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Controversies in the Treatment of Burkitt Lymphoma in AIDS

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Abstract

Purpose of review—The success of combined antiretroviral therapy (cART) has transformed HIV infection into a survivable chronic disease in developed countries. Increasingly then, the risks of HIV associated cancers become paramount. Burkitt lymphoma (BL) is one of the cancer subtypes highly disproportionately affecting HIV infected patients.

Recent findings—Recent conference proceedings appear to corroborate early reports that intensive therapy of HIV-BL is feasible and effective. An optimal approach is not defined due to the small numbers of patients in current trials and the absence of comparison studies. Moreover, while breakthroughs in the pathogenesis of lymphoma in general and BL in particular suggest that HIV infection plays a significant role, the opportunity for targeted therapy based on differences in biology are wholly untapped.

Summary—Advances are being made in HIV-BL, but future studies need to incorporate our expanding understanding of biology to improve efficacy and reduce toxicity, preferably by integrating a biologic approach to this curable disease.

Keywords

Burkitt; HIV; AIDS; Lymphoma

Introduction

Burkitt and atypical Burkitt lymphoma (BL) are highly aggressive tumors with nearly 100% growth fraction driven by the *myc* oncogene and highly curative with current therapy. The three major types include endemic African, sporadic and human immunodeficiency virus (HIV)-associated. Though relatively rare in the immunocompetent population, patients with HIV infection are at least 50 times more likely to get lymphoma in general. As 25-40% of these lymphomas will be BL,[1-3] this translates to a 10-20% individual life-time risk of BL for an HIV infected person. This is largely unaffected by combination anti-retroviral therapy (cART), as the risk of BL is independent of CD4 count.

In the immunocompetent setting, treatment for BL has evolved from single agent studies first conducted in endemic African BL[4] to often complex multi-agent regimens[5-10] none of which have been compared in randomized studies. The addition of high dose cytarabine

and methotrexate in doses sufficient to cross the blood-brain barrier and intrathecal prophylaxis led to an improvement in success of BL therapy[4] and most regimens in use to day incorporate these elements.

Early in the acquired immunodeficiency syndrome (AIDS) epidemic, the underlying comorbidities AIDS patients already had at the time of a lymphoma diagnosis, precluded intensive chemotherapy. In fact, standard regimens for diffuse large B cell lymphoma were eschewed because of treatment related mortality.[11] However, with the advent of combination antiretroviral therapy (cART), patients often presented with a lymphoma in the absence of previous opportunistic infections and even low CD4 counts at presentation were often reversible with the institution of cART during or at the completion of chemotherapy. Subsequently, at least three studies published from 2002-2004 supported treating AIDS related BL aggressively with standard intensive therapies[12-14], despite a prevailing view that treatment was futile.

The current manuscript will explore some of the current areas of interest in the treatment of HIV-BL. These include optimization of chemotherapy, incorporation of immunotherapy, age appropriate modifications, and biologic uniqueness of HIV-BL. As little has been published in manuscript form recently, this review will incorporate recent international conference proceedings.

Chemotherapy Backbone

As noted earlier, none of the standard multi-agent programs for the treatment of BL have been compared in randomized trials. Therefore, adapting a particular regiment to HIV-BL is somewhat dependent on a particular institution's predilection for one regimen over another. Two groups with a particular interest in HIV-BL have reported interim results in abstract form using very different approaches.

The AIDS Malignancy Consortium (AMC) built upon the Magrath National Cancer Institute regimen CODOX-M/IVAC (Table 1) [8] and modifications made by Lacasce (Table 2) [15] to improve tolerability in adults. Originally, Magrath was successful in a population of HIV negative children and young adults, but was associated with a nearly universal rate of pancytopenic complications in adults and severe mucositis. The Lacasce modifications included decreasing the dose of methotrexate, while maintaining central nervous system penetration, and capping vincristine; and consolidating some of the intrathecal therapies. AMC 048 (Table 3) [16] kept these changes and added some new ones with the intent to reduce further morbidity and mortality. For example, methotrexate was no longer given during the nadir from the first few days of therapy. In the hopes of improved efficacy, rituximab, the anti-CD20 antibody, was added and ifosfamide and etoposide were given as a five day infusion rather than bolus therapy.

