Relapsed and Refractory Hodgkin Lymphoma

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Contents

20.1 Introduction

High-dose therapy (HDCT) followed by autologous stem cell transplantation (ASCT) is the standard treatment for patients with relapsed Hodgkin lymphoma (HL). This is based on the results of two randomized controlled studies showing improved event-free survival (EFS) in the ASCT group compared to standard-dose salvage chemotherapy. There are a number of single-arm institutional and registry studies also showing an advantage for HDCT/ASCT [1, 2]. Many larger single-center studies have reported that HDCT/ASCT is the best treatment option for patients with primary refractory HL providing that the disease is chemosensitive to salvage chemotherapy (SC) [3–5]. Despite this evidence, many questions remain including the utility of pre-SC prognostic factors, type and number of salvage chemotherapy needed prior to HDCT, the use of pre-ASCT fludeoxyglucose-positron

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emission tomography (FDG-PET) scanning to determine ASCT eligibility, the role of radiotherapy during ASCT, and the need to consider allogeneic transplantation in selected patients. The objective of this chapter is to provide hematologists/oncologists with an up-to-date review of these issues; however, we will restrict the data to refractory or relapsing HL patients who are eligible for HDCT.

20.2 Prognostic Factors in Relapsed and Refractory Hodgkin Lymphoma

Several studies analyzed risk factors in relapsed and refractory HL. Time to relapse after first-line therapy was confirmed as important risk factor in virtually all analyses. The observation that the duration of remission has a marked effect on the ability of patients to respond to subsequent salvage treatment dates back to 1979 [6]. This finding was later confirmed in larger analyses [7–9]. In 422 patients with relapsed or refractory HL registered in the German Hodgkin Study Group (GHSG) database, patients with early (<12 months) and late relapse (>12 months) had a 4-year overall survival (OS) of 44% and 72%, respectively. This difference in outcome between early and late relapsed patients is also present when only patients treated with HDCT and ASCT were analyzed [7–9]. The prognosis of patients with primary refractory disease is particularly poor, as demonstrated in a large prospective multicenter trial with 157 patients receiving HDCT and ASCT after failure of first-line therapy [10]. The 5-year OS estimates were 30% and 76% for patients with refractory or relapsed disease, respectively. Many other prognostic factors have been described for patients relapsing after first-line chemotherapy. These include age, sex, histology, site of relapse, stage at relapse, bulky disease, B-symptoms, performance status, extranodal relapse, anemia, and chemosensitivity to salvage chemotherapy in patients receiving HDCT and ASCT. However, the impact of these factors on outcome was less consistent than time to relapse.

The GHSG performed a larger retrospective analysis on 422 relapsed patients [7] suggesting that the prognosis of these patients can be estimated according to a number of risk factors. The most relevant factors were combined into a prognostic score (Table 20.1). This score included duration of first remission, stage at relapse, and the presence or absence of anemia at relapse. Early recurrence within 3–12 months after the end of primary treatment, relapse stage III or IV, and hemoglobin <10.5 g/dL in female or <12 g/dL in male patients contributed to a score with values 0–3 in order of worsening prognosis. This prognostic score allowed distinguishing between different prognostic groups. The actuarial 4-year freedom from second failure (FF2F) and OS for patients relapsing after chemotherapy with three unfavorable factors was 17% and 27%, respectively. In contrast, patients with none of the unfavorable factors had an FF2F and OS of 48% and 83% at 4 years, respectively. In addition, the prognostic score was also predictive for patient subgroups such as those relapsing after radiotherapy, for patients relapsing after chemotherapy who were treated with conventional treatment or HDCT followed by ASCT, and for patients under 60 years having a Karnofsky performance status ≥90%. This prognostic score used clinical characteristics that can be easily collected at the time of relapse separating groups of patients with clearly different outcomes.

