Ewa Paszkiewicz-Kozik, Jan Walewski

Klinika Nowotworów Układu Chłonnego, Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie, Warszawa

Hodgkin lymphoma — closer to failure-free treatment

Address for correspondence:
Prof. Jan Walewski
Klinika Nowotworów Układu Chłonnego
Centrum Onkologii — Instytut
im. Marii Skłodowskiej-Curie
ul. W.K. Roentgena 5, 02–781 Warszawa
Phone: +48 (22) 546 3248
e-mail: jan.walewski@coi.pl

Oncology in Clinical Practice
2015, Vol. 11, No. 4, 199–210
Translation: GROY Translations

ISSN 2450–1554
www.opk.viamedica.pl

ABSTRACT

A major challenge in the clinical research on Hodgkin lymphoma is an optimization of the current treatment algorithms in a way that would reduce late toxicity without compromising efficacy. Population-based studies evaluating the late effects of treatment of Hodgkin lymphoma of a limited stage indicate a risk of relapse at 10% to 20%, mostly occurring within the first 3 years post-therapy, and on the other hand, a risk of second malignancy or cardiovascular disease increasing constantly and markedly exceeding the corresponding risk in healthy people. Although this elevated risk of late complications is attributed to the oncogenic potential of combined modality treatment including both cytotoxic agents and mediastinal irradiation, randomized trials successfully addressing radiation-free and/or alkylator-free regimens that could change the paradigm of combined chemo- and radiotherapy have not been performed. In this review, we present in brief guideline-based treatment outcomes, new data from recent studies related to risk-adapted therapy guided by the early response assessment with interim PET/CT, studies on recurrent disease as well as novel agents. It is hoped that recent advances in the field of immunotherapy including toxin conjugated anti-CD30 antibody and checkpoint inhibitor anti-PD1 antibody will drive progress in the systemic treatment of Hodgkin lymphoma has already happened in some solid tumours.

Key words: Hodgkin lymphoma, ESMO recommendations, combined modality treatment, risk adapted therapy, PET, brentuximab vedotin, nivolumab, panobinostat, CD30, PD1, HDACi

Oncol Clin Pract 2015; 11, 4: 199–210

Introduction

Most of the patients suffering from classical Hodgkin lymphoma (HL) are permanently cured after modern treatment adjusted to clinical stage and risk category. Although 10% to 30% of patients relapse depending on the risk factors and the type of the induction chemotherapy, the second-line therapy and autotransplantation of hematopoietic cells (auto-HCT) leads to long-term remission or cure of about half of the relapsed patients. Thus, in about 20% of patients the treatment ends in failure. The median survival of patients who relapse or have a disease progression after auto-HCT does not exceed 2–3 years. Therefore, this group of patients are at extremely high risk and requires the development of new therapeutic approaches. Unfortunately, the prognostic factors that would anticipate treatment failure with acceptable probability are unknown, although a number of clinical and biological factors such as the content of macrophages in the tumor tissue, expression of BCL2 or lack of satisfactory response after 2–3 cycles of initial treatment with ABVD regimen have a well-established adverse significance.

According to the current data of the Polish National Cancer Registry, 728 new cases of HL were registered in Poland in 2012 [1]. After the standard induction therapy (ABVD + radiotherapy), over 500 of those patients will be cured, and in over 200 cases, progression or relapse will occur within first 3 years from the start of treatment. Of these 200 patients, about 150 will obtain a second complete or partial remission after the re-induction therapy and, in most cases, will receive the consolidation high-dose chemotherapy with autologous hematopoietic cell transplantation. About half of them, thus over 70 patients, will be cured, while the remaining over 70 patients will suffer next relapses. These patients, along with about 60 patients with no response to the re-induction therapy, comprise a group of about 150 uncured patients.

Table 1. Categories of initial risk in patients with HL according to EORTC/LYSA and GHSG [2]

Risk group	EORTC/LYSA	GHSG
Limited stage	CS I–II, no risk factors (supradiaphragmatical locations)	CS I–II, no risk factors
Intermediate stage	CS I–II and ≥ 1 risk factors (supradiaphragmatical locations)	CS I, CS IIA and ≥ 1 risk factors CS IIB with factors C/D, but not A/B
Advanced stage	CS III–IV	CS IIB with factors A/B, CS III, IV
Risk factors	(A) — mediastinal mass	(A) — mediastinal mass
	(B) — age ≥ 50	(B) — extranodal location
	(C) — elevated ESR values	(C) — elevated ESR values
	(D) — ≥ 4 node areas	(D) — ≥ 3 node areas

EORTC — European Organisation for Research and Treatment of Cancer; LYSA — Lymphoma Study Association; GHSG — German Hodgkin Study Group; CS — clinical stage; mediastinal mass — more than 1/3 of the maximum horizontal chest diameter; B — systemic symptoms: night sweats, weight loss > 10%/6 months; elevated ESR values — > 50 mm/h if B not present, > 30 mm/h if B present

Table 2. The induction HL therapy regimens: ABVD and BEACOPPesc

ABVD	BEACOPPesc
Adriamycin — 25 mg/m² iv day 1 and 15	Bleomycin — 10 mg/m² iv day 8
Bleomycin — 10 mg/m² iv day 1 and 15	Etoposide — 200 mg/m² iv day 1–3
Vinblastin — 6 mg/m² iv day 1 and 15	Adriamycin — 35 mg/m² iv day 1
Dacarbazine — 375 mg/m² iv day 1 and 15 — every 28 days	Cyclophosphamide — 1250 mg/m² iv day 1
	Vincristine — 1.4 mg/m² iv day 8
	Procarbazine — 100 mg/m² iv after day 1–7
	Prednisone — 40 mg/m² iv after day 1–14
	G-CSF s.c. since day 8 — every 22 days

This review presents the results obtained with a standard treatment methods according to the current recommendations, and new data resulting from the controlled clinical trials announcing near-future changes in the clinical practice and new possibilities of preventing treatment failures.

Methods and results of treatment of patients with Hodgkin lymphoma according to the current recommendations

Treatment paradigms for HL are described in a number of guidelines that, in general, are consistent with each other and are regularly updated according to the new published data. The most recent recommendations of the European Society of Medical Oncology (ESMO) were published in 2014 [2].

Selection of induction therapy for patients with HL is guided by the disease stage (limited, intermediate, or advanced) depending on the clinical stage and clinical risk factors, including mediastinal mass of a width of more than 1/3 of the maximum horizontal chest diameter on the Th5–Th6 level, age of over 50 years, extranodal location, disease affecting more than 3 (or 4) nodal areas, and elevated ESR values (Table 1).

Induction therapy of HL includes chemotherapy combined with limited-field radiotherapy.