A planned interim analysis to exclude excess treatment related mortality (TRM) was reported at the 2009 American Society of Hematology (ASH) meeting. With 22 of 31 planned patients accrued as of June 2009 , baseline characteristics included: Classical Burkitt, 95%; Low/High Risk, 9/91%; Median (range) Age 40 (19 – 55); CD4 count 290 (0 – 1260), CD4 <100, 5 (27%); HIV viral load 15,600 (48 – 715,881). Thus far, the trial had no TRM, only four patients withdrew due to adverse events and one did not complete the protocol. The latter patient remained in remission, but had less than one year of follow up. Grade 3/4 toxicities were markedly reduced. With a median follow up of 17 months, the one-year overall survival (OS) (95% CI) was 85.7% (60%, 100%). Notably, despite concerns raised in a prior AMC study (010) of rituximab and cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) in DLBCL, rituximab did not appear to increase toxicity. These results compared favorably with two studies that excluded HIV + pts.

Magrath [8]originally reported 100% grade 4 hematologic and 20% mucositis in 39 adults, 33 children (92% 2 yr EFS) with CODOX-M/IVAC. The Medical Research Council/ National Cancer Research Institute Lymphoma 10 (MRC/NCRI LY10) trial [17] used the same regimen with reduced methotrexate(3gr/m2), but reported 9% treatment related deaths (64% 2 year OS). With ongoing enrollment of AMC 048 anticipated to be complete 2nd quarter 2010, it is possible the primary objective of 1 year OS of 85% may be achieved.

Using an entirely different approach, the United States National Institute of Health (US NCI) built upon its prior experience with rituximab and infusional etoposide, vincristine, doxorubicin with bolus rituximab and cyclophosphamide and oral prednisone (EPOCH-R) in DLBCL (Table 4). [18] The interim results with 25 patients were presented in Frankfort in 2009.[19] Baseline characteristics included HIV negative (n=17) and HIV positive (n=8), median age 30 (18-66), median ECOG PS 1 (1-3), Murphy stage III/IV 15 (56%), LDH>Normal, 14 (58%) and extranodal sites 19 (76%) with ileocecal disease 15 (60%). No patients had CNS disease at diagnosis. The 17 HIV negative patients received 6 cycles of dose adjusted (DA) EPOCH-R while HIV positive patients (n=8) received 3-6 cycles for a minimum of 3 cycles and 1 cycle beyond CR. All received prophylactic intrathecal therapy. Treatment was given as out-patient when feasible. 100% of patients achieved CR/ CRuncertain by clinical response criteria with 1 patient requiring consolidation radiation to a site of residual disease. At a median potential follow-up time of 35 months, OS and EFS are 100% and 96%. Toxicities were acceptable with zero TRM, 38% hospitalization, 45% grade IV neutropenia, 16% febrile neutropenia and only 5% (n=1) tumor lysis. Again rituximab was not felt to be contributing to increased toxicity.

The controversy surrounding these two regimens lies in whether infusional therapy designed to treat rapidly dividing tumors can stand alone without drugs that penetrate the CNS. The CNS has long been a known site of relapsed disease in BL and the incorporation of methotrexate and cytarabine at CNS penetrating doses has become dogma. This may be particularly problematic for patients with HIV infection which increases the risk of extranodal disease in lymphomas generally. With only 8 HIV infected patients in the NIH trial, no conclusions can be drawn.

