Hodgkin's lymphoma unmet medical needs in Brazil: experts' perspective

Necessidades médicas não atendidas no tratamento de linfoma de Hodgkin no Brasil: perspectiva de médicos

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ABSTRACT

Background: In 2016, Hodgkin's Lymphoma (HL) was responsible for 2,470 new cases in Brazil and, despite recent scientific advances, there are unmet medical needs that affects patients' outcome. Therefore, we aimed to explore the unmet medical needs in the management of HL patients in Brazil, based on experts' perspective. **Methods:** A questionnaire was developed to address the unmet medical needs including barriers for the diagnosis and treatment of HL in Brazil. The questionnaire results were presented in a panel discussion to validate participants' responses and to collect additional data. **Main results:** Eight experts participated in the panel. On both healthcare systems, public and private, a slight majority of patients was women and most of them were under 60 years-old. In addition, the majority of patients were referred from another specialty on both systems. The time from onco-hematologist appointment to diagnosis was different between public and private sector (median of 30 and 12.5 days, respectively). Most patients in the public sector were on stage III (33%) and IV (33%); in the private sector, most patients were on stages II (36%) and III (24%). The most common barriers were the delayed diagnosis and the unavailability of diagnostic procedures and treatment options. **Conclusion:** According to participants, issues related to infrastructure and healthcare resource allocation affects the management of HL. Improvements in the infrastructure and educational measures for physicians and patients may contribute to minimize the barriers.

RESUMO

Introdução: Em 2016, o Linfoma de Hodgkin (LH) foi responsável por 2.470 novos casos no Brasil e, apesar dos recentes avanços científicos, há necessidades médicas não atendidas que afetam os pacientes. Portanto, o estudo teve como objetivo explorar as necessidades médicas não atendidas no manejo de pacientes com LH no Brasil, com base na perspectiva de especialistas. **Métodos:** Um questionário foi desenvolvido para abordar as necessidades médicas não atendidas, incluindo as barreiras para o diagnóstico e tratamento do LH no Brasil. Os resultados do questionário foram

apresentados em um painel de discussão para validar as respostas dos participantes e coletar dados adicionais. **Principais resultados:** Oito especialistas participaram do painel. De acordo com os especialistas, em ambos os sistemas de saúde público e privado, uma pequena maioria dos pacientes era mulher e a maioria tinha menos de 60 anos. Além disso, a maioria dos pacientes foi encaminhada por outra especialidade em ambos os sistemas. O tempo entre a consulta com o onco-hematologista até o diagnóstico foi diferente entre o setor público e privado (mediana de 30 e 12,5 dias, respectivamente). A maioria dos pacientes do setor público apresenta estádios III (33%) e IV (33%); no setor privado, a maioria dos pacientes apresenta estádios II (36%) e III (24%). As barreiras mais comuns foram o atraso no diagnóstico e a indisponibilidade de procedimentos diagnósticos, e opções de tratamento. **Conclusão:** De acordo com os participantes, as questões relacionadas à infraestrutura e à alocação de recursos de saúde afetam o gerenciamento do LH. Melhorias na infraestrutura e medidas educacionais para médicos e pacientes podem contribuir para minimizar as barreiras.

Introduction

Hodgkin's lymphoma (HL), a B-cell malignancy, is a relatively rare disease: in Brazil, the National Institute of Cancer estimated 2,470 new cases in 2016, with approximately 60% of cases occurring in men and an estimated incidence of 1.46 new cases/100,000 men and 0.93 new cases/100,000 women. (Moskowitz *et al.* 2009) Fortunately, there is a high probability of cure with the available therapies, with more than 80% of all newly diagnosed HL patients aged 60 years or less likely to be cured with front-line therapy consisting of multi-agent chemotherapy alone or associated with radiotherapy. (Ansell 2016)

However, there is still an unmet medical need in the management of the disease, since approximately 5% to 10% of cases of HL may be refractory and 10% to 30% may experience a relapse. (Horning 2000, Diehl *et al.* 2001) Despite treatment options, outcomes remain suboptimal: approximately 50% of HL patients relapse after Autologous Stem Cell Transplant (ASCT) (Sureda *et al.* 2005, Majhail *et al.* 2006), and only a minority of patients is eventually cured. (Arai *et al.* 2013, Martinez *et al.* 2013)