This score was confirmed in the prospective European HDR2 trial that was conducted by the GHSG, EORTC, GEL/TAMO, and EBMT comparing two pre-HDCT regimens in 241 patients

Table 20.1 Prognostic score in relapsed Hodgkin lymphoma evaluated in 422 patients [7]

Factor		Groups with 4-year OS (%)
Duration of first remission	Early relapse vs.	47
	Late relapse	73
Stage at relapse	Stage III/IV vs.	46
	Stage I/II	77
Hemoglobin	F < 10.5 g/dL; M < 12.0 g/dL Vs. F > 10.5 g/dL; M > 12.0 g/dL	40 72

[11]. Stage III patients had a similar risk in terms of progression-free survival (PFS) compared to stage II patients in univariate analysis. Thus, the prognostic score was slightly modified in that only stage IV (and not stage III) was scored as additional risk factor. Moreover, both multiple relapses and early relapse were scored as risk factor. Patients with none of these risk factors (n = 117) had a PFS of 81% (95% CI, 72% to 87%) at 3 years (Fig. 20.1). Conversely, almost all patients in the small group of those having three risk factors (n = 14) relapsed or died within 3 years (PFS, 14%; 95% CI, 2% to 37%). Other analyses have identified extranodal disease [8, 12] and B-symptoms [8, 13] as risk factors. Moreover, in patients receiving HDCT and ASCT, chemosensitivity to salvage chemotherapy was described as an important prognostic factor in several reports [9, 12]. More recently, FDG-PET after salvage therapy has been established as prognostic tool that might overshadow classical risk factors (see Sect. 20.4) [14, 15].

Although a plethora of risk factors have been described in relapsed/refractory HL, there is currently no generally accepted risk-adapted treatment approach. The French Lymphoma Study Association (LYSA) has proposed a risk-adapted strategy based on the three risk factors—primary refractory disease, early relapse, and stage III/IV at relapse [16]. The lymphoma group of the Memorial Sloan-Kettering Cancer Center (MSKCC) used three risk factors (early relapse, extranodal disease, and B-symptoms) to stratify patients into three different treatment groups [8, 17]. Risk-adapted therapy with different SC and/or HDCT approaches should be further evaluated in prospective clinical trials.

To shed more light on the impact of different risk factors in relapsed/refractory HL and to better identify patients who might be candidates for intensification strategies, a large multinational cooperative study recently reassessed 23 patients with known risk factors who received ASCT [18]. In a retrospective analysis of 656 patients with a median follow-up of 60 months after ASCT, the multivariate analysis identified stage IV disease, time to relapse ≤3 months, ECOG performance status ≥1, bulk ≥5 cm, and inadequate response to salvage chemotherapy (<PR by CT) as significant and nonredundant risk factors for PFS. Validation in 389 independent international patients with evaluation of response to salvage therapy by functional imaging instead of CT confirmed the excellent discrimination of risk groups and significant prognostication of PFS and OS after ASCT (HR = 1.70 and HR = 1.63, respectively; $p < 0.0001$). Especially, patients with 3–5 risk factors had a dismal prognosis (HR = 4.8 for PFS in 690 patients treated predominantly in routine care, Fig. 20.2), and

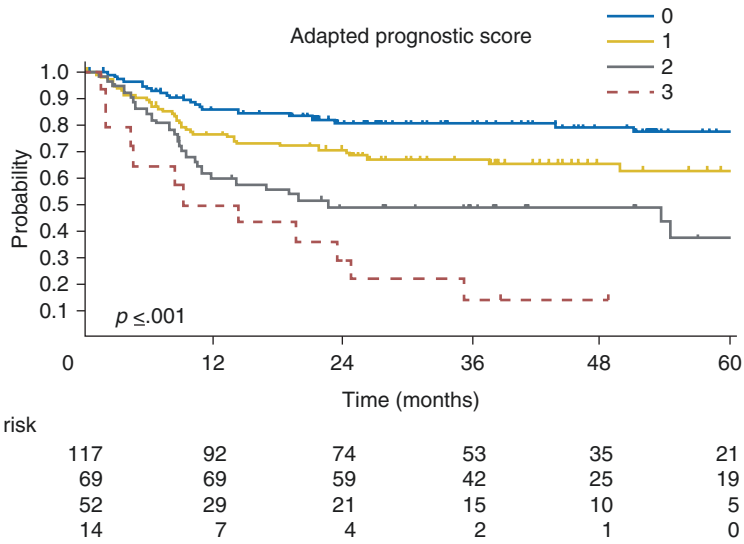

Fig. 20.1 Kaplan–Meier curves of progression-free survival in four groups of patients differentiated with an adapted prognostic score. Presence of stage IV disease, early or multiple relapse, and anemia summed up to a score ranging from 0 to 3 [11]

