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Review Article

Post ASH 2022: Hodgkin lymphoma, what' new?

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ABSTRACT:

Research in Hodgkin lymphoma (HL) is rapidly evolving as novel combinations and therapeutic strategies are constantly emerging. In the latest 65th annual meeting of the American Society of Hematology (ASH), several ground-breaking abstracts were presented with clinical practice-changing implications. Among the most remarkable abstracts are the development of Advanced-Stage Hodgkin Lymphoma International Prognostic Index (A-HIPI), the safety results of HD21 study, the integration of PD1 inhibitors in ABVD backbone through various schedules, the combination of nivolumab/ICE (NICE) in second-line setting and the first results of dual PD-1 and LAG-3 blockade with favezelimab. In this review we aim to summarize the key findings and critically comment on these studies, which reflect the current and future trends in HL treatment landscape.

KEY WORDS: *Hodgkin lymphoma, A-HIPI, prognostic factors, novel agents, brentuximab vedotin, nivolumab, pembrolizumab, favezelimab*

INTRODUCTION

The treatment of Hodgkin Lymphoma (HL) has rapidly evolved during the last decades passing from monotherapy with radiation (RT) and single-agent or non-anthracycline combination chemotherapy, to anthracycline-based combined modality schedules, risk-adapted approaches, intensification of chemotherapy in the form of BEACOPP-escalated, interim PET-adapted strategies and, recently, to incorporation of targeted agents into the first-line and salvage therapy. Owing to this progress, HL has been converted to a highly curable lymphoid malignancy. However, there are still various unmet clinical needs and several issues to be addressed, which briefly lie on improving patients' outcome, while reducing toxicity. Several abstracts focusing on latest developments of HL were presented in the latest 65th annual meeting of the American Society of Hematology (ASH). This review summarizes the most ground-breaking studies presented in the fields of prognostication and management of HL in the first-line and in the relapsed/refractory (r/r) setting.

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Prognostic factors for the outcome of first-line therapy

Baseline prognostication in advanced-stage HL remained unchanged during the last two decades. The International Prognostic Score (IPS), developed through an international effort led by the German Hodgkin Study Group (GHSG) (Hasenclever and Diehl, 1998), was the only validated clinical tool for predicting progression free survival (PFS).[1] Other conventional and biological prognostic factors were not adopted in clinical practice,[2]

while abbreviated versions of the IPS, as the IPS-3[3-5] were simpler but not better than the original version.

The IPS eventually became outdated due to several reasons including the progress in the treatment strategies since the era that the analyzed patients had been treated and the dichotomous categorization of some variables, which might have obscured some information. Subsequent studies suggested that, under modern anthracycline-based treatment, the outcome of the higher IPS-defined risk groups may be significantly better than predicted by the original dataset.[6,7] In fact neither the IPS nor the IPS-3 were able to define a sizeable subgroup of patients with sufficiently poor prognosis under modern treatment. In addition they were not able to define any very low risk subgroup.

The international consortium "Hodgkin Lymphoma International Study for Individual Care" (HoLISTIC) developed a new clinical prediction model called "Advanced-stage cHL International Prognostication Index" (A-HIPI), to predict 5-year PFS and overall survival (OS). The results were presented in ASH 2022 and were also recently published.[8,9] Researchers included a population of 4.027 patients with advanced-stage HL, derived from 8 phase 3 clinical trials (ECOG 2496, SWOG 0816, HD2000, HD9601, HD0607, HD0801, UK Stanford V, RATHL) between 1996 and 2012.[10-17] The median age of the patients was 33 years, 55% were male, 73% had B-symptoms, 35% had bulky disease and 33% had stage IV disease. Kaplan-Meier estimators at 5 years were 77% for PFS and 92% for OS. Age and absolute lymphocyte count (ALC) as continuous variables had nonlinear, U-shaped relationship with PFS and OS. Age, stage, ALC, and albumin were significant for both 5-year PFS and OS whereas sex, bulky disease, and hemoglobin were significant only for 5-year OS. C-statistics for the A-HIPI model were 0.590 for 5-year PFS and 0.730 for 5-year OS compared to 0.597 and 0.692 for IPS.[9] This new prognostic model appears to be promising as a clinical tool for predicting the outcome of patients with advanced HL.

