutropenia — no. of cycles (%)				
Nadir <500 cells/mm³	72 (46)	60 (52)	12 (31)	0.03
Nadir <100 cells/mm³	26 (17)	20 (17)	6 (15)	1.00
Thrombocytopenia — no. of cycles (%)				
Nadir <50,000 platelets/mm³	12 (8)	7 (6)	5 (13)	0.18
Nadir <25,000 platelets/mm³	3 (2)	2 (2)	1 (3)	1.00
Fever and neutropenia necessitating hospital admission				
Any patient — no. of cycles (%)	30 (19)	26 (22)	4 (10)	0.11
Patients ≥40 yr of age — no. of cycles/total no. (%)	4/54 (7)	2/30 (7)	2/24 (8)	1.00
Gastrointestinal event — no. of cycles (%)†				
Mucositis	8 (5)	7 (6)	1 (9)	0.68
Constipation	2 (1)	0	2 (5)	0.06
Ileus	2 (1)	2 (2)	0	1.00
Neurologic event — no. of patients/total no. (%)‡				
Sensory impairment	5/30 (17)	4/19 (21)	1/11 (9)	0.63
Motor impairment	2/30 (7)	2/19 (11)	0/11	0.52

* NA denotes not applicable.
† All the gastrointestinal events were grade 3.
‡ All the sensory-impairment events were grade 3, and all the motor-impairment events were grade 2.

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A Study of Rituximab and Ifosfamide, Carboplatin, and Etoposide Chemotherapy in Children with Recurrent/Refractory B-cell (CD20+) Non-Hodgkin Lymphoma and Mature B-Cell Acute Lymphoblastic Leukemia: A Report from the Children's Oncology Group

Timothy C. Griffin, MD[1], **Sheila Weitzman, MD**[2], **Howard Weinstein, MD**[3], **Myron Chang, PhD**[4], **Mitchell Cairo, MD**[5], **Robert Hutchison, MD**[6], **Bruce Shiramizu, MD**[7], **Joseph Wiley, MD**[8], **Deborah Woods**[9], **Margaret Barnich**[10], and **Thomas G. Gross, MD, PhD**[11]

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Table III

Reported Toxicities

Targeted Toxicities	Grade 3	Grade 4	All Grades
Neutrophils	1	3	36
Platelets	1	4	37
Allergy/Hypersensitivity	5	0	5
Rash	1	0	1