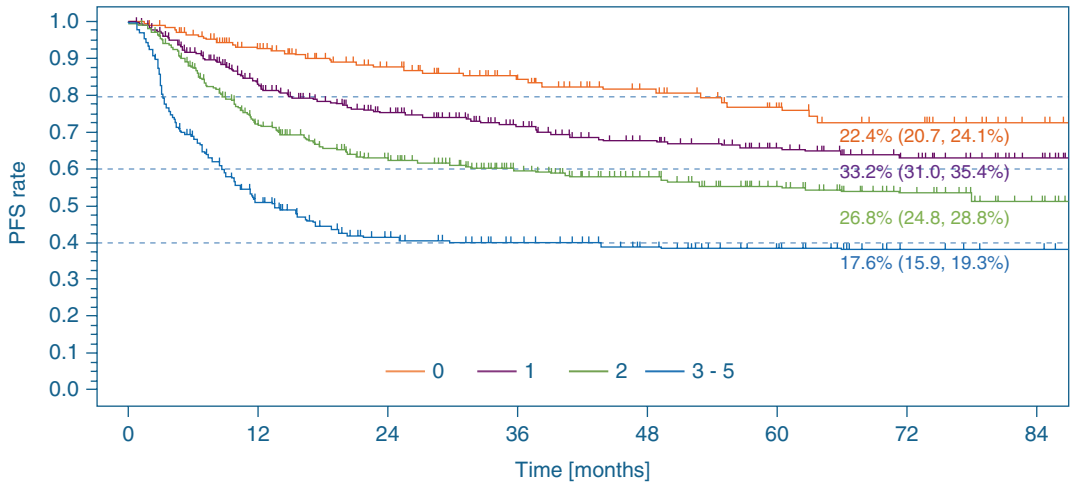

Fig. 20.2 Kaplan–Meier curves of progression-free survival (PFS) after autologous stem cell transplant (ASCT) in four risk groups of the risk score in patients treated predominantly in routine clinical care [18]

therefore, ultrahigh-risk patients can reliably be identified. This might allow for a more reasonable selection of patients for alternative salvage strategies in clinical trials or consolidation strategies (see Sects. 20.7 and 20.8) in routine care.

20.3 Salvage Therapy

Possibly the most important goal in the management of patients with relapsed or primary refractory HL is establishing chemosensitive disease with SC. It has been clearly demonstrated in multiple studies that chemorefractory disease to SC predicts for a poor long-term PFS [18, 19]. An effective salvage regimen must have a favorable toxicity profile, in addition to having a high response rate. Older regimens such as mini- or dexa-BEAM have limited utility in 2019 because of toxicity to hematopoietic stem cells, leading to an inadequate stem cell harvest [20–22]. The optimal choice of a salvage regimen is unclear, because different regimens have not been directly compared with one another and in general, as opposed to diffuse large B cell lymphoma, response rates are quite high approaching 80%. Unfortunately, the clinician is left to choose from a variety of reasonable salvage options without clear knowledge of the superiority of one regimen vs. another. At MSKCC, the ICE (ifosfamide, carboplatin, etoposide) chemotherapy regimen has been used since 1994 and has become the standard SC used in the United States [3, 8, 19]. ICE is regularly administered as an inpatient treatment for 2 cycles. In a series of prospective clinical trials, the complete response (CR) rate is approximately 50% and the overall response rate is 80%. An augmented dosing has been evaluated in patients with unfavorable risk factors [8, 17] with the following doses: ifosfamide 10 g/m^2 as a 48-h continuous infusion, etoposide 200 mg/m^2 for 3 doses, and carboplatin at an AUC of 5. It is likely that cytarabine-based regimens such as DHAP (dexamethasone, high-dose ara-C [=cytarabine], cisplatin), ESHAP (etoposide, methylprednisolone, high-dose ara-C [=cytarabine], cisplatin), and DHAX (dexamethasone, high-dose ara-C [=cytarabine], oxaliplatin) have similar response rates, and centers tend to be passionate concerning the type of salvage regimen that is employed. The GHSG and other European cooperative groups regard DHAP as standard SC [23, 24].

