REVIEW ARTICLE
ARTIGO DE REVISÃO

Treatment patterns of Hodgkin's lymphoma in Brazil: experts' perspective

Padrões de tratamento do linfoma de Hodgkin no Brasil: a perspectiva dos especialistas

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ABSTRACT

Background: Hodgkin's Lymphoma (HL) is a curable type of cancer, with a wide variety of therapies, especially for refractory/relapsing cases. Therefore, the study aims to explore the treatment patterns used in the management of HL patients in Brazil. **Methods:** A survey was developed to explore the treatment patterns in Brazil, addressing topics such as clinical characteristics, lines of therapy, transplant information and cure rates. Then, results were presented in a panel discussion to validate participants' responses and gain additional insights. **Main results:** The eight experts reported that most patients are women and under 60 years old. In both private and public healthcare systems, ABVD was the most commonly used first-line therapy for patients of all stages. The median cure rates for patients in stages I and II were 80% and 87.5%, and for stages III and IV 60% and 67.5%, respectively, in public and private sectors. For the subsequent lines of therapy, different regimens such as DHAP, GVD, GEV, ICE and allogeneic transplant are used, among others. Brentuximab vedotin was present mainly in the private sector. In the public sector, 70% of the patients are eligible for autologous stem cell transplant; of them, 75% actually receive the transplant. In the private sector, 80% of the patients are eligible, and 100% of them receive the transplant. **Conclusion:** Similarities were found between the public and private sectors in first-line therapy and cure rates. However, barriers for subsequent lines of therapy are more evident in the public system.

Palavras-chave:
linfoma de Hodgkin, quimioterapia, investigações de saúde, opinião de especialista

RESUMO

Introdução: O linfoma de Hodgkin (LH) é um tipo de câncer curável, com ampla variedade de terapias, especialmente para casos refratários/recidivantes. Portanto, o estudo visa explorar os padrões de tratamento utilizados no manejo de pacientes com LH no Brasil. **Métodos:** Uma pesquisa foi desenvolvida para explorar os padrões de tratamento no Brasil, abordando tópicos como: características clínicas, linhas de terapia, informações sobre transplantes e taxas de cura. Em seguida, os resultados foram apresentados em um painel de discussão para validar as respostas dos partici-

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pantes e coletar os *insights* adicionais. **Principais resultados:** Os oito especialistas relataram que a maioria dos pacientes é composta por mulheres com idade menor de 60 anos. Em ambos os sistemas de saúde, privado e público, ABVD foi a terapia de primeira linha mais comumente usada para pacientes de todos os estágios. As medianas das taxas de cura para pacientes nos estágios I e II foram de 80% e 87,5%, e para os estádios III e IV, de 60% e 67,5%, nos setores público e privado, respectivamente. Para as linhas subsequentes de terapia, diferentes regimes como DHAP, GVD, GEV, ICE e transplante alogênico são utilizados, entre outros. Brentuximabe vedotina estava presente principalmente no setor privado. No setor público, 70% dos pacientes são elegíveis para transplante autólogo de células-tronco; deles, 75% recebem o transplante. No setor privado, 80% dos pacientes são elegíveis e 100% recebem o transplante. **Conclusão:** Foram encontradas semelhanças entre o setor público e privado na terapia de primeira linha, bem como nas taxas de cura. No entanto, as barreiras para as linhas subsequentes de terapia são mais evidentes no sistema público.

Introduction

Hodgkin's lymphoma (HL) is a B-cell malignancy that represents 0.5% of all new cancer cases (NCI – US). In Brazil, the National Institute of Cancer estimated 2,470 new cases in 2016—1,460 in men and 1,010 in women (Martinez *et al.,* 2013). The disease is currently considered to be a cancer with a high probability of control and cure with the available therapies. The National Cancer Institute maintains that more than 80% of all newly diagnosed HL patients aged 60 years or less are likely to be cured following frontline therapy (Ansell 2016).

