Safety and efficacy of CHOP or R-CHOP based regimens for treatment of diffUse large B-cell Lymphoma protease inhibitor or non-protease inhibitor based antiretroviral Treatment regimens in HIV-infected patients receiving: SCULPT study

Submitted to the

HIV Residency Advisory Committee
Toronto General Hospital/McGill University Health Centre
Toronto, ON & Montréal, QC, and the
Leslie Dan Faculty of Pharmacy, University of Toronto

In Partial Fulfillment of the Requirements of the
HIV Pharmacy Specialty Residency Program

By

Alison YJ Wong, B.Pharm., M.Sc.
HIV Pharmacy Resident
November 25, 2011

Co-investigators:
Suzanne Marcotte, B.Pharm, M.Sc[4], Mathieu Laroche, B.Pharm, M.Sc[4], Nancy L Sheehan, B.Pharm, M.Sc[3], Vishal Kukreti, MD, FRCPC[1,5], Jean-Pierre Routy, MD[3,6], Bernard Lemieux, MD, FRCPC[4], Jack Seki, B. Pharm, Pharm D[1], Danielle Rouleau, MD, Msc FRCPC[4,7,8], Alice Tseng, Pharm D., FCSHP[1,2]

Affiliations:
[1]University Health Network, Toronto, Ontario
[2]University of Toronto, Toronto, Ontario
[3]Immunodeficiency service, McGill University Health Centre, Montréal, Québec
[4]Centre hospitalier de l'Université de Montréal, Montréal, Québec
[5]Department of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, Ontario
[6]Division of hematology, McGill University Health Centre, Montréal, Québec
[7]UHRESS, Centre hospitalier de l'Université de Montréal, Montréal, Québec
[8]Université de Montréal, Montréal, Québec

ABSTRACT

Background: Despite successful combination antiretroviral therapy (cART), HIV-infected patients remain at greater risk of diffuse large B-cell lymphoma (DLBCL) than the non-HIV infected population. Concomitant use of cART and cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab (CHOP+/-R) substantially increases response rates but may also increase toxicity, possibly due to antiretroviral-antineoplastic drug interactions. The influence of different cART combined with CHOP+/-R, however, remains largely unknown. We evaluated the frequency of confirmed or unconfirmed complete remission (CR/CRu) of DLBCL in patients treated with CHOP+/-R while receiving a protease inhibitor (PI) versus a non-PI based cART.

Methods: A retrospective multi-centered pilot study was conducted in HIV-infected patients on cART who were treated for DLBCL with CHOP+/-R between 2002-2010 in three academic hospitals. Percentage of CR/CRu, one-year and two-year disease free survival (DFS) and overall survival (OS), median disease free survival and overall survival time were evaluated. Overall percentage of intended chemotherapy dose delivery and the number of delayed cycles, frequency of severe adverse events, HIV virological control and CD4 count were also evaluated. Preliminary comparisons between patients receiving PI and non-PI based cART were made using Fisher's exact test and Wilcoxon's test. Possible predictors of CR/CRu between groups were evaluated by univariate logistic regressions.

Results: A total of 34 patients were included with 65% and 35% of patients receiving a PI and non-PI based cART, respectively. Baseline characteristics were similar between both groups; 85% of patients were male, median age 43 years, 50% with International Prognostic Index (IPI) score 2-3, median 7 years since HIV diagnosis and a median $CD4^+$ of 225 cells/mm^3 at baseline.

CR/CRu was achieved in 77% and 58% of patients in the PI and non-PI group, respectively (p=0.21), with 65% and 63% of patients achieving 2-year overall survival (p=1.00). Univariate analyses showed that a lower IPI score and a higher total number of received chemotherapy cycles were significantly associated with higher CR/CRu rates (p=0.02 and 0.03, respectively). Toxicity was similar between both groups with the exception of decreased frequency of anemia in the PI group (23% versus 37%, p=0.04).

Conclusion: Similar efficacy of CHOP+/-R was observed in patients receiving a PI and a non-PI based cART. Response rates appear to be higher in patients receiving a PI based cART although this requires confirmation with larger studies. No significant increase in toxicity was observed in patients receiving a PI based cART; furthermore, less anemia was observed in comparison to those on a non-PI based cART.

TABLE OF CONTENTS

INTRODUCTION

Since the advent of combination antiretroviral therapy (cART), a decrease of up to 70% in the incidence of non-Hodgkin's lymphoma (NHL) in the HIV-infected population has been observed (1-3). Nonetheless, NHL remains one of the most frequently diagnosed malignancies and contributes to up to 22% of those diagnosed in this population (2-4). In addition these individuals remain at greater risk for developing NHL than non-infected persons (5). The most frequent type of NHL remains diffuse large B-cell lymphoma (DLBCL) which is commonly treated with a standard regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) with or without rituximab (+/- R), an anti-CD20, B-cell antibody (3, 6-9).

The concomitant use of cART and CHOP+/-R, in comparison to the use of chemotherapy alone, has shown substantially increased rates of complete remission from 20-36% to 51-77% (6, 7, 10-13). Some studies showed similar rates as non-HIV infected patients when cART was co-administered with chemotherapy (6, 10); however, several studies and case reports presented below have shown increased toxicity and decreased plasma concentrations of antiretroviral drugs thereby illustrating the potential interaction between cART and chemotherapy (14-18).

Interactions may be classified into pharmacodynamic and pharmacokinetic interactions. The first consists of concomitant use of drugs with similar side effects thereby leading to increased toxicity. For instance, both chemotherapy and zidovudine are likely to cause hematologic toxicity and the latter is therefore avoided. Didanosine and stavudine are also avoided with chemotherapy agents due to the cumulative risk of peripheral neuropathy. (19)

Pharmacokinetic interactions, consisting of modified metabolism of the drugs, could lead to decreased drug efficacy and/or increased toxicity. Non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens are considered as inducers of CYP3A4. This may result in

increased drug elimination thereby potentially resulting in decreased drug efficacy of doxorubicin, vincristine and prednisone(20). Regarding cyclophosphamide, induction of CYP 3A4 may result in increased transformation to inactive toxic metabolites, thereby leading to increased toxicity and decreased efficacy. No studies regarding the pharmacokinetic or clinical impact of NNRTIs on CHOP+/-R were found, however. Protease inhibitor (PI) based regimens, on the other hand, are considered as potent inhibitors of enzymes including CYP3A4 and 2B6 (20). The elimination of doxorubicin, vincristine and prednisone may therefore be decreased, possibly leading to increased toxicity. Regarding cyclophosphamide, its metabolism via CYP 3A4 to inactive metabolites may be decreased, thereby potentially leading to an increase in transformation to its active metabolite via CYP 2B6 therefore increased efficacy and toxicity could be possible if co-administered with PIs. Particular mention of ritonavir is required as it is often used as a pharmacokinetic enhancer to increase the plasma concentration of other PIs (commonly known as “boosting”) and is also the most potent CYP 3A4 inhibitor amongst the PIs but also acts as a CYP 2B6 inducer. As other PIs, it may therefore increase the toxicity of doxorubicin, vincristine and prednisone. Regarding cyclophosphamide however, increased activation is possible, leading to potential increased efficacy and increased toxicity. (20, 21) Pharmacokinetic studies have shown an unchanged doxorubicin clearance rate (18, 22) but a 50% decrease of cyclophosphamide clearance in comparison to historical cohorts when CHOP was co-administered with a non-boosted PI based regimen consisting of indinavir, saquinavir or nelfinavir (18). This result, however, did not translate to excessive hematologic toxicity nor decreased efficacy (18).