The induction therapy includes 2 or 3 cycles of the ABVD chemotherapy (Table 2), and radiation therapy (RT) of the involved-fields (IFRT) with 20 Gy in the disease limited stages or 4 cycles of ABVD and IFRT with 30 Gy in the intermediate stages. In the advanced stage, patients receive 6–8 ABVD cycles and IFRT of potential residual changes (dimension > 1.5 cm). This algorithm of combined modality treatment results in cure of about 75% of patients in all stages [3]. Two-week interval between ABVD cycles irrespective of leukocyte count on day 14 is important for treatment outcome. It was shown that using full-dose ABVD independently from the number of neutrophiles on the day of chemotherapy administration and without G-CSF prophylaxis was associated with the treatment compliance of 95%, and generally no infectious complications. Neutropenic fever occurred in only 0.57% of cases, although grade III/IV neutropenia occurred in almost 80% of patients [4, 5].

Table 3. Treating patients with HL, ESMO 2014 recommendations

Limited stage	2–3 × ABVD + IFRT 20 Gy or ISRT
Intermediate stage, age of patients > 60 years old	4 × ABVD + IFRT 30 Gy or ISRT
Intermediate stage, age of patients ≤ 60 years old	2 × BEACOPPesc + 2 × ABVD + IFRT 30 Gy or ISRT
Advanced stage, age > 60	6–8 × ABVD + IFRT (> 1.5 cm)
Advanced stage, age of patients ≤ 60 years old	6 × BEACOPPesc + IFRT in patients with active residual changes in PET scan > 2.5 cm

The ESMO recommendations include alternative use of the multi-drug BEACOPP regimen (Table 2) in the escalated version (esc) in patients ≤ 60 years old — in the intermediate stage, the BEACOPPesc × 2 + ABVD × 2 + IFRT 30 Gy, and in the advanced stage, BEACOPP × 6 + IFRT of the residual PET-positive changes of > 2.5 cm diameter. This option is based on the extensive experience of the German group (GHSG, *German Hodgkin Lymphoma Study Group*) indicating better disease control (progression-free survival, PFS) in comparison to the ABVD [2]. However, this approach is not commonly accepted due to the lack of convincing evidence of the survival advantage to the BEACOPPesc, and significantly higher toxicity, compared to the ABVD, manifest by neutropenia complications, frequent infertility, and elevated risk of myelodysplastic syndrome or acute myeloid leukaemia (MDS/AML). Currently, the GHSG group is conducting trials on the BEACOPP totally remodeled in the direction of improving the therapeutic index.

Radiotherapy in the context of combined modality treatment of limited stage HL is evolving in the direction of reducing the irradiated volume and the dose. Major advances in the imaging techniques (contrast-enhanced computed tomography, positron emission tomography — PET), multidimensional planning and intensity modulated radiation therapy allow to significantly reduce the exposure of healthy tissue. Until recently, irradiation as part of the combined modality treatment included the involved fields (IFRT), i.e. area of initial involvement with a margin (involved field). Recently, the recommendations of the International Lymphoma Radiation Oncology Group (ILROG) include irradiation of the affected sites (involved site, ISRT) or even affected lymph nodes (involved node, INRT) in cases when using optimal imaging for planning the radiotherapy is possible. However, these techniques have not yet been verified in prospective trials [6–8].

Current ESMO recommendations regarding the induction therapy of patients with HL are shown in the Table 3.

During the past several decades, although numerous attempts were made to develop a different chemotherapy regimen that would be more effective than ABVD and less toxic than BEACOPP, no success was achieved.

A hybrid program of MOPP/ABVD showed similar efficacy but higher early and late toxicity (risk of MDS/AML) in comparison to ABVD in patients with advanced stage HL in the randomised trial [9].

Moreover, new regimens of multi-drug alternating chemotherapy were developed on the basis of pharmacological background of drug interactions: ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone), PABIOE (prednisolone, adriamycin, bleomycin, vincristine, etoposide), hybrid ChlVPP/EVA (etoposide, vincristine, adriamycin), or the complex combined modality treatment regimen Stanford V (mechlorethamine, adriamycin, vincristine, bleomycin, vinblastine, etoposide, prednisolone) or the first remission consolidation with high-dose chemotherapy with auto-HCT, had efficacy comparable to the ABVD but at the same time, higher toxicity [10–13].

Systematic long-term prospective GHSG trials including large groups of patients led to the widespread use of the BEACOPPesc regimen in a number of European centres [14]. The first randomised trial of this series compared 3 regimens of induction chemotherapy: COPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisolone), BEACOPP and BEACOPPesc, and included 1196 patients with advanced HL. After 10 years of follow up, the freedom from treatment failure (FFTF) and overall survival (OS) was the highest in the BEACOPPesc group, and the lowest in COPP/ABVD (FFTF: 64%, 70%, 82%, and OS 75%, 80%, 86%, respectively) [15]. The same group (GHSG), based on the data from *Medline* and the Cochrane Library, carried out a network meta-analysis of the overall survival in 14 randomised trials conducted from 1980 to 2013 in patients with advanced HL where one of the randomisation arms included ABVD and/or BEACOPP in different combinations and sequences, and of different number of cycles. These trials *per se* did not have enough statistical power to assess the OS. The treatment regimens included MOPP, MOPP/ABV, C(M)OPP/ABVD, BEACOPP × 8, BEACOPPesc × 8, Stanford V, C(M)OPP/EBV/CAD, BEACOPPesc × 4 + BEACOPP × 2–4, BEACOPP-14 × 8, BEACOPPesc × 6, and ABVD as the comparator. Basing on an analysis of the integrated data including the total of almost 10,000 patients, the lowest hazard ratio (HR)

Table 4. The 5-point scale (5-PS) of PET interpretations [31]

Points	Description	Result	Interpretation
1	No uptake	Negative	Complete metabolic response
2	Uptake ≤ mediastinal blood pool	Negative	Complete metabolic response
3	Uptake > mediastinal blood pool, but liver	Intermediate	Uncertain
4	Uptake moderately higher than liver	Positive	Failure, disease progression
5	Uptake markedly higher than liver and/or new lesions	Positive	Failure, disease progression

was assigned to the BEACOPPesc × 6 regimen with the probability of being the best regimen of 63%. The OS improvement against the comparator (ABVD) was 7% (95% vs. 88%) [16, 17]. No differences in the death incidence due to toxicity, and AML/MDS were found.

New clinical data concerning the Hodgkin lymphoma induction therapy

High efficacy of modern combined modality treatment of HL is associated with a significant increase of the risk of the late complications including second primary malignancies and cardiovascular complications. Population based studies indicate that during 30 years post-treatment, the risk of the second malignancy increases by about 1% a year. In females treated with mediastinal irradiation at the age of 30 or less, the risk of developing breast cancer after a 25-year observation, is 30–40% [18].

Recently published or presented developments include the results of prospective studies designed to evaluate treatment modifications guided by early response assessment using FDG-PET method (positron emission tomography with 18-fludeoxyglucose) after initial cycles of chemotherapy.