However, refractory and relapsed patients historically present significantly worse outcomes, even after autologous stem cell transplantation (ASCT) (Crump, 2008, Arai *et al.,* 2013). For this reason, these patients are the focus of the recent development of new therapies. Among them, brentuximab vedotin is an option for use after failure of ASCT (or in patients not eligible for ASCT), or as a consolidation therapy following ASCT for patients with a high risk of relapse (Moskowitz *et al.,* 2015). Other new therapies include immunotherapeutic agents, known as checkpoint inhibitors (such as nivolumab and pembrolizumab), and other approaches, such as allogeneic stem cell transplant.

Several treatment recommendations for HL are available and include these new therapeutic options. However, compliance with guidelines is not always optimal, as they may not fill the gap between evidence and the management of individual patients with specific medical needs. Moreover, real-life issues, such as access to medical care and new technologies, can significantly impact the actual management and outcomes of patients, especially in countries with socioeconomic disparities like Brazil. Although expert surveys and panels are not substitutes for clinical data, they are effective in gathering input on real-life issues that could be used to generate new studies and to inform health policies.

Objective

The present study aimed to explore the real-life scenario of the management of Hodgkin's lymphoma in Brazil from an expert perspective and to generate additional insights into HL treatment.

Methods

This is a cross-sectional study that was divided into two steps: a questionnaire (survey) followed by a panel discussion. Eight experts in the treatment of HL, from the private and public healthcare systems, were invited to participate in the experts' panel in 2017. The participants were from different Brazilian regions, representing the South, Southeast and Northeast regions. No ethics approval and informed consent to participate were necessary, as no patients were participating in the study and real patients' data was not used.

After the physicians accepted to participate in the study, a questionnaire was sent to each one of them. The participants were instructed to answer the questionnaire according to their experience and perspectives. Subsequently, the answers were compiled and presented to all of the participants in an in-person panel discussion. The panel discussion was conducted to validate their opinions, debate topics related to HL treatment and to gather possible strategies to minimize these barriers.

Questionnaire development

An 86-question questionnaire was developed by specialists based on the main treatment strategies found in the literature and validated by an internal expert. The questionnaire, containing multiple-choice and one open question, was divided into three main topics:

- Participants' characterization: specialty; experience time; mean number of HL patients seen per month; healthcare system.
- Patients' characterization: number of HL patients from each healthcare systems; gender; age; number of refractory and relapsing patients.
- Treatments: regimens, cycles and cure rate on each line of therapy (first, second and subsequent); factors related to patients, disease and treatment that impact the treatment choice; follow up time;

main reasons to change therapies; autologous stem cell transplantation (ASCT) information; salvage, induction and consolidation/maintenance therapies, reasons for patients' ineligibility to ASCT; allogeneic stem cell transplantation information.

After its development in an online platform, the questionnaire was sent by e-mail to eight physicians and completed within two weeks.

Panel meeting

All the participants were invited to participate in an in-person panel discussion to debate their point of view over the Hodgkin's Lymphoma treatment. The eight specialists agreed to participate in the panel approximately one week after sending the filled questionnaire. The meeting took place in São Paulo and the results from the questionnaire were presented. The specialists had the opportunity to debate and validate their answers, sharing their experience and commenting on the differences between the Brazilian scenarios. During the meeting, the participants addressed issues related to treatment patterns, difficulties and barriers to the treatment of patients with Hodgkin's Lymphoma, and possible measures to improve their scenarios.

Data analysis

Descriptive statistics were used to analyze the results. The responses from questionnaire were extracted with counting/ranking for multiple-choice questions and categorization for open questions. Subsequently, the results from all responses were summarized using frequency analyses, with descriptive purposes only. All results are reported as rate of respondents with multiple choices for several questions.

Results

Participant's characteristics

Eight physicians from three different Brazilian geographic regions (South, Southeast and Northeast) responded to the questionnaire. Six of them are hematologists / onco-hematologists; one is a pathologist and one is a nuclear medicine specialist. The median time of experience was ten years, ranging from 10 to 35 years. Almost all participants reported working on both public and private healthcare systems; one of them works exclusively in the private sector.