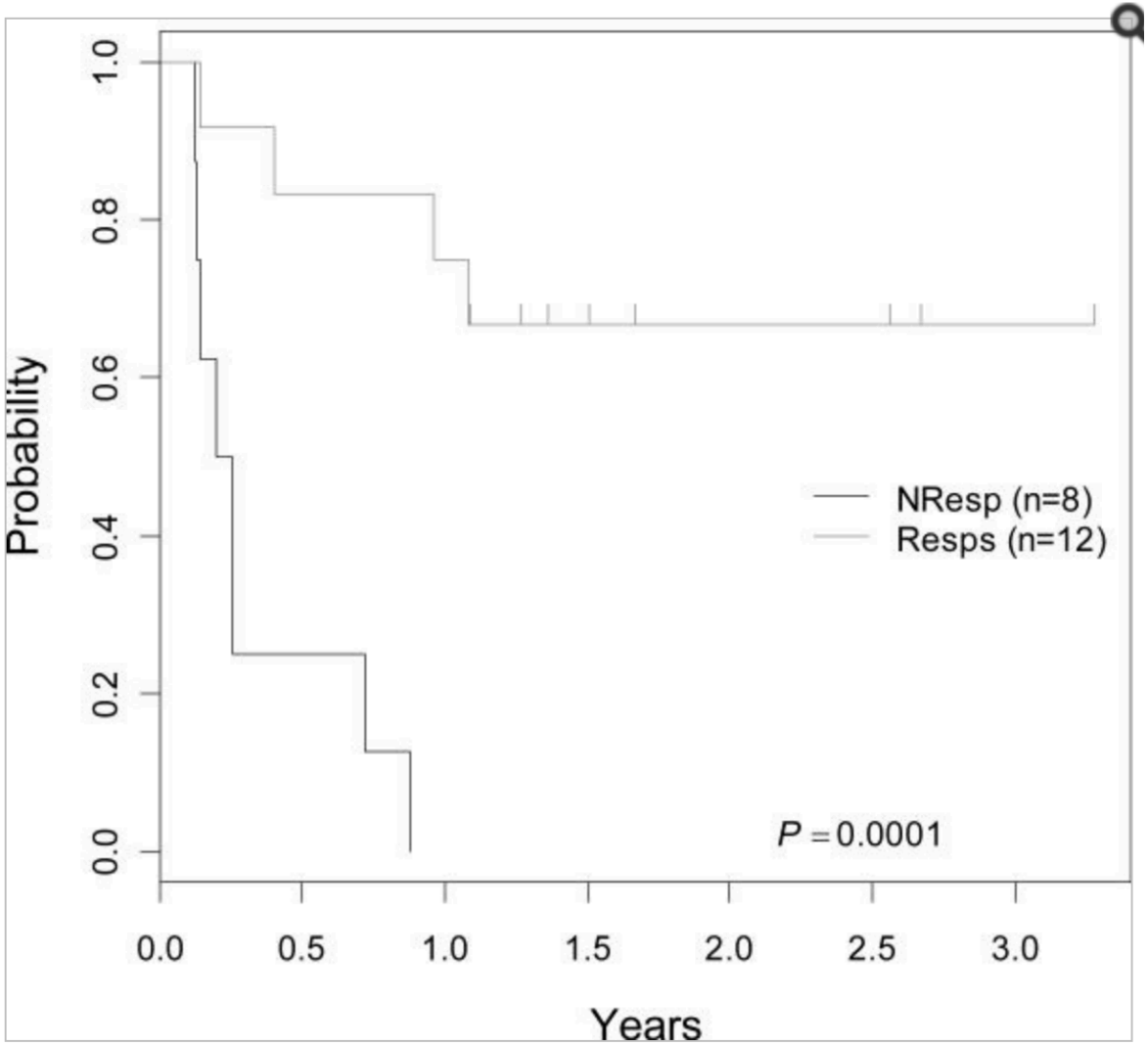
Other Toxicities	Grade 3	Grade 4	
Vomiting	7	0	
Nausea	5	0	
Infection	5	1	
Febrile Neutropenia	4	0	
Hypokalemia	2	3	
Hemoglobin	0	3	
Hemorrhage	2	0	

One episode of grade 3 toxicity each reported for elevated SGOT, renal insufficiency, dehydration, acidosis, seizure, somnolence, syncope, hematemesis, lymphopenia, bilirubin

Pediatr Blood Cancer. 2009 Feb; 52(2): 177–181.
doi: 10.1002/pbc.21753

Overall Survival: Responders vs. Non-Responders

Figure 2



Pediatr Blood Cancer. 2009 Feb; 52(2): 177–181.
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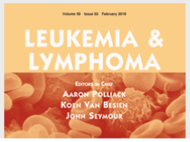
Additional Articles on Treatment Management



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Original Article

Modified Magrath Regimens for Adults with Burkitt and Burkitt-Like Lymphomas: Preserved Efficacy with Decreased Toxicity

A Lacasce, O Howard, S Li, D Fisher, A Weng, D Neuberg & ...show all

Pages 761-767 | Received 14 Aug 2003, Published online: 03 Aug 2009

Download citation http://dx.doi.org/10.1080/1042819031000141301

Long-Term Outcome after Hyper-CVAD and Rituximab Chemoimmunotherapy for Burkitt (BL) or Burkitt-Like (BLL) Leukemia/Lymphoma and Mature B-Cell Acute Lymphocytic Leukemia (ALL).

Deborah A. Thomas, Hagop M. Kantarjian, Jorge Cortes, Stefan Faderl, William G. Wierda, Farhad Ravandi, Maria Alma Rodriguez, Luis Fayad, and Susan O'Brien

Blood 2008 112:1929;

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