Dose-related toxicities of vinca alkaloids, such as anemia, neutropenia, peripheral or autonomic neuropathy, have been shown to increase during co-administration with PI based

regimens (14, 15, 17). Vaccher et al evaluated the safety of CHOP alone or with zidovudine monotherapy in comparison to co-administration of CHOP and a PI based cART (indinavir, saquinavir, nelfinavir, ritonavir at treatment doses) (15). The latter group showed a 29% increase in use of colony stimulating factor (granulocyte macrophage-colony stimulating factor or granulocyte-colony stimulating factor) and an increase in grade 3 or 4 adverse events such as anemia (7% vs 33%; $p = 0.001$) and autonomic neurotoxicity (0% vs 17%; $p = 0.002$) (15). The authors concluded that the combination of CHOP and cART was feasible but careful monitoring of cross toxicity and possible pharmacokinetic interactions would be necessary (15). Another study evaluating the effect of non-PI vs PI based cART (not specified) on a chemotherapy regimen consisting of infusional cyclophosphamide, doxorubicin and etoposide also showed a higher incidence of severe neutropenia (38% vs 54%; $p = 0.05$) and serious infections (25% vs 48%; $p = 0.025$) (16). The authors concluded that physicians may want to consider alternative regimens to PI based cART when prescribing that chemotherapy regimen (16).

It is important to note, however, that these studies have numerous limitations. When specified, the antiretroviral agents evaluated were unboosted indinavir, saquinavir, nelfinavir or ritonavir at treatment doses in combination with two nucleoside reverse transcriptase inhibitors (NRTI) (often including stavudine, didanosine and zidovudine), all of which are now less commonly used. The effects of other antiretroviral agents such as lopinavir, darunavir and raltegravir remain largely unknown. In addition, all studies often included multiple chemotherapy regimens and several histological subtypes of NHL, thereby introducing potential bias. The number of pharmacokinetic studies evaluating the impact of cART on CHOP+/-R is also extremely limited. Finally, there have been no studies to our knowledge that compare

directly the effect of different cART regimens on CHOP+/-R therapy in HIV-infected patients with DLBCL.

Despite the limitations of the studies, PI based regimens may increase CHOP+/-R toxicity. Hematologic and autonomic toxicities secondary to CHOP are often managed by delays in chemotherapy cycles or dose reductions of chemotherapy, both of which may lead to decreased clinical efficacy. The main objective of this pilot study was therefore to determine the rate of complete remission or unconfirmed complete remission (CR/CRu) of DLBCL in patients treated with CHOP+/-R and receiving a PI based cART or a non-PI based cART.

METHODS

Patients

We conducted a retrospective multi-centered observational study using data from 3 different academic centres that included the Montreal Chest Institute Immunodeficiency Service (MCI), Montreal, the *Centre Hospitalier de l'Université de Montréal (CHUM)*, Montreal and the Princess Margaret Hospital (PMH), Toronto. The MCI is an urban hospital clinic that offers clinical follow-up for ambulatory HIV-infected patients and a prospective clinical database is maintained on all patients since 1989. Patients with a diagnosis of non-Hodgkin's lymphoma documented in the database were screened for eligibility. The CHUM is a network of three urban hospitals that includes outpatient HIV and oncology clinics as well as inpatient services. All patients who had a concomitant diagnosis of previous HIV or AIDS and new DLBCL were identified through the archive's diagnosis coding system and were screened for eligibility. Prior to April 1st, 2006, the coding system used was CIM-9 (HIV: B24, AIDS Z21 and DLBCL: 9680). Thereafter, the coding system was changed to CIM-10 (HIV: 795.6, AIDS: 042.9, DLBCL:

9680). Finally, PMH is a tertiary hospital specialized in the treatment of cancer. All patients who received CHOP+/-R at this center were identified through the pharmacy dispensing system and screened manually for eligibility.

Eligible patients were HIV-infected adults who started CHOP+/-R chemotherapy between January 1st, 2002 and January 1st, 2010 for the treatment of DLBCL. Diagnosis of DLBCL was reassessed on an individual basis if documentation by the treating physician was unclear. Diagnosis of HIV infection could be as late as 6 months after DLBCL diagnosis. Concomitant cART (defined as the use of three or more antiretroviral agents) by the second cycle of chemotherapy treatment was mandatory for patients to be included in the study. Exclusion criteria included documented diagnosis of Burkitt's lymphoma or plasmablastic lymphoma, history of prior chemotherapy treatment unless treated for Kaposi's sarcoma and the use of delavirdine in cART. Delavirdine was excluded as it is considered to be an enzyme inhibitor (23) in contrast to the other NNRTIs, considered to be inducers (19). Other exclusion criteria consisted of increased bilirubin or serum aspartate aminotransferase level considered unrelated to DLBCL or atazanavir use (for increased bilirubin) requiring chemotherapy dose adjustments. Patients with renal failure at DLBCL diagnosis defined as an estimated glomerular filtration rate less than, or equal to 30 mL/min/1.73m^2 (calculated with the 4-variable modification of diet in renal disease formula(24)) were also excluded. Finally, patients who received an empiric reduction in dosage of CHOP at the first cycle unrelated to increased liver function tests were also excluded. Laboratory values immediately prior to chemotherapy initiation were used to assess patient eligibility.

Endpoints

The primary endpoint was CR/CRu as documented by the treating physician at the time of treatment. If documentation was unclear, a hemato-oncologist was consulted for clarification. Objective assessment of response according to the Cheson criteria (25) was not considered feasible due to the retrospective nature of the study as all required parameters were not systematically assessed and documented in the charts. Secondary endpoints were overall survival (OS), disease free survival (DFS), overall percent of intended chemotherapy dose delivery and number of chemotherapy cycles delayed for 7 days or more. OS was assessed in all patients and was measured from the date of first chemotherapy treatment to the date of death whereas DFS was assessed in patients who achieved CR/CRu and was measured from the date of last chemotherapy treatment to the date of disease relapse or death. Other secondary endpoints included CD4 count and HIV virological response for assessment of HIV control. For patients with detectable HIV viral loads (VL) at baseline, virological response was defined as a decrease in HIV VL of more than 2 $\log_{10}$ copies/mL from baseline or undetectable VL at weeks 4 – 8 after chemotherapy initiation. At 20 – 28 and 44 – 52 weeks after chemotherapy initiation, adequate virological response was defined as undetectable VL alone. For those with undetectable VL at baseline, all VLs reported during chemotherapy were analyzed to determine if the patient experienced virological breakthrough defined as a detectable VL (> 40 or >50 copies/mL depending on local assay). Safety was assessed by the frequency of grade 3 or 4 adverse events (anemia, acute kidney injury, ALT or AST increase, blood bilirubin increase, constipation, diarrhea, febrile neutropenia, infection, noninfective cystitis or hematuria, infusion related reaction, nausea, vomiting) as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.2010(26).

Patients were followed through the earliest of the following: a change of cART between the 2nd and last chemotherapy cycle leading to a change of treatment arm (eg: change from a PI based regimen to a non-PI based regimen), two-year follow-up after the end of chemotherapy, death or until January 1st, 2011.

Data collection

Demographics (age, gender), DLBCL related characteristics (Ann Arbor stage, age-adjusted International Prognostic Index [IPI] score (27), B symptoms, extranodal, bone marrow or central nervous system involvement), HIV infection related characteristics (time since HIV diagnosis, prior AIDS defining illness, prior cART exposure, time since cART initiation, change of cART between date of DLBCL diagnosis and chemotherapy initiation) and concomitant infection with hepatitis B or C infection were collected at DLBCL diagnosis. cART regimen used, change of cART, chemotherapy doses, delays in chemotherapy cycles, total number of chemotherapy cycles, use of any rituximab and primary prophylaxis with granulocyte colony stimulating factor (GCSF) at the first chemotherapy cycle were collected while the patient received chemotherapy. Regarding HIV laboratory values, all VLs were collected from baseline until the end of chemotherapy and CD4 counts were collected at baseline and between chemotherapy cycles in order to assess the effect of chemotherapy. The first CD4 count within the month after the last cycle of chemotherapy was also collected in an attempt to capture the cumulative effect of chemotherapy. Laboratory values for toxicity outcomes were collected during chemotherapy and for the two-year follow-up period. Data was collected from local databases and completed with a review of the medical records. A copy of the data collection form is attached in Appendix A.

