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Survival and consolidative radiotherapy in patients living with HIV and treated for diffuse large B-cell lymphoma

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ABSTRACT

Objectives: Current guidelines tend to treat HIV positive (HIV+) patients as their seronegative counterparts with diffuse large B-cell lymphoma (DLBCL) but little is known about their radiotherapy responses differences.
Patients and Methods: A retrospective cohort of all consecutive HIV+ DBCL patients treated with chemotherapy between 2004 and 2018 was assessed. All patients had biopsy-proven lymphomas. They were included if the proposed radical treatment was done without progression or death during chemotherapy and had at least 6 months of follow-up or were followed until death.
Results: Fifty-three (53) patients were selected, with a median age at diagnosis of 41.39 years (20–65 years). Median follow-up of 35.16 months (1.4–178.7 months). Male patients accounted for 54.7% and most had a good performance in the ECOG scale at diagnoses (81.1% are ECOG 0–1). Median overall survival was not reached. Mean OS was 41.5 months with 16 deaths. Age had an impact on OS, with patients older than 60 years at more risk ($p = 0.044$), as did longtime use of HAART, with those that started antiretroviral therapy within the diagnose of the lymphoma at greatest risk ($p = 0.044$). RT did not have an impact on OS ($p = 0.384$) or PFS ($p = 0.420$), although survival curves show better OS in the radiotherapy group. Toxicities were rare, since none of the patients had grade 3 or superior toxicity.
Conclusion: RT did not impact survival or progression in our limited sample, but a longer OS may occur after the first-year post RT. RT should be tested in prospective data in the HIV+ population with DLBCL.

1. Introduction

The role of radiotherapy (RT) in the treatment of non-Hodgkin diffuse large B-cell lymphomas (DLBCL) has been tested over the years. Prior to the development of rituximab, radiotherapy has been a consistent option of consolidative therapy for initial disease over the years. The GELA group[1] trial that tried to compare an extensive arm of chemotherapy (CHT) with insufficient CHT followed by RT, concluded that RT cannot replace inadequate CHT regimens. Better evidence came from the Eastern Oncology Group (ECOG)[2] as the randomization after the same schemes of CHT with complete response between radiation or no longer treatment. In that trial, RT showed an increase in disease-free survival (DSF). Following the MabThera[3] trial, radiation had yet again to prove its use. The UNFOLDER[4] trial showed more results on the role of RT, especially because the no-RT arms were prematurely closed due to improved EFS in the RT arm. Another issue altogether is the use of RT in the advanced disease setting. The International Lymphoma Radiation Oncology Group (ILROG) has proposed guidelines to its use in this population.[5] Nowadays, RT is an accepted option for consolidation in DLBCL.

In the population of people living with HIV that are diagnosed with DLBCL, this information is particularly relevant, since for a long time the use of rituximab in this population has been avoided and

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the impact of radiotherapy in this set is yet to be measured. Large research groups have made recommendations for treatment in this subset, such as the German AIDS Society (DAIG),[6] but little evidence is available and it is limited to small series,[7] and little attention is given to the role of radiotherapy.

Since it is a consolidative therapy, it is important to address the correct indication and expected toxicities of RT in DLBCL patients. It is a consensus that not every patient should receive RT and that better knowledge of the disease and the effects of radiation is the way that must be taken to improve patients' outcomes.

An important, yet understudied, part of DLBCL patients are those infected with the human immunodeficiency virus (HIV). An important French prospective cohort has shown that survival among patients living with HIV and that are diagnosed with DLBCL are similar to HIV negative patients.[8] In this cohort, nevertheless, radiotherapy was not part of the treatment. Therefore, its use and indications, as its toxicities, are unknown. This study aims to cast some light on this issue.

2. Patients and methods

All consecutive patients that were diagnosed with DLBCL and were people living with HIV virus treated with radiotherapy between 2004 and 2018 were retrospectively assessed. Patients that died before receiving any kind of treatment or died during chemotherapy were not included. Previous evidence[9] showed that most patients had died during first course of chemotherapy. Therefore, including those patients would be a bias since not all of them received radiotherapy. Only patients that had reached the consolidation phase of their treatment were included then. Patients with only CNS disease who had received primary CNS lymphoma treatments were also excluded. All patients had biopsy-proven DLBCL. Patients had to have 6 months of follow up after the completion of either RT or chemotherapy or were followed until death. Survival (both OS and PFS) was assessed from the diagnosis date. Fifteen patients (28.3%) were staged with Positron-emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and the others (71.7%) with whole-body tomography (CT). Both methods were valid and their use was also assessed in this population. All patients were also assessed with the International Prognostic Index (IPI) and all were re-classified by the current classification.[10] Radiotherapy technique consisted of involved-field treatments for all patients treated before 2015, which was changed after publication by Specht et al.[11] and involved-site techniques were preferred. When available, PET-CT images were used for delineation.

