UPDATE ARTICLE
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New treatment approaches for relapsing/refractory Hodgkin's lymphoma: An overview of the Brazilian scenario

Novas abordagens de tratamento para o linfoma de Hodgkin recidivante/refratário: uma revisão

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ABSTRACT

Hodgkin's lymphoma (HL) is a B-cell malignancy with a classical bimodal distribution with incidence peaking in the third and sixth decades of life. The purpose of this review is to describe the current unmet medical need for relapsing/refractory HL and the main data of emerging treatments, including brentuximab vedotin, the immune checkpoint inhibitors nivolumab and pembrolizumab, as well as other compounds in development. Available guidelines for relapsing/refractory HL are discussed.

Palavras-chave:
linfoma de Hodgkin, necessidades médicas não atendidas, tratamentos

RESUMO

O linfoma de Hodgkin (LH) é uma neoplasia de células B com distribuição bimodal clássica com pico de incidência na terceira e sexta décadas de vida. O objetivo desta revisão é descrever as atuais necessidades médicas não atendidas dos pacientes com LH recidivante/refratário e os dados principais dos tratamentos emergentes, incluindo brentuximabe vedotina, os inibidores do ponto de verificação imunológico, nivolumabe e pembrolizumabe, bem como outros compostos em desenvolvimento. Além disso, discutem-se as diretrizes disponíveis para LH recidivante/refratário.

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Hodgkin's lymphoma: Do we still have remaining unmet medical needs?

Hodgkin's lymphoma (HL) is a B-cell malignancy separated into two major subtypes: Nodular Lymphocyte Predominant (NLP) and Classical Hodgkin Lymphoma. (Kuppers *et al.* 2012) NLP is characterized by the presence of lymphocyte-predominant cells (known as popcorn cells), whereas CHL – which accounts for 95% of the cases – shows the presence of characteristic neoplastic cells, known as Reed-Sternberg cells and Hodgkin cells, respectively. (Kuppers *et al.* 2012) In both diseases, the neoplastic cells are scattered in a background of non-neoplastic cells that differ in each subtype. HL affects mainly the lymph nodes, but extra-lymphatic organs such as bone marrow, liver and lungs can also be involved. (Kuppers *et al.* 2012)

While the cause of HL remains unknown, familial history, viral infections and immune suppression are known to increase the risk of the disease. A classical bimodal distribution is observed, with a first peak of incidence in the third decade of life and a second peak after the age of 50. The US National Cancer Institute estimates 8,260 new cases of HL in 2017, representing 0.5% of all new cancer cases. The last prevalence data estimated 204,065 people living with the disease in the US during the year of 2014 (National Cancer Institute 2017). In Brazil, there are few epidemiologic data; the National Institute of Cancer (Instituto Nacional do Câncer José de Alencar Gomes da Silva (INCA) 2018) estimated 2,530 new cases in 2018, affecting 1,480 men and 1,050 women.

HL has been a field for extensive research and clinical improvements over the last several years and is currently considered to be a cancer with a high probability of control and cure. In fact, the National Cancer Institute shows that the percentage of HL patients surviving 5 years, between 2007 and 2013, was 86.4%—including patients with advanced disease at presentation (National Cancer Institute 2017)—and shows that currently more than 80% of all newly diagnosed HL patients aged 60 years or less are likely to be cured following front-line therapy consisting of multi-agent chemotherapy and radiotherapy. (Ansell Stephen 2012, Borchmann *et al.* 2012)