Statistical analysis

Descriptive analyses were stratified by cART received (PI vs non-PI based cART) and presented as median ± interquartile range (IQR) for continuous variables, and proportions for categorical variables.

Regarding chemotherapy related outcomes, rates of CR/CRu, one-year and two-year DFS and OS rates, median time to disease relapse or death and median time to death were analyzed. Overall percentage of dose received and the number of chemotherapy cycles delayed for 7 days or more were also described. Regarding HIV related outcomes, CD4 counts, virological response for patients with detectable VL at baseline and maintenance of undetectable VL for those with undetectable VL at baseline were also described.

Baseline characteristics and exploratory comparisons between PI and non-PI based cART were analyzed using the Fisher's exact test and Wilcoxon test for categorical and continuous outcomes, respectively. Univariate analyses were done by use of logistic regression to estimate odds ratios (OR) for having CR/CRu. Two-tailed exact p-values (or Monte Carlo estimate of p-value if exact was not possible) less than or equal to 0.05 were considered statistically significant. Analyses were conducted with SPSS Statistics 19.0 (SPSS Inc., Chicago. Illinois).

Ethical considerations

The retrospective use of data from the MCI, PMH and CHUM was approved by the research ethics board of each centre. In addition, a data transfer file agreement was signed between the investigators from the three sites.

RESULTS

A total of 34 patients were included, of whom 22 (65%) and 12 (35%) patients received a PI-based and non-PI based cART respectively. Patients were predominantly male (85%) with a median age of 43 years (IQR 38; 53) and a median CD4 count of 225 cells/mm^3 (IQR 113; 440) at baseline. PI use was separated as follows: lopinavir/ritonavir (32%) and atazanavir/ritonavir (23%), darunavir/ritonavir BID dosing (9%), fosamprenavir/ritonavir (9%), nelfinavir (9%), lopinavir/ritonavir and nevirapine (9%), lopinavir/ritonavir and indinavir (5%). Patients who received a non-PI based cART received either an efavirenz-based therapy (50%) or a raltegravir-based therapy (50%). In regards to the nucleoside reverse transcriptase backbone, zidovudine, stavudine and didanosine were used respectively in 1, 4 and 1 patients in the PI group and 1, 1 and 0 patients in the non-PI group. Those receiving a PI-based cART had a more advanced HIV disease than those receiving a non-PI based cART as reflected by a lower CD4 count, a longer time since HIV diagnosis and higher proportion of history of AIDS-defining illness although these differences were not statistically significant (Table 1.). In contrast, the extent of DLBCL was less severe in the PI group as reflected by the lower IPI score and the lower proportion of patients with bone marrow or CNS involvement although these differences were also not statistically significant (Table 1). The proportion of patients who received concomitant rituximab chemotherapy (55% and 50% in the PI and non-PI group respectively; p = 1.00) and primary GCSF prophylaxis (73% and 67%, respectively; p = 0.71) was similar in both groups.

Overall CR/CRu was achieved in 24 (71%) patients with a total of 17 (77%) and 7 (58%) patients achieved CR/CRu in the PI and non-PI groups, respectively, (p=0.21) (Table 2). Three patients were censored prior to the evaluation of response to therapy, two of whom received a PI-

based cART and were switched to a non-PI based cART after the 2nd cycle of chemotherapy to avoid drug-drug interactions and one in the non-PI group who was lost to follow-up immediately after receiving the last cycle of chemotherapy. Median duration of follow-up was 27 (IQR 8; 29) and 22 (IQR 3; 28) months for the PI group and non-PI group, respectively (p = 0.36). Median survival time was 27 months (IQR 8; 28) and 21 months (IQR 2; 28) for PI and non-PI groups, respectively (p = 0.44). One-year and two-year OS rates were similar between both groups (68% vs 67%; p = 1.00 and 65% vs 63%; p = 1.00; Figure 1a). Reason for censor did not differ between both groups (Table 2). A total of 8 patients died during the follow-up period, among whom the cause of death was DLBCL related for 3 patients in each group (disease progression or relapse). The two remaining patients were on a PI based cART and died of non-DLBCL malignancy and syndrome of inappropriate antidiuretic hormone secretion, respectively, while in CR/CRu.

Amongst those who achieved CR/CRu, median DFS was 24 months (IQR 20; 24) and 19 months (IQR 14; 24) for PI and non-PI groups, respectively (p=0.38). One-year and two-year DFS rates were respectively 88% vs 100% (14/16 vs 6/6 patients; p = 0.54) and 87% vs 75% (13/15 vs 3/4 patients; p = 0.53) for those receiving a PI-based and non-PI based therapy (Figure 1b). In addition to the two patients who died while in CR/CRu as mentioned above, one patient on a non-PI based cART had disease relapse 18 months after the last cycle of chemotherapy. Univariate analyses showed that only lower IPI score and higher total number of chemotherapy cycles received were associated with CR/CRu (Table 3).

Regarding chemotherapy, a total of 201 cycles of chemotherapy were administered, with 133 and 68 cycles of chemotherapy in the PI and non-PI groups, respectively, of which 18 (14%) and 4 (6%) were delayed (p=0.27). Neutropenia, febrile neutropenia or infection was the reason

for delayed chemotherapy cycles in 13 (72%) and 2 (50%) patients (p=0.57). A median of 6 chemotherapy cycles was administered for patients in each group (IQRs 6 – 8 vs 4 – 8; p=0.63 for PI and non-PI based cART, respectively). At least one cycle of chemotherapy was delayed in 9 (41%) and 4 (33%) patients in the PI and non-PI groups (p = 0.73). Dose reductions of chemotherapy agents were similar in both groups although a greater proportion of patients receiving a PI based cART required vincristine dose reductions (36% vs 8%; p = 0.11) (Table 4). Seventy-eight percent of vincristine dose reductions was due to neurotoxicity.

With regards to the efficacy of cART, 70% (7/10) of those who had undetectable VL at baseline remained virologically suppressed throughout (67% [4/6] vs 75% [3/4] in the PI and non-PI group, respectively; p = 1.00). The remaining 3 patients each had an isolated virologic blip with a VL less than 200 copies/mL. For patients with a detectable or unknown VL at chemotherapy initiation, similar virological response was observed in both groups (Table 5). In order to better evaluate the impact of chemotherapy on CD4 count, the latter is shown in relation to the chemotherapy cycle received (Figure 2).

The rate of adverse events during chemotherapy was similar in both groups (Table 6) with the exception of grade 3 or 4 anemia that occurred less frequently in patients receiving a PI based cART than a non-PI based cART (23% and 37% of total cycles, respectively; p = 0.04). Occurrence of febrile neutropenia was numerically higher in patients receiving a PI based cART in comparison to a non-PI based cART although this did not reach statistical significance (13% and 7%; p = 0.34). During the two-year follow-up period, two patients (one in each group) were diagnosed with doxorubicin induced cardiomyopathy.