However, the A-HIPI has several limitations. First, it is a continuous score requiring a dedicated calculator to be computed, so that it is not readily applicable. Such a calculator can be found at https://qxmd.com/calculate/calculator_869/a-hipi and displays the exact predicted 5-year PFS and OS for any individual patient. There is no risk-group classification. Second, if patients are classified based on their predicted survival rates, the worst 25% of the patient population still had a 5-year PFS of 71.7% and the best 25% (Q1) 86.9%, which are not optimal for a potent prognostic classification. Third, whether A-HIPI is applicable within the patient population with a negative interim PET or simply predicts the interim PET status is also unknown, as is its applicability under novel-agent containing first-line therapy.

The role of novel agents in first-line treatment

The balance between treatment efficacy and toxicity has emerged as the most crucial issue in the first-line management of HL. The incorporation of novel agents to ABVD or BEACOPP backbones is the core idea of current research as an attempt to reduce cytotoxic drugs or to establish radiotherapy-sparing approaches, while maintaining and even improving survival. The combination of Brentuximab Vedotin (BV) with doxorubicin, vinblastine and dacarbazine (BV-AVD) has already proved to be superior to conventional ABVD in terms of PFS and OS based on the results of ECHELON-1 study.[18-20]

Beyond BV-AVD, the GHSG incorporated BV to a BEACOPP-escalated backbone by introducing two novel regimens, namely BreCAPP and BreCADD. In the first combination, vincristine and bleomycin were replaced by BV in order to avoid the overlapping neurotoxicity and pulmonary toxicity. In addition to these modifications, in the BreCADD regimen, procarbazine is replaced by the less gonadotoxic and leukemogenic dacarbazine with a 4-day dexamethasone course instead of the 14-day prednisone schedule in order to avoid prolonged high-dose steroid exposure, especially during periods of severe neutropenia. BreCAPP and BreCADD were directly compared in a randomized phase 2 trial exhibiting the same efficacy[21,22], but BreCADD had a better safety profile and was selected for further investigation. Thus, the HD21 trial attempted to compare the traditional BEACOPP-escalated regimen with 4 or 6 cycles of BreCADD, according to the results of iPET in both arms. The primary endpoints were the non-inferiority of PFS and the reduction of treatment-related morbidity (TRMB) in terms of organ toxicity (grade 3-4) and hematologic toxicity (grade 4 anemia, thrombocytopenia, infections). In ASH 2022 the GHSG presented the safety and toxicity results: TRMB was documented in 59% versus 42% of patients in the BEACOPP-escalated and BreCADD arm, and hematological TRMB events were documented in 52% versus 31% respectively ($p<0.001$). Only 8% and 6% of patients required at least one red cell and platelet transfusion in the BreCADD arm compared to 22% and 13% in patients, who received BEACOPP-escalated. TRMB organ toxicity did not differ significantly between the two arms.[23] The results from the subsequent interim efficacy analysis at 40 months, presented at the Lugano meeting on June 2023, were even more impressive. The 3-year PFS was 94.9% versus 92.3% for the BreCADD and BEACOPP groups respectively and OS at 3-years was 98.5% for both arms.[24] Overall, the BreCADD regimen showed a clinically meaningful reduction of TRMB and impressive efficacy in terms of PFS compared to BEACOPP-escalated in patients with newly diagnosed advanced cHL and 4 or 6 cycles of BreCADD -depending on interim PET results- constitute the new standard of the GHSG for advanced-stage cHL.

