

How I treat HIV-associated lymphoma

Kieron Dunleavy¹ and Wyndham H. Wilson¹

¹Center for Cancer Research, National Cancer Institute, Bethesda, MD

Over the past 10 years, significant progress has been made in understanding HIV-associated lymphomas and improving the prognosis of these diseases. With the advent of combination antiretroviral therapy and the development of novel therapeutic strategies, most patients with HIV-associated lymphomas are cured. The outcome for the majority of patients with HIV-associated diffuse large B-cell lymphoma and Burkitt lymphoma in particular, is excellent, with recent studies supporting the role of rituximab in these diseases. Indeed, in the combination antiretroviral therapy era, the curability of many patients with HIV-associated lymphoma is similar to their HIV-negative counterparts. New treatment frontiers need to focus on improving the outcome for patients with advanced immune suppression and for those with adverse tumor biology, such as the activated B-cell type of diffuse large B-cell lymphoma and the virally driven lymphomas. Future clinical trials need to investigate novel targeted agents alone and in combination with chemotherapy. (*Blood*. 2012;119(14): 3245-3255)

phoma and Burkitt lymphoma in particular, is excellent, with recent studies supporting the role of rituximab in these diseases. Indeed, in the combination antiretroviral therapy era, the curability of many patients with HIV-associated lymphoma is similar to their HIV-negative counterparts. New treatment frontiers need to focus on improving the outcome for patients with advanced immune suppression and for those with adverse tumor biology, such as the activated B-cell type of diffuse large B-cell lymphoma and the virally driven lymphomas. Future clinical trials need to investigate novel targeted agents alone and in combination with chemotherapy. (*Blood*. 2012;119(14): 3245-3255)

pression and for those with adverse tumor biology, such as the activated B-cell type of diffuse large B-cell lymphoma and the virally driven lymphomas. Future clinical trials need to investigate novel targeted agents alone and in combination with chemotherapy. (*Blood*. 2012;119(14): 3245-3255)



blood

Common Types of HIV-Associated Lymphomas

- DLBCL – includes primary CNS lymphoma (PCNSL)
- Burkitt Lymphoma
- HIV-positive patients have a 60-200 fold increased incidence of non-Hodgkin Lymphoma.
 - Majority of which are DLBCL.
- Less frequent:
 - Primary Effusion Lymphoma (PEL)
 - Plasmablastic Lymphoma
 - Classical Hodgkin Lymphoma (HL)
 - Follicular Lymphoma
 - Peripheral T-Cell Lymphoma
- Risk of systemic or primary CNS lymphoma in HIV-infected persons is closely associated with the CD4 count!

Pathobiology

- Involves complex biologic factors that play a role
- Chronic antigen stimulation
- Co-infecting oncogenic viruses (EBV)
- Genetic abnormalities
- Cytokine dysregulation
- Most lymphomas are B-cell lineage
 - Rearrangement of immunoglobulin genes
- Occasional T-cell lymphomas
 - T-cell receptor gene rearrangements

Viral and genetic abnormalities in HIV-associated NHL

Histologic subtype	EBV +	KSHV/HHV-8+	Common recurring chromosomal abnormalities
Diffuse large B-cell lymphoma			<i>MYC</i> (10%); <i>BCL6</i> (20% of centroblastic DLBCL) ^{19,20} <i>TP53</i> (40%) ^{5,88}
Centroblastic	30% ^{2,10,11}	0	
Immunoblastic	80-90% ^{2,10,11}	0	
Plasmablastic lymphoma	> 50% ²	80% ⁸¹	None
Primary effusion lymphoma	100% ^{2,8}	100% ^{2,8}	None
Burkitt lymphoma	30-50% ^{2,9}	0	<i>MYC</i> (100%) ² ; <i>TP53</i> (50-60%) ^{5,88}
Primary CNS lymphoma	100% ¹⁰	0	<i>BCL6</i> (30-40%) ²
Hodgkin lymphoma	80-100% ²	0	None