DISCUSSION

This retrospective, multi-centered pilot study was conducted in order to determine the response rates of DLBCL to CHOP+/-R in HIV-infected patients receiving either a PI-based cART or a non-PI based cART. We report a response rate (CR/CRu) of 77% and 58% in patients receiving concomitant chemotherapy with a PI and non-PI based cART, respectively. These results are consistent with those reported in the literature (51 – 77%) regarding the response of NHL to CHOP+/-R (6-8, 10-12). The 2-year overall survival rate of 63 – 65% observed in our study is also similar to that reported in the literature (60 – 75%) (6, 7, 11). The variable response and survival rates may be explained by the different baseline characteristics of the studied population (DLBCL vs Burkitt's lymphoma, IPI score, use of rituximab, baseline CD4 count, previous AIDS diagnosis and time since cART initiation). It is also interesting to note that despite the use of effective cART, the response rates remain slightly lower than those achieved with CHOP+/-R in the non-HIV infected population (63% - 86%) although these studies excluded patients with high IPI scores (28, 29).

The different response rates, 77% and 58% for patients on a PI based and non-PI based cART respectively, did not reach statistical significance ($p = 0.21$) although this is likely due to the limited power of the study. A post-hoc analysis revealed that for the rates reported within this study, a sample size of 74 patients in each group would be necessary to have a power of 80% with a confidence level of 95%. Nonetheless, CR/CRu rates were numerically higher in patients receiving PI based cART than those receiving non-PI based cART. This may be due to the increased presence of poor prognostic factors in patients receiving a non-PI based cART as reflected by the higher IPI score. The limited sample size of the study unfortunately precluded

any multivariate analysis. Another possibility is increased efficacy of CHOP+/-R in the PI group due to decreased metabolism of chemotherapy agents. Induction of chemotherapy agents by NNRTIs in the non-PI group may also have decreased CR/uCR in this group. Further details regarding the metabolism effect of PIs and NNRTIs on CHOP+/-R are discussed when evaluating safety.

Lower IPI score and higher number of chemotherapy cycles received were the only characteristics that were associated with a better response to therapy in the univariate analyses. DLBCL prognosis did not appear to depend on any HIV characteristics such as CD4 count and time since HIV diagnosis. Current literature suggests that, in addition to lower IPI score, CD4 count and previous cART may also be associated with increased response to chemotherapy (7, 8). The lack of association between HIV baseline characteristics and response rates may be explained by better control of HIV infection in our population as reflected by higher CD4 counts (median CD4 >200 cells/mm^3), a limited proportion of patients with prior AIDS-defining illnesses (18%) and a high proportion of patients treated with cART prior to chemotherapy initiation (65%). Rituximab use was not associated with increased CR/CRu ($p = 0.18$) although the OR was 3.5 (95% confidence interval [CI]; 0.59 – 21.81). Indeed, certain studies in HIV-uninfected patients reported an increase in CR/CRu rate of 13 – 18% (28, 29) and our lack of statistical significance may have been due to our limited sample size. Other studies in HIV-infected patients, however, showed no benefit (8) or even an increased risk of infectious death when used to treat NHL particularly in patients with CD4 below 100 cells/mm^3 (8, 30).

Regarding safety, the overall rate of febrile neutropenia is at the lower range of those reported in the literature (11% vs 11-31%) despite lower use of GCSF for primary prophylaxis (8, 12). The other studies, however, evaluated the impact of CHOP+/-R on NHL, including other

lymphoma subtypes with poorer prognosis (such as Burkitt's lymphoma). The main reason for chemotherapy delay was neutropenia, febrile neutropenia or infection. The proportion of chemotherapy cycles delayed was numerically greater in patients receiving a PI based cART (14%) compared to a non-PI based cART (6%). Indeed, a greater proportion of patients had documented febrile neutropenia in those receiving a PI based therapy compared to those receiving a non-PI based therapy. These findings are supported by a study by Bower et al that reported a higher incidence of severe neutropenia and serious infections in patients receiving a PI based cART compared to those receiving a non-PI based cART during chemotherapy treatment with cyclophosphamide, doxorubicin and etoposide. This may be explained by a possible reduction of doxorubicin metabolism via inhibition of CYP 3A4 due to PI based cART, thereby increasing exposure to doxorubicin, enhancing its toxicity(20). Nonetheless, pharmacokinetic studies with unboosted PIs (weaker CYP 3A4 inhibitors) did not show any change in doxorubicin clearance rate in comparison to patients not on cART (18, 22). NNRTI based cART may have also increased doxorubicin elimination via induction of CYP 3A4, potentially decreasing doxorubicin toxicity (20). This effect, however, may have been diluted by the neutral influence of raltegravir based cART (50% of non-PI based cART) on doxorubicin metabolism. A final possibility is induction of cyclophosphamide activation via CYP 2B6 by ritonavir boosted PI regimens thereby leading to increased efficacy and toxicity (20). No pharmacokinetic data regarding coadministration of cyclophosphamide and a ritonavir-boosted PI based therapy was found.

The proportion of patients requiring a vincristine dose reduction was also numerically greater in patients receiving a PI based cART compared to a non-PI based cART although this did not reach statistical significance. The main reason for vincristine dose reductions was

neurotoxicity. This is consistent with the findings of Vaccher et al who observed an increased risk of autonomic toxicity when CHOP was co-administered with a non-boosted PI based cART in comparison to CHOP alone (17% vs 0%; $p < 0.01$) (15). This may be explained by PI inhibition or NNRTI induction of vincristine metabolism via CYP3A4 as described above (20).

The rate of grade 3 or 4 anemia was significantly higher in this study in comparison to previous studies (27% vs 5-8%) (7, 8). It is difficult to interpret these findings however as data regarding the use of erythropoiesis-simulating agents was not collected. In addition, the CTCAE v4.0 definition included blood transfusions as grade 3 anemia whereas previous versions do not. Nonetheless, we observed a higher rate of anemia in patients receiving a non-PI based cART in comparison to a PI based cART despite similar exposure to zidovudine (1 patient in each group). This is in contrast to a study by Vaccher et al who reported an increased risk of anemia (33% vs 1%; $p < 0.01$) in patients receiving a PI based cART in comparison to no cART(15). Their observation, however, was likely due to the significant proportion (58%) of patients who received zidovudine as part of cART(15). The increased rate of anemia in patients receiving non-PI based cART may be explained by the more advanced stage of DLBCL in this group as reflected by the Ann Arbor stage and IPI score(31). Another possibility is that NNRTI based cART may induce cyclophosphamide transformation to inactive and possibly toxic metabolites via CYP3A4, thereby increasing its bone marrow toxicity and potentially decreasing its efficacy as shown by the decreased CR/CRu rate in the non-PI group compared to the PI group (21).

Finally, we also showed that adequate virological control during chemotherapy is possible for those with undetectable VL prior to chemotherapy initiation as no patient met the criteria for virological failure defined as an HIV RNA level above 200 copies/mL (32). This shows that adequate control of HIV remains possible despite the possibility of low tolerability

and adherence. Due to the large amount of missing data, no conclusion regarding the virologic efficacy of cART in patients with detectable VL at chemotherapy initiation can be drawn. The same can also be said in regards to the impact of chemotherapy on CD4 count.

Several major limitations of this study should be noted, including the retrospective design and the small sample size. The small sample size precluded the possibility of any multivariate analyses that could adjust for differences in baseline characteristics between the groups and greatly limited the power of the study. An attempt to include the most patients was made as shown by the large eligibility time frame and the multi-centered design. The latter, however, could have also introduced a confounding bias for plausible clustering effect by site.

CONCLUSION

This is the first study to our knowledge that reports the response rates of DLBCL to CHOP+/-R according to the type of cART received. Similar rates of CR/CRu were observed in both groups despite a numerically greater proportion of patients on a PI based regimen who experienced chemotherapy cycle delays and vincristine dose reductions. In contrast, a greater proportion of patients on a non-PI based regimen experienced anemia. Further studies including new classes of antiretroviral agents are required to determine the optimal choice of cART when co-administered with chemotherapy.

