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Editorial

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Recent Advances in Hodgkin Lymphoma

Theodoros P Vassilakopoulos[1*] and Sotirios G Papageorgiou[2]

Introduction

Hodgkin lymphoma (HL) is considered as a highly curable malignancy, but successful treatment can be associated with significant long-term toxicity [1]. Traditional treatment modalities include chemotherapy, radiotherapy (RT) and salvage chemotherapy with autologous stem cell transplantation (ASCT). The goal of modern treatment is focused on tailoring each patient's approach according to age, risk of relapse and risk of short- and long-term toxicity.

Recent major advances in HL include the use of positron emission tomography/computed tomography (PET/CT) for individualization of first-line therapy and the development of novel agents for patients with relapsed/refractory disease. PET/CT-based individualization of treatment aims to select high-risk patients who would benefit from intensified chemotherapy and avoid overtreatment of low risk patients, a strategy possibly contributing to the reduction of long-term complications.

The Role of PET/CT in First-line Treatment

Early stages

Despite the high success rate in the treatment of early stage HL by the combination of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and involved field radiotherapy (IFRT), long-term treatment-related complications remain a significant concern, with mortality unrelated to HL exceeding that directly attributed to the disease beyond 10 years from diagnosis [1]. Accordingly, it has long ago proposed to omit RT in patients without bulky disease in an attempt to avoid occurrence of secondary solid tumors as well as cardiovascular and other important complications [1]. Indeed, omission of RT in stage I/IIA patients with non-bulky disease was rather associated with lower than increased overall 12-year mortality, despite significantly higher relapse rates compared to extended field RT [2]. Two recent randomized trials, the RAPID [3] and the EORTC H10 study [4], evaluated the omission of IF [3] or involved node (IN) RT [4] in patients with complete metabolic response, i.e. a negative PET/CT, after 3 or 2 ABVD cycles, respectively. In the RAPID trial, 3 cycles of ABVD were administered in all PET/CT-negative patients [defined as Deauville 5-point scale score (D5PS) 1 or 2]. In the H10 trial, a total of 3 or 4 ABVD cycles were administered in patients randomized in the RT arms and 4 or 6 in those randomized to ABVD alone, depending on the initial prognostic classification (early favorable or early unfavorable stages respectively). Notably, while the RAPID trial included only non-bulky CS IA/IIA patients, H10 did include patients with bulky disease and/or B-symptoms. Both trials have shown that, even if PET/CT converts to negative after 3 or 2 cycles of ABVD, the omission of IF(IN)RT is associated with higher relapse rates in patients with localized HL. However, short-term overall survival (OS) is not compromised. In addition, most patients do not really need RT, since the 3-year progression free survival (PFS) can be as high as 91% in non-irradiated patients with non-bulky disease who become PET/CT-negative after ABVD [3]. Therefore, even in the PET/CT era, the need of IF or INRT in the treatment of PET/CT-negative early stage HL without bulky disease appears to be a matter of physician's choice and patients' informed decision. The long-term results of the above trials as well as those of the ongoing HD16 study by the German Hodgkin Study Group (GHSG) are expected to shed more light in this area [5].

Advanced stages

In advanced-stage HL, GHSG data suggest that 6 cycles of the more intensive combination BEACOPP-escalated (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) provide better disease control than 6-8 cycles of ABVD. However, the effect on OS remains controversial, while the resulting acute and late toxicity is much higher than ABVD [6-8]. Moreover, robust clinical data show that PET/CT performed after 2 cycles of ABVD (PET2) may effectively discriminate patients with advanced-stage HL (and even early-stage patients with unfavorable risk profile) into 2 groups with highly different 2-year PFS: 85-90% in PET2-negative versus 25-35% in PET2-positive cases [7,9-11]. Therefore, administration of BEACOPP-escalated and its variants could be limited to PET2-positive patients, producing long-term remissions in 65% of cases as compared to 25-35% with continued ABVD. However, no randomized controlled trials are available to prove this benefit, especially regarding OS. A major limitation of the PET2-based strategy remains its relatively low negative predictive value. Indeed, while in early unfavorable HL a negative PET2 is associated with 2-year PFS of approximately 90%, in advanced stage (III/IV) HL the 2-year PFS may be even less than 80-85% [10,11]. Therefore, the reverse treatment strategy is also being tested in advanced stage HL, i.e. initial administration of 2 cycles of BEACOPP-escalated is followed by either 4 further cycles in patients with persistently positive PET2, or de-escalation to 4 ABVD cycles in patients achieving a negative PET2 [12]. Ongoing and future trials will hopefully provide definitive answers.

