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Rituximab in combination with chemotherapy versus chemotherapy alone in HIV-associated non-Hodgkin lymphoma: A pooled analysis of 15 prospective studies

Jorge J. Castillo* and Ignacio A. Echenique

In HIV-positive patients with non-Hodgkin lymphoma (NHL), no benefit of adding rituximab to chemotherapy was seen in a randomized controlled trial (RCT). We performed a meta-analysis of prospective studies to ascertain outcomes in HIV-positive NHL patients treated with chemotherapy (chemo) versus rituximab and chemo (R-chemo). A literature search through September 2011 was performed using the key search "(HIV OR AIDS) AND lymphoma". The main outcomes were overall response rate (ORR), complete response rate (CRR) and 2-year overall survival (OS) and are reported as non-adjusted odds ratio (OR). We identified 15 prospective studies including 1,060 HIV-positive NHL patients, 675 treated with chemo and 385 with R-chemo. There was a higher proportion of HAART in R-chemo patients (82% *vs.* 68%; $p < 0.01$) but there were no differences in proportion of patients with advanced stage or high/high-intermediate age-adjusted International Prognostic Index (aaIPI) scores. Meta-analysis showed the OR for ORR, CRR and 2-year OS in patients treated with R-chemo was 1.39 (95% CI 0.79-2.47; $p = 0.26$), 1.66 (95% CI 0.98-2.82; $p = 0.06$) and 2.19 (95% CI 1.68-2.86; $p < 0.001$), respectively. HIV-positive lymphoma patients treated with R-chemo had higher odds for CR and 2-year OS when compared to chemo but also had a higher proportion of HAART usage.

Since the mid-nineties until few years ago, the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) had been considered the standard of care for immunocompetent patients with a diagnosis of diffuse large B-cell lymphoma (DLBCL) [1]. Recent trials have demonstrated improved response and survival rates with the addition of rituximab (Rituxan®, Genentech, South San Francisco, CA) to CHOP (R-CHOP) in immunocompetent patients with DLBCL [2–4]. In HIV-positive patients, however, the benefit of adding rituximab is less clear. Prior to the era of highly active antiretroviral therapy (HAART), treatment of HIV-associated NHL was marred by high rates of toxicity and dismal outcomes [5]. With the advent of HAART, outcomes have improved substantially [6–8]. However, in a randomized controlled trial (RCT) by the AIDS Malignancy Consortium (AMC), the addition of rituximab to CHOP showed no survival advantage, likely due to the increased death rate from infections [9]. A meta-analysis by the Cochrane Database could not accurately determine superior clinical effectiveness from any particular regimen in patients with HIV-associated NHL [10]. Such analysis did not specifically examine regimens containing rituximab against those that did not. We have performed a study-level meta-analysis of prospective studies to ascertain the efficacy and outcomes in HIV-positive NHL patients treated with R-chemotherapy (R-chemo) versus chemotherapy alone (chemo).

From a total of 267 publications, we identified 15 prospective studies, 14 single-arm [11–24] and 1 RCT [9], providing pertinent data. Four prospective studies provided clinical and outcome data on R-chemo and ten on chemo. The RCT provided data clinical and outcome data on chemo and R-chemo. Seven studies originated from Europe, six from the US, one from South America, and one was a multinational study with centers from Europe and the US. Twelve studies (80%) administered mandatory *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, seven studies (47%) administered central nervous system (CNS) prophylaxis with each cycle of systemic chemotherapy, and eight studies (53%) administered granulocyte-colony stimulating factor (G-CSF) routinely. The regimens investigated were CHOP, CDE (cyclophosphamide, doxorubicin, and etoposide), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) with and without rituximab. Selected characteristics of the studies are shown in Table I.

A total of 1,060 HIV-positive NHL patients were studied, 675 (64%) treated with chemo and 385 (36%) with R-chemo. There was a male predominance of 6:1 but there was no difference in proportion of men between the R-chemo and chemo groups (84% vs. 85%; $P = 0.52$). With regard to antiretroviral therapy, 757 patients (71%) were treated with HAART; R-chemo patients had a higher proportion of HAART than chemo patients (82% vs. 68%; $P < 0.01$). Seventy percent of patients ($n = 705$) presented with clinical Stages 3 or 4; there was no difference on the proportion of advanced stage between the R-chemo and chemo groups (58% vs. 73%; $P = 0.08$). High and high-intermediate aaIPI scores were seen in 460 patients (54%); there was no difference between the R-chemo and chemo groups (49% vs. 44%; $P = 0.11$). Selected characteristics of the patients are shown in Table II.