ACKNOWLEDGMENTS

We graciously thank Benoît Crevier and Jordan Pelletier, B.Sc., for their help with data collection. We thank Jeanne Chu, Manhim Chau, Costa Pexos, Andrée Séguin, Pascale Guillemette, Micheline Daneau and Lyne Sergerie for their work on data extraction and access to charts. We thank the McGill University Health Center, the *Centre Hospitalier de* l'*Université de Montréal* and Princess Margaret Hospital for allowing us access to patient charts.

REFERENCES

1. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer burden in the HIV-infected population in the United States. Journal of the National Cancer Institute. 2011;103(9):753-62.

2. Franceschi S, Lise M, Clifford GM, Rickenbach M, Levi F, Maspoli M, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. British journal of cancer. 2010;103(3):416-22.

3. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. International journal of cancer. Journal international du cancer. 2008;123(1):187-94.

4. Lanoy E, Spano JP, Bonnet F, Guiguet M, Boue F, Cadranel J, et al. The spectrum of malignancies in HIV-infected patients in 2006 in France: the ONCOVIH study. International journal of cancer. Journal international du cancer. 2011;129(2):467-75.

5. StatBite: Lymphoma incidence in HIV patients vs. general population. J Natl Cancer Inst;102(14):1003.

6. Ribera JM, Oriol A, Morgades M, Gonzalez-Barca E, Miralles P, Lopez-Guillermo A, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol. 2007;140(4):411-9.

7. Boue F, Gabarre J, Gisselbrecht C, Reynes J, Cheret A, Bonnet F, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol. 2006;24(25):4123-8.

8. Kaplan LD, Lee JY, Ambinder RF, Sparano JA, Cesarman E, Chadburn A, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood. 2005;106(5):1538-43.

9. Navarro WH, Kaplan LD**.** AIDS-related lymphoproliferative disease. Blood. 2006;107(1):13-20.

10. Diamond C, Taylor TH, Im T, Anton-Culver H**.** Presentation and outcomes of systemic non-Hodgkin's lymphoma: a comparison between patients with acquired immunodeficiency syndrome (AIDS) treated with highly active antiretroviral therapy and patients without AIDS. Leuk Lymphoma. 2006;47(9):1822-9.

11. Navarro JT, Ribera JM, Oriol A, Romeu J, Sirera G, Mate JL, et al. Favorable impact of virological response to highly active antiretroviral therapy on survival in patients with AIDS-related lymphoma. Leuk Lymphoma. 2002;43(9):1837-42.

12. Weiss R, Mitrou P, Arasteh K, Schuermann D, Hentrich M, Duehrsen U, et al. Acquired immunodeficiency syndrome-related lymphoma: simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival--results of the German Multicenter Trial. Cancer. 2006;106(7):1560-8.

13. Navarro JT, Lloveras N, Ribera JM, Oriol A, Mate JL, Feliu E**.** The prognosis of HIV-infected patients with diffuse large B-cell lymphoma treated with chemotherapy and highly active antiretroviral therapy is similar to that of HIV-negative patients receiving chemotherapy. Haematologica. 2005;90(5):704-6.

14. Makinson A, Martelli N, Peyriere H, Turriere C, Le Moing V, Reynes J**.** Profound neutropenia resulting from interaction between antiretroviral therapy and vinblastine in a patient with HIV-associated Hodgkin's disease. Eur J Haematol. 2007;78(4):358-60.

15. Vaccher E, Spina M, di Gennaro G, Talamini R, Nasti G, Schioppa O, et al. Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. Cancer. 2001;91(1):155-63.

16. Bower M, McCall-Peat N, Ryan N, Davies L, Young AM, Gupta S, et al. Protease inhibitors potentiate chemotherapy-induced neutropenia. Blood. 2004;104(9):2943-6.

17. Kotb R, Vincent I, Dulioust A, Peretti D, Taburet AM, Delfraissy JF, et al. Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. Eur J Haematol. 2006;76(3):269-71.

18. Ratner L, Lee J, Tang S, Redden D, Hamzeh F, Herndier B, et al. Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. J Clin Oncol. 2001;19(8):2171-8.

19. Mounier N, Katlama C, Costagliola D, Chichmanian RM, Spano JP**.** Drug interactions between antineoplastic and antiretroviral therapies: Implications and management for clinical practice. Crit Rev Oncol Hematol. 2009;72(1):10-20.

20. Antoniou T, Tseng AL**.** Interactions between antiretrovirals and antineoplastic drug therapy. Clin Pharmacokinet. 2005;44(2):111-45.

21. Antoniou T, Tseng A**.** Potential interactions between antineoplastics and antiretrovirals. In: Tseng A, Foisy M, eds. Handbook of HIV drug therapy. 2010 ed. Toronto; 2010:373-92.

22. Toffoli G, Corona G, Cattarossi G, Boiocchi M, Di Gennaro G, Tirelli U, et al. Effect of highly active antiretroviral therapy (HAART) on pharmacokinetics and pharmacodynamics of doxorubicin in patients with HIV-associated non-Hodgkin's lymphoma. Ann Oncol. 2004;15(12):1805-9.

23. Rescriptor. Product Monograph. ViiV Healthcare ULC; 2010.

24. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clinical chemistry. 2007;53(4):766-72.

25. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999;17(4):1244-53.

26. Common Terminology Criteria for Adverse Events (CTCAE). In: Services USDoHaH, ed. 4.03 ed; 2009.

27. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. The New England journal of medicine. 1993;329(14):987-94.

28. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. The lancet oncology. 2006;7(5):379-91.

29. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. The New England journal of medicine. 2002;346(4):235-42.

30. Spina M, Jaeger U, Sparano JA, Talamini R, Simonelli C, Michieli M, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood. 2005;105(5):1891-7.

31. Haioun C, Salar A, Pettengell R, Johnsen HE, Duehrsen U, Rossi FG, et al. Anemia and erythropoiesis-stimulating agent administration in patients with non-Hodgkin lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone +/- rituximab chemotherapy: results from an observational study. Leukemia & lymphoma. 2011;52(5):796-803.

32. Panel on Antiretroviral Guidelines for Adults and Adolescents**.** Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; 2011:1-166.

TABLES

Table 1. Baseline characteristics

	All, n (%)	PI, n (%)	Non-PI, n (%)	p-value
N	34	22	12	
Age (years)*	43 (38; 53)	42 (38; 50)	44 (35; 55)	0.85
Male gender	29 (85)	19 (86)	10 (83)	1.00
Time since HIV diagnosis (years)*	7 (1;16)	11 (1; 19)	6 (1; 11)	0.36
Prior AIDS-defining **Unknown**	6 (18) 4 (12)	5 (23) 2 (9)	1 (8) 2 (17)	0.63
cART initiated prior to DLBCL diagnosis	22 (65)	14 (64)	8 (67)	1.00
Time since cART initiation (years) [∫,]	5 (2; 10)	7 (2; 11)	3 (2; 6)	0.31
Change of cART prior to chemotherapy initiation[∫]	11 (50)	5 (36)	6 (75)	0.18
CD4 (cells/mm^3)* **Unknown**	225 (113; 440) 7 (21)	206 (98; 392) 5 (23)	330 (143;530) 2 (17)	0.39
Undetectable viral load **Unknown**	10 (29) 11 (32)	6 (27) 6 (27)	4 (33) 5 (42)	0.65
Viral load if detectable (log_{10}) *,[¥]	3.89 (2.32; 4.40)	4.14 (2.46; 4.41)	2.99 (2.01; -)	0.81

	All	PI	Non-PI	p-value
Ann Arbor stage				
I / II	12 (35)	9 (41)	3 (25)	0.47
III / IV	22 (65)	13 (59)	9 (75)	
Age adjusted IPI score				
0 – 1	17 (50)	13 (59)	4 (33)	0.14
2	9 (27)	6 (27)	3 (25)	
3	8 (24)	3 (14)	5 (42)	
B-symptoms	16 (47)	9 (41)	7 (58)	0.48
Extranodal involvement	24 (71)	16 (73)	8 (67)	0.71
Bone marrow involvement	3 (9)	1 (5)	2 (17)	0.70
CNS involvement	4 (12)	1 (5)	3 (25)	0.18
Use of rituximab	18 (53)	12 (55)	6 (50)	1.00
GCSF primary prophylaxis	24 (71)	16 (73)	8 (67)	0.71
HBV	2 (6)	2 (9)	0 (0)	0.53
HCV	6 (18)	2 (9)	4 (33)	0.15

* Reported as medians (interquartile range)

∫ Calculated for patients with prior cART exposure.