Hodgkin lymphoma is a highly FDG-avid neoplasm, and the newest recommendations for initial staging and evaluation of response to treatment — the Lugano classification [19] — include FDG-PET examination as a standard, both initially and at the end of the treatment. Uniform criteria of response assessment with PET/CT method are established as a 5-point scale (5-PS) based on a visual assessment of the intensity of FDG uptake by the lymphoma lesions in comparison to the uptake by the mediastinal blood pool and by the liver (Table 4) [20, 21]. The retrospective trials show that the positive result of PET scan performed after 2 cycles of ABVD has a highly significant unfavourable prognostic value [22]. In the trial by an Italian group performed on 260 patients with HL, including 207 with an advanced stage, the frequency of positive results (5-PS: 4 or 5) of PET after 2nd cycle ABVD (PET-2) was 17%. After a median of 37 month follow up, 3-year progression free survival (PFS) in the whole group of patients was 83% and in patients with negative and positive results of PET-2 — 95% and 28%, respectively ($p < 0.0001$). The prognostic value of PET scan in this trial was significantly higher than the value of the International Prognostic Score for advanced disease — IPS [23].

The RAPID trial of the British group NCRI UK (National Cancer Research Institute UK), compared the IFRT (standard approach) to observation without radiotherapy in a group of 602 patients with early stage HL, without systemic symptoms and without bulky mediastinal mass, who had negative PET (5-PS: 2) after the 3rd cycle of ABVD. After a median 60-month follow up, 3-year PFS of patients irradiated and observed was 94.5% and 90.8% ($p = 0.02$), respectively, and OS — 97.1% and 99% ($p = 0.27$), respectively. The authors conclude that PET response evaluation after 3 cycles of ABVD allows to identify a group of patients with excellent prognosis who constitute 75% of all patients, and who may be safely spared from IFRT [24].

The equivalence of the efficacy of ABVD chemotherapy without IFRT with the standard treatment in patients with limited stage HL was not confirmed in trial H10 of the EORTC/LYSA/FIL group (European Organisation for Research and Treatment of Cancer/Lymphoma Study Association/Fondazione Italiana Linfomi) where the standard treatment was compared with the treatment adapted to PET result after 2 cycles of ABVD. Patients with supradiaphragmaticHL in the clinical stage I and II were stratified by risk, favourable (F) or unfavourable (U) (Table 1), and randomised to the standard treatment ABVD × 3 (F) or × 4 (U) + INRT 30+6 Gy or adapted to PET-2 result where PET-negative patients received ABVD next cycles — 2 (F) or 4 (U) without INRT, and PET-positive patients received treatment of increased intensity BEACOPPesc × 2 + INRT. A preplanned interim analysis after occurrence of the first 34 events in patients with negative PET-2 result showed that the number of events in treatment arms without INRT was significantly higher than in the standard arms (F: 9 vs. 1, U: 16 vs. 7). In effect of this interim analysis, design of the study was modified so that the patients with negative PET-2 result continue the standard

treatment (INRT) while randomised are PET-positive patients only, i.e. they receive intensified treatment [25]. The results in PET-2 positive patients were presented during the International Conference on Malignant Lymphoma (ICML) in Lugano in 2015. In a total of 361 patients with positive PET-2 results, after a median 4.5-yearfollow up, the 5-year PFS and 5-year OS in the standard arm was 77% and 89%, respectively, and in the experimental arm — 91% and 96%, respectively. Survival benefit to patients in the experimental arm who received the intensified treatment (5-year PFS, p = 0.02, 5-year OS, p = 0.062) was significant [26].

PET-guided, response-adapted therapy is a subject of clinical trials in advanced HL as well. Recently, preliminary results of the international RATHL (Response-adapted therapy of HL) trial coordinated by the Cancer Research UK group were presented where the safety and efficacy of treatment modifiied according to interim PET was evaluated. The trial included patients with HL in CS IIB-IV and IIA with bulky disease or the number of involved sites ≥ 3. PET/CT scan was performed at baseline and after 2 cycles of ABVD (PET-2). PET imaging was evaluated centrally with negative result defined as 5-PS score from 1 to 3. Patients with a negative PET-2 result were randomized to receive 4 further cycles of ABVD or AVD. Patients with positive PET-2 result received intensified BEACOPP-14 treatment (cycle every 14 days) × 4 or BEACOPPesc × 3, and a further PET/CT scan was performed (PET-3). Patients with negative PET-3 result received 2 consolidating cycles of BEACOPP-14 or 1 cycle of BEACOPPesc. In the PET-negative cases, radiotherapy was not used. The PET-2 result was negative in 954 of 1 137 patients (84%). 952 patients continued the ABVD or ABV chemotherapy randomly. After a median 32-month follow up, the 3-year PFS after ABVD and ABV treatment were comparable, 85.45% and 84.48%, respectively, and the 3-year OS — 97.0% and 97.5%, respectively. In patients treated with the ABVD regimen, pulmonary toxicity occurred more frequently. Out of 174 patients with a positive PET-2 result who received intensified treatment, 74% obtained negative PET-3 result. The 3-year PFS and 3-year OS of these patients was 68% and 86%, while the 3-year PFS and 3-year OS of the whole patient population was 83% and 95%. This trial showed that excluding bleomycin from further treatment in the patients who obtained a negative PET result after 2 cycles of ABVD and who are a vast majority of the whole group, leads to non-inferior outcome and allows reducing the pulmonary toxicity. The efficacy of treatment escalation in patients with a positive PET-2 result is less convincing and requires further assessment [27].

Relapsed and refractory disease

Approach to HL patient who fails initial therapy due to relapse or refractory disease depends on specific risk factors at the time of failure.

The most powerful risk factor is a resistance defined as disease progression during or within 3 months from completing the initial treatment (combined modality treatment or radical chemotherapy) or by a non-response to treatment with at least partial remission (PR) (Table 5) [28]. If PET/CT is used for response evaluation, the resistance is defined as a positive result (5-PS: 4 or 5) consistent with the presence of abnormal lesion in the CT scan after 3–4 cycles of induction chemotherapy. In case of equivocal interpretation of imaging examinations, a confirmation biopsy is recommended.

In case of recurrent disease other than resistant to initial therapy, significant risk factors include: time to relapse less than 12 months (early relapse), advanced clinical stage (CS III, IV) at relapse, impaired performance status (ECOG PS > 0), anemia, extranodal sites involved, and systemic symptoms. A number of international research groups have elaborated prognostic models for recurrent disease based on the results of prospective trials (Table 6) [28–31]. These models generally distinguish 3 risk categories depending on the number of adverse prognostic factors present: standard risk: 0, intermediate risk: 1–2, and high risk: 3 factors.