For R-CHOP, the nonadjusted OR for ORR, CRR and 2-year OS were 1.05 (95% CI 0.71–1.55; $P = 0.81$), 1.42 (95% CI 1.04–1.93; $P = 0.03$) and 2.37 (95% CI 1.73–3.25; $P < 0.001$), respectively. For R-CDE, the nonadjusted OR for ORR, CRR, and 2-year OS for R-CDE were 2.33 (95% CI 1.20–4.54; $P = 0.01$), 2.90 (95% CI 1.53–5.49; $P < 0.01$) and 1.96 (95% CI 1.06–3.61; $P = 0.03$), respectively. For R-EPOCH, the nonadjusted odds ratio for ORR, CRR and 2-year OS were 1.10 (95% CI 0.79–2.47; $P = 0.26$), 1.00 (95% CI 0.39–2.62; $P = 0.99$), and 1.50 (95% CI 0.62–3.63; $P = 0.37$). When pooling all studies, R-chemo was associated with OR for ORR of 1.39 (95% CI 0.79–2.47; $P = 0.26$); there was moderate heterogeneity ($I^2 = 61\%$) and the trim-and-fill analysis detected 1 imputed study, which would not have altered our results (OR 1.49, 95% CI 0.81–2.73). For CRR, the OR for R-chemo was 1.66 (95% CI 0.98–2.82; $P = 0.06$); there was moderate heterogeneity ($I^2 = 58\%$) but no publication bias was detected. Finally, the OR for 2-year OS was 2.19 (95% CI 1.68–2.86; $P < 0.001$) without heterogeneity ($I^2 = 0\%$); the trim-and-fill analysis detected two imputed studies, which could have not altered our results (OR 2.37, 95% CI 1.87–3.0). Forest plots are shown in Fig. 1.

In this meta-analysis of prospective studies examining R-chemo and chemo for HIV-associated NHL, we were able to note an advantage to rituximab-containing regimens for ORR, CRR, and 2-year OS rates, but our observations did not reach statistical significance in all measures. Regarding ORR, only R-CDE was superior whereas for CRR both R-CHOP and R-CDE exhibited an advantage. Similarly, both R-CHOP and R-CDE exhibited advantages in 2-year OS rates. However, there was no apparent benefit from the addition of rituximab to EPOCH. These findings could be explained by the heterogeneity of the studies or the fact that the present dataset proceeded from a pooled analysis of study-level data. Additionally, the comparison between EPOCH and R-EPOCH was based on a smaller sample ($n = 90$) when compared to R-CHOP vs. CHOP ($n = 779$) and R-CDE vs. CDE ($n = 193$).

TABLE I. Selected Characteristics of the Studies Included

Author	Country	Year published	Study period	Regimen	PJP prophylaxis	CNS prophylaxis	G-CSF	Number of patients
Vaccher [23]	Italy	2001	1988–1998	CHOP	Yes	Yes	No	104
Ratner [16]	USA	2001	1998–1999	CHOP	Yes	Choice	Yes	23
Simonelli [18]	Italy	2003	1997–1998	CHOP/R-CDE	No	No	No	38
Little [14]	USA	2003	1995–2000	EPOCH	Yes	No→Yes	Yes	39
Levine [13]	USA	2004	1999–2002	CHOP	Yes	Yes	Yes	24
Sparano [19]	USA	2004	1995–1999	CDE	Yes	Yes	Yes	98
Toffoli[[22]	Italy	2004	NR	CHOP	No	No	No	19
Kaplan [9]	USA	2005	1998–2002	CHOP/R-CHOP	Yes	Choice	Yes	150
Spina [21]	Europe/USA	2005	1998–2003	R-CDE	Yes	Yes	Yes	74
Weiss [24]	Germany	2006	1997–2001	CHOP	Yes	Yes	No	72
Mounier [15]	France	2006	1993–1999	CHOP	Yes	Yes	Yes	204
Boue [11]	France	2006	NR	R-CHOP	Yes	Choice	G3/G4	61
Hernandez [12]	Venezuela	2006	NR	CHOP	No	No	No	22
Ribera [17]	Spain	2008	2001–2006	R-CHOP	Yes	Yes	G3/G4	81
Sparano [20]	USA	2010	2002–2006	R-EPOCH	Yes	Choice	Yes	51

PJP, *Pneumocystis jiroveci* pneumonia; CNS, central nervous system; G-CSF, granulocyte-colony stimulating factor; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; EPOCH, infusional etoposide, cyclophosphamide, doxorubicin, vincristine, and dexamethasone; CDE, infusional cyclophosphamide, doxorubicin, and etoposide; R, rituximab; Choice: investigator's choice; G3/G4: if grade 3 or 4 neutropenia during previous cycle; NR, not reported.