Although much more clinical experience with PET2 has been accumulated in advanced stage HL, only one randomized trial has been reported thus far, which included only early stage patients with adverse prognostic factors. In the EORTC H10 study, patients who remained PET2-positive after 2 cycles of ABVD were randomized to receive either 2 more ABVD cycles or 2 cycles of BEACOPP-escalated before scheduled INRT. Preliminary results presented in the 2015 Lugano International Conference on Malignant Lymphomas have

***Corresponding author:** Theodoros P Vassilakopoulos, MD, Assistant Professor in Haematology, Department of Haematology, National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, 17, Agiou Thoma str, Goudi, 11527, Athens, Greece, Tel: 0030210- 7456899; Fax: 0030210-7456698; E-mail: tvassilak@med.uoa.gr; theopvass@hotmail.com

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shown that BEACOPP-escalated improved disease control and marginally OS compared to continue ABVD. Detailed final results of the trial have not been published yet.

Novel Agents in Relapsed/Refractory HL

Despite usually successful first-line treatment, 20-30% of HL patients progress or relapse. Most of them are eligible for salvage chemotherapy and autologous stem cell transplantation (ASCT), but chemorefractory, elderly and unfit patients cannot be selected for this procedure and typically have a poor outcome. Most importantly, almost half of chemosensitive, young and fit patients who are treated with ASCT experience further disease progression or relapse and also have poor outcomes with a median survival of 2-3 years. These poor prognosis patients are in urgent need for novel treatment strategies, mostly targeted therapies.

Several targeted agents were tested with moderate or promising efficacy during the last 10 years, but did not enter into phase 3 trials, probably because of the development of other highly active agents [13]. Everolimus, an orally administered mTOR kinase inhibitor, was active in relapsed/refractory HL in a phase II study of 52 heavily pretreated patients (58% after ASCT), in which 42% responded (9% CRs) and 35% had stable disease, with a median PFS of 9 months [14]. Panobinostat, a histone deacetylase inhibitor, was active in a phase 2 trial of 129 heavily pretreated patients (median of 4 previous therapies) who had failed ASCT: The overall response rate (ORR) was 27% including 4% CRs and 55% of the patients had stable disease; the median duration of response was 6.9 months and the median PFS 6.1 months [15]. However, a trial comparing panobinostat with placebo as consolidation therapy in patients at high risk of relapse/progression after ASCT was prematurely terminated due to slow recruitment [16]. Two other histone deacetylase inhibitors, mocetinostat and resminostat, have been administered in heavily pretreated patients, mostly after ASCT failure, with reported response rates of 25-35% including cases of CR. Lenalidomide, an immunomodulatory and antiangiogenic factor, also appears effective in multiply pretreated patients, although with heterogeneous results that require further confirmation [13]. Except of targeted therapies, bendamustine, a conventional cytotoxic agent, appears to be active in phase II trials of relapsed/refractory Hodgkin lymphoma, but has not received official approval for this indication at the time being [17]. Despite the above results, the promises gained from these agents and their development have been overdriven by the rapid emergence of highly active CD30 and Programmed Death-1 (PD-1) targeted agents, as discussed below.

The first very important progress in relapsed/refractory classical HL was achieved with the development of Bentuximab Vedotin (BV), an antibody-drug conjugate formed by the conjunction of an anti-CD30 monoclonal antibody (cAC10) with monomethyl Auristatin E (MMAE), a microtubule-disrupting cytotoxic agent [18]. In the pivotal phase II trial of 102 patients, in whom ASCT had failed and had received a median of 3.5 lines of treatment, BV was given intravenously at a dose of 1.8 mg/kg (maximum 180 mg) every 3 weeks for a total of 16 infusions [19]. The ORR was 75% including 34% complete remissions (CR) were achieved in 34% of cases [19]. The median PFS was 9.3 months and the 5-year PFS 22% [20], while the median duration of response was 11.2 months, but has not yet been reached for complete responders [20,21]. It should be noted that 9% of patients (9/102) remain in CR for >5 years without any further treatment (i.e. allogeneic SCT), suggesting that BV might ultimately cure a subgroup of heavily pretreated patients with HL [20]. Furthermore, BV was tested as consolidation therapy in ASCT-treated patients with relapsed/refractory HL, who were considered to be at high risk of relapse/progression after ASCT based on established conventional prognostic factors [21]. In the AETHERA study, 329 HL patients who had been treated with ASCT and were considered at high-risk of further relapse (primary refractory disease, early relapse or relapse beyond 1 year with extranodal disease) were randomized to receive either BV (at the dose and duration described above) or placebo within 45 days after ASCT [21]. Treatment with BV improved PFS compared with placebo (hazard ratio [HR] 0·57, 95% CI 0·40-0·81; p=0·0013). The benefits were higher in higher-risk patients. However, OS was not different between BV and placebo at the time of study publication [22]. Moreover, BV can be successfully combined with salvage chemotherapy such as the combination of ifosfamide, carboplatine and etoposide (ICE) before ASCT [23], with bendamustin in relapsed/refractory disease [24], and can be administered as bridge to allogeneic SCT [25]. In an attempt to further improve the efficacy of first-line treatment, BV was shown to be safely combined with ABVD, if bleomycin was omitted due to unacceptably high incidence of pulmonary toxicity [26]. Thus, the combination BV-AVD is currently being compared against ABVD in the ongoing ECHELON-1 study in patients with advanced HL. It should however be noted that, despite the encouraging results from the above combinations of chemotherapy with BV, its indications in HL are limited to: (a) relapsed/refractory CD30+ HL after ASCT; (b) relapsed/refractory CD30+ HL after at least 2 prior lines of therapy, when ASCT or multi-agent chemotherapy is not an option; and (c) CD30+ HL at increased risk of relapse/progression following ASCT.