Statistical analyses were made with descriptive statistics and frequencies analysis were conducted with calculation of means, standard deviations (SD), medians and interquartile ranges (IQR). Survival estimates were calculated using the Kaplan-Meier method starting from diagnosis date and the log-rank test was used for comparisons between variables. All variables with clinical significance or $p \leq 0.10$ in the univariate analysis were included in the multivariate analysis. The Cox regression method was used for the multivariate analysis. Significance level was set at 5% ($p < 0.05$).

Ethics committee authorization was obtained in the local ethics committee according to Brazilian law and the Declaration of Helsinki. We were granted a waiver by the ethics committee to request each patient consent due to the retrospective nature of this study.

3. Results

Patients were retrospectively analyzed. Fifty-three patients met the inclusion criteria and had their data collected. All patients were people living with HIV. Median age at diagnosis was 41.39 years (interquartile range 34.90–48.20). 54.71% of the patients were male. There was one transgender female patient in this sample. Most patients (81.12%) had performance grade 0 or 1 in the ECOG scale. Most patients were not staged with positron-emission tomography with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) (28.3%). Patients were graded according to the International Prognostic Index (IPI) and those with scores of 0 or 1 were a minority (28.3%), with most patients graded 3 (41.5%). Most patients were also advanced stage according to the Lugano system (66.0% were stage III and IV). More information about patients' characteristics and their impact on overall survival can be seen in Table 1.

HIV characteristics were also assessed. Median CD4+ cells count at diagnosis was 215 cells/mm^3. Most patients had undetectable viral loads, but 43.40% were with a median value of 221.5 copies/mL. Most patients (75.47%) were long time users of highly

Table 1
Patient characteristics and outcomes.

Patient characteristics	RT		p
	No N = 25 (47.17%)	Yes N = 28 (52.83%)	
ECOG			
0	15 (60.0%)	20 (71.4%)	0.624
1	5 (20.0%)	3 (10.7%)	
2 or lower	5 (20.0%)	5 (17.9%)	
Staging			
PET	5 (20.0%)	10 (35.7%)	0.093
CT	20 (80.0%)	18 (64.3%)	
IPI			
Low	4 (16.0%)	11 (39.3%)	0.135
Intermediate	10 (40.0%)	5 (17.8%)	
High-intermediate	11 (44.0%)	11 (39.3%)	
High	0 (0%)	1 (3.6%)	
Stage			
I	0 (0%)	4 (14.3%)	0.726
II	6 (24.0%)	8 (28.6%)	
III	4 (16.0%)	3 (10.7%)	
IV	15 (60.0%)	13 (46.4%)	
Localization			
Above diaphragm	6 (24.0%)	12 (42.9%)	0.957
Below diaphragm	4 (16.0%)	6 (21.4%)	
Both sides	15 (60.0%)	10 (35.7%)	
Bulky disease			
No	19 (76.0%)	11 (39.3%)	0.468
Yes	6 (24.0%)	17 (60.7%)	
Extranodal disease			
No	15 (60.0%)	6 (21.4%)	0.233
Yes	10 (40.0%)	22 (78.6%)	
B Symptoms			
No	18 (72.0%)	12 (42.9%)	0.279
Yes	7 (28.0%)	16 (57.1%)	
HAART			
No use	5 (20.0%)	2 (7.2%)	**0.044**
At lymphoma diagnosis	0 (0%)	5 (17.8%)	
Long-term user	20 (80.0%)	20 (71.4%)	
No information	0 (0%)	1 (3.6%)	
Response to chemotherapy			
Complete response	23 (92.0%)	17 (60.7%)	0.615
Partial response	2 (8.0%)	11 (39.3%)	
Disease Progression			
No	21(84.0%)	21 (75.0 %)	
Yes	4 (16.0 %)	7 (25.0 %)	
Death			
No	16 (64.0%)	21 (75.0%)	
Yes	9 (36.0%)	7 (25.0%)	

Bold value are significant value ($p < 0.05$).