Characterization of physicians' patients

The participants reported a median number of seven new patients with HL per month. Seventy percent of them were from the public healthcare system. Regarding patients' age, a median of 87.5% and 75% of HL patients, in the public and private sectors, respectively, were under 60 years old. In addition, there is almost an equal number of female patients in both healthcare systems (median of 55% in the public sector and 50% in the private sector).

Treatments

First line therapies

The participants reported the main factors related to patients, disease and treatment that influence the choice of therapy for HL, as shown in Table 1.

According to participants, the most common first-line therapies for patients at stages I and II was ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine), with a median of 4 cycles and half of them combining radiotherapy, on both healthcare systems. For patients at stages III and IV, ABVD was still the most common regimen used; however, with a median of 6 cycles on both systems (Table 2). Regarding patients' cure rate after first-line therapy, similar results were reported in the public and private healthcare systems for patients at stages I and II as well as III and IV (Table 2).

After the first-line therapy, patients were followed up every 3 months (median) in the first five years; and every twelve months (median) after the initial five-year period, in both sectors. The most common reasons to change thera-

Table 1. The main factors related to patients, diseases and treatments influencing the therapy choice in both healthcare systems, according to physicians' perspectives.

	Public healthcare system			Private healthcare system		
Rank	**Patient**	**Disease**	**Treatment**	**Patient**	**Disease**	**Treatment**
1	Performance Status	Disease stage	Toxicity	Performance Status	Disease stage	Toxicity
2	Accessibility to the healthcare institution	Disease-related complications	Pharmacokinetic characteristics of the medication	Comorbidities	Disease-related complications	Pharmacokinetic characteristics of the medication
3	Patients' age	Risk	Costs	Patients' age	Risk	Costs
4	Comorbidities	Previous response to treatments	Availability of the service	Patients' preference	Previous response to treatments	Availability of the service
5	Access to treatment		Route of administration	Previous treatments toxicity		Route of administration

Table 2. The most common regimens used as first-line therapies, as well as the median number of cycles and cure rate of each group, according to physicians perspectives.

First-line therapy	Public healthcare system		Private healthcare system	
Patients stages I and II		%		%
Most common regimens	ABVD	50	ABVD	50
	ABVD + Radiotherapy	50	ABVD + Radiotherapy	50
Cycles (median)	4		4	
Cure rate (median)		80		87.5
Patients stages III and IV		%		%
Most common regimens	ABVD	83	ABVD	67
	BEACOPP	17	ABVD + Radiotherapy	17
			BEACOPP	17
Cycles (median)	6		6	
Cure rate (median)		60		67.5

py in the public and private sectors were lack of response to treatment, disease progression and toxicity. In the public sector, drug unavailability was also mentioned as a reason for therapy change.

The experts reported that the median rate of refractory disease following first-line therapy is 17.5% in the public sector and 10% in the private sector. Regarding relapsing disease, they reported rates of 25% for the public sector and 20% for the private sector. Figure 1 shows the distribution of the relapsed patients according to each period.

Subsequent lines of therapy

DHAP (Dexamethasone, Cisplatin, Cytarabine), ICE (Ifosfamide, Carboplatin, Etoposide) and GEV (Ifosfamide, Gemcitabine, Vinorelbine) were the most common salvage regimens in the public sector, with 33% each. In the private sector, the same regimens were reported, but with different proportions (ICE 50%, GEV 33% and DHAP 17%). A median of three cycles was reported on both healthcare systems.