In the recent two years, a new category of targeted therapies have been developed with impressive results in relapsed/refractory HL. The monoclonal antibodies nivolumab and pembrolizumab inhibit PD-1, which is expressed in the surface of cytotoxic T-lymphocytes. In classical HL, PD-1 ligands (PDL-1 and PDL-2) are overexpressed by Hodgkin-Reed-Sternberg (HRS) cells due to the presence of copy number gains in the 9p24.1 locus [27]. PD-1/PDL interaction inhibits T-cell function allowing immune escape of HRS cells. Inhibition of PD-1 by nivolumab or pembrolizumab is blocking this deleterious interaction between the HRS cells and T-cells and restores immune responses against the neoplastic cells. In phase I trials these drugs have shown high response rates in heavily pretreated patients with an acceptable safety profile [28,29]. In one of the four arms of the CHECKMATE-205 phase II study, 80 patients with ECOG performance status 0-1 in whom both ASCT and BV had failed and had received a median of 4 prior lines of therapy (range; 3-15), nivolumab was administered intravenously at a dose of 3mg/kg every 2 weeks up to disease progression or unacceptable toxicity [30]. The ORR was 66% according to an independent committee and 73% according to the investigators, while CR rates were 9% and 28%, respectively. The median PFS was 10.0 months and the median duration of response was 7.8 months. Similarly, in one of the 3 arms of the KEYNOTE-87 phase II study, approximately 60 patients with ECOG performance status 0-1 in whom both ASCT and BV had failed, were scheduled to receive intravenous pembrolizumab at a dose of 200 mg every 3 weeks up to disease progression or unacceptable toxicity or up to 2 years [31]. In a preliminary analysis of 30 patients who had received a median of 5 cycles (range; 3-12), the ORR was 73% according to the investigators, while the CR rate was 27%. Similar response rates were reported in the other two treatment arms, each including 30 patients: One of these arms recruited patients not suitable for ASCT (mostly chemo-resistant); while the other included patients who had relapsed

after ASCT but had not received BV thereafter (BV prior to ASCT was permitted). The final results of KEYNOTE-87 in >180 patients across all three arms including data for PFS and duration of remission are expected soon. However, all these results are quite preliminary and cannot fully define the expected response rates and, more importantly, response duration in various specific patient subgroups. Overall, nivolumab and pembrolizumab appear highly effective in heavily pretreated patients with relapsed/refractory HL and urgently deserve further evaluation.

Conclusions

In the recent years, considerable progress has been made in the management of patients with HL and will hopefully result in improvements of survival. Ongoing and future large clinical trials will lead to the expansion of the indications of currently available agents. Enrolment of patients in well-designed clinical trials is expected to permit the rational incorporation of PET/CT and novel agents in treatment approaches of HL aiming to achieve maximal efficacy, minimal short- and long-term toxicity and cost-effectiveness [32].