Rituximab

Rituximab, an anti-CD20 antibody, has become a ubiquitous part of regimens directed against B cell lymphomas which are largely universally positive for the target cell surface molecule. In randomized studies this antibody when added to a chemotherapy backbone has variously increased response rates, progression free survival and overall survival in a wide variety of indolent and aggressive lymphomas, exclusive of BL, and chronic lymphocytic leukemia. This immunotherapy is not specific to the malignant cell and results in temporary ablation of the normal mature B cell compartment. This raised the concern that patients with already compromised immune systems secondary to HIV might be vulnerable to further immuosuppression. AMC 010 which randomized patients to CHOP with or without rituximab reported an excess number of deaths in those with CD4 counts less than 50 cell/ ml[20]. Subsequently, however, both AMC 034[21] and US NIH[22] reported excellent results with EPOCH-R. Nonetheless, AMC 034 randomized patients receiving concurrent or sequentially rituximab and patients with a baseline CD4 count < 50/uL had a high infectious death rate in the concurrent arm. Thus, for many investigators the true balance of risk and benefit in this highly select group of patients remains unclear. Notably, a retrospective analysis of immunocompetent BL patients treated with CODOX-M/IVAC with (n=47) and without rituximab (n=40) simply based on the year of presentation, showed only a trend towards improvement in response rate and survival suggesting that increased patient

numbers may be needed to demonstrate significance.[23] With the rarity of BL, it is unlikely this will be resolved in future trials.

The impact of age on therapy and outcome

The initial studies in BL were predominantly on children and younger adults. This was in part due to the incidence of the disease and the fear that older patients would not tolerate such intensive therapies. However, with an aging population, both immunocompetent and HIV infected, the question of age appropriate therapy for BL becomes salient. In fact, a recent epidemiologic study suggests BL may have a geriatric peak.[24-25] Moreover, the HIV population is aging with fewer years of life lost attributable to HIV[25] and some projections of normal life expectancy in a significant proportion of treated individuals.[26] A recent attempt to review the treatment of BL in individuals over 40 primarily highlighted the paucity of available data.[27] The impact of aging vis a vis HIV and BL remains to be elucidated.

Does HIV status matter?

Implicit in these discussions is that treatment of HIV-BL can be imported from studies in the immunocompetent patient population. However, this may not be entirely true. First, one notes the issues raised earlier of toxicity with anti-CD20 therapy in the most immunocompromised. Perhaps more importantly, the pathobiology of HIV lymphomas is not necessarily identical to those presenting in the absence of HIV despite their shared similarities under the microscope. Several observations suggest this to be true. First is the well described predilection of HIV-lymphoma to present with extranodal involvement. Second, the proportion of Epstein-Barr Virus (EBV) infection in DLBCL and BL differs with respect to HIV infection. Lastly, early reports demonstrate that different pathways of intracellular events occur in the presence of HIV, perhaps partly influenced by the presence of EBV infection which is known to carry oncogenic proteins. For example, preliminary preclinical studies have suggested that B-cell receptor related signaling is often disrupted in DLCBL cell lines with concomitant EBV from HIV-infected individuals,[28] in contrast to frequent intact signaling in DLBCL lines derived from immunocompetent individuals.[29] The multi-drug resistance P-glycoprotein (Pgp) may also be much higher in HIV positive lymphomas influencing response to chemotherapy. Epigenetic changes (such as silencing of the o-6 methylguanine methyl transferases)[30] may additionally play a role, although the relationship to HIV infection and immunohistochemical subtypes is incompletely explored. Finally, a recent analysis using single nucleotide polymorphism (SNP)-based microarray comparative genomic hybridization of AIDS and immunocompetent DLBCLs revealed significant differences between subtypes of lymphoma and differences between those with and without host HIV infection.[31] Elucidating these pathways could reveal new targets for therapy with small molecule inhibitors or other strategies. These could prove to augment current strategies or replace them with less toxic options.

Studies in Africa

It bears mention BL was originally discovered in Africa by Dennis Burkitt and many of the original single agent trials were conducted there, the benefits of multi-agent therapy have only rarely been applicable to endemic BL. It remains to be seen whether the increasing availability of cART in Africa will facilitate the treatment of BL.[32] It is also possible that improved life expectancy from an HIV perspective will result in a surge in the incidence of BL.