Table 2
HIV characteristics.

HIV characteristics	RT		p
	No N = 25 (47.17%)	Yes N = 28 (52.83%)	
HAART			
No use	5 (20.0%)	2 (7.2%)	**0.044**
At lymphoma diagnosis	0 (0%)	5 (17.8%)	
Long-term user	20 (80.0%)	20 (71.4%)	
No information	0 (0%)	1 (3.6%)	
NRTI in the current scheme			
Yes	19 (76.0%)	4 (14.3%)	**0.041**
No	5 (20.0%)	23 (8.1%)	
No information	1 (4.0%)	1 (3.6%)	
NNRTI in the current scheme			
Yes	19 (76.0%)	17 (60.7%)	0.503
No	5 (20.0%)	10 (35.7%)	
No information	1 (4.0%)	1 (3.6%)	
Protease inhibitors in the current scheme			
Yes	14 (56.0%)	15 (53.6%)	0.150
No	10 (40.0%)	12 (42.8%)	
No information	1 (4.0%)	1 (3.6%)	
Integrase inhibitors in the current scheme			
Yes	2 (8.0%)	5 (78.6%)	0.942
No	22 (88.0%)	22 (17.8%)	
No information	1 (4.0%)	1 (3.6%)	
Fusion inhibitors in the current scheme			
Yes	0 (0%)	0 (0%)	–
No	24 (96.0%)	27 (96.4%)	
No information	1 (4.0%)	1 (3.6%)	
CCR5 antagonist in the current scheme			
Yes	0 (0%)	0 (0%)	–
No	24 (96.0%)	27 (96.4%)	
No information	1 (4.0%)	1 (3.6%)	

Bold values are significant values (p < 0.05).

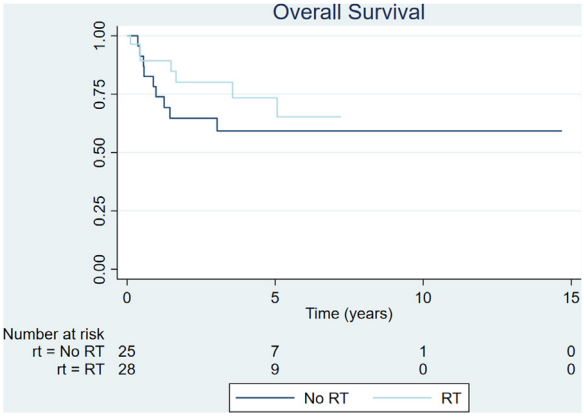

Fig. 1. Overall Survival (p = 0.384).

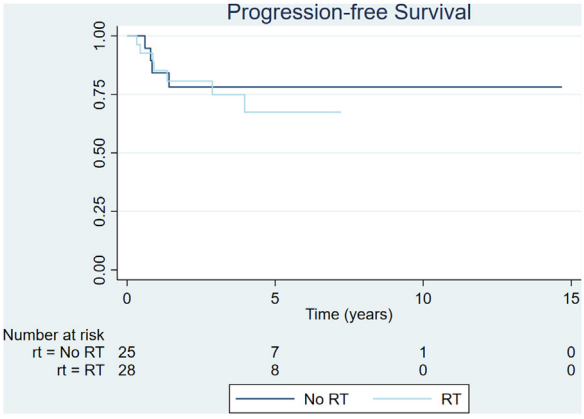

Fig. 2. Progression-Free Survival (p = 0.420).

active antiretroviral therapy (HAART), with impact on overall survival (p = 0.044) but no impact on disease progression (p = 0.261). Long-term users had a statistically lower chance of dying after first-line treatment for DLBCL. Seven patients (13.20%) were receiving integrase inhibitors as dolutegravir at lymphoma diagnosis and most patients were in use of older drug associations as their HAART treatment. More data on HIV treatments for these patients and their impact on overall survival can be seen in Table 2. An important toxicity outcome found was the drop on the CD4+ cell count. Median CD4+ cell count drop was 25.5 cells/mm^3 (from an enhance of 269 to a drop of 370 cell/mm^3 at diagnosis and at end of treatment) and did not impact survival outcomes (p = 0.06).