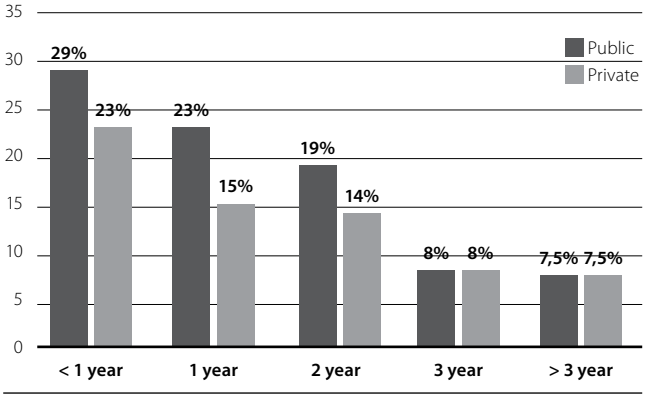

Figure 1. The mean distribution of relapsed patients separated by the respective period in each healthcare system (mean percentage).

Autologous Stem Cell Transplant

Among the five main criteria for ASCT ineligibility, comorbidities, patients' preference, performance status and age were reported in both healthcare systems. The difference was disease stage and chemosensitivity, reported in the public and private sectors, respectively. As induction therapy, the participants reported the use of several different regimens, such as ICE, GEV, Mini-BEAM, BEAM and CBV and a median of 1 cycle, on both healthcare systems; of note, the experts reported periods of shortage of etoposide in the market.

Significant discrepancies between the public and private systems were found regarding the actual rate of performance of ASCT: while a median of 80% of the private patients are eligible for ASCT and all of them (100%) actually undergo the procedure, in the public sector, these rates reduce to 70% and 75%, respectively. The reasons for not performing ASCT in eligible patients are related to the system infrastructure: some transplant centers were closed and not all reference centers perform transplants. Of note, there is only one public center that performs transplants in the Northeast region; so many patients need to move to the South and Southeast to receive it. In addition, HL patients compete with patients with other diseases that also require a transplant. The median time to receive the ASCT in the private sector is 1.5 months, while in the public sector it is 4.5 months. The experts note that this scenario could be improved with the performance of ASCT on an outpatient basis, similar to what is already done in other countries. The use of consolidation therapy following ASCT was also discussed: while none of the participants reported to use it for public patients, all of them reported to use it, with brentuximab vedotin, for patients with a high risk of relapse, including those who had not reached complete response following salvage chemotherapy.

According to the experts, the median cure rate of the ASCT is 50% in the public healthcare system and it slightly increases to 55% in the private sector. Table 3 shows the main subsequent therapies for transplant-eligible patients.

For patients who eventually relapse after ASCT, the main treatment options include allogeneic transplant, different chemotherapy regimens, and brentuximab vedotin. Table 4 shows the main therapies used following relapse after ASCT in both scenarios.

Allogeneic Stem Cell Transplant

Performance status was the main factor for patients' ineligibility for allogeneic steam cell transplant on both healthcare systems. In the public sector, it was followed by insufficient

Table 3. The most common regimens used as induction and consolidation in transplant-eligible patients, according to physicians perspectives.

	Public healthcare system		Private healthcare system	
Induction regimens		%		%
Most common regimens	Other*	50	Other*	50
	ICE	17	ICE	17
	GEV	17	GEV	17
	Mini-BEAM	17	Mini-BEAM	17
Cycles (median)	1		1	
Consolidation/maintenance regimens				
Most common regimens		0	Brentuximab Vedotin	100

Table 4. The most common regimens used as subsequent-line therapies, as well as the median number of cycles, following relapse after ASCT.

	Public healthcare system		Private healthcare system	
		%		%
Most common regimens	Allogeneic stem cell transplant	50	Brentuximab Vedotin	83
	DHAP	33	Allogeneic stem cell transplant	50
	GVD	33	DHAP	17
	GEV	33	Radiotherapy	17
	Radiotherapy	33	Other	0
	ICE	17		
	Brentuximab Vedotin	17		
	Other*	17		
Cycles (median)	3		8	

*Other: at this stage, the treatment of patient individualized, depending of prior treatments and toxicity, for instance. Median cycles refers to systemic therapies.

biological function (pulmonary, cardiovascular, renal and hepatic), lack of psychosocial support, age, lack of financial support and lack of a compatible donor. In the private sector, it was followed by age, insufficient biological function, lack of psychosocial support and lack of a compatible donor. In the public sector, a median of 22.5% of the patients have the transplant indication and only 10% receive it. In the private sector, the median rates change to 15% and 35%, respectively. The reasons for the lower rate of allogeneic transplant in the public system include the same infrastructure issues discussed above. The mean cure rate of allogeneic transplant was reported to be 20% in both sectors.