TABLE II. Selected Characteristics of the Patients Included in This Study

	R-CHOP		CHOP			R-CDE		CDE			R-EPOCH		EPOCH		
Characteristic	*N*	%	*N*	%	*P*	*N*	%	*N*	%	*P*	*N*	%	*N*	%	*P*
Total	241	31	538	69	–	95	49	98	51	–	51	57	39	43	–
Median age (years)	43		38		–	38		40		–	44		40		–
Median $CD4^+$ count	136/uL		109/uL		–	161/uL		160/uL		–	181/uL		198/uL		–
Sex															
Men	121	85	356	86	0.98	60	81	82	84		43	84	36	92	0.41
Women	21	15	59	14		14	19	16	16	0.86	8	16	3	8	
HAART															
Yes	222	92	368	68	<0.01	42	57	71	74	0.05	36	71	18	46	0.03
No	19	8	170	32		32	43	27	37		15	19	21	54	
Clinical stage															
Early (1 and 2)	63	26	178	35	0.02	22	30	25	24	0.66	8	16	13	33	0.09
Advanced (3 and 4)	178	74	333	65		52	70	73	76		43	84	26	67	
aaIPI scores															
Low/low-int risk	108	45	190	54	0.03	42	57	62	67	0.48	35	69	23	59	0.39
High/high-int risk	133	55	161	46		32	43	36	33		16	31	16	41	

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R, rituximab; CDE, infusional cyclophosphamide, doxorubicin, and etoposide; EPOCH, infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; HAART, highly active antiretroviral therapy; aaIPI, age-adjusted International Prognostic Index.

Overall, it is not surprising that the addition of rituximab to chemo is associated with an improved CR and 2-year OS rates, as in several RCTs in immunocompetent population R-chemo has consistently been associated with improved response rates and outcome [2,4]. Our discussion, however, will focus on the potential reasons behind the apparent benefit found in our study. On the basis of the data presented here, there did not seem to be an apparent difference with regards to age and $CD4^+$ counts, although due to the level-study nature of our analysis no additional statistical adjustments could be made to investigate the role of these factors in response and outcome. Furthermore, there was no statistical difference between the R-chemo and chemo groups regarding advanced stage and aaIPI scores.

The clear difference was seen in the proportion of patients on the R-chemo group receiving HAART. Since the introduction of HAART, the prognosis of patients with HIV-associated NHL has improved significantly [8]. The reasons behind this improvement include virological and immunological responses, which would not only allow for a better control of the HIV infection, but also decrease the rates of potentially life-threatening infections. This effect has facilitated the administration of standard doses of chemotherapy, which was associated with a large proportion of deaths from chemotherapy in the pre-HAART era. Some authors have posited that the mere use of HAART without necessary improvement in viral replication is sufficient to favor complete remission [13,14]. On the other hand, few groups have shown that either a virological or an immunological response to HAART is necessary to improve survival in patients with HIV-associated NHL treated concurrently with chemotherapy [6,7,17]. Of additional importance is that early studies using CHOP did not routinely administer G-CSF [12,18,22–24], PJP prophylaxis [12,18,22] or CNS prophylaxis [12,18,22]. This could have also influenced on the better outcomes seen in patients treated with R-CHOP, as these studies were designed to include better supportive measures.

Our study has several strengths, which include the first attempt to evaluate the role of rituximab by studying exclusively prospective trials, the side-to-side comparison of specific chemotherapeutic regimens with and without rituximab, and the large sample size. Our study included 15 prospective studies from different parts of the world. Prospective studies are less likely to carry several of the inherent problems of a retrospective design, as objectives and outcomes are defined a priori and data are usually complete. However, single-arm prospective studies carry their own limitations in comparison with RCTs, such as selection bias, heterogeneity and, obviously, the lack of a controlled arm. Additional imitations of our study are the lack of sufficient data to analyze the cause of mortality among the studied population, specifically with regards to infectious complications, the fact that the patients were not actually randomized to R-chemo or chemo groups, and our inability to adjust our results for potentially important prognostic markers. These limitations could be better addressed by a patient-level meta-analysis.