However, despite a high likelihood of success with front-line treatment, approximately 5% to 10% of cases of HL may be refractory to the initial chemotherapy or radiation therapy and approximately 10% to 30% may experience relapse after a complete initial response to treatment. (Horning 2000, Diehl *et al.* 2001) Both groups represent a challenging population to treat, with less well–defined prognostic models and poor therapeutic results. (Collins *et al.* 2014) Primary resistance is generally considered to be of poor prognosis; many patients do not undergo autologous stem cell transplantation (ASCT) due to rapidly progressive disease, poor performance status or other comorbidities, and until recently, virtually no patient (0–8%) survived more than 8 years using conventional chemotherapy alone. (Longo *et al.* 1992, Bonfante *et al.* 1997, Josting *et al.* 2000) Relapsed disease is also associated with worse prognosis in the long term, especially if relapse occurs early following response to first-line therapy. A large retrospective analysis performed by the German Hodgkin Study Group (GHSG) identified that failure to attain a temporary remission on first-line treatment in addition to the low-performance status at the time of progression and age above 50 years predicted poor 5-year freedom from second failure (FF2F). (Josting *et al.* 2000) Other studies also showed that relapsing within 12 months of first-line therapy leads to worse prognosis (Brice *et al.* 1997, Wheeler *et al.* 1997, Sureda *et al.* 2001) compared to an 80% chance of a second remission for patients with a late relapse. (Longo *et al.* 1992)

In general, the treatment of R/R HL starts with salvage chemotherapy, followed by HDT and ASCT. Nevertheless, long-term results are still suboptimal even with this approach: approximately 50% of HL patients relapse after ASCT (Sureda *et al.* 2005, Majhail *et al.* 2006) and their prognosis is generally poor, with a median survival of 25 months (Moskowitz *et al.* 2009), with only a minority or no patients being cured. (Arai *et al.* 2013, Martinez *et al.* 2013). To manage this unmet medical need, new therapeutic approaches have been implemented in recent years, with the development of brentuximab vedotin and checkpoint inhibitors. Most of these innovative therapies have recently been approved for HL treatment and have been implemented in international guidelines.

Guidelines for Treatment of Relapsing/ Refractory Hodgkin Lymphoma

The 2017 edition of the NCCN guidelines (National Comprehensive Cancer Network (NCCN) 2017) recommends that patients with primary refractory or relapsed disease should start second-line systemic therapy, which includes several cytotoxic multidrug regimens; patients should be then re-staged and referred to HDT and ASCT if responding; treatment with brentuximab vedotin for one year as a consolidation therapy after ASCT should be considered, especially for patients with Deauville 4 prior to ASCT. PD-1 blocking antibodies should be used after BV. The European recommendations were last updated in 2014 (Eichenauer *et al.* 2014); they also recommended HDT and ASCT for patients with R/R disease, and even tandem ASCT for high-risk patients. BV was recommended in patients failing ASCT or at least two lines of previous therapy if they are not candidates to ASCT.

Although international guidelines provide orientation on disease management, there are no current national treatment guidelines in Brazil for the treatment of Hodgkin's lymphoma.

Therefore, we reviewed the clinical information of these innovative therapies for the management of R/R HL.

Brentuximab Vedotin

Brentuximab vedotin (BV) is an antibody-drug conjugate (ADC) comprising an anti-CD30 antibody conjugated by a protease cleavable linker to the potent antimicrotubule agent, monomethyl auristatin E (MMAE). It selectively binds to the CD30 receptor, a member of the tumor necrosis factor (TNF) superfamily, expressed by malignant RS cells. After binding to the cell surface, the ADC-CD30 complex initiates internalization and trafficking to the lysosomal compartment, releasing MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell. This is a targeted mechanism of action, as the normal CD30 expression is restricted to a relatively small proportion of activated B cells, T cells, and eosinophils. (Younes *et al.* 2012)

Brentuximab vedotin was originally granted accelerated approval by the Food and Drug Administration (FDA) in August 2011, by the European Medicines Agency (Moskowitz *et al.*) in 2012, and by the Brazilian Health Authority (ANVISA) in 2015. Brentuximab vedotin is approved in Brazil for HL patients that are relapsing or refractory after ASCT or at least two prior therapies, when ASCT or polychemotherapy is not an option, and as a consolidation therapy for patients at high risk of relapse or progression after ASCT. It is also approved for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma, both in Brazil and in the US. The main trials that investigated BV in HL are described below.