Transplant-ineligible patients

The most common second-line therapies for transplant-ineligible patients were GEV, GCD, GVD, DHAP, ICE and brentuximab vedotin, with a median of 6 cycles in both sectors. Of note, one expert only mentioned the use of Brentuximab vedotin as a second-line therapy; this indication is not approved in Brazil. Subsequent lines of therapies further highlight the discrepancies between both systems, with brentuximab vedotin commonly used in private patients (consistent with the approved use of the drug in the country - after 2 previous chemotherapy regimens in transplant-ineligible patients) while the drug is not used in the public system. Table 5 shows the second and subsequent lines of therapies for the transplant-ineligible patients.

Overall, refractory/relapsing Hodgkin's lymphoma patients were followed every 3 months (median) on both healthcare systems. Table 6 shows the physicians' perspective on the cure rate on each line of therapy. According to participants, the main reasons to change therapy were toxicity, lack of response and disease progression on both therapies.

Table 5. Regimens used as second and subsequent lines of therapy for transplant-ineligible patients, according to physicians perspectives.

Second line	**Public healthcare system**		**Private healthcare system**	
		%		%
Most common regimens	GEV	33	GEV	60
	GCD	17	ICE	20
	GVD	17	Brentuximab vedotin (off label use)	20
	DHAP	17		
	DHAP + Radiotherapy	17		
Cycles (median)	6		6	
Subsequent lines	**Public healthcare system**		**Private healthcare system**	
Most common regimens	ICE	67	Brentuximab Vedotin	67
	Radiotherapy	50	GVD	33
	DHAP	33	DHAP	17
	GVD	33	GCD	17
	GCD	17	GEV	17
	GEV	17	Radiotherapy	17
			Others*	17
Cycles (median)	3.5		4	

*Others: GEMOX and GDP regimens. Median cycles refers to systemic therapies.

Table 6. The cure rate reported by the participants for each line of therapy.

	Public healthcare system		Private healthcare system	
Cure rate	Mean (%)	Med (Min-Max) (%)	Mean (%)	Med (Min-Max) (%)
Transplant Eligible patients				
After second line	52.5	50 (45-60)	58	55 (45-70)
After subsequent line	17	15 (0-40)	18	15 (0-40)
Transplant Ineligible patients				
After second line	17.5	20 (0-30)	13	10 (0-25)
After subsequent line	7	5 (0-20)	2	0 (0-10)

Discussion

Although Hodgkin's lymphoma is a type of cancer with high rates of cure, it is still a complex disease to manage, which requires highly specialized clinical teams and continuing medical education. In Brazil, these experts usually work at both the public and private healthcare systems that coexist in the country: the public healthcare system is funded by the government and available to all citizens, and the private system is comprised of private insurance companies and out-of-pocket expenses with healthcare. These specialized teams present a good level of medical education and large clinical experience in the area of Hodgkin's lymphoma, making use of the best available evidence and international guidelines such as the NCCN guidelines.

The experts reported a high consistency between the public and private healthcare systems with regard to the first line treatment of Hodgkin's lymphoma. The regimen used more often was ABVD (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine): for 4 cycles in patients at stages I and II (half of them with combined radiotherapy) and for 6 cycles for patients at stages III and IV. This result is consistent with treatment recommendations and with data obtained from the Brazil registry, which showed that ABVD was the front-line treatment in 93% of the patients (Follows *et al.,* 2014, Biasoli *et al.,* 2017). A potential consequence, the cure rates achieved after first-line therapy are also perceived as similar between the systems: 80–87.5% for patients at stages I and II, and 60–67.5% for stages III and IV. Of note, results from the Brazil registry are consistent with this perception: the rate of complete responses (CR) among the 652 evaluable patients was 73%, plus 12% of unconfirmed CRs (Biasoli *et al.,* 2017).