Missing data for 4 patients in PI group and 2 patients in non-PI group.

¥ Viral load available for 13 patients (10 and 3 in the PI and non-PI groups, respectively)

Table 2. Response to chemotherapy and reason for censoring

	All, n(%)	PI, n(%)	Non-PI, n(%)	p-value
Response to chemotherapy				
(Un)confirmed complete remission	24 (71)	17 (77)	7 (58)	0.21
Partial response	1 (3)	1 (5)	0 (0)	1.00
Progression	6 (18)	2 (9)	4 (33)	0.15
Unknown	3 (9)	2 (9)	1 (8)	
Reason for censor				
Prior to end of study or 2-year follow-up	14 (41)	9 (41)	5 (42)	
Change of cART after 2nd cycle of chemotherapy	2 (6)	2 (9)	0 (0)	
Death	8 (24)	5 (23)	3 (25)	
Lost to follow-up	4 (12)	2 (9)	2 (17)	0.10
End of study or 2-year follow-up	20 (59)	13 (59)	7 (58)	
2-year follow-up	17 (50)	13 (59)	4 (33)	
End of study	3 (9)	0 (0)	3 (25)	

Table 3. Univariate analyses for (un)confirmed complete remission

	Odds ratio (95% CI)	p-value
Protease inhibitors based cART	3.24 (0.57; 18.39)	0.19
Age	1.14 (0.99; 1.31)	0.08
Male gender	4.40 (0.49; 39.21)	0.18
IPI	0.25 (0.08; 0.80)	0.02
Total number of chemotherapy cycles received	1.81 (1.07; 3.06)	0.03
Rituximab	3.50 (0.56; 21.81)	0.18

cART (combination antiretroviral therapy)

Other variables tested: Previous AIDS diagnosis, use of granulocyte colony stimulating factors, delay of any cycle of chemotherapy, undetectable viral load prior to chemotherapy, years since HIV diagnosis, CD4 count. All had p-values > 0.20.

Table. 4 Chemotherapy related outcomes

	All, n (%)	PI, n (%)	Non-PI, n (%)	p-value
Median number of cycles received[¥]	6 (6; 8)	6 (6; 8)	6 (4; 8)	0.63
Any chemotherapy cycle delay	13 (38)	9 (41)	4 (33)	0.73
Dose reductions				
Cyclophosphamide	1 (3)	1 (5)	0 (0)	1.00
Doxorubicin	4 (12)	3 (14)	1 (8)	1.00
Vincristine	9 (27)	8 (36)	1 (8)	0.11
Peripheral neuropathy	4 (44)*	3 (38)*	1 (100)*	
Constipation	3 (33)*	3 (38)*	0 (0)*	1.00
Increased bilirubin	1 (11)*	1 (13)*	0 (0)*	
Neutropenia	1 (11)*	1 (13)*	0 (0)*	
Median dose received[¥, ∫]				
Cyclophosphamide	100 (100; 100)	100 (100; 100)	100 (100; 100)	0.85
Doxorubicin	100 (100; 100)	100 (100; 100)	100 (100; 100)	0.68
Vincristine	100 (90;100)	100 (75; 100)	100 (100; 100)	0.23

[¥] Reported as medians (interquartile range)

* Percentage according to number of patients who had vincristine dose reductions

∫ Reported as percentage of full dose

Table 5. Virologic response for patients with detectable or unknown viral load at chemotherapy initiation

	All, n (%)	PI, n (%)	Non- PI, n (%)	p-value
N	24	16	8	
Weeks 20-28				
Virologic suppression	5 (21)	4(25)	1 (13)	
No	3 (13)	5 (31)	0 (0)	0.63
Unknown	16 (67)	7 (44)	7 (88)	
Weeks 44-52				
Virologic suppression	2 (8)	2 (13)	0 (0)	
No	2 (8)	1 (6)	1 (13)	0.50
Unknown	20 (83)	13 (81)	7 (88)	

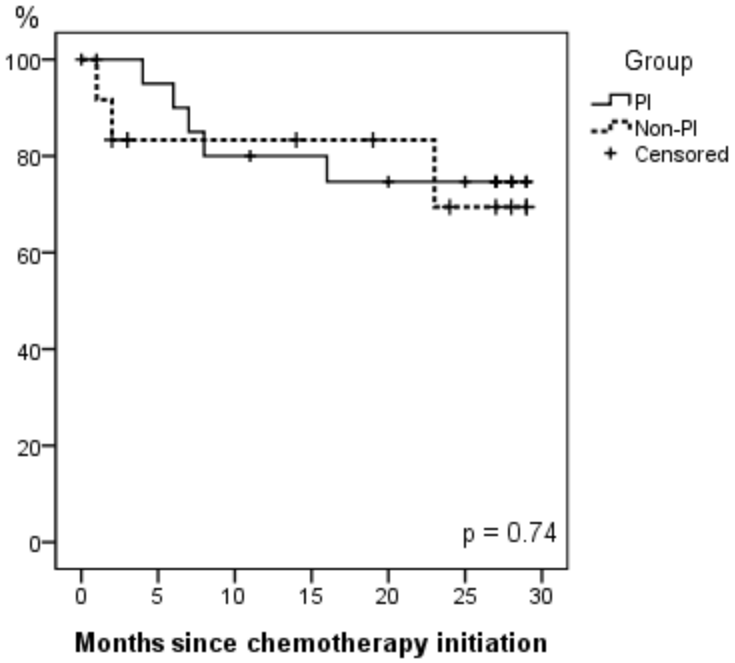
Virologic suppression < 40 copies/mL or < 50 copies/mL depending on local assay.

Table 6. Grade 3 or 4 adverse events

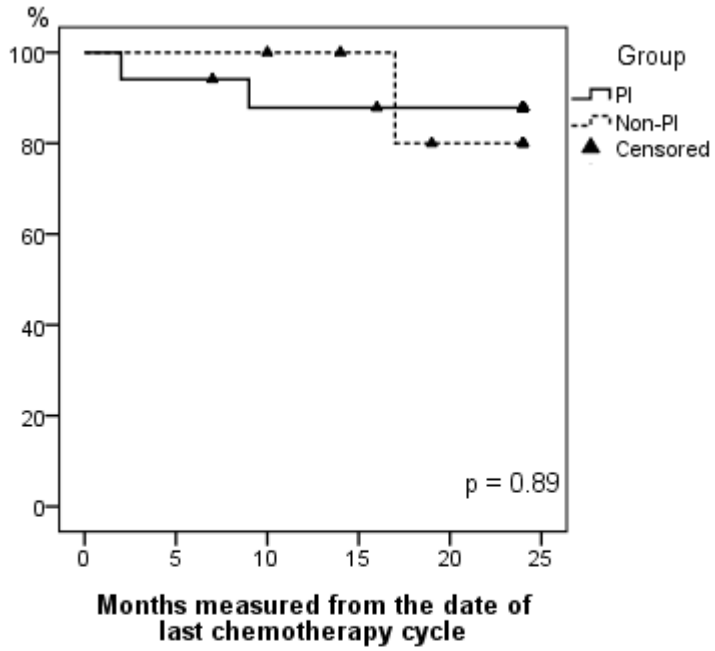
	All, n(%)	PI , n (%)	Non-PI, n(%)	p-value
Total number of cycles	201	133	68	
Anemia	55 (27)	30 (23)	25 (37)	0.04
Acute kidney injury	2 (1)	1 (1)	1 (2)	1.00
ALT/AST	7 (4)	4 (3)	3 (4)	0.69
Bilirubin	5 (3)	4 (3)	1 (2)	0.66
Febrile neutropenia	22 (11)	17 (13)	5 (7)	0.34
Non-infective cystitis or hematuria	1 (1)	0 (0)	1 (2)	0.34
Vomiting	1 (1)	0 (0)	1 (2)	0.34
Emergency visit*	6 (3)	2 (2)	4 (6)	0.18
Infection	9 (4)	7 (5)	2 (3)	0.72
Any AE during cycle	**88 (44)**	**57 (43)**	**31 (46)**	**0.77**