Pivotal phase II study in relapsing/ refractory Hodgkin lymphoma

Younes and colleagues conducted the pivotal phase II, single-arm study that established the efficacy and safety of BV in patients with relapsed or refractory HL after ASCT. In the study, a total of 102 patients with histologically documented HL, measurable disease $\geq$ 1.5 cm by computed tomography (CT), PET (positron emission tomography)-positive disease and performance status of 0 or 1 were included. Overall, the study population comprised of patients with poor prognosis: 71% had a primary refractory disease and 42% had a disease that was refractory to the most recent prior therapy. The median number of previous chemotherapy regimens excluding ASCT was 3.5 and the median time to relapse after ASCT was only 6.7 months, with most patients (71%) having relapsed within a year of ASCT. All 102 patients were treated with at least one infusion of brentuximab vedotin 1.8 mg/kg every 3 weeks; in the absence of disease progression or prohibitive toxicity, patients received a maximum of 16 cycles. The overall response rate (ORR – primary endpoint) was 75%, with complete remission (Armand *et al.*) in 34% of patients. The median time to the objective and to complete response were 5.7 and 12 weeks, respectively. The median duration of response was 6.7 months among all responders, while it was 20.5 months for those who achieved a CR. Responses occurred in different subgroups, including relapsed and primary refractory disease. The median progression-free survival (PFS) for all patients was 5.6 months and for patients who achieved a CR was 21.7 months. Median overall survival (OS) was 22.4 months, with an estimated 1-year survival rate of 89%. These responses seen with BV were superior to responses observed with other single agents. In addition, PFS was longer than the PFS observed with the previous systemic therapies (for patients who received systemic therapy following ASCT). Most adverse events (AEs) associated with BV were grade 1 or 2 and manageable through standard supportive care. They included peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. Neuropathy was the most clinically meaningful AE although it was largely reversible and considered to be a class effect of antimicrotubule agents. (Younes *et al.* 2012)

Follow-up data

At 5 years, patients from the pivotal phase II study of BV for R/R HL received a median of nine cycles of BV with an ORR of 72% and the CR rate of 33%. The median OS and PFS were 40.5 and 9.3 months, respectively, and the estimated 5-year OS and PFS rates were 41% and 22%. Interestingly, patients who had achieved a complete response with brentuximab (N = 34) had estimated 5-year OS and PFS rates of 64% and 52%, respectively, without achieving the median OS and PFS. This final analysis showed that 13 patients (38% of all CR patients) were still on follow-up and remission at study closure; 9 of them in sustained CR without receiving any further anticancer therapy (4 received allogeneic stem cell transplant [allo-SCT]). These patients in long-term remission represent 9% of the enrolled study population and provide a new perspective on the belief that allo-SCT was the only option for long-term disease control. The most common treatment-related AEs were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. Grade 3 or higher AEs occurred in ≥5 percent of patients and included neutropenia, peripheral sensory neuropathy, thrombocytopenia, and anemia. Of the patients who experienced treatment-emergent peripheral neuropathy, 88% achieved either resolution (73%) or improvement (14%) in symptoms. (Chen *et al.* 2016)

The encouraging experience with BV in the setting of relapse or refractory disease led to its investigation in the consolidation of remission and prevention of relapse in high-risk patients following ASCT.

Brentuximab vedotin as consolidation following ASCT

Patients with HL who relapse after ASCT have a poor outcome with very few effective therapeutic options. A study in

this population showed a median time to progression after the next therapy of only 3.8 months and a median survival after the ASCT of 26 months. (Kewalramani *et al.* 2003) Patients who underwent a reduced-intensity allogeneic transplant had a treatment-related mortality at 1 year of 20% and a 2-year OS of 50%. (Robinson *et al.* 2002) In fact, no completed randomized trials of maintenance or consolidation therapy after ASCT had been reported and no treatment was approved in this setting, and the standard of care for these patients was observation and best supportive care until disease progression. The unmet need of this population coupled with the success of BV in the relapsed and refractory HL setting raised the prospect of its use in prolonging remission and preventing relapse in high-risk patients following ASCT.