In case of standard risk relapse, like a late relapse of limited stage, outside the irradiation field, without a bulky mass and without systemic symptoms, the right treatment is a second line chemotherapy (BEACOPPesc) with or without IFRT if CR is achieved (PET-negative) [32]. In individual cases of late, isolated

Table 5. Definitions of the HL treatment failures [28]

Primary refractoriness	Progression during treatment or within 3 months from its completion and/or persistent FDG uptake (PET) > 3 (5-PS) in accordance with the CT image. In questionable cases, biopsy of the PET+ lesion is recommended
Early relapse	Relapse within 3–12 months from the 1st line treatment
Late relapse	Relapse within > 12 months from the 1st line treatment

5-PS — 5-point scale

Table 6. Risk factors of failure of 2nd line treatment of patients with relapsed HL

Risk factor	LYSA [28]	PMHT [29]	GHSG [30]	MSKCC [31]
Primary refractoriness	•	•	•	
Early relapse	•	•	•	•
CS III, IV	•	•	•	
ECOG PS > 0		•	•	
Hb < 10.5 (K) < 12.0 (M) g/dl			•	
Extranodal site				•
Systemic symptoms				•

relapse, long-term remission may be obtained with radiotherapy alone [33].

In relapse of intermediate risk (1–2 risk factors) the optimal approach is the second line chemotherapy and in patients responding with at least partial remission, consolidation with high-dose chemotherapy (HDT) and auto-HCT. Around 50% of patients will have long-term disease-free survival and will likely be cured after this treatment [34, 35]. Regimens used in the second line treatment usually contain platinum compounds or gemcitabine (e.g. DHAP — dexamethasone, cytarabine, cisplatinum, ICE — ifosfamide, carboplatinum, etoposide, IGEV — ifosfamide, gemcitabine, vinorelbine) with objective response rates (CR+PR) of 80–90% and CR — 20–50%. Comparative data on clinical activity of second line regimens in HL is not available [2]. Recently, promising results were presented of using bendamustine combined with brentuximab vedotin antibody in the second line treatment before the consolidation with HDT/auto-HCT; the CR rate after this treatment was 80% [36].

Experience of the French LySA group justify using the tandem consolidation HDT/auto-HCT in cases of relapse of intermediate risk where the response was obtained only after the 3rd line treatment (resistance to 2nd line treatment) and in cases of high risk (3 or more risk factors) [37].

In case of HL relapse after HDT/auto-HCT, the median survival does not exceed 2–3 years, although this is highly dependent on the risk factors, and is significantly shorter in very early relapse. According to the registry data of EBMT [38], the following factors additionally increase the risk in this situation: impaired performance status (ECOG PS > 1), the presence of a bulky mass at relapse, clinical stage IV, age ≥ 50 years old, time to relapse < 6 months from HCT. The probability of 5-year survival depending on the number of risk factors 0, 1 and ≥ 2 is 62%, 37%, and 12%, respectively. Comparison of the results of the conventional chemotherapy and radiotherapy with the results of allotransplantation (in majority with reduced intensity conditioning, RIC-Allo) showed a tendency in the direction of longer survival after the RIC-Allo that after 5 years was 48%, and in the case of the conventional treatment — 32%, although the difference was not statistically significant ($p = 0.08$).

In cases of relapse after HDT/auto-HCT with response to subsequent treatment line, RIC-Allo is a justified option that should, however, be taken within the prospective clinical trial protocol as it is not considered a standard treatment [2]. Allotransplantation after full myeloablation is not accepted due to the high risk of fatal complications dependent on the procedure (NRM, non-relapse mortality) approaching about 50%, and disappointing 3-year overall survival, below 20% [39, 40].

The role of allotransplantation of hematopoietic cells in relapsed HL was a subject of prospective trial of the Spanish group GEL/TAMO (Grupo Español de Linfomas/Transplante de Médula Osea) and EBMT (European Blood and Marrow Transplantation). The trial included 92 patients with relapsed HL, including 86% after HDT/auto-HCT for whom the bone marrow donors were identified, sibling compatible in the HLA system or unrelated donor compatible or not-compatible in 1 antigen. After the re-induction chemotherapy, 14 patients did not obtain a response and died after 6–17 months, 50 patients obtained partial or complete remission, and 28 — stabilisation of the disease, and 78 patients were subjected to RIC-Allo. For the conditioning, fludarabine and melphalan were used, for GVHD (graft versus host disease) prophylaxis — antithymocyte globulin was used in recipients of the cells from the unrelated donors (29%). The main cause of treatment failure was disease progression. PFS after 1 year and 4 years was 48% and 24%, respectively. NRM within 100 days, within 1 year, and within 4 years from RIC-Allo was 8%, 15% and 19%, respectively, thus it was low in comparison to the previous data. The 4-year OS was 43% [41]. A multivariate analysis of the main trial endpoints: OS, PFS, NRM and subsequent relapse rate showed that resistance to the re-induction therapy (lack of PR or CR) was the highly significant unfavourable prognostic factor for all of the 4 parameters, increasing the risk 2–3 fold. Moreover, the impaired performance status (ECOG PS ≥ 2) was the especially

unfavourable factor for the OS, PFS and NRM, and the age > 45 — for the NRM.

This trial showed that the RIC-Allo method is relatively safe in patients with relapsed HL, 45 years old or younger, of good performance status, who obtained PR or CR after the re-induction therapy. Almost half of the patients meeting these criteria have a chance for long-term survival after RIC-Allo.

New drugs

Brentuximab vedotin

Brentuximab vedotin (BV) is a human, chimeric monoclonal IgG1 anti-CD30 antibody , covalently bound with a peptide linker with 4 molecules of the antitubulin drug — monomethyl auristatin E (MMAE). The antigen CD30, the target for BV is a membrane peptide from the family of the TNF receptors (tumor necrosis factor), occurring on the surface of the activated T lymphocytes, B and the NK cells on the germ cell tumor, head and neck tumors, lymphoma cells, and in over 90% on the Reed-Syernberg cells (HRS) in HL [42–46]. In the HRS cells, the CD30 is found in the cell membrane or inside the cytoplasm in the Golgi apparatus. CD30 stimulates the HRS growth by activating the transcription factor NF-KB. In addition, CD30 stimulates the adjacent B and T lymphocytes to produce the cytokines (IL5, INF-γ) and immunoglobulins, promoting the HRS cell survival and growth. BV molecule after binding the CD30 antigen is internalized by endocytosis. Lysosome enzymes cleave the linker, and released MMAE molecules bind to tubulin leading to the microtubule network dearrangement, cell cycle arrest in the G2/M phase and apoptosis [47, 48]. BV was approved by the FDA (Food and Drug Administration, USA) in 2011, and by the EMA (European Medicines Agency) in 2012 for use in monotherapy of patients with CD30 positive HL relapsed or refractory to treatment, after HDT/auto-HCT or after at least two previous chemotherapy lines in cases when HDT/auto-HCT or multi-drug chemotherapy is not a treatment option. Approval was granted with an accelerated procedure based on the results of phase II trial. The BV registration trial included 102 patients with relapsed/primary refractory HL, after HDT/auto-HCT. The patients received BV monotherapy at the standard dose of 1.8 mg/kg i.v. every 3 weeks to the maximum of 16 administrations (median dose number — 9). Majority of patients had primary refractory HL (72 patients), the average number of prior chemotherapy lines was 3.5 (1–13). The average time to relapse after HDT/auto-HCT was 6.7 months (0–131) [49]. At a median follow up of 33 months (1.8–57.3), 48 patients were alive (47%), and median OS for the whole group was 40.5 months. The complete remission rate (CR) after end of treatment was 33%, and partial remission rate (PR) — 38%. The median remission duration for the patients who obtained CR was not reached, and was 11.2 months (95% CI: 7.7, 18.70) for all patients. The median PFS and OS were 9.3 and 40.5 months, respectively, for the whole group of patients. 3-year PFS and OS for patients with CR after completed BV treatment was 58% (95%CI: 41%, 76%) and 73% (95%CI: 57%, 88%), respectively. 8 patients received the consolidation allo-HCT. 3-year PFS in 6 patients after allo-HCT performed in CR was 80% (95% CI: 45%, 100%), and in the remaining 28 patients in CR — 53% (95% CI: 34%, 73%). A young age, good performance status, the limited stage at BV treatment start was a favorable prognostic factor for survival [50].