BEACOPP regimen was also mentioned in the questionnaire for the treatment of patients with HL stages III and IV. The experts clarified that the use of this regimen is very limited in Brazil; it is usually recommended only when ABVD is not available in the institution. In the literature, BEACOPP regimen showed higher freedom from first progression compared to ABVD regimen, with a similar 7-year overall survival rate between both regimens (Viviani *et al.,* 2011). However, BEACOPP showed itself as a more aggressive treatment with serious adverse events occurring more frequently (Viviani *et al.,* 2011), which may be an important issue for patients in the public sector who have limited access to healthcare institutions.

However, discrepancies in the standard of care offered to private and public patients become more profound as patients relapse or are refractory to the first-line therapy. Access to ASCT is an important example: among the transplant-eligible patients, the procedure takes longer to occur in the public system, with some patients even dying while on the line (median of 4.5 months to ASCT *versus* 1.5 in the private system). Moreover, it happens less often: while 100% of the private patients actually undergo the procedure, 75% of the public patients are transplanted—which is mainly due to problems in the infrastructure of the public system. Despite ASCT being recommended for the treatment of relapsed/refractory patients (Andre *et al.,* 1999, Josting *et al.,* 2000), only a few medical institutions are certified to perform transplant and some institutions have terminated their transplant program, which places an enormous burden on the centers that have hospital beds available. Lastly, according to the experts, the rate of cure following transplant is 55% for private patients while it is 50% for public patients.

Regarding consolidation therapy, there is evidence showing that it is beneficial for HL patients. For instance, studies showed that brentuximab vedotin, after ASCT, improved progression-free survival in patients with a high risk of relapse (Moskowitz *et al.,* 2015). Interestingly, there is no use of consolidation therapy with brentuximab vedotin after ASCT for high-risk patients treated in the public healthcare system due to the lack of availability of this therapy in the system. In contrast, around 30% of private patients receive consolidation therapy (high-risk patients) with brentuximab vedotin. This result is an example of the discrepancies observed in the treatment of HL patients between the public and private systems.

Upon failure of ASCT, access to allogeneic stem cell transplant seems to be unequal in healthcare settings (median of 10% and 35% in the public and private sectors, respectively). Moreover, the use of brentuximab vedotin remains almost limited to private patients (83% of private patients versus only 17% of public patients)—which is truly detrimental to public patients, as the use of BV in this situation delivered an ORR of 72% and a CR rate of 33% after 5 years of follow-up, with estimated 5-year OS and PFS rates of 41% and 22%, respectively (Chen *et al.,* 2016).

Several other regimens are used as subsequent lines of therapy, according to individual medical conditions or availability of drugs in the system. The experts did not mention

the use of other new, innovative therapies for Hodgkin's lymphoma, such as the checkpoint inhibitors nivolumab and pembrolizumab They are available in Brazil for certain types of solid tumors, and at the time of the panel, they were not approved for use in Hodgkin's lymphoma (nivolumab has been recently approved).

This study presents some limitations. As only eight experts participated in the panel discussion, the representativeness of the results is limited. The sample did not cover the entire Brazilian territory, although they represent three geographic regions of the country (out of five). The results were obtained from a questionnaire and a panel discussion that reflects the experts' point of view. Therefore, the certainty of the values may be affected and should not be overgeneralized. Nevertheless, this panel discussion has an exploratory objective to help guide further studies of the scenario over HL patients' treatment.

Conclusion

Overall, the present data showed good consistency in regard to first-line therapy for HL in Brazil in the public and private health systems. However, for the more severe cases (patients with refractory or relapsing disease) there are significant discrepancies between these systems regarding access to transplant and innovative new therapies, which pose an important challenge to the management of these patients in the public healthcare system. Suggestions from the experts to improve this scenario include better allocation of the healthcare budget, improvement in the system infrastructure, and the adoption of outpatient facilities for autologous stem cell transplantation.

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