In this scenario, the most recent developments in HL have focused on these refractory or relapsing patients. For instance, Brentuximab Vedotin induced an overall objective response in 75% of relapsed/refractory HL patients after ASCT, being 34% and 40% of patients with complete and partial response, respectively. (Younes *et al.* 2012) In addition, Brentuximab Vedotin delivered a 5-year overall survival (OS) and progression-free survival (PFS) rates of 41% and 22%, respectively, in relapsed/refractory patients after ASCT. (Chen *et al.* 2016) Another example is the checkpoint inhibitors (PD-1 blocking agent), nivolumab and Pembrolizumab. (Timmerman *et al.* 2016, Chen *et al.* 2017) A phase II clinical study with Nivolumab in refractory/relapsed HL patients after ASCT and Brentuximab (Checkmate 205B) demonstrated a 68% objective response, being 8% of complete response and 60% of partial response. PFS and OS at 12 months were 54.6% and 94.9%, respectively, (Timmerman *et al.* 2016).

Despite the outcomes' improvement, managing patients in real life is subject to variables such as the clinical condition of these patients, the level of medical literacy, features of the healthcare setting, as well as socioeconomic and health policy issues. (Ellis *et al.* 2012, Gomez *et al.* 2015, Parikh *et al.* 2015, Adam *et al.* 2016, Karalexi *et al.* 2016, Mogensen *et al.* 2016) These variables have a significant impact on treatment outcomes; therefore, it remains critical to understand what these real-life issues are and how to overcome them to achieve the best standard of care.

Objectives

Although surveys and panel discussions do not substitute clinical data, they are good methods to explore the real-life scenario and gather information for future studies. Therefore, the present panel discussion aimed to collect input from experts about the management of HL in the Brazilian heterogeneous scenario.

Methods

This panel study was developed to explore the unmet medical needs and the difficulties in the diagnosis and treatment of HL patients in the Brazilian healthcare scenario, based on experts' perspective. The study was divided into two main steps: a questionnaire and a panel discussion. Eight experts were invited to participate in the study in 2017. The participants worked in the private and public healthcare systems, and they were spread across the Brazilian territory, coming from 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.

Following the study participation acceptance, a questionnaire was sent to the physicians. Then, the questionnaire answers were presented in the panel discussion, where the participants validated their opinions, debated topics related

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to unmet HL medical needs, and suggested measures to minimize these difficulties.

Questionnaire development

A 62-question survey was developed in an online platform by specialists based on the main unmet medical needs found in a literature review. After questionnaire development, it was validated by an internal expert and sent to all the participants through e-mail invitation. The questionnaire was responded to in one week. In the e-mail and before starting the questionnaire, the participants were instructed to answer the questionnaire according to their experience and perspectives.

The questionnaire aimed to elucidate the barriers to diagnosing and treating HL patients in the Brazilian healthcare scenario. For this reason, the questionnaire was divided into two sections, public and private healthcare systems, and each section into three main topics containing multiple-choice and four open questions:

- 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; patients' referral; disease stage; time of disease; time of diagnosis.
- Unmet medical needs: adherence and needs from guidelines; tests used for diagnosis; availability of diagnostic procedures; barriers for diagnosis; time to initiate treatment; treatment availability for HL and refractory/relapsing patients; treatment adherence; reasons for non-adherence; barriers and factors influencing autologous and allogeneic stem cell transplantation; hospitalization barriers; barriers for diagnosis and treatment; measures to minimize barriers.

Panel Meeting

After completing the questionnaire, a panel discussion was performed for the participants to debate their perspective on barriers related to management of HL patients. All experts participated in the panel, which took place in São Paulo, one week after receiving the experts' responses. The questionnaire answers were compiled and presented to all of the participants on the day of the panel discussion. During the panel, the participants shared their experience and commented the different scenarios in the Brazilian healthcare systems. Issues related to the diagnosis and treatment of HL were debated and they suggested measures to minimize the current difficulties and barriers.