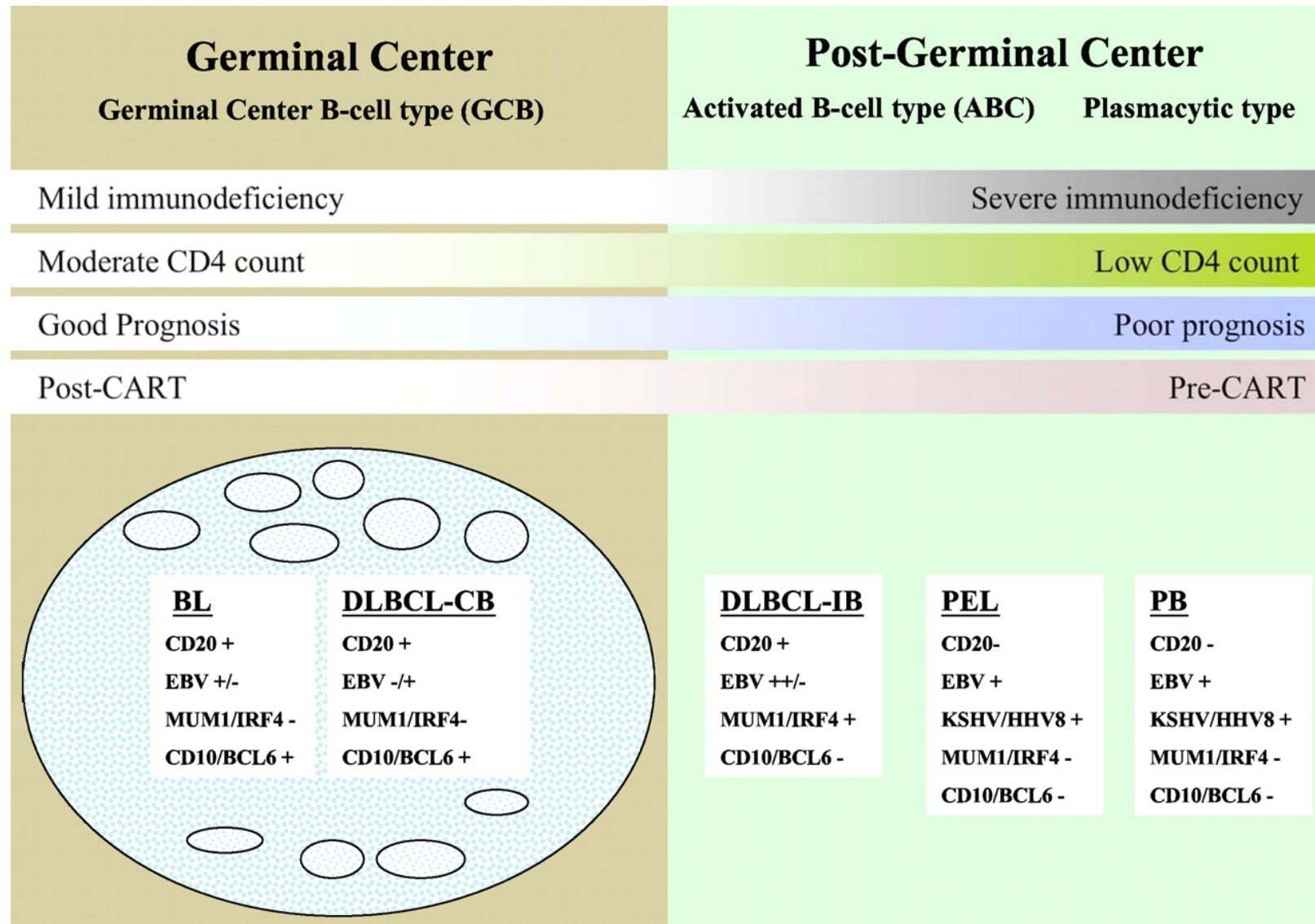
EBV, Epstein-Barr virus; KSHV/HHV-8, Kaposi sarcoma herpes virus/human herpes virus 8; CNS, central nervous system.

Kieron Dunleavy, and Wyndham H. Wilson Blood 2012;119:3245-3255

Diagnosis

- Most important: Adequate and properly evaluated biopsy
- Excisional biopsies
- Core or Fine needle aspirate biopsies are inadequate.
- Centroblastic → characterized by diffuse sheets of large lymphoid cells with round or oval nuclei & prominent nucleoli.
- Express germinal center-associated markers
 - CD10
 - BCL6
 - CD20+
- Immunoblastic variant → cases containing more than 90% immunoblasts and exhibits features of plasmacytoid differentiation.
 - CD10-
 - *MUM1/IRF4+*
 - CD138/syndecn-1

A model for the histogenesis of HIV-associated lymphomas showing molecular and viral pathogenesis and DLBCL taxonomy



Kieron Dunleavy and Wyndham H. Wilson
Blood 2012;119:3245-3255

Evaluation

- Physical examination → include careful assessment of lymph node regions, liver & spleen.
- Laboratory studies:
 - CBC
 - Chemistry profile (LDH, uric acid levels, CD4 count & HIV viral load)
- Serology:
 - Hepatitis B & C
- Bone marrow aspirate and biopsy performed at initial diagnosis
 - 20% of cases - lymphoma will be detected
- LP in aggressive B-cell lymphomas
 - Analysis by flow cytometry and cytology
- CT & [MRI]
 - [FDG-PET if available]

Treatment Questions

- Treatment for HIV-associated lymphoma has evolved significantly over the past 30 years.
- Therapeutic Questions:
 - Should lower doses of chemotherapy be used to reduce toxicity and immune suppression?
 - What is the role of rituximab and the optimal regimen?
 - Should CART be suspended during lymphoma therapy?