Despite our shortcomings, we were able to show an improvement in response and survival rates in patients with HIV-positive NHL with R-chemo, supporting its use as the standard of care for these patients. Our results should be taken with caution, as they conflict with a published RCT and data arising from an RCT are more reliable than pooled analyses. However, given the specific issues with the study by Kaplan et al. [9], such as lack of antibiotic prophylaxis and the administration of rituximab to patients with CD4 counts <50 cells/mm^3, our study likely reflects the actual clinical practice. A true answer, however, should come from a carefully designed RCT. Our

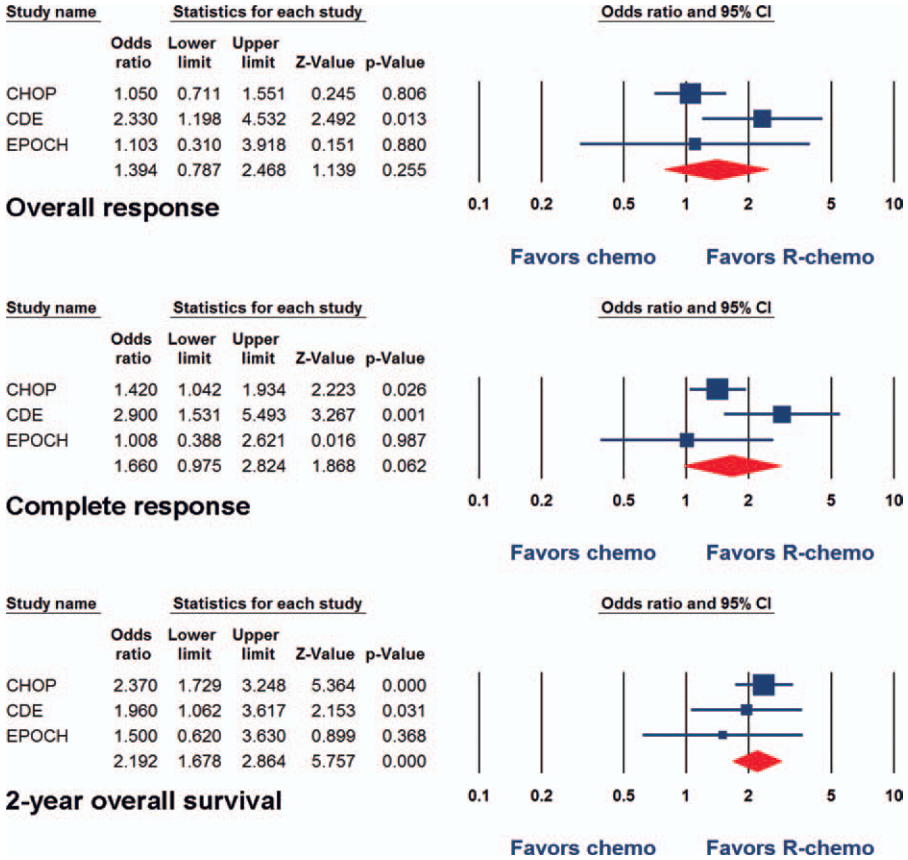

Figure 1. Forest plots showing the pooled odds ratio and 95% confidence interval for overall response (top), complete response (center) and 2-year overall survival (bottom) for chemo and R-chemo from prospective studies in patients with HIV-associated non-Hodgkin lymphomas. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

study does not address the administration of a specific R-chemo regimen over another. Other authors have suggested the current standard of care for the therapy of HIV-associated NHL is R-EPOCH [25]. Because of the scarcity of patients, comparative prospective studies are difficult to perform in HIV-infected population. For this purpose, multi-institutional collaboration is warranted.