*Not graded according to the Common Terminology Criteria for Adverse Events.

FIGURES

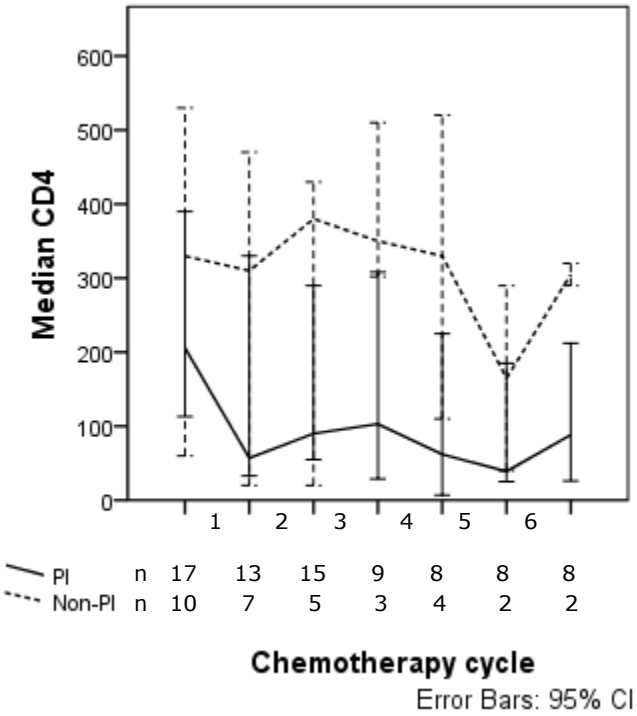


a) Overall survival

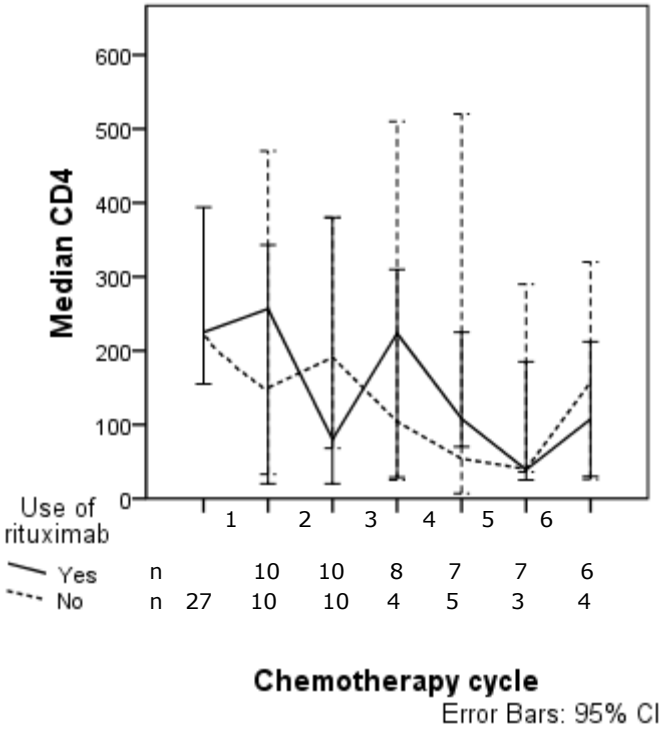


b) Disease free survival

Figure 1. Kaplan Meier survival curves



a) CD4 according to cART received



b) CD4 according to the use of rituximab

Figure 2. Change in median CD4 according to chemotherapy cycle

APPENDIX A. DATA COLLECTION FORM

ID #:	Site:	PMH CHUM CHEST

Screening criteria:

HIV-infected patients diagnosed with non-Hodgkin's lymphoma between 01/01/2002 and 01/01/2010.

REMINDER: DO NOT LEAVE ANY BLANKS

Inclusion criteria: (evaluate at DLBCL diagnosis)

			Not valid
≥ 18 years-old	Yes	No	☐
Positive HIV serology or documented HIV (diagnosed up to 6 months after DLBCL diagnosis)	Yes	No	
Documented DLBCL	Yes	No	
Cyclophosphamide/Cytoxan/Neosar/Procytox	Yes	No	
Doxorubicin/Adriamycin/Caelyx/Myocet/Rubex	Yes	No	
Vincristine/Oncovin/Vincasar	Yes	No	
Prednisone	Yes	No	
Receiving cART (≥ 3 ARV agents) at the **2nd cycle** of CHOP+/-R	Yes	No	

DLBCL: diffuse large b-cell lymphoma; cART: combination antiretroviral therapy; ARV: antiretroviral

REMINDER: DO NOT LEAVE ANY BLANKS

Exclusion criteria: (evaluate at first chemotherapy cycle)

				Excluded
Cyclophosphamide 750 mg/m^2 IV If no, dose: _____ mg/m^2 IV		Yes	No	☐
If dose decreased, related to increased bilirubin or AST	N/A	Yes	No	
Doxorubicin 50 mg/m^2 IV If no, dose: _____ mg/m^2 IV		Yes	No	
If dose decreased, related to increased bilirubin or AST	N/A	Yes	No	
Vincristine 1.4 mg/m^2 IV or 2 mg IV If no, dose: _____ mg/m^2 IV		Yes	No	
If dose decreased, related to increased bilirubin, AST or fluconazole use	N/A	Yes	No	
Prednisone 40 – 45 mg/m^2 or 100 mg po x5 d If no, dose: _____ mg/m^2 IV		Yes	No	
If dose decreased, related to increased bilirubin or AST	N/A	Yes	No	
Increased serum bilirubin level: _____ µmol/L		Yes	No	
Increase related to DLBCL or atazanavir use	N/A	Yes	No	
Increased serum AST level requiring chemotherapy dose adjustments: _____ U/L		Yes	No	
Increase related to DLBCL	N/A	Yes	No	
History of prior chemotherapy		Yes	No	
If yes, history of Kaposi's sarcoma	N/A	Yes	No	
eGFR (MDRD) ≤ 30 mL/min/m^2 = _____mL/min/1.73m^2		Yes	No	
Use of delavirdine in cART		Yes	No	
Diagnosis of Burkitt's lymphoma		Yes	No	
Diagnosis of plasmablastic lymphoma		Yes	No	

N/A: not applicable; AST: aspartate aminotransferase; ULN: upper limit of the normal; DLBCL: diffuse large b-cell lymphoma; eGFR: estimated glomerular filtration rate; MDRD: modification of diet in renal disease; cART (combination antiretroviral therapy)

REMINDER: DO NOT LEAVE ANY BLANKS

Baseline demographics (at DLBCL diagnosis)