Data analysis

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

Results

Participant's characteristics

The participants were from the South, Southeast and Northeast geographic regions of Brazil. Four of them reported being onco-hematologists, two hematologists, one pathologist and one from nuclear medicine. The median time of experience was ten years, ranging from 10 to 35 years. Seven participants worked on both the public and private healthcare systems; only one participant worked exclusively in the private healthcare system.

Characterization of physicians' patients

The participants reported a median of seven new HL patients per month. The majority of them were under 60 years old, with a median of approximately 87.5% and 75% from the public and private sectors, respectively. About patients' gender, they presented a similar profile on both healthcare systems, a median of 55 and 50% from public and private sectors, respectively. The participants also reported that a median of 95% of HL patients from the public sector, and 100% from the private sector, are referred from different specialties.

Figure 1 shows the specialties that refer patients for treatment. The option "other" was the most reported in both healthcare systems, which includes surgeons, for instance. Figure 2 shows the disease stage at diagnosis in each healthcare system, where higher percentages of stages III and IV were found in the public system. It was also reported that the median time of disease at the diagnosis was 6.5 and 1.5 months in the public and private sectors, respectively.

Unmet medical needs

According to physicians, the most used guideline was the National Comprehensive Cancer Network (NCCN), followed by European Society for Medical Oncology (ESMO), World Health Organization (WHO), institution's internal guidelines and Brazilian Clinical Oncology Guideline (Manual de Oncologia Clínica do Brasil – MOC). Most participants consider that the guidelines fit in the private sector scenario, but not regarding treatment of refractory/relapsed patients in the public segment.

Unmet medical needs – diagnosis

Participants reported having a good availability of diagnostic procedures in the public and private sectors. Table 1 shows the most used tests for diagnosis according to their
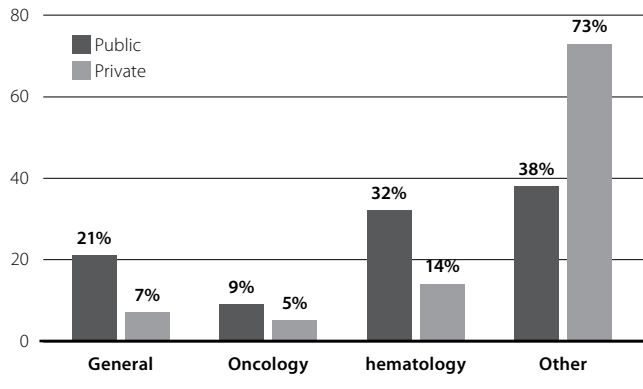
Figure 1. The mean percentage of patients referred from different specialties according to physicians' perspective. (Other: other specialties such as surgeons)
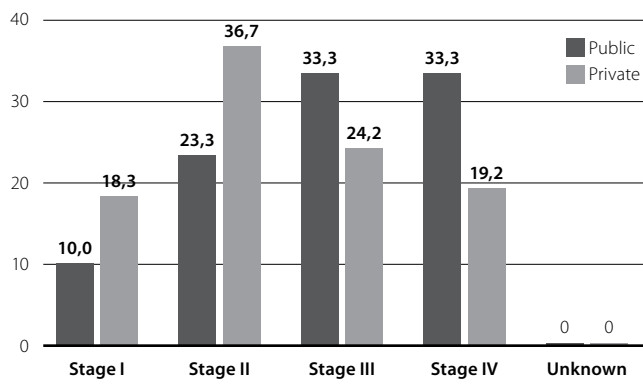

Figure 2. The mean percentage of patients with each stage of the disease at diagnosis, according to physicians' perspective.