Methods

The authors performed independent literature searches using Pubmed/MEDLINE from January 1980 through September 2011 using the terms "(HIV OR AIDS) AND lymphoma" with limits "Clinical Trial". We limited our results to prospective trials in English language in which HIV-positive NHL patients were treated with chemo or R-chemo. Retrospective case series and case reports were excluded. The reference lists of the included studies were scrutinized for additional studies. Any discrepancies between reviewers were resolved by joint re-evaluation of the full-text manuscript. Patients' characteristics and outcomes were collected from published data. Data extraction was performed independently by the two reviewers and included author, year of publication, country of origin, study design, sample size, use of HAART, PJP prophylaxis, CNS prophylaxis, use of G-CSF, age, sex, $CD4^+$ counts, clinical stage, aaIPI score, ORR, CRR, and 2-year OS. Any discrepancies were addressed by a joint re-evaluation of the original article. Clinical characteristics are presented using descriptive statistics (i.e., medians for continuous and proportions for categorical variables). Chi-square was used to compare categorical characteristics between groups. The main outcomes were ORR, CRR, and 2-year OS rates and will be reported as nonadjusted OR (95% CI). All ORs were calculated comparing R-chemo versus chemo. Meta-analyses using the random effect model [26] were used to estimate the outcomes. Heterogeneity was measured using the I^2 index [27]; I^2 values of 25, 50, and 75% reflect mild, moderate, and severe heterogeneity, respectively. Publication bias was addressed by using the trim-and-fill analysis [28], which assumes that the effect sizes of all the studies distribute normally around the center of a funnel plot; if asymmetry is found, it adjusts for the potential effect that nonpublished (imputed) studies might have had on the measured outcome. All calculations were obtained using the MedCalc (MedCalc Software, Mariakerke, Belgium) and Comprehensive Meta-Analysis (Biostat, Englewood, NJ).

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Inpatient management of sickle cell pain: A 'snapshot' of current practice

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The Sickle Cell Disease Clinical Research Network (SCDCRN) designed the PROACTIVE Feasibility Study (ClinicalTrials.gov NCT00951808) to determine whether elevated serum levels of secretory phospholipase A2 (sPLA2) during hospitalization for pain would permit preemptive therapy of sickle cell acute chest syndrome (ACS) by blood transfusion [1,2]. While PROACTIVE was not designed to assess pain management and was terminated early due to inadequate patient accrual, collection of clinical data allowed a "snapshot" of current care by expert providers. Nearly half the patients admitted for pain were taking hydroxyurea; hydroxyurea did not affect length of stay. Providers commonly administered parenteral opioid analgesia, usually morphine or hydromorphone, to adults and children, generally by patient-controlled analgesia (PCA). Adult providers were more likely to prescribe hydromorphone and did so at substantially higher morphine equivalent doses than were given to adults receiving morphine; the latter received doses similar to children who received either medication. All subjects treated with PCA received higher daily doses of opioids than those treated by time-contingent dosing. Physicians often restricted intravenous fluids to less than a maintenance rate and underutilized incentive spirometry, which reduces ACS in patients hospitalized for pain [3].

The most common cause of hospitalization of people with sickle cell disease (SCD) is the acute pain episode [4]. ACS is defined as new clinical pulmonary findings and a new infiltrate on chest radiograph [5], nearly 50% of ACS is diagnosed during hospitalization for other complications [6]. The 237 patients (169 SS, 42 SC, 15 $S\beta^0$-thalassemia, 11 $S\beta^+$-thalassemia) enrolled in PROACTIVE from 25 centers included 118 males and 119 females. Mean age of enrolled patients was 19.3 years (range 2.0–68.0); there were 122 children and 115 adults (age =18 years). One hundred one enrolled on the day of admission and 114 the day after; 22 enrolled on day 3. Ten subjects were randomized to receive transfusion or not; the remainder were monitored in an "Observation" arm of the study. Mean duration of hospitalization was 4.1 days (range 1–11) for children and 5.0 days (range $<$1–40) for adults. This average length of stay for pediatric subjects is comparable to that estimated from the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID): 4.4 days [7] in 1997 and 4.7 days in 2000 [8].

Pain most commonly occurred in the lower extremities in both adults (66%) and children (54%) (Supporting Information Table I). Back pain was second most prevalent (44%), especially seen in adults over age 35 (73%). Abdominal pain was most common in children aged 2–9 years (25%). Seventy-seven percent of all patients complained of chest or back pain. Incentive spirometry administered at 10 puffs every two hours while patients were awake was shown in 1995 to significantly reduce the risk of ACS in patients hospitalized with pain at these sites; many now use incentive spirometry on all inpatients requiring opioid analgesia. Underutilization of this safe, inexpensive intervention has been reported [9]; only 54% of our patients (60% of children and 47% of adults) and 56% of those with chest/back pain received protocol-recommended spirometry. Spirometry prescription differed between