Further retrospective and prospective trials confirmed the efficacy of the BV monotherapy in patients with relapsed HL (Table 7). As the CD30 antigen is permanently expressed on the HRS cells, administration of the BV in cases of progression after previous treatment with BV may also lead to subsequent responses in a proportion of patients. In the phase II trial on the secondary BV treatment in 21 patients, the average time from the last BV dose was 8 months (2–45), ORR was obtained in 60% of patients, and the median PFS was 9.9 months [56].

The published data clearly indicate that although a significant number of patients with HL relapsed after auto-HCT achieve an objective response to BV treatment, majority of them will relapse or progress after several months again. Therefore, after achieving the best response to BV, patients should proceed — if at all possible, to the consolidating treatment, optimally allo-HCT. The retrospective trial evaluated 17 patients with HL recurrent after the auto-HCT, who received RIC-allo after achieving the best response (CR — 6, PR — 8) to BV. After one-year follow up, 92.3% of patients were disease-free, 1-year OS was 100%, NRM — 0, and the previous BV treatment had no influence on the frequency of acute and chronic GVHD [57]. Similar results of retrospective reports were also published by other research groups [58, 59]. BV can be also safely administered in case of relapse after allo-HCT. The retrospective data indicate that response rate and duration are comparable to the results from the registration trial: ORR 58%, CR 38%, PFS 7.8 months [60]. Considering the CD30 expression by activated T lymphocytes, there is a hypothetical possibility of modulation of the GVHD and GVL (graft versus lymphoma) effects by using the anti-CD30 antibody [61]. Recently, several attempts of this kind were described. 4 patients received BV in early post-transplantation period after allo-HCT, including 3 patients receiving the standard BV dose with a donor lymphocyte infusion (DLI), while 1 patient, due to the presence of GVHD, received only

Table 7. Selected clinical trials concerning the BV monotherapy of refractory/relapsed (R/R) HL

Author	Publication year	Group of patients	Trial type	n	ORR/CR (%)	Parameters of survival
Younes [51]	2010	R/R*	Phase I	42	36/21	Response duration 9.7 m
Younes [49]	2012	R/R after auto-HCT	Phase II	102	75/34	PFS 5.6 (5–9) m
Rothe [52]	2012	R/R	Retrospective	45	60/22	Response duration 8 m
Zinzani [53]	2013	R/R	Retrospective	65	71/21	20 m PFS 24.2% 20 m OS 73.8%
Gibb [54]	2013	R/R	Retrospective	18	72/17	Median PFS 5.1 m (including ALCL)
Salihoglu [55]	2015	R/R	Retrospective	58	63/26	Response duration 9 m 12 m PFS 33% 12 m OS 71%
Gopal [50]	2015	R/R after auto-HCT	Phase II**	102	75/34	PFS 9.3 m (95% CI: 7.1–12.2) OS 40.5 m (95% CI: 28.7–)

*Data for patients with HL; **update of the registering trial; BV — brentuximab vedotin; n — number of patients; m — months

BV. Early GVHD occurred in all of the patients with the objective response to the treatment, lasting on average for 349 days (259–366 days). One patient died due to acute GVHD complicated by sepsis [62].

The optimal place of BV in a complex treatment algorithm for HL is a subject of a number of currently conducted prospective clinical trials.

One of the rational approaches is to increase efficacy (by eliminating failures occurring in about 30% of cases) of ABVD regimen by adding a highly active drug such as BV. This combination, however, turned out to increase the pulmonary toxicity of bleomycin and cannot be used which is why in further trials on the optimisation of the induction regimen, bleomycin was excluded and the BV is evaluated in combination with the AVD regimen [63]. A randomised global trial including Poland, comparing ABVD and BV+ABV is currently recruiting patients with HL in advanced stages [64]. Also phase II trials of the GHSG group on the new version of the BEACOPP regimen, including BV, cyclophosphamide, etoposide, doxorubicin, dacarbazine, and dexamethasone, are in advanced stages [65, 66].

Prospective trials are also ongoing for patients of age over 60, evaluating activity of BV+AVD regimen in this age group and the efficacy of induction therapy with BV and bendamustine [67, 68].

A number of trials focus on using BV in relapsed HL before auto-HCT. In a phase II trial, 37 patients received 4 doses of BV every 3 weeks. ORR in the whole group was 68% (CR — 13, PR — 12), and 33 patients were referred to auto-HCT consolidation that was performed in 18 patients [69].

In another phase II trial, patients in the first relapse had BV administered at 1.2 mg/kg on day 1, 8, and 15, every 4 weeks in 2 cycles. Patients with negative PET result (5-PS: 1 or 2) were subject to auto-HCT and the remaining patients received 2 additional cycles of ICE chemotherapy. Of 45 patients included, 12 (27%, 95% CI 13–40) obtained a negative PET result after BV, and in the remaining patients, who received ICE chemotherapy, a metabolic response occurred in 22 cases, while all the patients received auto-HCT consolidation [70]. Both cited studies showed that BV can be considered as a rescue therapy in first relapse. In this way, some patients (about 30%) can avoid the administration of multi-drug chemotherapy before the auto-HCT. However, this approach requires confirmation [71].

A number of other studies evaluated the possibility of increasing the CR rate with re-induction therapy before auto-HCT by combining BV with the standard chemotherapy regimens — DHAP, ESHAP, ICE [72–74]. It was already shown that BV in combination with bendamustine results in CR rate of 80% before auto-HCT [36].

A different approach to improve results of auto-HCT for recurrent disease is administering BV after transplantation to prevent subsequent relapse or progression of the disease. This approach was a subject of recently published randomised, double-blind trial (AETHERA) in which patients with relapsed HL and risk factors for failure after auto-HCT were randomly assigned to the consolidating treatment after auto-HCT using up to 16 administrations of a standard dose BV or a placebo. After a 2-year observation, the PFS (the trial main endpoint) was 65% and 45% in patients treated with BV and placebo, respectively, and the difference was highly statistically significant [75]. The results of AETHERA trial, with participating centres also from Poland, were the basis for FDA approval of a new indication for

brentuximab vedotin — a consolidation treatment after auto-HCT in patients with HL at risk for subsequent relapse or progression (17.08.2015).