Pivotal trials in HIV-associated lymphomas

Study	Study type	Study design	Results
Kaplan et al ⁵³	Prospective multicenter randomized phase III (n=192)	Randomization to standard-dose m-BACOD with GM-CSF versus low-dose m-BACOD without GM-CSF. No cART	Similar efficacy of both regimens but less hematological toxicity with low-dose m-BACOD
Ratner et al ⁶²	Prospective multicenter sequential phase II (n=65)	First 40 patients received modified-dose (m) CHOP (50% cyclophosphamide and doxorubicin) and the next 25 patients received standard-dose CHOP. cART was administered	CR higher with full dose CHOP compared to mCHOP (48% vs 30%). Authors concluded that concomitant cART was safe but unable to conclude superiority of one regimen over another
Sparano et al ⁶⁵	Prospective multicenter sequential phase II (n=98)	First 43 patients received didanosine and the next 55 patients received cART with CDE	At 2 years, FFS and OS were 36% and 43%. Patients receiving concomitant cART had better survival and less toxicity
Mounier et al ⁵⁶	Prospective multicenter phase III study	485 patients were randomly assigned to different CHOP-based chemotherapy regimens according to an HIV score that was based on performance status, prior AIDS and CD4 count	Though HIV score, IPI score and cART affected survival, the intensity of CHOP-based chemotherapy had no effect on survival
Little et al ³⁷	Prospective single center phase II (n=39)	All patients received EPOCH and G-CSF with cART suspension	CR was 74%. At 53 months, DFS and OS were 92% and 60%. Patients in CR achieved CD4 recovery and HIV control following treatment. Conclusion that EPOCH with cART suspension is feasible and highly effective
Kaplan et al ⁵⁸	Prospective multicenter randomized phase III (n=150)	Randomization (2:1) to R-CHOP versus CHOP with concomitant cART. Some patients received maintenance rituximab.	CR rate higher with R-CHOP compared to CHOP (57.6% vs 47%). Increased infectious deaths with R-CHOP mostly in patients with low CD4 counts. Conclusion that rituximab does not improve clinical outcome
Boue et al ⁶³	Prospective multicenter phase II (n=61)	All patients received R-CHOP	CR in 77% of patients. Estimated 2 year OS was 75%
Spina et al ⁶⁰	Retrospective analysis of 3 phase II trials	Pooled results from 3 trials of CDE with rituximab	CR rate was 70%. At 2 years, FFS and OS were 59% and 64%. Conclusion that R-CDE is effective but rituximab may increase infections
Sparano et al ⁴⁹	Prospective multicenter phase II study	101 patients were randomized to receive either concurrent or sequential rituximab with DA-EPOCH	There was a superior outcome with concurrent rituximab and DA-EPOCH (CR rate 75%) and this was considerably better when compared to the previous ANC results with CHOP +/- R
Dunleavy et al ⁴⁷	Prospective single center phase II (n=33)	All patients received SC-EPOCH-RR with cART suspension	79% of patients needed only 3 cycles of treatment. At 5 year follow-up, PFS and OS were 84% and 68%. Outcome was better for GCB versus non-GCB DLBCL (5 year PFS of 95% versus 44%).

GM-CSF, granulocyte macrophage colony-stimulating factor; G-CSF, granulocyte colony stimulating factor; cART, combined anti-retroviral therapy; CR, complete remission; FFS, failure-free survival; OS, overall survival; DFS, disease-free survival; m-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; R, rituximab; CDE, Cyclophosphamide, doxorubicin, and etoposide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DA, dose adjusted; SC short course

Kieron Dunleavy, and Wyndham H. Wilson
Blood 2012;119:3245-3255

Outcome of CART and role of Rituximab

- Variety of trials performed to evaluate dose modifications and effects of CART on treatment.
- French group performed phase 2 study of CHOP + rituximab in HIV-associated NHL.
 - CR rate of 77%
 - 2-year survival rate of 75%
 - Suggested rituximab was beneficial and could be given safely.
- Additional phase 2 randomized study performed.
 - Randomized patients to receive concurrent versus sequential rituximab with EPOCH
 - Concurrent rituximab was not associated with increased infectious deaths
 - Examined whether the complete response rate with EPOCH-R was superior to CHOP with or without rituximab
 - Also whether concurrent vs. sequential rituximab was more toxic/or more effective.
 - No difference in toxicity.
- Based on study → unwise to omit rituximab from upfront therapy in HIV-associated lymphomas.
- Results suggest EPOCH-based treatment of HIV-associated lymphoma may be an optimal treatment regimen.