SGN35-027 is a phase 2 single-arm study including three parts: part A aims to explore the efficacy and safety of the combination BV-AVD when administered with growth factor prophylaxis; part B evaluates the efficacy and tolerability of the combination of BV, nivolumab, doxorubicin and dacarbazine (AN+AD), in patients with disease stage III/IV or stage I/II with bulky mediastinal disease; part C focuses on the efficacy and tolerability of AN+AD in patients with stage I/II non-bulky cHL. The primary objective of parts B and C was to estimate the complete metabolic response (CMR) rate at end-of-treatment (EoT) in previously untreated patients with HL. The preliminary results of the SGN35-027 study were presented in ASH 2022. In part B, 57 patients were enrolled with a median age of 35 years; 51% had stage IV disease. The CMR rate was 88% at EoT. With a median follow-up of 15.1 months, 7% of the patients had progressive disease and 2% died. The estimated 1-year PFS was 93%. Four patients discontinued early due to treatment-emergent adverse events (TEAEs). Overall, 51% of patients experienced TEAEs of grade ≥3. Of note, there no cases of febrile neutropenia and only 2 patients experienced peripheral sensory neuropathy of grade ≥3, while 74% of patients had any dose modification.[25] In the part C of the study, 125 patients were enrolled with a median age of 33years. The CMR rate was 91% at EoT. No patients discontinued treatment early due to TRAEs.[26] Overall, the investigators concluded that AN+AD is promising in terms of efficacy and also well tolerated.

NIVAHL is a randomized phase 2 study, which explored the efficacy and safety of nivolumab plus AVD (N-AVD) with additional consolidation with RT patients with "intermediate" stage cHL, as defined by GHSG; namely early unfavorable patients with 3 or more involved nodal sites or elevated erythrocyte sedimentation rate (according to B-symptoms) or bulky mediastinal or extranodal extension of the disease. In total, 109 patients were randomized in two groups, both containing 8 doses of nivolumab given either as concomitant treatment with N-AVD for 4 cycles or as sequential treatment starting with 4 infusions of nivolumab at 14-day schedule, followed by two additional cycles of N-AVD and two AVD cycles. All patients received consolidative RT after the completion of immunochemotherapy. Bröckelmann et al presented the follow-up analysis of NIVAHL in ASH 2022. After 2 cycles of N-AVD patients achieved a high early CMR rate of 87%, similarly to standard ABVD treatment. Interestingly, more than half (51%) of the patients who received 4 infusions of nivolumab alone also achieved an early CMR. At the end of systemic therapy the CR rate was similar in the 2 groups (83% and 84%).[27] The study was recently published as a full paper reporting a 3-year PFS of 98% and 100% in the concomitant and sequential treatment group respectively and a 3-year OS of 100%.[28]

In an effort to assess the effect of BV and examine whether RT could be omitted in localized stages even with bulky disease, Kumar et al. enrolled 116 patients with intermediate (early unfavorable) stage HL according to the GHSG criteria in a study of 4 cycles of BV-AVD with no iPET-based design and RT in various dose and field schedules (cohorts 1-3) or no RT at all (cohort 4).[29] Of note, 86% of patients had a large nodal mass (≥7cm), 27% had traditionally defined bulky disease (≥10 cm) and 23% had stage IIB with bulky or extranodal disease. Notably, all patients in cohort 4 had nodal masses ≥7cm. The rate of iPET negativity was 87%, while EoT-PET (after 4 cycles) was negative in 93-100% of the patients. The 2-year PFS were similar (93%-100%) among cohorts 1-3 and was also similar (96.6%) in RT-free cohort 4, showing a remarkable efficacy which comes in contrast with the impaired outcome of patients with nodal masses >5cm in the RAPID trial.[30,31] In ASH 2022, Stuver et al presented the results of an extended 4-year follow-up showing a sustained long-term disease control rates even in the RT-free cohort and confirming the activity of BV in absence of RT consolidation in patients with bulky disease; 4-year PFS was 92.5% in RT-free cohort and 89.7-93.1% in cohorts 1-3. The authors also aimed to describe the prognostic significance of baseline TMV. The 4-year PFS in the MTV-high (defined as >150 cm^3) group was significantly lower than that in the MTV-low group (91% versus 100%, respectively). Taking into account both MTV and PET2, the 4-year PFS for the MTV-low and PET2-negative, MTV-low/PET2-positive, MTV-high/PET2-negative, and MTV-high/PET2-positive groups was 100%, 100%, 95%, and 60%, respectively (p=0.001).[32]