Although the tolerance of BV treatment is generally acceptable , the main adverse effect is reversible peripheral neuropathy. Indeed, the most frequent adverse effects noted in the BV registration trial were: sensory peripheral polyneuropathy (42%), nausea (35%), hyposthenia (34%), neutropenia (19%), diarrhoea (18%). Toxicity grade 3 and 4 occurred in 56% of patients. No treatment related deaths occurred within 30 days treatment completion [49]. In the AETHERA trial, sensory polyneuropathy occurred in 56%, and neutropenia in 35% of patients [75]. Polyneuropathy is reversible in most cases, more often it occurs during the second administration of BV and in elderly patients who also suffer from other adverse effects of BV e.g., anemia, fatigue [56, 76].

The following serious adverse events attributed to BV treatment were also sporadically reported: a few cases of reactivation of John Cunningham virus (JC) and progressive multifocal leukoencephalopathy (PML) which is often a fatal complication, acute pancreatitis, pulmonary toxicity in cases of combined use of BV with bleomycin, severe bacterial and protozoan infections.

Anti-PD1 antibodies

Increased expression of PD-L1 and PD-L2 molecules by the HRS cells is one of the reasons why T lymphocytes are anergic to Hodgkin and Reed-Sternberg cells (HRS), despite the fact that T lymphocytes and other cells of the immune system significantly outnumber the lymphoma cells. These molecules are ligands of the PD1 (programmed death 1) receptor expressed on activated T lymphocytes. Natural role of the PD1/PD-L1/2 interaction is to limit activation of cytotoxic T lymphocytes and prevent autoimmune responses in the course of developing of the e response to specific antigen. Excess PD1 activating ligand in the micro-environment cells switches off the immunological response of the T lymphocytes against the HRS cells. In the majority of HL cases the 9p24.1 amplifications leading to over-expression of PD-L1 and PD-L2 are noted. The factor increasing the ligands expression can be the latent infection with the Epstein-Barr virus (EBV) occurring in some HL cases. Antibodies blocking the PD1 — PD-L1/2 junction can activate or intensify the T lymphocytes activation and lead to developing the cytotoxic anti-tumor response. A number of anti-PD1 and anti-PD-L1 antibodies have been created and two anti-PD1 antibodies — nivolumab and pembrolizumab were recently proved to be highly active in relapsed HL.

Nivulomab, a fully human IgG4 kappa monoclonal anti-PD1 antibody was evaluated in a phase I trial in 26 patients with HL who received 3 or more lines of previous treatment. Nearly 80% of patients failed BV treatment or auto-HCT. Antibody was administered at a dose of 3 mg/kg i.v. on day 1, 28, and then every 2 weeks until progression, complete remission or for a maximum of 2 years. A median (range) of nivulomab doses was 16 (6–37). ORR and CR rate was 87% and 17%, respectively, and PFS after 24 weeks — 86%. Adverse events occurred in 78% of patients, including erythema (22%) and thrombopoenia (17%). Grade 3 events occurred in 5 patients: myelodysplastic syndrome, pancreatitis, pneumonia, stomatitis, colitis, serum lipase elevation, and thrombocytopenia, lymphopenia, and leukopenia. No grade 4 or 5 events were reported. Treatment was terminated prematurely in 12 patients: due to adverse events in 2, progressive disease — in 4, and allo- or auto-transplantation in 6 patients [77].

Pembrolizumab is a humanized IgG4 type anti-PD1 humanized antibody that in a phase I trial in 31 patients with relapsed/primary refractory HL after BV and/or auto-HCT failure administered at a dose of 10 mg/kg i.v. every 2 weeks up to 2 years of the treatment also showed substantial activity (ORR 66%, CR 21%). The most frequent grade 1–2 adverse events were related to respiratory system and thyroid. Grade 3 toxicity occurred in 3 patients including pain, hypoxemia, arthroid edema or pneumonia [78].

Histone deacetylase inhibitors

A number of phase II trials showed significant activity of oral histone deacetylase inhibitors (HDACi) in patients with the recurrent HL. Deacetylase inhibition leads to hyperacetylation of histones and transforming a condensed chromatin structure into relaxed structure associated with higher levels of gene transcription. As a consequence, expression of a number of genes is modified what results in the inhibition of cell cycle and angiogenesis, among others. HDACi increase expression of CD134(OX40) ligand for the regulatory T lymphocytes on HRS cells, decrease the expression of PD1 on T lymphocytes, and also increase the secretion of TNF alfa and interleukin 17. Moreover, HDACi inhibit secretion of interleukin 10 which disturbs the regulatory functions of type-1 T lymphocytes [79, 80]. In a phase II trial, 129 patients with relapsed HL, after multiple treatment lines, received panobinostat at a dose of 40 mg 3 days a week. ORR was obtained by 35 patients (27%), including PR — 30 (23%) and CR — 5 (4%). The median PFS was 6.1 months [81]. A promising activity was shown with a combination of HDACi with chemotherapy and mTOR inhibitors. In a phase I trial, a combination of panobinostat with ICE chemotherapy was evaluated as re-introduction treatment before auto-HCT. ORR rate in the group of 21 patients was 81% including

CR — 71% [82]. In a similar trial, a combination of vorinostat with mTOR inhibitor — sirolimus was tested in a group of 57 patients after multiple treatment lines and ORR was 57% [83].

Summary

Over 50 years since the introduction of the first multi-drug chemotherapy regimen — MOPP in hemato-oncology and 40 years after introducing the ABVD regimen and adopting the commonly accepted paradigm of the combined modality treatment of patients with Hodgkin lymphoma, in recent years, data are emerging that probably will lead to significant changes in near future. New clinical data justify the modification of the intensity of treatment — in the limited stage, as well as in the advanced stage of HL depending on the PET/CT scan result after 2–3 induction treatment cycles. If the initial results of the first trials of this kind are confirmed (EORTC H10, RAPID, and RATHL), the risk-adapted treatment strategy will lead to the use of intensive or combined with irradiation treatment more selectively, and in the appropriate group of patients.

Some monoclonal antibodies have emerged of unheard of activity as single agents in high-risk HL, and have even received their first approvals for usage.

Brentuximab vedotin, currently approved for monotherapy of the recurrent disease after auto-HCT or resistant to two treatment lines and in consolidation treatment after auto-HCT in patients with high risk for relapse/progression, is the subject of trials in variety of clinical situations and in variable combinations with other drugs — in the first remission induction in the advanced and limited stages, in the second-line treatment before auto-HCT, in consolidation therapy after auto-HCT, in relapse after auto-HCT, before and after allo-HCT. Many of these trials may soon be published and provide new clues for defining a proper place for this and other antibodies in the complex HL treatment algorithm.

The emergence of a new-class anti-PD1 antibodies able to induce anti-tumor immunological response with efficacy at least comparable to BV in HL will change the landscape of treatment options for these patients. If further developed, these antibodies, along with BV, may change the standard treatment to less toxic and more efficient.