Chemotherapy consisted mostly of protocols containing etoposide. No patient received rituximab in our sample and it is a common practice in our institution to improve the common CHOP regimen with the addition of etoposide (CHOEP) according to older data for aggressive lymphomas[12] (43.39% received etoposide containing regimens). Most patients received 6–8 cycles of chemotherapy (45.28% and 43.39%, respectively). Response to primary chemotherapy treatment was also assessed. Complete response was acquired for 75.47% in their first line treatment. Patients that progressed were excluded from analysis since they would impact negatively the no-RT group and would create bias, so the remaining patients reached partial response. Toxicities due to chemotherapy were common, with 73.35% of patients having grade 3 or superior toxicities requiring pauses or treatment dose reduction and 28.30% having grade 4 hematological toxicity. All patients with grade 5 toxicities were excluded from analysis.

Radiotherapy was standard when delivered. Twenty-eight patients (52.83%) received RT as a consolidative therapy. RT consisted of involved site for 12 patients that were stage I or II and treatment to bulky, extranodal or partial response sites to 16 patients with advanced stage disease. Standard dose was 30 or 30.6 Gy to complete response sites and 36 Gy to partial response sites. 22 patients were treated with the involved-field technique, most before 2015, and the remaining 31 were treated with the involved-site technique. RT was included in multivariate analysis and did not impact any outcome. Consolidative radiotherapy did not impact the outcome either (p = 0.33). Figs. 1 and 2 graphically describe the difference between patients that did and did not receive radiotherapy. Toxicities due to RT were rare and minor. Only 39.2% of patients had any grade 2 toxicities, mostly fatigue and skin alterations, with no patients having grade 3 or higher toxicities.

Median follow-up was 35.16 months. Mean overall survival and progression-free survival for the entire cohort were 41.60 and 39.04 months, respectively. No median values were reached. Univariate analysis and multivariate analysis on overall survival results can be seen in Table 3.

4. Discussion

The association of HIV and DLBCL is a novel issue that lacks good quality data. The French cohort described by Besson et al.[8] is the best evidence nowadays of this interaction. Although small, it is good quality data acquired prospectively with current standards of the treatment of HIV infection. Regardless, the question addressed by these authors do not apply to most centers since no patient received radiotherapy as a consolidation treatment. Therefore, information on the way people living with HIV deal with toxicities and their prognoses is still absent in this treatment scenario. Our study is the first one to our knowledge to address this

Table 3
Univariate and multivariate analysis on overall survival.

Variable	Categories	Univariate analysis		Multivariate analysis	
		n	p	p	CI (95)
Gender	Male	30	0.88	–	
	Female	23			
Age	<60 years	42	0.10	–	
	>60 years	11			
ECOG	0–1	43	0.34	–	
	2–4	10			
Staging exam	PET-CT	15	0.13	–	
	CT	38			
IPI	Low	15	0.40	–	
	Low-intermediate	15			
	High-intermediate	22			
	High	1			
Stage	I	4	**0.44**	0.53	−0.30 to 0.685
	II	14			
	III	7			
	IV	28			
Localization	Above diaphragm	18	0.63	–	
	Below diaphragm	10			
	Both sides	15			
Bulky disease	No	30	0.58	–	
	Yes	23			
Extranodal disease	No	21	0.22	–	
	Yes	32			
B Symptoms	No	30	0.24	–	
	Yes	23			
HAART	No use	7	**0.04**	0.10	−1.16 to 0.00
	Started at diagnosis	5			
	Long-time user	40			
	No information	1			
Chemotherapy	CHOP based	30	**0.06**	0.09	−2.12 to 0.14
	Others	23			
Radiotherapy	No	25	**0.95**	0.33	−1.47 to 0.50
	Yes	28			
Response to chemotherapy	Complete	40	0.68	–	
	Partial	13			

Bold values are significant values ($p < 0.05$).

issue. As it can be seen from our data, the most important interaction with HIV and the treatment for DLBCL is that people that are receiving HAART at lymphoma diagnosis tend to do better. This information is new and not reported previously. In the French cohort, this information was mentioned as 79% of their patients were receiving HAART at enrolment but no association was made between HIV treatment and outcomes.

Another question that must be addressed is that RT did not interfere with the outcomes. The rationale of omitting RT in HIV positive patients to make treatment less toxic is not true. In our sample, no patient had enhanced toxicities due to RT. No secondary malignancies were reported. The impact of HIV on toxicities from consolidative RT has been reported in a large sample of DLBL patients[13] but they are limited to increased fatigue and altered blood cell count. The rationale, therefore, to omit RT based on HIV status alone cannot be supported.