Keynote-C11 is another phase 2 study aiming to assess the efficacy of pembrolizumab plus chemotherapy with an iPET-based approach. The study included patients with early unfavorable and advanced stage disease. All patients will undergo PET/CT after 3 infusions (PET3) of pembrolizumab and 2 subsequent AVD cycles (phase 1). Patients with a negative PET3 will continue with 2-4 cycles of AVD (phase 2) depending on stage and bulky disease, whereas patients with a positive PET3 will receive 2-4 cycles of BEACOPP-escalated or 4 AVD cycles for patients for patients < or 0>60 years respectively. All patients will receive 4 cycles of pembrolizumab at a dose of 400 mg, every six weeks as consolidation therapy, which corresponds to 8 standard pembrolizumab cycles. Advani et al presented the results of an interim efficacy analysis. The study has included 146 patients so far. The median age was 34.5 years, 20% of patients had bulky disease, while 55% and 42% had advanced and early unfavorable disease respectively. The median follow-up was only 3.2 months with 32% of the patients being on pembrolizumab monotherapy, 29% on chemotherapy phase 1, 23% on chemo-

therapy phase 2, and 7 on pembrolizumab consolidation. Grade ≥3 TRAEs were reported in 14% of patients who received pembrolizumab monotherapy or consolidation, 54% of patients who received AVD, and in 1 of 2 patients who received BEACOPP-escalated. Immune-mediated events were reported in 19% of patients who received pembrolizumab monotherapy or consolidation. Efficacy results are pending.[33]

Finally, BV-AVD followed by nivolumab consolidation with an upfront PET-based schedule, was recently evaluated in a study of 75 patients with early-stage disease. Treatment included 3 cycles of BV-AVD as induction, followed by either nivolumab consolidation for iPET3-negative patients or additional 4 cycles of BV-AVD and subsequent nivolumab consolidation for iPET3-positive patients. Impressively, 97% of the patients achieved a negative iPET3 after BV-AVD induction with a CMR rate of 100% at EoT-PET. With a median follow-up of 22 months, there has been no event of disease progression or death in all eligible patients.[34]

New insights in relapsed/refractory setting

R/r cHL has become exceptionally manageable during the last years, mainly due to the approval of BV and PD-1 inhibitors.[35-40] Pembrolizumab has been approved as monotherapy for r/r-cHL in general by the FDA based on the results of the KEYNOTE-204 trial, while EMA granted approval for pembrolizumab monotherapy in transplant-ineligible patients after 2 or more lines of therapy.[41,42] BV has been tested in combination with conventional salvage regimens or with nivolumab in the second-line setting but has not yet gained approval.[43-49] Currently, the scientific interest is shifting towards moving anti-PD-1 treatment to first salvage therapy prior to ASCT or developing novel schedules of PD-1 blockade in order to overcome unmet clinical needs and to further improve patients' outcome. Two studies presented in the oral session of ASH 2022 reflect these trends and provide interesting insights in r/r HL.

The combination of nivolumab plus ifosfamide, carboplatine and etoposide (NICE) was evaluated as a first salvage therapy in 35 patients with r/r cHL, among whom 34 were evaluable for toxicity and 32 had completed treatment and were evaluable for efficacy. Eligible patients should carry at least one of the "high-risk" features including primary refractory disease, relapse within 1 year of completing front-line therapy, B-symptoms or extranodal disease at relapse, and prior exposure to BV as part of initial therapy. Patients were to receive a single nivolumab infusion followed by NICE for 2-3 cycles at the discretion of the treating physician. PET/CT was performed after Nx1+NICEx2 and was evaluated according to the 2014 Lugano criteria. Responding patients were intended to proceed to ASCT. The results were impressive with an ORR of 100% including 88% CR rate and 29/32 patients who completed therapy undergoing autologous stem cell transplantation (ASCT; 25 after 2 and 7 after 3 NICE cycles). There were no stem cell mobilization failures and the median time of neutrophil and platelet recovery were not different from those expected from the usual clinical practice. With a median follow-up of 12.8 months and a median post-ASCT follow-up of 12.5 months, the 1-year PFS and OS were 90% and 100% respectively.[50] The whole N+NICE procedure was well tolerated. These exciting results coupled with the similar results obtained with pembrolizumab-GVD and pembrolizumab-ICE and the previously reported nivolumab monotherapy with or without NICE, provide novel -not yet approved- options for pre-ASCT salvage in r/r cHL and -probably- the road for a transplant-free cure.[51-53] Following these impressive results, we have adopted the N+NICE approach as second-line (first salvage) therapy in r/r cHL in our Department and 6 patients have been treated under this approach during the last 3 months following a case by case regulatory approval.