The randomized, placebo-controlled Aethera trial (Moskowitz *et al.* 2015) investigated the use of BV after ASCT in 329 patients with a high risk of relapse following ASCT. Risk factors for relapse following ASCT were based on data from multiple series of ASCT patients and validated prognostic models and were defined as one of the following: primary refractory HL (failure to achieve complete remission), early relapsed disease (remission lasting less than 1 year) or the presence of extranodal disease at the start of salvage therapy. However, patients included had to have had at least stable disease after salvage. A standard regimen of BV was started 30–45 days after ASCT. CT scans were used to assess disease progression according to an independent review and the Revised Response Criteria for Malignant Lymphoma.

BV appeared to be well-tolerated in this setting, with nearly 50% of patients completing 16 cycles of therapy and a toxicity profile that was consistent with previous studies. Peripheral neuropathy was the most common AE, with resolution or improvement in most patients. Consolidation treatment with BV provided a statistically and clinically significant improvement in PFS versus placebo. After a median follow-up of 30 months, PFS was significantly improved in the BV group, with a 43% reduction in the risk of progression (HR: 0.57; 95% CI 0.40-0.81; p=0.0013). Median PFS with brentuximab vedotin was 42.9 months versus 24.1 months in the placebo group, with estimated 2-year rates of PFS of 63% and 51%, respectively. PFS was consistent across all subgroups. Overall, there was high concordance (87%) between central and investigator assessments with more progression events being recorded by the investigators (for 13% of the patients in the placebo group and 4% of the patients in the BV group). The authors recorded only four PFS events after the 24-month assessment period, encompassing 108 patient-years of follow-up.

There was no difference in OS between treatment groups in the interim analysis, probably due to the high crossover rate of patients in the placebo group. Although more follow-up data is needed to evaluate long-term survival, the authors consider that many patients who were progression-free at 24 months might be cured, since relapse or progression after ASCT usually happens early (71% within 1 year and 90% within 2 years of ASCT). (Majhail *et al.* 2006, Arai *et al.* 2013) Lastly, a post-hoc analysis conducted by the authors showed that the PFS and OS benefits with BV increased with an increase in the numbers of risk factors for relapse after ASCT; however, further analysis of risk factors is needed to define better the population that is most likely to benefit from consolidation therapy with BV after ASCT.

At 3 years, in the Aethera trial follow-up, it was observed that the PFS rate was 61% (95% CI 53–68) for the BV arm and 43% (95% CI 36–51) for the placebo group. The PFS was similar to the one observed in the 2-year follow up, with a HR of 0.58 (95% CI 0.41–0.82). (Sweetenham 2016) Also, another study showed that BV presents a stronger impact in HL patients with more than 2 risk factors. (C. Moskowitz 2016)

Retreatment with Brentuximab Vedotin

Retreatment with BV in patients with HL(n=20) who had achieved CR or PR during initial BV therapy and subsequently relapsed was associated with a high overall objective response rate, with the same rate of CR and PR (both 30%) and 20% of patients experiencing stable disease as a best response. The median time between the last dose of BV given during the initial study and the first dose of retreatment was 11.4 months (range 4–45 months). No patients with HL were retreated with BV more than once (permitted if required). At this time point, the median OS had not yet been reached. (Bartlett *et al.* 2014)

Checkpoint Inhibitors

Over the past several years, a greater understanding of the regulatory pathways of the immune system and the mechanisms that allow tumor escape, including tumor augmentation of ligands to the T cell-programmed cell death 1 (PD-1) receptor known as PD-L1 and PD-L2 have led to the development of new immunotherapeutic options to treat solid tumors. This approach is especially interesting to treat hematologic malignancies based on the efficacy of immunologic approaches such as allogeneic transplantation, immunomodulatory drugs and adoptive cellular therapies (Tai *et al.* 2005, Maus *et al.* 2014) and the expression of PD-L1 and PD-L2. (Bryan and Gordon 2015) Specifically in HL, other factors provide further support to immunologic treatment such as the high expression of the immunoregulatory glycan-binding protein and galectin-1 (resulting in a type 2 T-helper cell and T-regulatory cell skewed tumor micro-environment), immunoregulatory gene alterations such as amplification at the 9p24.1 locus (resulting in increased JAK-STAT signaling and high expression of PD-L1 and PD-L2 on the tumor cell

surface) (Green *et al.* 2010) and the presence of latent Epstein–Barr virus infection in around 40% of HL cases, which is also thought to contribute to high expression of PD-L1 and PD-L2. (Paydas *et al.* 2015) Therefore, tumor-immune evasion through PD-1 augmentation appears to play a major role in the oncogenesis of HL and has consequently led to considerable interest in immune checkpoint inhibition using anti-PD-1 and anti-PD-L1 immunotherapy. Increasing data have been presented in the last few years about the use of checkpoint inhibitors, mainly on the anti-PD1 monoclonal antibodies nivolumab and pembrolizumab in the treatment of R/R HL.