SC-EPOCH-RR drug doses and schedule

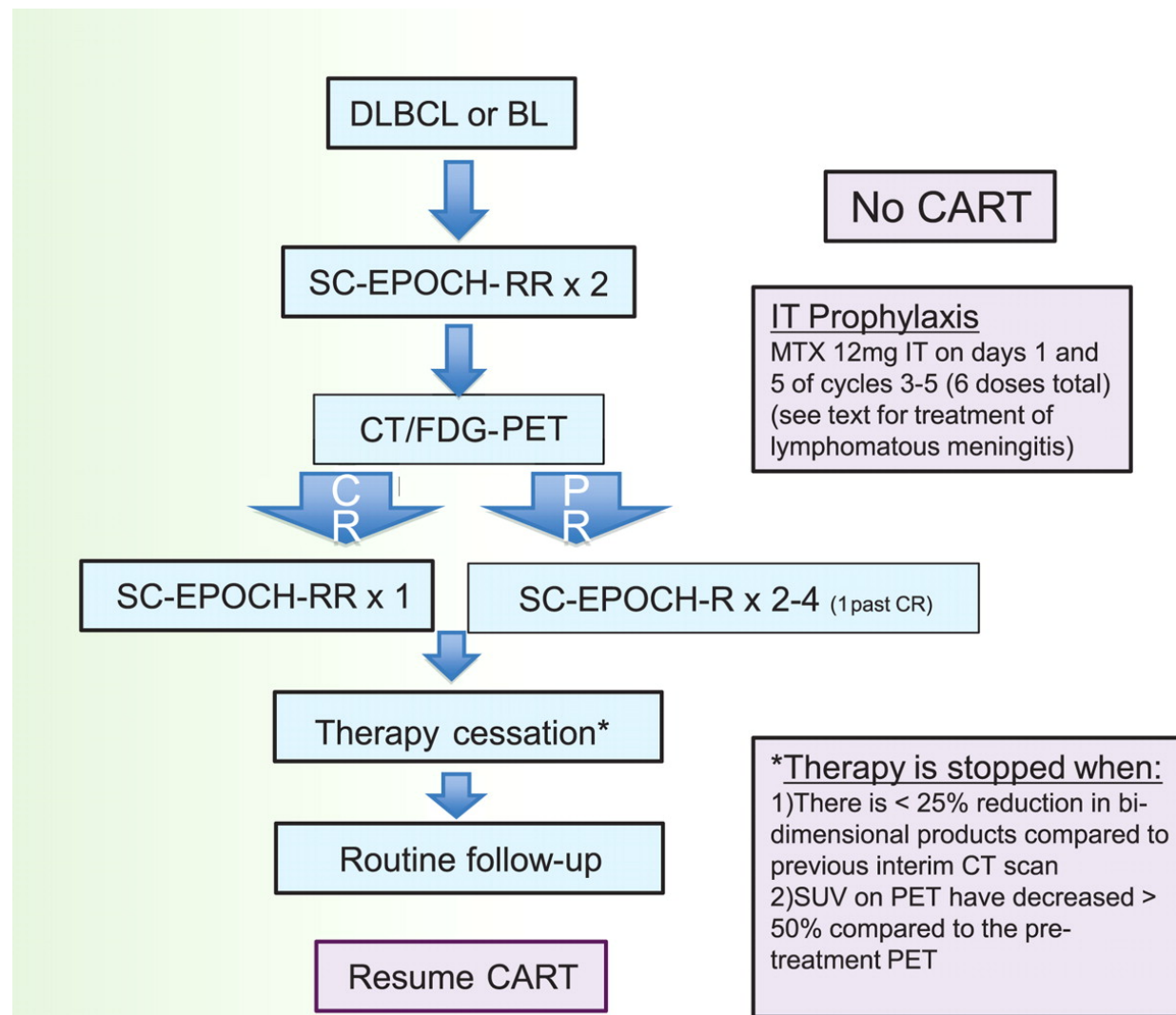
	Dose mg/m ² /day	Treatment Days		
Infusional Agents				
Etoposide	50	Days 1 to 4	Cycle 21 days	
Vincristine	0.4			
Doxorubicin	10			
Bolus Agents				
Cyclophosphamide	750	Day 5		
Prednisone	60 od	Days 1 to 5		
Biologic Agents				
G-CSF	300 mcg	Days 6 to 15		
Rituximab	375	Days 1 and 5		