Finally, Timmerman et al presented the results of a phase I/II study using favezelimab, a novel anti-LAG-3 inhibitor. LAG-3 is a T-cell immune-checkpoint receptor, which negatively regulates T-cell proliferation and activation in a similar way to CTLA-4 and PD-1. Dual PD-1 and LAG-3 blockade has already been successful in the treatment of some solid tumors.[54] The study presented in ASH 2022 evaluated the safety and efficacy of favezelimab in combination with pembrolizumab in 34 patients with cHL (dose-expansion cohort), who had relapsed after ASCT or were ineligible for ASCT, and had progressed after ≥2 doses of anti-PD-1 therapy. Favezelimab was administered at the dose of 800mg every 3 weeks, in a concomitant schedule with pembrolizumab at the usual dose, for up to 35 cycles. The median age of the patients was 37.5 years and 94% had received at least 4 prior lines of therapy. Interestingly, response was assessed by the 2007 International Working Group (IWG) criteria, which were more strict than the 2014 Lugano criteria.[55,56] With median follow-up of 19.0 months, the objective response rate was 29% with 9% CR. However, 89% of evaluable patients had any degree of reduction of baseline target lesions. The median duration of response was 19.4 months with 65% of patients maintained their response for at least 12 months. The median PFS and OS were 10.7 months and 25.7 months with 1-year rates of 39% and 91% respectively. Interestingly, 70% of responders had previously received anti-PD1 treatment as their most recent therapy. Only 6 patients discontinued treatment due to therapy-related adverse events and no treatment-related deaths were recorded.[57] These results point out to the ability of maintaining at least mid-term tumor control in patients who have failed PD-1-inhibitor therapy. However, given

that treatment with nivolumab beyond progression may be beneficial[39] and that overall survival at 5 years is ~70% with both PD-1 inhibitors,[58,59] the comparative efficacy of the favezelimab plus pembrolizumab combination versus pembrolizumab monotherapy should be explored. For this reason an indirect comparison was attempted between patients receiving the combination favezelimab plus pembrolizumab versus patients of the KEYNOTE-07 trial who received pembrolizumab beyond progression. In the study presented at the 2023 ICML Lugano Meeting, favezelimab appeared to contribute to further and deeper responses compared to continued pembrolizumab.[60]

CONCLUSION

The latest results from the clinical trials and studies presented at ASH 2022 and the subsequent EHA, ASCO and Lugano ICML Meetings are ground-breaking and will have tremendous impact in HL treatment landscape. The integration of novel agents in the first-line treatment has yielded impressive results. Further to those presented here, the combination of nivolumab-AVD proved better than BV-AVD in the SWOG S1826 trial of advanced Hodgkin lymphoma and may become the new standard of care.[61] All the developments with the integration of novel agents in the first-line treatment are reviewed in detail in a recent review from our group.[62] Apart from improved PFS rates, prognostication and survival patterns are expected to be much different in the long-term. Current biological and clinical prognostic factors may be less relevant and also, the decrease of early treatment failures could possibly be replaced by late relapses.[63-66] More time is needed to redefine new risk factors and prognostic models. Relapsed and refractory disease, especially after the novel combinations or under checkpoint inhibitor treatment still remains a major unmet clinical need.

Conflict of Interest: TPV has participated in advisory boards and received honararia by Takeda and Merck.

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