Nivolumab

Nivolumab is a fully human monoclonal IgG4 antibody directed against PD-1. It has been approved by the FDA for HL adult patients who relapsed or progressed after hematologic stem cell transplantation (HSCT) and BV, or after at least 3 lines of systemic therapy, including HSCT. It has also been approved by the EMA for patients with relapsed or refractory HL after ASCT and BV. Nivolumab was approved by ANVISA in October 2017 for the treatment of patients with relapsing or refractory HL after ASCT followed by therapy with brentuximab vedotin.

Phase II: Nivolumab after failure of ASCT and brentuximab vedotin

The phase II CheckMate 205 study was a multi-cohort study evaluating nivolumab in HL; data from the cohort of patients with prior failure of both ASCT and subsequent BV has been published (Timmerman *et al.* 2016). Patients were included regardless of their PD-L1 status and received nivolumab 3mg/kg every 2 weeks. They were required to have received previous BV but were not required to be refractory to it. The median number of previous therapies was four. The median time between the most recent BV treatment and the first dose of nivolumab was 0.7 years, and the median time between HDT / ASCT and the first dose of nivolumab was 3.4 years.

At the time of analysis, 64% of patients remained on treatment and the median number of nivolumab doses received was 17. The primary outcome was ORR assessed by a central, independent review group. At a median follow-up of 8.9 months, 66.3% of the 80 patients achieved an objective response, which included CR in seven (9%) patients and PR in 46 (58%) patients. Overall, responses were quick, with a median time to first objective response of 2.1 months, and profound, with tumor reductions of at least 50% from baseline in all but one patient. The median duration of objective response was 7.8 months. Similar to what has been seen in solid tumors, there were some atypical response patterns to PD-1 blockade, including the appearance of new lesions followed by negative PET scan and responses after initial progression. Of note, response to nivolumab was reported in more than two-thirds of patients who had not responded to the most recent BV treatment before trial enrolment. At 6 months, the PFS rate was 76.9% and OS rate was 98.7%. At 12 months, median PFS was 10·0 months (95% CI 8·41–not reached). Some patients discontinued treatment with nivolumab and were referred to stem cell transplant (5 allo-SCT and one ASCT); one of them was in CR by the time of referral, 2 were in PR and one in stable disease. All patients who had transplantation after nivolumab treatment were alive at the time of analysis; however, there is a risk of complication in patients receiving allo-SCT, and they should be monitored for complications such as hyperacute graft-versus host-disease (GVHD), grade 3–4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions as four of five patients died from complications of allo-SCT in the phase 1 study. Overall, the most common drug-related AES (≥15% of patients) included fatigue (25%), infusion-related reaction (20%), and rash (16%), and the most common drug-related grade 3 or 4 AEs were neutropenia (5%) and increased lipase concentrations (5%). AEs of special interest, which are possibly inflammatory in nature and due to the enhancement of the immunologic activity following PD1 blockade were skin abnormalities (41%); gastrointestinal abnormalities (26%); hypersensitivity or infusion-related reaction (21%); and endocrine (18%), hepatic (10%), renal (5%), and pulmonary (1%) events. Pneumonitis was reported in two (3%) patients (one grade 2 and one grade 3) between the first dose and 35 days after the last dose; both cases were judged to be drug-related and both resolved with corticosteroid treatment. Most select AEs of special interest reported were of grades 1 or 2, and most were considered by the investigators to be drug-related.