Table 1. The most common tests used in the diagnosis and staging of HL. The percentage represents the rate of participants using each test

Tests	Public healthcare system	Private healthcare system
	%	%
Blood count	100	100
Biochemical markers	100	100
PET-TC	100	100
Lymph node biopsy	100	100
Immunohistochemistry	100	100
Erythrocyte sedimentation rate (ESR)	83.3	100
Chest x-ray	66.7	33.3
Other	66.7	50
TC	50	50
Bone marrow biopsy	50	50
Magnetic Resonance Imaging	0	0

Other: Serologies, Doppler echocardiography, B2 microglobulin.

reported frequency. However, it was emphasized by physicians that, in the public sector, it takes a median of 30 days to receive the tests results and make the diagnosis; in the private sector, this number drops to 12.5 days. Regarding immunohistochemistry results, the participants also reported that 26.7% of the results are not reliable in the public sector; in the private sector, this number drops to 8.3%.

The participants reported that the main barriers for the diagnosis in the public sector are the delay in making an appointment with a specialist, delay in performing diagnostic procedures, and lack of infrastructure to perform the biopsy. In the private sector, the majority of the participants reported not having difficulties with the diagnosis. Table 2.

Unmet needs—Treatment

For patients at diagnosis, the participants reported that it takes a median of 1.5 and 1 months in the private and public sector, respectively, to begin the treatment. In the public healthcare system, 83.3% of the participants reported having all necessary treatments available for HL patients; in the private healthcare system, all treatments were available. However, when treatment of refractory/relapsing HL patients is considered, only 16.7% of the participants reported having all treatments available in the public sector while 83.3 % reported having treatments available in the private sector.

Regarding patients' adherence to treatment, participants believe that most patients are adherent to both healthcare systems, with 85.8% and 93.3% in the public and private sectors, respectively. Patients' lack of information (66.7%), adverse events (50%), treatment unavailability (50%), socio-economic factors (50%), forgetfulness of the therapy (16.7%) and symptoms of the disease (16.7%) were considered the main reasons for non-adherence in the public healthcare system. In the private sector, adverse events were the main reason for non-adherence (80%), followed by forgetfulness of the therapy (20%) and patients' lack of information (20%).

The delay in scheduling preparatory procedures and exams was mentioned by half of the participants as the main barrier for the Autologous Stem Cell Transplant (ASCT) in the public sector, followed by the unavailability of the procedure (33.3%) and lack of specialized centers (33.3%). In the private sector, 75% of the participants mentioned that they do not have difficulties in the ASCT; the only barrier was the unavailability of the procedure (25%). The main factor influencing the ASCT procedure results was the performance status, reported by all participants for both healthcare systems. This was followed by chemosensitivity (83.3%), absence of extra-nodal involvement and bulky disease (50%), time to relapse higher than 6 months (33.3%) and absence of B symptoms (16.7%), in the public sector; and chemosensitivity (83.3%), absence of extra-nodal involvement and bulky disease (66.7%), time to relapse higher than 6 months

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Table 2. The most reported barriers to the diagnosis and staging of HL, based on physicians' perspective. The percentage represents the rate of participants reporting each barrier.

Barriers	Public healthcare system %	Private healthcare system %
Delay in scheduling consultation with specialists	83.3	0
Delay in the scheduling of PET-CT	83.3	0
Delay in scheduling the biopsy	66.7	20
Delay in computed tomography scheduling	66.7	0
Lack of structure / human resources / devices needed for biopsy	66.7	0
Lack of structure / human resources / devices required for immunohistochemistry	50	0
Lack of structure / human resources / devices needed for computed tomography	50	0
Delay in the scheduling of immunohistochemistry	33.3	20
Lack of structure / human resources / devices needed for PET-CT	33.3	0
Delay in X-ray scheduling	16.7	0
Lack of specialists	16.7	0
Others	16.7	60
Delay in MRI Scheduling	0	0
Lack of structure / human resources / devices needed for X-ray	0	0
Lack of structure / human resources / devices needed for MRI	0	0

Others: There are no barriers in the private healthcare system.

(66.7%) and absence of B symptoms (50%), in the private sector.