On the other hand, RT did not significantly impact survival. This issue might be a consequence of the small sample size. It is known from the pre and post MabThera radiotherapy trials that the impact of RT on survival is limited and cannot be seen in small patient groups. Nevertheless, the overall survival Kaplan-Meyer curves showed can raise the question of whether RT can really improve outcomes in this population. This subject should be, therefore, addressed by prospective trials.

5. Conclusion

In conclusion, patients living with HIV have similar outcomes when treated with or without radiotherapy as consolidative treatment after chemotherapy for DLBCL. Prospective data with larger samples are needed to really understand the impact of this treatment in this special population.

Authors contributions

Carolina Medici and Geovanne Mauro were responsible for study design and ethics committee approval. Carolina Medici and Lucas Casimiro were responsible for data collection. Geovanne Mauro were responsible for statistics analysis. Geovanne Mauro, Carolina Medici and Lucas Casimiro were responsible for writing manuscript. Eduardo Weltman was responsible for overall orientation and manuscript review.

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Conflict of interest

None declared.

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References

1. Bonnet C, Fillet G, Mounier N, et al. CHOP alone compared with CHOP plus radiotherapy for localized aggressive lymphoma in elderly patients: a study by

the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 2007;25(March (7)):787–792, http://dx.doi.org/10.1200/JCO.2006.07.0722.
2. Horning SJ, Weller E, Kim K, et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: eastern cooperative oncology group study 1484. *J Clin Oncol*. 2004;22(August (15)):3032–3038, http://dx.doi.org/10.1200/JCO.2004.06.088.
3. Pfreundschuh M, Trümper L, Österborg A, 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. *Lancet Oncol*. 2006;7(May (5)):379–391, http://dx.doi.org/10.1016/S1470-2045(06)70664-7.
4. Pfreundschuh M., Murawski N., Ziepert M., et al. Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: Results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA.
5. Ng AK, Yahalom J, Goda JS, et al. Role of radiation therapy in patients with relapsed/refractory diffuse large B-cell lymphoma: guidelines from the international lymphoma radiation oncology group. *Int J Radiat Oncol Biol Phys*. 2018;100(March (3)):652–669, http://dx.doi.org/10.1016/j.ijrobp.2017.12.005.
6. Hentrich M, Hoffmann C, Mosthaf F, et al. Therapy of HIV-associated lymphoma—recommendations of the oncology working group of the German Study Group of Physicians in Private Practice Treating HIV-Infected Patients (DAGNÄ), in cooperation with the German AIDS Society (DAIG). *Ann Hematol*. 2014;93(June(6)):913–921.
7. De Felice F, Di Mino A, Grapulin L, et al. Head and neck diffuse large B cell lymphomas (HN-DLBCL) in human immunodeficiency virus (HIV) positive patients: long-term results in the highly active antiretroviral therapy (HAART) era. *Eur Arch Oto-rhino-laryngology*. 2017;274(October (10)):3735–3739.
8. Besson C, Lancar R, Prevot S, et al. Outcomes for HIV-associated diffuse large B-cell lymphoma in the modern combined antiretroviral therapy era. *AIDs*. 2017;31(November (18)):2493–2501, http://dx.doi.org/10.1097/QAD.0000000000001652.
9. Tanaka PY, Pracchia LF, Bellesso M, et al. A prognostic score for AIDS-related diffuse large B-cell lymphoma in Brazil. *Ann Hematol*. 2010;89(January (1)):45, http://dx.doi.org/10.1007/s00277-009-0761-3.
10. Montalbán C, Díaz-López A, Dlouhy I, et al. Validation of the NCCN-IPI for diffuse large B-cell lymphoma (DLBCL): the addition of β2-microglobulin yields a more accurate GELTAMO-IPI. *Br J Haematol*. 2017;176(6):918–928. Mar.
11. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). *Int J Radiat Oncol Biol Phys*. 2014;89(July (4)):854–862.
12. Köppler H, Pflüger KH, Eschenbach I, et al. Randomised comparison of CHOEP versus alternating hCHOP/IVEP for high-grade non-Hodgkin's lymphomas: treatment results and prognostic factor analysis in a multi-centre trial. *Ann Oncol*. 1994;5(January (1)):49–55, http://dx.doi.org/10.1093/oxfordjournals.annonc.a058690.
13. Medici CT, Mauro GP, Casimiro LC, et al. Impact of HIV infection on consolidative radiotherapy for non-Hodgkin diffuse large B-cell lymphoma. *Radiat Oncol*. 2020;15(December (1)):1–7.