References

1. Nowotwory złośliwe w Polsce w 2012 roku. Krajowy Rejestr Nowotworów, http://onkologia.org.pl/raporty/; 7.08.2015.
2. Eichenauer DA, Engert A, André M et al. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 (Suppl 3): iii70–iii75.
3. Santoro A, Bonadonna G, Valagussa P et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 1987; 5: 27–37.
4. Boleti E, Mead GM. ABVD for Hodgkin's lymphoma: full-dose chemotherapy without dose reductions or growth factors. Ann Oncol 2007; 18: 376–380.
5. Smith TJ, Bohlke K, Lyman GH et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015; Epub Jul 13, doi: 10.1200/JCO.2015.62.3488.
6. Kaplan HS. Clinical evaluation and radiotherapeutic management of Hodgkin's disease and the malignant lymphomas. N Engl J Med 1968; 278: 892–899.
7. Campbell BA, Voss N, Pickles T et al. Involved-nodal radiation therapy as a component of combination therapy for limited-stage Hodgkin's lymphoma: a question of field size. J Clin Oncol 2008; 26: 5170–5174.
8. Specht L, Yahalom J, Illidge T et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys 2014; 89: 854–862.
9. Duggan DB, Petroni GR, Johnson JL et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. J Clin Oncol 2003; 21: 607–614.
10. Johnson PW, Radford JA, Cullen MH et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). J Clin Oncol 2005; 23: 9208–9218.
11. Gordon LI, Hong F, Fisher RI et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol 2013; 31: 684–691.
12. Advani RH, Hong F, Fisher RI et al. Randomized Phase III Trial Comparing ABVD Plus Radiotherapy With the Stanford V Regimen in Patients With Stages I or II Locally Extensive, Bulky Mediastinal Hodgkin Lymphoma: A Subset Analysis of the North American Intergroup E2496 Trial. J Clin Oncol 2015; 33: 1936–1942.
13. Carella AM, Bellei M, Brice P et al. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long--term results. Haematologica 2009; 94: 146–148.
14. Diehl V, Franklin J, Hasenclever D et al. BEACOPP: a new regimen for advanced Hodgkin's disease. Ann Oncol 1998; 9 (Suppl 5): 67–71.
15. Engert A, Diehl V, Franklin J et al. Escalated-Dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol 2009; 27: 4548–4554.
16. Skoetz N, Trelle S, Rancea M. Effect of initial treatment strategy on survival of patients with advanced-stage Hodgkin's lymphoma: a systematic review and network meta-analysis. Lancet Oncol 2013; 14: 943–952.
17. Wongso D, Fuchs M, Plütschow A et al. Treatment-related mortality in patients with advanced-stage Hodgkin lymphoma: an analysis of the German Hodgkin Study Group. J Clin Oncol 2013; 31: 2819–2824.
18. Armitage JO. Early-stage Hodgkin's lymphoma. N Engl J Med 2010; 363: 653–662.
19. Cheson BD, Fisher RI, Barrington SF et al.; for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014; 32: 3059–3067.
20. Meignan M, Gallamini A, Haioun C et al. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8–9 April 2010. Leuk Lymphoma 2010; 51: 2171–2180.
21. Barrington SF, Mikhaeel NG, Kostakoglu L et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol 2014; 32: 3048–3058.
22. Hutchings M, Mikhaeel NG, Fields PA et al. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol 2005; 16: 1160–1168.
23. Gallamini A, Barrington SF, Biggi A et al. 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 2014; 99: 1107–1113.
24. Radford J, Illidge T, Counsell N et al. Results of a Trial of PET-Directed Therapy for Early-Stage Hodgkin's Lymphoma. N Engl J Med 2015; 372: 1598–1607.
25. Raemaekers JMM, André MPE, Federico M et al. 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 2014; 32: 1188–1194.