Follow-up data

Follow-up data from CheckMate 205 has recently been presented. (Timmerman *et al.* 2016) For the cohort of patients who failed ASCT and BV, 43 patients (54%) remained on therapy after a median follow-up of 15.4 months. The ORR was 68%, with a CR rate of 8% and a PR rate of 60%. The median duration of response was prolonged to 13.1 months (95% CI, 8.7 months—not reached; range, 0.0–14.2 months) and the median duration of CR was not reached. Median PFS was 14.8 months; 12-month PFS was 54.6% and 12-month overall survival (OS) was 94.9%, with median OS not reached. The most common reasons for discontinuation were disease progression (24%), allogeneic SCT (9%) and AEs (6%). The most common drug-related AEs were fatigue (28%), infusion reaction (20%), arthralgia (15%), and rash (15%). Twenty-nine percent of patients had Grade 3–4 drug-related AEs; the most common were increased lipase (8%), neutropenia (5%), and increased aspartate aminotransferase (4%).

Pembrolizumab

Pembrolizumab is a humanized immunoglobulin G-1 kappa monoclonal antibody targeting the PD-1 receptor, which has also demonstrated a significant effect in HL. The FDA approved it for the treatment of adult and pediatric patients with refractory disease or who have relapsed after 3 or more prior lines of therapy. EMA has approved the drug for adult patients with R/R HL who have failed autologous ASCT and BV, or who are transplant-ineligible and have failed BV. Until the approval of this article for publication, pembrolizumab had not been approved for treatment of HL in Brazil.

Phase II: Pembrolizumab in different cohorts of relapsed/refractory patients

Keynote 087 was a single-arm phase II study which investigated pembrolizumab at the fixed dose of 200 mg every 3 weeks in 210 heavily pretreated patients with R/R HL. Patients were grouped in cohorts based on disease progression: if they had progressed after ASCT and subsequent BV (cohort 1), after salvage chemotherapy and BV (ineligible to ASCT—cohort 2) or after ASCT but without BV (cohort 3). The primary end points were ORR by central review and safety. The population included 35% of patients with primary refractory disease and 14% whose disease was chemo-refractory to all prior regimens; 61% had undergone prior ASCT and 83% had received prior BV at some point, including 41.7% of patients in cohort 3, who had received BV treatment before ASCT. Across all cohorts, 90% of the patients had some level of decrease in the tumor burden. Most responses were reported at the first assessment and ORR was 69%, with a CR rate of 22.4%. An analysis by cohort was prespecified; although the patients had received different prior treatments, their response rates were similar (from 64% for cohort 2 to 73.9% for cohort 1), as well as the rates of CR (20% to 25%). The median duration of response was not reached in any of the cohorts by the time of the analysis. At 6 months, the OS rate was 99.5% (median OS not reached) and the PFS rate was 72.4%. Due to the short follow-up, more accurate estimations of OS and PFS, as well as durability of response, are needed.

The safety profile was largely consistent with previous studies, with the most common treatment-related AEs being 11%, hypothyroidism 10.5%, diarrhea 6.7%, fatigue 6.7%, headache 6.2%, rash 6.2% and nausea 5.7%. Importantly, 14 patients in this study went on to receive a stem cell transplant, including 10 patients undergoing allogeneic SCT; one of these patients died due to graft-versus-host disease. Similar to nivolumab, it is recommended to monitor patients for complications of allo-SCT after treatment with pembrolizumab, including hepatic veno-occlusive disease, grade 3–4 acute GVHD, including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. (Chen *et al.* 2017).

Conclusion

HL is currently considered a cancer with a high probability of cure with front-line therapy based on multiagent chemotherapy and radiotherapy. However, up to 30% of patients will be refractory to frontline therapy or present with disease relapse following initial response to therapy. Salvage chemotherapy followed by high dose therapy and ASCT is the standard of care for this population, but outcomes are inferior to front-line therapy, with approximately half of the patients relapsing after ASCT. New therapies for R/R HL such as brentuximab vedotin and checkpoint inhibitors provide new therapeutic options for patients, with good tolerability, high response rates and promising survival results, even after failure of ASCT. For patients with a high risk of relapse following ASCT, the positive data of brentuximab vedotin in the consolidation setting also provides a new standard of care in the management of the disease.

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