od=once daily

Kieron Dunleavy, and Wyndham H. Wilson
Blood 2012;119:3245-3255

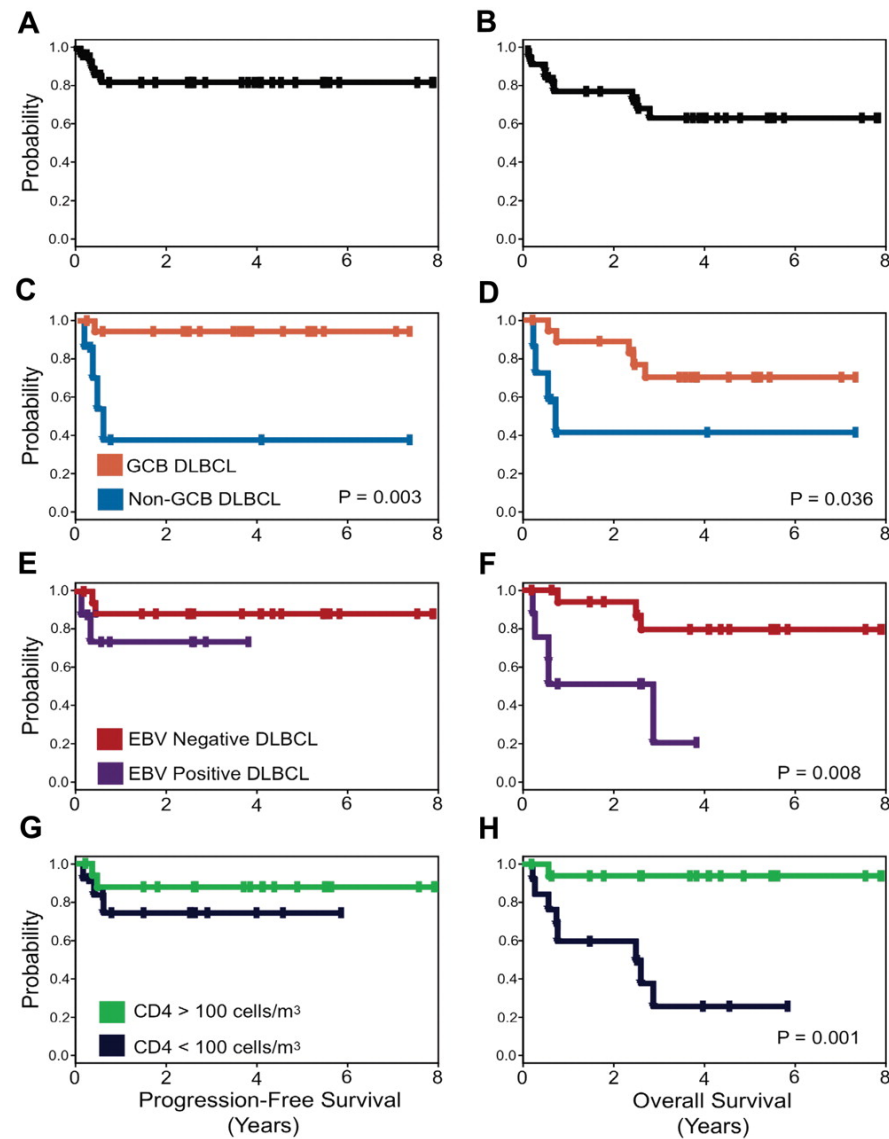
SC-EPOCH-RR treatment paradigm

To determine how many cycles of SC-EPOCH-RR are needed



Kieron Dunleavy, and Wyndham H. Wilson
Blood 2012;119:3245-3255

PFS and OS Kaplan-Meier curves



Kieron Dunleavy, and Wyndham H. Wilson
Blood 2012;119:3245-3255

Treatment of Relapse

- Usually associated with a poor prognosis.
- Median survival tends to be <1 year
- Italian study presented high-dose therapy and transplantation.
 - Median OS was 33 months
 - Chemo-sensitive disease had a relatively favorable outcome.
 - Disease free at 44 months of follow-up
- Reasonable to approach relapsed HIV-associated lymphomas similarly to their HIV-negative counterparts.