26. Raemaekers JMM. 13th International Conference on Malignant Lymphoma, Lugano 17–20 June 2015, an oral presentation at the plenary session.
27. Johnson PW, Federico M, Fossa A et al. Response-adapted therapy based on interim FDG-PET scans in advanced Hodgkin Lymphoma: first analysis of the safety of de-escalation and efficacy of escalation in the international RATHL study (CRUK/07/033). Hematol Oncol 2015; 33 (Suppl 1): 102, abstract 8.
28. Van Den Neste E, Casasnovas O, André M et al. Classical Hodgkin's lymphoma: the Lymphoma Study Association guidelines for relapsed and refractory adult patients eligible for transplant. Haematologica 2013; 98: 1185–1195.
29. Kuruvilla J, Keating A, Crump M. How I treat relapsed and refractory Hodgkin lymphoma. Blood 2011; 117: 4208–4217.
30. Josting A, Franklin J, May M et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's lymphoma study group. J Clin Oncol 2002; 20: 221–230.
31. Moskowitz CH, Nimer SD, Zelenetz AD et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001; 97: 616–623.
32. Sieniawski M, Franklin J, Nogova L et al. Outcome of patients experiencing progression or relapse after primary treatment with two cycles of chemotherapy and radiotherapy for early-stage favorable Hodgkin's lymphoma. J Clin Oncol 2007; 25: 2000–2005.
33. Josting A, Nogová L, Franklin J et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol 2005; 23: 1522–1529.
34. Schmitz N, Pfistner B, Sextro M et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet 2002; 359: 2065–2071.
35. Linch DC, Winfield D, Goldstone AH et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 1993; 341: 1051–1054.
36. LaCasce A, Bociek RG, Matous J et al. Brentuximab vedotin in combination with bendamustine for patients with Hodgkin lymphoma who are relapsed or refractory after frontline therapy. Blood 2014; 124: 293.
37. Morschhauser F, Brice P, Fermé C et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. J Clin Oncol 2008; 26: 5980–5987.
38. Martínez C, Canals C, Sarina B et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Ann Oncol 2013; 24: 2430–2434.
39. Milpied N, Fielding AK, Pearce RM, Ernst P, Goldstone AH. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. European Group for Blood and Bone Marrow Transplantation. J Clin Oncol 1996; 14: 1291–1296.
40. Gajewski JL, Phillips GL, Sobocinski KA et al. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease J Clin Oncol 1996; 14: 572–578.
41. Sureda A, Canalas C, Arranz R et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study: a prospective clinical trial by the Grupo Español de Linfomas/ Trasplante de Médula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica 2012; 97: 310–317.
42. Deutsch YE, Tadmor T, Podack ER, Rosenblatt JD. CD30; an important new target in hematologic malignances. Leukemia Lymphoma 2011; 52: 1641–1654.
43. Podack ER, Strbo N, Sotosec V, Muta H. CD30-governor of memory T cells? Ann N Y Acad Sci 2002; 975: 101–113.
44. Kneile JR, Tan G, Suster S, Wakely PE. Expression of CD30 (Ber-H2) in nasopharyngeal carcinoma, undifferentiated type and lymphoepithelioma-like carcinoma. A comparison study with anaplastic large cell lymphoma. Histopathology 2006; 48: 855–861.
45. Somada S, Muta H, Nakamura K et al. CD30 Ligand/CD30 interaction is involved in pathogenesis of inflammatory Bowel disease. Dig Dis Sci 2012; 57: 2031–2037.
46. Sabattini E, Pizzi M, Tabanelli V et al. CD30 expression in peripheral T-cell lymphomas. Haematologica 2013; 98: e81–e82.
47. Francisco JA, Cerveny CG, Meyer DL et al. cAC10-vcMMAE, an anti--CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 2003; 102: 1458–1465.
48. Hamblett KJ, Senter PD, Chace DF et al. Effects of drug loading on the antitumor activity of a monoclonal antibody drug conjugate. Clin Cancer Res 2004; 10: 7063–7070.
49. Younes A, Gopal AK, Smith SE et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol 2012; 30: 2183–2189.
50. Gopal AK, Chen R, Smith SE et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood 2015; 125: 1236–1243.
51. Younes A, Bartlett NL, Leonard JP et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 2010; 363: 1812–1821.
52. Rothe A, Sasse S, Goergen H et al. Brentuximab vedotin for relapsed or refractory CD30+ hematologic malignancies: the German Hodgkin Study Group experience. Blood 2012; 120: 1470–1472.
53. Zinzani PL, Viviani S, Anastasia A et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica 2013; 98: 1232–1236.
54. Gibb A, Jones C, Bloor A et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. Haematologica 2013; 98: 611–614.
55. Salihoglu A, Elverdi T, Karadogan I et al. Brentuximab vedotin for relapsed or refractory Hodgkin lymphoma: experience in Turkey. Ann Hematol 2015; 94: 415–420.
56. Bartlett NL, Chen R, Fanale MA et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol Oncol 2014; 7: 24.
57. Chen R, Palmer JM, Thomas SH et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood 2012; 119: 6379–6381.
58. Gibb A, Jones C, Bloor A et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. Haematologica 2013; 98: 611–614.
59. Garciaz S, Coso D, Peyrade F et al. Brentuximab vedotin followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma. Hematol Oncol 2014; 32: 187–191.
60. Gopal AK, Ramchandren R, O'Connor OA et al. Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. Blood 2012; 120: 560–568.
61. Blazar BR, Levy RB, Mak TW et al. CD30/CD30 ligand (CD153) interaction regulates CD4+ T cell-mediated graft-versus-host disease. J Immunol 2004; 173: 2933–2941.
62. Theurich S, Malcher J, Wennhold K et al. Brentuximab vedotin combined with donor lymphocyte infusions for early relapse of Hodgkin lymphoma after allogeneic stem-cell transplantation induces tumor--specific immunity and sustained clinical remission. J Clin Oncol 2013; 31: e59–e63.
63. Younes A, Connors JM, Park SI et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. Lancet Oncol 2013; 14: 1348–1356.
64. https://www.clinicaltrials.gov: Phase 3 Frontline Therapy Trial in Patients With Advanced Classical Hodgkin Lymphoma, NCT01712490.
65. https://www.clinicaltrials.gov: Brentuximab Vedotin Combined With AVD Chemotherapy and Involved-Site Radiotherapy in Patients With Newly Diagnosed Early Stage, Unfavorable Risk Hodgkin Lymphoma. NCT01868451.
66. https://www.clinicaltrials.gov: Targeted BEACOPP Variants in Patients With Newly Diagnosed Advanced Classical Hodgkin Lymphoma. NCT01569204.
67. https://www.clinicaltrials.gov: Brentuximab Vedotin and Combination Chemotherapy in Treating Older Patients With Previously Untreated Stage II-IV Hodgkin Lymphoma. NCT01476410.
68. https://www.clinicaltrials.gov: A Study of Brentuximab Vedotin in Adults Age 60 and Above With Newly Diagnosed Hodgkin Lymphoma (HL). NCT01716806.
69. Chen R, Palmer JM, Martin P et al. Results of a multicenter phase II trial of brentuximab vedotin as second-line therapy before autologous transplantation in relapsed/refractory Hodgkin Lymphoma. Biol Blood Marrow Transplant 2015; Jul 23. [Epub ahead of print].

70. Moskowitz AJ, Schöder H, Yahalom J et al. 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 2015; 16: 284–292.
71. https://www.clinicaltrials.gov: Brentuximab Vedotin Before Autologous Stem Cell Transplant in Treating Patients With Hodgkin Lymphoma. NCT01393717.
72. https://www.clinicaltrials.gov: Phase I/II Feasibility Study Combining Brentuximab Vedotin With Second Line Salvage Chemotherapy (DHAP) in Hodgkin Lymphoma Patients. NCT02280993.
73. https://www.clinicaltrials.gov: Evaluation Study of Brentuximab Vedotin in Pre-transplant Induction and Consolidation for Relapsed or Refractory HL. NCT02243436.
74. https://www.clinicaltrials.gov: Brentuximab Vedotin, Ifosfamide, Carboplatin, and Etoposide in Treating Patients With Relapsed or Refractory Hodgkin Lymphoma (BV-ICE). NCT02227199.
75. Moskowitz CH, Nademanee A, Masszi T et al. 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 2015; 385: 1853–1862.
76. Gopal AK, Bartlett NL, Forero-Torres A et al. Brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30-positive lymphomas: a retrospective evaluation of safety and efficacy. Leuk Lymphoma 2014; 55: 2328–2334.
77. Ansell SM, Lesokhin AM, Borrello I et al. PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. N Engl J Med 2015; 372: 311–319.
78. Moskowitz CH, Ribrag V, Michot JM et al. PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma after Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013). Blood 2014; 124: abstract 624.
79. Oki Y, Buglio D, Zhang J et al. Immune regulatory effects of panobinostat in patients with Hodgkin lymphoma through modulation of serum cytokine levels and T-cell PD1 expression. Blood Cancer J 2014; 4: e236.
80. Buglio D, Khaskhely NM, Voo KS et al. HDAC11 plays an essential role in regulating OX40 ligand expression in Hodgkin lymphoma. Blood 2011; 117: 2910–2917.
81. Younes A, Sureda A, Ben-Yehuda D et al. Panobinostat in patients with relapsed/refractory Hodgkin's lymphoma after autologous stem--cell transplantation: results of a phase II study. J Clin Oncol 2012; 30: 2197–2203.
82. Oki Y, Fanale MA, Westin JR et al. A phase I study of panobinostat in combination with ICE (Ifosfamide, Carboplatin and Etoposide) In patients with relapsed or refractory classical Hodgkin lymphoma (cHL). Blood 2013; 122: 252.
83. Janku F, Oki Y, Falchook GS et al. Activity of the mTOR inhibitor sirolimus and HDAC inhibitor vorinostat in heavily pretreated refractory Hodgkin lymphoma patients. ASCO Meeting Abstracts 2014; 32: 8508.