Conclusions

Burkitt lymphoma is a rare disease in the immunocompetent population, but is disproportionally common in the HIV infected population. Epidemiology suggests the incidence may further increase with the aging population. Early studies in the cART era refute the nihilistic approach to this disease prior to cART. More recently trials are largely borrowing from those conducted in the immunocompetent population, although changes are being tested to reduce the morbidity of treatment for all patients. Whether high dose methotrexate and cytarabine can be eliminated, facilitating outpatient therapy, remains an open question. The impact of rituximab also remains undefined. Finally, the pathobiologic influence of HIV and the opportunity for future targeted therapy remains largely unexplored.

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Table 1

Regimen A: R-CODOX-M[a]														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Cyclophosphamide 800mg/m^2 IVPB	X													
Cyclophosphamide 200mg/m^2 IVPB		X	X	X	X									
Vincristine 1.4 mg/m^2 IVP (no cap)	X							X						X (D15, cycle 3 only)
Doxorubicin 40 mg/m^2 IVP	X													
Methotrexate 1200 mg/ m^2 over 1 hour, then 240 mg/ m^2 each hour for 23 hours										X				
Leucovorin (rescue until methotrexate clearance)													X	
Cytarabine 70 mg IT	X		X											X (D15)
Methotrexate 12 mg IT														X (D15)
G-CSF[g](until ANC >1000)												X	X	X[g](ApproxD18)

Regimen B: IVAC[a]														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Ifosfamide 1500 mg/m^2 IVPB	X	X	X	X	X									
Mensa 360 mg/m^2 every 3 hours	X	X	X	X	X									
Etoposide 50mg/m^2 IVPB	X	X	X	X	X									
Cytarabine 2000mg/m^2 IVPB (no cap) q12h × 4 doses	X	X	X	X										
Methotrexate 12 mg IT					X									
Neulast a or GM-CSF[b]							X	X	X	X	X	X	X	

[a]Low risk disease patients receive three cycles of regimen A (A-A-A). High Risk patients receive four alternating cycles of regimen A and B (A-B-A-B).

[b]Original regimen published with patients randomized to GM-CSF or observation

Table 2

Regimen A: R-CODOX-M[a]														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Cyclophosphamide 800mg/m^2 IVPB	X	X												
Vincristine 1.4 mg/m^2 IVP	X									X				
Doxorubicin 50 mg/m^2 IVP	X													
Methotrexate 3000mg/m^2 IVPB										X				
Leuc ovorin IVPB (rescue until methotrexate clearance)											x			
Cytarabine 50 mg IT	X		X											
Methotrexate 12 mg IT	X													
GM-CSF (until ANC>1000)		X	X	X	X	X						X		

Regimen B: IVAC[a]														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Ifosfamide 1500 mg/m^2 IVPB	X	X	X	X	X									
Mensa IVPB[b]	X	X	X	X	X									
Etoposide 60mg/m^2 IVPB	X	X	X	X	X									
Cytarabine 2000mg/m^2 IVPB (no cap) q12h × 4 doses	X	X												
Methotrexate 12 mg IT					X									
Neulasta or GM-CSF					X	X	X	X	X	X	X	X	x	

[a]Low risk disease patients receive three cycles of regimen A (A-A-A). High Risk patients receive four alternating cycles of regimen A and B (A-B-A-B).

[b]Mensa given as total daily dose in divided doses

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Table 3

Regimen A: R-CODOX-M[a]														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Rituximab 375 mg/m^2 IVPB	X[b]													
Cyclophosphamide 800mg/m^2 IVPB	X	X												
Vincristine 1.4 mg/m^2 IVP[c]	X							X						
Doxorubicin 50 mg/m^2 IVP	X													
Neulasta[h]			X											
Methotrexate 3000mg/m^2 IVPB[d]														X **(D15)**
Leucovorin IVPB														X[e]
Cytarabine 50 mg IT	X[f]		X[I]											
Methotrexate 12 mg IT	X[f]													
G-CSF[g]														X[g] **(ApproxD18)**