For the Allogeneic stem cell transplant, the reported barriers for the procedure in the public sector were the delay in scheduling donation procedure (50%) and difficulty in finding a donor and specialized centers (33.3%). Sixty-six percent of the participants reported having no difficulties in the private sector; the other factors mentioned were delay in scheduling donation procedure (33.3%) and difficulty in finding a donor (16.7%). In the public sector, the main factors that affect the procedure success were performance status

(100%), chemosensitivity (83.3%), time to relapse higher than 6 months and absence of Bulky disease (50%), and absence of extra-nodal involvement (33.3%). In the private sector, the factors most mentioned were performance status and chemosensitivity (100%), followed by time to relapse higher than 6 months (66.7%), absence of Bulky disease (50%), absence of extra-nodal involvement (33.3%) and B symptoms (16.7%).

For hospitalization of HL patients, the only reported barrier in the public sector was the lack of hospital beds, mentioned by all participants. In the private sector, 75% of participants mentioned that there is no barrier in hospitalizing patients; the only barriers reported were the lack of hospitals near patient's residence and poor condition of hospital beds (25%).

Table 3 shows the most common barriers for treatment initiation in both healthcare systems.

Suggestions to minimize barriers

In table 4, there are the main measures to minimize barriers for diagnosis, patients' non-adherence and treatment.

Discussion

International treatment guidelines for HL are well established and, for the patients with a refractory or relapsing disease, significant progress has been made in recent years. Our panel discussion successfully explored the current Brazilian scenario over the management of HL, evidencing the unmet medical needs and barriers for HL diagnosis and treatment.

According to the results obtained, the referral from other specialties represents an important role in the management of HL patients. During the panel, the participants agreed that, in the public sector, patients initially visit general practitioners, then undergo diagnostic procedures and, finally, visit the onco-hematologist for treatment. In the private sector, there is a similar path, but it is more common to have patients directly visiting the onco-hematologist/oncologist than in the public sector. This process is observed in the questionnaire results, where surgeons (others) were the most common area to refer patients to onco-hematologists, usually with the diagnosis already done. Also, general practitioners also present an important role in patient referral, especially in the public sector. The importance of patient referral was previously reported in the literature (Zeichner and Montero 2016), where the different specialties present key role in the time to diagnosis and, consequently, in patients stage and cure rates.

Real life issues in the management of HL patients in Brazil start at diagnosis: although tests are usually available even in the public system (PET and CT less than in the private system), it takes a long time to receive test results, with a worse scenario in the public system. During the panel, the participants mentioned that the diagnosis time could reach more than 5

Table 3. The most reported barriers to the treatment of HL, based on physicians' perspective. The percentage represents the rate of participants reporting each barrier.

Barriers	Public healthcare system	Private healthcare system
	%	%
Delay in diagnosis	66.7	25
Delay in the staging process	66.7	0
Unavailability of appropriate treatment (chemotherapeutic or immunotherapeutic)	33.3	0
Delay in scheduling radiotherapy sessions	33.3	0
Delay in obtaining treatments (chemotherapeutic or immunotherapeutic)	16.7	25
Others	16.7	50

Others: There are no barriers in the private healthcare system.

months when considering the time from the first visit to a non-specialist until disease diagnosis. Among the critical steps, the participants mentioned the time of appointments with specialists or to undergo diagnostic procedures, such as biopsy. These barriers for the access of patients to healthcare system certainly contributes to the differences observed between the two systems regarding disease stage at diagnosis—with public patients usually presenting with more advanced disease at diagnosis. Indeed, results from the Brazil registry showed that the median time from the onset of symptoms to diagnosis was 6 months and that 65% of the patients had advanced disease at diagnosis. (Biasoli *et al.* 2017)

As mentioned by the participants, most of the diagnostic procedures are available for them, even in the public sector. One of the exceptions is the PET-CT, which is not available for all of the participants, being present only in specific healthcare institutions in the public sector. PET-CT is an important tool that helps physicians to stage HL and to monitor and manage the patients' treatment. (Ansell 2016) For instance, as agreed by the participants in the panel, interim PET may be used to monitor an early disease response. However, several participants reported having difficulty in scheduling the PET-CT in the correct period of the treatment. Regarding immunohistochemistry, the participants reported that around 25% and 8% of the results in the public and private sectors, respectively, are not reliable. During the panel discussion, the experts mentioned that most immunohistochemistry tests are made through core biopsy. It was agreed that core biopsy should be used in the diagnosis, as in relapse there may be

Table 4. The main measures to minimize barriers for diagnosis, patients' non-adherence and treatment. The percentage represents the rate of participants reporting each measure.