The other popular choice is to incorporate gemcitabine into the SC program. Gemcitabine-based regimens are better tolerated, show similar activity, and have the advantage of easier outpatient administration. GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin) was

evaluated in 91 patients with relapsed or refractory HL, and overall response rate (ORR) was 70%, albeit with a modest 19% CR rate based upon CT imaging [25]. Another program, IGEV (ifosfamide, prednisolone, gemcitabine, and vinorelbine), was administered to 91 patients of which 49 (54%) achieved a CR and 25 patients (27.5%) had a PR for an ORR of 81.3%, based upon PET imaging [26]. Lastly, Kuruvilla et al. compared GDP (gemcitabine, dexamethasone, and cisplatin) with mini-BEAM; response rates were similar but GDP was far less toxic [27]. A more recent report supports the tolerability and efficacy of GDP in patients with relapsed or refractory HL [28].

Depending upon prognostic factors, favorable risk patients are likely to have a high CR rate to any of these regimens and it is prudent to minimize toxicity if possible. Recently, several studies have incorporated brentuximab vedotin (BV) either sequentially or in combination with chemotherapy as part of a salvage strategy prior to ASCT [29–32]. BV comprises an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). BV demonstrated substantial efficacy, including an objective response rate of 75% and complete remission (CR) rate of 34%, in a pivotal phase two study of patients with CD30-positive HL who had failed HDCT and ASCT therapy and is approved in this setting [33]. As a targeted therapy with minimal hematologic toxicity, BV may provide a unique opportunity to deliver therapy pre-ASCT. Two studies confirmed a single-agent response rate of >80% as first salvage treatment in transplant-eligible patients; however, the complete response rate is <40% [29, 30]. Sequential treatment with platinum-based salvage treatment to patients lacking a PET-negative response (Fig. 20.3) increases the CR rate to >80% [30]. Other studies have combined BV with either bendamustine, ICE, DHAP (Fig. 20.4), or ESHAP and all trials demonstrated feasibility and favorable results as compared to historical data [34–37]. Interestingly, patients achieving a CR to either single-agent BV, sequential BV and chemotherapy, or concomitant BV and chemotherapy all have similar 2-year PFS data post-ASCT: >80% of patients are progression-free. Clearly, single BV therapy

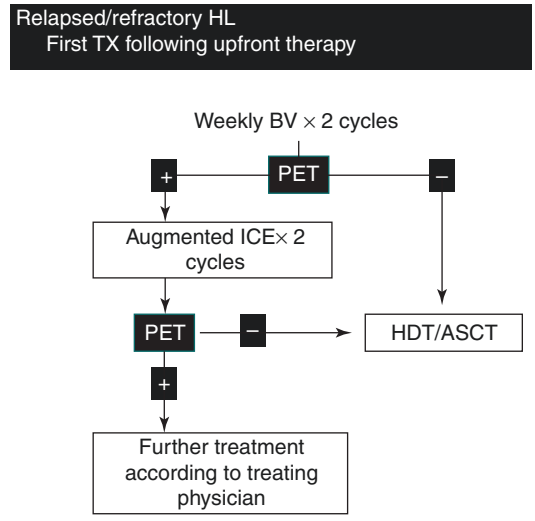

Fig. 20.3 Brentuximab vedotin as initial salvage therapy in relapsed/refractory HL. *HL* Hodgkin lymphoma, *TX* chemotherapy, *BV* brentuximab vedotin, *PET* positron emission tomography, *ICE* ifosfamide, carboplatin, and etoposide, *HDCT* high-dose therapy, *ASCT* autologous stem cell transplant [30]

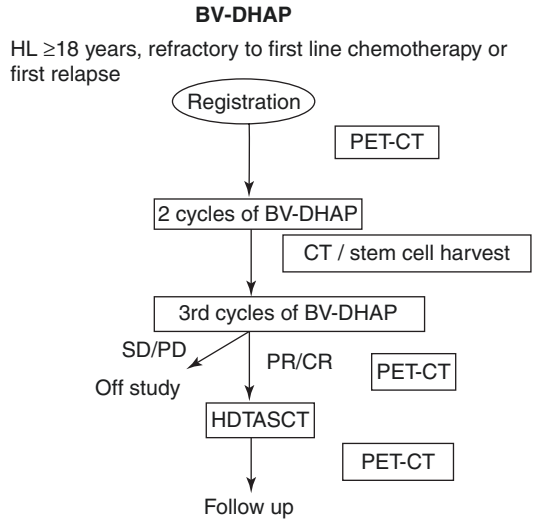

Fig. 20.4 Brentuximab vedotin-DHAP as salvage therapy in relapsed/refractory HL. *BV* brentuximab vedotin, *DHAP* dexamethasone, high-dose ara-C, Cisplatinum, *HL* Hodgkin lymphoma, *yr* year, *PET-CT* positron emission tomography/computed tomography, *SD* stable disease, *PD* progressive disease, *PR* partial remission, *CR* complete remission [35]