Regimen B: IVAC[a]														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Rituximab 375 mg/m^2 IVPB	X													
Ifosfamide 1500 mg/m^2 IVCI	X	X	X	X	X									
Mensa 1500 mg/m^2 IVCI	X	X	X	X	X									
Etoposide 60mg/m^2 IVCI	X	X	X	X	X									
Cytarabine 2000mg/m^2 IVPB (no cap) q12h × 4 doses	X	X												
Methotrexate 12 mg IT					X									
Neulasta[h]						X								

[a]Low risk disease patients receive three cycles of regimen A (A-A-A). High Risk patients receive four alternating cycles of regimen A and B (A-B-A-B).

[b] Rituximab should be given once each cycle. It is recognized that the acute presentation of high grade lymphoma and scheduling constraints may make it difficult to administer rituximab on the first day of each cycle. The rituximab can be given up to 3 days before a chemotherapy cycle and anytime within the cycle such that a total of four doses are given with this regimen for patients with high-risk disease. A missed dose can be made up within 28 days of the last dose of IVAC.

[c] Vincristine maximum 2 mg dose. May be delayed by a few days to accommodate scheduling or treatment for constipation.

[d] Methotrexate levels should be drawn 24, 48 and 72 hours post treatment with anticipated decrement in levels of 10 fold every 24 hours. Guidelines for fluid repletion and leucovorin rescue are listed in Section 10.3.

[e] Leucovorin: 24 hours post methotrexate administration, leucovorin is initiated with a dose of 200 mg/m^2 IV followed by 25 mg/m^2 IV every 6 hours until the methotrexate level < 50 nmol/L.(See Section 9.0 for guidelines).

[f] Methotrexate (12 mg IT) mixed with cytarabine (50 mg IT) given on Day 1. Hydrocortisone 50mg should be given to reduce arachnoiditis. Drugs may be given mixed in one syringe or sequential as per local pharmacy practice.

[g] G-CSF: investigators should restart G-CSF after methotrexate levels have dropped below 50 nmol/L and continue until absolute neutrophil count (ANC) >1000.

[h] Pegfilgrastim (Neulasta).- If not available G-CSF daily until ANC>1000 cell/μL can be substituted.

[I] High risk patients receive an additional cytarabine 50 mg IT on Day 3.

Table 4

Regimen : Dose-Adjusted EPOCH														
Treatment	**Day**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14-28**
Vincristine 0.4 mg/m^2 IVPB[a,b]	X	X	X	X										
Doxorubicin 10 mg/m^2 IVP[a]	X	X	X	X										
Etoposide 50mg/m^2 IVCI[a]	X	X	X	X										
Cyclophosphamide 375mg/m^2 IVPB (cycle 1, CD4$^+$ cells ≥ 100mm^3)					X									
Cyclophosphamide 187mg/m^2 IVPB (cycle 1, CD4$^+$ cells < 100mm^3)					X									
Cyclophosphamide ↑187mg/m^2 IVPB above previous cycle(**dose-adjusted after cycle 1**, nadir ANC >500μL)[c]					X									
Cyclophosphamide ↓ 187mg/m^2 IVPB below previous cycle (**dose-adjusted after cycle 1**, nadir ANC <500μL or platelets <25,000) [c]					X									
Prednisone 60 mg/m^2	X	X	X	X	X									
GM-CSF (until ANC>1000)						X	X	X	X	X	X	X	X	

Data are for cycle 1, except where noted in “Cyclophosphamide dose-adjustment.” --- represents not applicable

[a]Etoposide, doxorubicin, and vincristine can be admixed in the same solution. Etoposide, doxorubicin and vincristine are never dose-adjusted for hematologic toxicity.

[b]Vincristine dose should never be routinely capped

[c]Dose based on previous cycle absolute neutrophil count (ANC) nadir (CBC BIW); maximum cyclophosphamide dose 750 mg/m^2

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