Measures to minimize barriers for diagnosis and staging	Public healthcare system	Private healthcare system
Measures	%	%
Providing adequate infrastructure	100	0
Providing adequate equipment	83.3	0
Continuing medical education for specialists (oncologists / hematologists)	66.7	20
Continuing medical education for general practitioners / basic care	66.7	20
Increased population awareness of LH-related signs and symptoms	50	20
Making more specialists available	33.3	0
Others	33.3[a]	40[b]
Measures to minimize barriers for treatment		
Measures	%	%
Providing appropriate treatments	100	20
Providing adequate infrastructure	100	0
Continuing medical education for specialists (oncologists / hematologists)	66.7	40
Making more specialists available	33.3	0
Continuing medical education for general practitioners / basic care	33.3	40
Increased awareness of the population of signs and symptoms related to LH	16.7	60
Others	0	0
Measures to improve patients' adherence		
Measures	%	%
Availability of treatment	100	0
Better management of adverse events	66.7	60
Better communication with patient	33.3	60
Treatment of disease symptoms	16.7	0
Others	16.7[c]	0

a. Other includes: Continuing medical education and training of the pathologists.
b. Other includes: Absence of barriers to diagnosis in the private system; type of health plan coverage
c. Other includes: facilitating patient transportation.

only a partial impairment of the lymph node. Moreover, the importance of pathologist training was highlighted, as immunohistochemistry from core biopsy is only reliable when performed by trained professionals.

Despite the delayed diagnosis, the participants agreed that the healthcare system is reasonably efficient in starting therapy once diagnosis has been established—within a median of 1.5 and 1 months in the public and private sectors, respectively. The availability of treatment options, however, varies significantly between the two systems, specifically after the first-line therapy. While 83.3% of the experts reported no issues in treatment availability for the refractory/relapsing patients in the private system, only 16.7% of experts in the public system reported the same.

For instance, despite the benefits of ASCT in relapsing/refractory HL patients (Ansell 2016), there are important non-medical barriers to access to ASCT, especially in the public system, that show a complex scenario for transplants. As mentioned by the participants, there is only a small number of institutions that specialize in ASCT poorly distributed in the Brazilian regions, which results in the lack of hospital beds for these patients. In addition, HL's patients compete with different pathologies that also require transplants, making it even more difficult to manage. These non-medical issues influence the rate of allogeneic transplant in the system. Another example of difficulties in treating relapsing/refractory patients is the absence of brentuximab, which is rarely available in the public system even for patients who relapse after ASCT. In the private system, participants reported that Brentuximab is often available or reimbursed both for patients relapsing after ASCT or as a consolidation therapy after ASCT. The checkpoint inhibitors nivolumab and pembrolizumab are commercially available in Brazil, and nivolumab has been recently approved for Hodgkin's lymphoma up to this date. As a result, the treatment of relapsing/refractory HL is performed using what is available on each institution, according to the experts.

Based on these results, the main barriers for the management of HL patients rely in the access for diagnostic and treatment procedures. To minimize these barriers, the participants agreed that diagnostic procedures and treatments should be available in a homogenized way across the institutions. Moreover, continuing medical education for specialists and primary care physicians is fundamental to minimize barriers such as the delayed diagnosis.

This study presents some limitations. The representativeness of the results is limited as only eight experts participated in the panel discussion. Despite covering three geographic Brazilian regions (out of five), the sample did not cover the entire territory. Another important limitation is the generalizability of the results. 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' diagnosis and treatment.

Conclusion

In summary, the experts conclude that the management of HL patients is different among public and private patients and the main differences are the delays in initial diagnosis and lack of therapeutic options for refractory or relapsing patients in the public system. They point out that impactful measures to improve this scenario would include the establishment of adequate healthcare infrastructure and equipment for this complex disease, coupled with investments in continuous medical education in HL for both specialists and general practitioners. These are essentially the same areas of improvement highlighted by the experts participating in the Brazilian registry for Hodgkin's lymphoma.

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