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

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 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.
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].
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 chemotherap y 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, vinblinlastine, 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/ABV, 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>
<thead>
<tr>
<th>Table 3. Treating patients with HL, ESMO 2014 recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited stage</strong></td>
</tr>
<tr>
<td><strong>Intermediate stage, age of patients &gt; 60 years old</strong></td>
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<tr>
<td><strong>Intermediate stage, age of patients ≤ 60 years old</strong></td>
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<tr>
<td><strong>Advanced stage, age &gt; 60</strong></td>
</tr>
<tr>
<td><strong>Advanced stage, age of patients ≤ 60 years old</strong></td>
</tr>
</tbody>
</table>
Table 4. The 5-point scale (5-PS) of PET interpretations [31]

<table>
<thead>
<tr>
<th>Points</th>
<th>Description</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No uptake</td>
<td>Negative</td>
<td>Complete metabolic response</td>
</tr>
<tr>
<td>2</td>
<td>Uptake ≤ mediastinal blood pool</td>
<td>Negative</td>
<td>Complete metabolic response</td>
</tr>
<tr>
<td>3</td>
<td>Uptake &gt; mediastinal blood pool, but liver</td>
<td>Intermediate</td>
<td>Uncertain</td>
</tr>
<tr>
<td>4</td>
<td>Uptake moderately higher than liver</td>
<td>Positive</td>
<td>Failure, disease progression</td>
</tr>
<tr>
<td>5</td>
<td>Uptake markedly higher than liver and/or new lesions</td>
<td>Positive</td>
<td>Failure, disease progression</td>
</tr>
</tbody>
</table>

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 supradiaphragmatic HL 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
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

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

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

5-PS — 5-point scale
Table 6. Risk factors of failure of 2nd line treatment of patients with relapsed HL

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Primary refractoriness</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
</tr>
<tr>
<td>Early relapse</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>CS III, IV</td>
<td>•</td>
<td>•</td>
<td>•</td>
<td></td>
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<tr>
<td>ECOG PS &gt; 0</td>
<td></td>
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<td>•</td>
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</tr>
<tr>
<td>Hb &lt; 10.5 (K) &lt; 12.0 (M) g/dl</td>
<td></td>
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<tr>
<td>Extranodal site</td>
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<tr>
<td>Systemic symptoms</td>
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</table>

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 surface of the activated T lymphocytes, B and the NK cells on the germ cell tumour, head and neck tumours, lymphoma cells, and in over 90% on the Reed-Sternberg 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 rearrangement, 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

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

*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 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%), hypotension (34%), neutropenia (19%), diarrhea (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 a consequence of expression 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 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 nivolumab 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 thrombocytopenia (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 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, and 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


41. Gibb A, Jones C, Bloor A et al. Brentuximab vedotin in refractory Hodgkin lymphoma — closer to failure-free treatment