<table>
<tr><td colspan="2">Baseline demographics</td></tr>
<tr><td>Date of birth:
(MM/YYYY) _____</td><td rowspan="5">Transmission risk factor for HIV infection:
☐ MSM
☐ IDU
☐ Heterosexual (non endemic)
☐ Heterosexual (endemic)</td></tr>
<tr><td>Gender: M F</td></tr>
<tr><td>Ethnicity: _____</td></tr>
<tr><td>Weight (Ibs / kg) :</td></tr>
<tr><td>Height (cm / in) :</td></tr>
<tr><td>History of positive HBV surface antigen or HBV DNA:
☐ yes ☐ no</td><td>History of positive HCV antibody or HCV DNA:
☐ yes ☐ no</td></tr>
<tr><td colspan="2">HIV related baseline demographics</td></tr>
<tr><td>Date of HIV diagnosis: _____
(MM/YYYY) ☐ unknown</td><td>Previous cART exposure:
☐ yes ☐ no ☐ unknown</td></tr>
<tr><td>Prior opportunistic infection
☐ yes : _____ ☐ no ☐ unknown</td><td>Date of cART initiation: _____
(MM/YYYY) ☐ unknown</td></tr>
<tr><td>Prior AIDS status:
☐ yes : _____ ☐ no ☐ unknown</td><td>Change of cART between date of DLBCL diagnosis and chemotherapy initiation:
☐ yes ☐ no ☐ unknown</td></tr>
<tr><td colspan="2">DLBCL related baseline demographics</td></tr>
<tr><td rowspan="2">Presence of B symptoms: ☐ none
☐ unexplained fever >38 degrees
☐ night sweats
☐ unexplained weight loss > 10% of body weight < 6 mo</td><td>☐ Ambulatory ☐ Hospitalized</td></tr>
<tr><td>Extranodal involvement:
☐ yes ☐ no</td></tr>
<tr><td>Ann arbor stage:
(I-IV) _____</td><td>Bone marrow involvement:
☐ yes ☐ no</td></tr>
<tr><td>Serum lactate dehydrogenase level > upper limit of the normal:
☐ yes : _____ ☐ no</td><td>Central nervous system involvement
☐ yes ☐ no</td></tr>
</table>

Laboratory values to be extracted:

Extract all the information available during the follow-up time period:

Start: Most recent value <3 months of chemotherapy initiation

End: the earliest of the following

- change of cART during chemotherapy leading to a change of treatment arm
- 2 year follow-up after end of chemotherapy
- death
- 01/01/2011

- CD 4
- CD 4 percentage
- CD 8
- CD 8 percentage
- CD 4: CD 8 ratio
- HIV viral load

- Toxicity outcomes
  - Hemoglobin
  - Serum creatinine
  - ALT
  - AST
  - Bilirubin
  - Absolute neutrophil count
  - Temperature (provide temperature if ≥ 38 degrees C)
  - Hematuria

- Other
  - beta-2 microglobulin
  - C reactive protein
  - D-dimers

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #1

<table>
<tr><td colspan="2">Date:</td><td colspan="2">Serum creatinine: _____ µmol/L</td></tr>
<tr><td colspan="2">Weight:</td><td colspan="2">eGFR: _____ mL/min/1.73m²</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="2">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="2">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td>☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td>☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #2

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td colspan="2">Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="3">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="3">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="3">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td colspan="2">☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td colspan="2">☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #3

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td>Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="2">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="2">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="2">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td>☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td>☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #4

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td>Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="2">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="2">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="2">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td>☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td>☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #5

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td colspan="2">Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="3">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="3">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="3">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td colspan="2">☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td colspan="2">☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #6

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td>Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="2">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="2">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="2">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td>☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td>☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #7

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td colspan="2">Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="3">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="3">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="3">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td colspan="2">☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td colspan="2">☐ yes ☐ no</td></tr>
</table>

REMINDER: DO NOT LEAVE ANY BLANKS

Chemotherapy cycle #8

<table>
<tr><td>Date:</td><td colspan="2">> 28 days after the first day of the previous cycle
☐ yes Reason:
☐ no</td><td colspan="2">Weight:</td></tr>
<tr><td colspan="2">Chemotherapy dosages</td><td colspan="3">Antiretroviral therapy</td></tr>
<tr><td>Cyclophosphamide</td><td>☐ 750 mg/m² IV
☐ Other: _____</td><td colspan="3">☐ PI based (includes PI+NNRTI based regimen)
☐ NNRTI based
☐ Other</td></tr>
<tr><td>Doxorubicin</td><td>☐ 50 mg/m² IV
☐ Other: _____</td><td>Zidovudine use
☐ yes ☐ no</td><td rowspan="5">Regimen used (dosage):

Previous regimen:
☐ same</td></tr>
<tr><td>Vincristine</td><td>☐ 1.4 mg/m² IV or 2 mg IV
☐ Other: _____</td><td>Stavudine use
☐ yes ☐ no</td></tr>
<tr><td>Prednisone</td><td>☐ 40 – 45 mg/m² or 100 mg po x5 d
☐ Other: _____</td><td>Didanosine use
☐ yes ☐ no</td></tr>
<tr><td>Rituximab</td><td>☐ 375 mg/m² IV
☐ Other: _____ ☐ none</td><td>Zalcitabine use
☐ yes ☐ no</td></tr>
<tr><td colspan="2">Reason for dose reduction if applicable:
☐ Toxicity: _____
☐ Known drug interaction (preventive reduction): _____
☐ Other: _____</td><td colspan="3">Reason for change of ARV regimen if applicable:
☐ Toxicity: _____
☐ Interaction: _____
☐ Other: _____</td></tr>
<tr><td>CNS prophylaxis</td><td>☐ yes ☐ no</td><td>Use of fluconazole</td><td colspan="2">☐ yes ☐ no</td></tr>
<tr><td>G-CSF</td><td>☐ yes ☐ no</td><td>Use of TMP-SMX</td><td colspan="2">☐ yes ☐ no</td></tr>
</table>

Adverse events between 1st chemotherapy cycle and end of follow-up

Adverse event	Grade 3	Grade 4	Date(s) of occurrence Specify grade 3 or 4
Anemia	Hemoglobin <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	
Acute kidney injury	Creatinine > 3 x baseline or > 353.6 µmol/L; hospitalization indicated	Life-threatening consequences; dialysis indicated	
ALT or AST increased	5.0 – 20.0 x upper limit of the normal	> 20.0 x upper limit of the normal	
Blood bilirubin increased	3.0 – 10.0 x upper limit of the normal unless patient is on atazanavir (Reyataz ®)	> 10.0 x upper limit of the normal unless patient is on atazanavir (Reyataz ®)	
Constipation	Constipation with manual evacuation indicated; limiting self care activities of daily life	Life-threatening consequences; urgent intervention indicated	
Diarrhea	Increase of ≥ 7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily life	Life-threatening consequences; urgent intervention indicated	
Febrile neutropenia	ANC< 1000/mm^3 with a single temperature of >38.3 degrees C or a sustained temperature of ≥ 38 degrees C for more than one hour	Life-threatening consequences; urgent intervention indicated	
Cystitis noninfective or hematuria	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	
Infusion related reaction	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	
Nausea	Inadequate oral caloric or fluid intake; tube feeding, TPN or hospitalization indicated	Not applicable	
Peripheral neuropathy	Defined as present or absent	Defined as present or absent	
Vomiting	≥ 6 episodes (separated by 5 minutes) in 24 hours; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	

Censor points

Date: _____

Reason (choose one):

☐	**Change of cART during chemotherapy leading to a change of treatment arm** **Reason for change:**
☐	**2 year follow-up after end of chemotherapy**
☐	**Death**
☐	**01/01/2011**