References

1. Ng AK, van Leeuwen FE (2016) Hodgkin lymphoma: Late effects of treatment and guidelines for surveillance. Semin Hematol 53: 209-215.
2. Meyer RM, Gospodarowicz MK, Connors JM, Pearcey RG, Wells WA, et al. (2012) ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366: 399-408.
3. Radford J, Illidge T, Counsell N, Hancock B, Pettengell R, et al. (2015) Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 372: 1598-1607.
4. Raemaekers JM, André MP, Federico M, Girinsky T, Oumedaly R, et al. (2014) Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 32: 1188-1194.
5. Engert A, Raemaekers J (2016) Treatment of early-stage Hodgkin lymphoma. Semin Hematol 53: 165-170.
6. Engert A, Haverkamp H, Kobe C, Markova J, Renner C, et al. (2012) Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. Lancet 379: 1791-1799.
7. Vassilakopoulos TP, Johnson PWM (2016) Treatment of advanced-stage Hodgkin lymphoma. Semin Hematol 53: 171-179.
8. Skoetz N, Trelle S, Rancea M, Haverkamp H, Diehl V, et al. (2013) Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: A systematic review and network meta-analysis. Lancet Oncol 14: 943-952.
9. Gallamini A, Barrington SF, Biggi A, Chauvie S, Kostakoglou L, et al. (2014) The predictive role of interim positron emission tomography for Hodgkin lymphoma treatment outcome is confirmed using the interpretation criteria of the Deauville five-point scale. Haematologica 99: 1107-1113.
10. Johnson P, Federico M, Kirkwood A, Fosså A, Berkahn L, et al. (2016) Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma. N Engl J Med 374: 2419-2429.
11. Press OW, Li H, Schöder H, Straus DJ, Moskowitz CH, et al. (2016) US Intergroup Trial of Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose-Positron Emission Tomography Imaging: Southwest Oncology Group S0816. J Clin Oncol 34: 2020-2027.
12. Casasnovas O, Brice P, Bouabdallah R, Salles GA, Stamatoullas A, et al. (2015) Randomized phase III study comparing an early PET driven treatment de-escalation to a not PET-monitored strategy in patients with advanced stages Hodgkin lymphoma: Interim analysis of the AHL2011 Lysa study. Blood 126: 577.
13. Younes A, Ansell SM (2016) Novel agents in the treatment of Hodgkin lymphoma: Biological basis and clinical results. Semin Hematol 53: 186-189.
14. Johnston PB, Pinter-Brown L, Rogerio J, Warsi G, Chau Q, et al. (2012) Everolimus for relapsed/refractory classical Hodgkin lymphoma: Multicenter, open-label, single-arm, phase 2 study. Blood 120: 2740.
15. Younes A, Sureda A, Ben-Yehuda D, Zinzani PL, Ong TC, et al. (2012) Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem-cell transplantation: results of a phase II study. J Clin Oncol 30: 2197-2203.
16. von Tresckow B, Morschhauser F, Szer J, Eichenauer DA, Abramson JS, et al. (2016) Panobinostat consolidation in patients with Hodgkin lymphoma at risk for relapse after high dose chemotherapy and autologous stem cell transplant: final results after early trial discontinuation. Leuk Lymphoma 17: 1-4.
17. Moskowitz AJ, Hamlin PA Jr, Perales MA, Gerecitano J, Horwitz SM, et al. (2013) Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol 31: 456-460.
18. Vassilakopoulos TP, Angelopoulou MK (2013) Advanced and relapsed/refractory Hodgkin lymphoma: what has been achieved during the last 50 years. Semin Hematol 50: 4-14.
19. Younes A, Gopal AK, Smith SE, Ansell SM, Rosnblatt JD, et al. (2012) Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 30: 2183-2189.
20. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, et al. (2016) Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood.
21. Gopal AK, Chen R, Smith SE, Ansell SM, Rosenblatt JD, et al. (2015) Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood 125: 1236-1243.
22. Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, et al. (2015) Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 385: 1853-1862.
23. Moskowitz AJ, Schöder H, Yahalom J, McCall SJ, Fox SY, et al. (2015) PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. Lancet Oncol 16: 284-292.
24. LaCasce AS, Bociek G, Sawas A, Caimi PF, Agura E, et al. (2015) Brentuximab vedotin plus bendamustine: A highly active salvage treatment regimen for patients with relapsed or refractory Hodgkin lymphoma. Blood 126: 3982.
25. Chen R, Palmer JM, Thomas SH, Tsai NC, Farol L, et al. (2012) Brentuximab vedotin enables successful reduced-intensity haematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood 119: 6379-6381.
26. Younes A, Connors JM, Park SI, Fanale M, O'Meara MM, et al. (2013) Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase1, open-label, dose-escalation study. Lancet Oncol 14: 1348-1356.
27. Roemer MG, Advani RH, Ligon AH, Natkunam Y, Redd RA, et al. (2016) PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome. J Clin Oncol 34: 2690-2697.
28. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, et al. (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372: 311-319.
29. Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, et al. (2016) Programmed Death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol epub Jun 27, pii: JCO673467.
30. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, et al. (2016) Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. Lancet Oncol 17: 1283-1294.

31. Chen RW, Zinzani PL, Fanale MA, Armand P, Johnson N, et al. (2016) Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study. J Clin Oncol 34: 7555.

32. Engert A, Vassilakopoulos TP (2016) Hodgkin lymphoma: Introduction. Semin Hematol 53: 137-138.

Author Affiliations

Top

[1]*Department of Haematology, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece*

[2]*Second Department of Internal Medicine, Propaedeutic, Hematology Unit, University General Hospital "ATTIKON", Athens, Greece*

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