will have the least side effects, but the lowest CR rate and likely prognostic factor analyses should determine the optimal salvage program. BV might also be an alternative for patients not tolerating salvage combination chemotherapy due to lymphoma-associated morbidity and for patients not responding to conventional therapy. Therefore, BV as salvage therapy was assessed in a phase IV trial for patients with relapsed HL and a history of ≥1 prior systemic chemotherapy regimen who were deemed transplant-ineligible at trial entry. After treatment with BV, 47% of patients finally received HDCT [38].

Besides BV, the anti-programmed cell death receptor 1 (PD1) antibodies nivolumab and pembrolizumab were also evaluated as preparative therapy before curative HDCT due to their excellent tolerability and high efficacy [39, 40]. The chemotherapy-free combination of BV and nivolumab was tested in 62 patients who failed induction therapy in a phase 1/2 trial [41]. With an ORR of 82% and a CR rate of 61%, the tumor control rate was high; however, these numbers are in the range of what can be achieved with a combination of BV and chemotherapy. Another trial assessing different combinations of nivolumab, ipilimumab, and BV in multiple cohorts including transplant-naïve patients is currently enrolling in the randomized phase 2 part of the trial that compares nivolumab plus BV to a combination of nivolumab, ipilimumab, and BV (ClinicalTrials.gov Identifier: NCT01896999).

Importantly, no randomized phase III trials with BV or anti-PD1 treatment as part of the salvage program were conducted so far and therefore superiority of these newer strategies over conventional treatment has yet to be proven. Additionally, BV and anti-PD1 treatment are not approved for the use in first salvage therapy in relapsed HL. In summary, several reasonable salvage options were evaluated in prospective nonrandomized clinical trials, and the clinician is left to choose based on the characteristics of the individual patient, personal experience, availability of drugs, and the standards of a specific center.

20.4 Pre-ASCT FDG-PET

FDG-PET-CT has revolutionized the way oncologists manage HL. FDG-PET-CT imaging is more sensitive and specific than either modality alone, and in 2019, most HL patients have a combined FDG-PET-CT scan for staging and to determine remission status at the conclusion of a chemotherapy program [42]. It is also recommended that the CT component include intravenous and oral contrast which can be helpful for patients requiring subsequent consolidative radiotherapy. Some of the basic "rules" in PET scanning for HL is that it is always abnormal at diagnosis and normalization after therapy is highly predictive of a good outcome. However, controversy remains concerning its role for interim evaluation.

Since second-line treatment employs a comprehensive approach, the pre-ASCT PET in reality is an interim PET (iPET). Reporting should be similar to that of untreated HL, scores 1–3 are considered negative via the 5-point or Deauville scale, and 4/5 are positive [43]. The question that investigators face is should a patient who is deemed chemosensitive by CT but with an abnormal iPET be excluded from curative therapy? Thirty percent of patients achieve long-term EFS if there is tumor shrinkage after one course of salvage therapy despite an abnormal iPET.

Recent studies have reported that chemosensitive disease should be defined by pretransplant PET status; those patients with a negative scan have a 5-year EFS of approximately 75% compared to 30% for those patients with improvement of CT but with persistent PET positivity [14, 44, 45]. This data was confirmed by the MD Anderson group where 3-year PFS and OS rates were 69% and 87%, respectively, vs. 23% and 58%, respectively, for patients with positive functional imaging. MSKCC investigators recently reported the results of a large phase II second-line treatment program where iPET was prospectively evaluated. Patients that achieved normalization of the post-ICE PET scan were transplanted with the expected 77% long-term EFS. Patients achieving cytoreduction to ICE but with a persistently abnormal PET received a

second, non-cross-resistant salvage treatment with four doses of GVD administered biweekly. Interestingly, 50% of patients had a PET-negative response to GVD and these patients also had a 77% long-term PFS. Patients with a persistently positive PET scan after two salvage chemotherapy programs had only 22% 5-year EFS [46].

In our opinion, the goal of salvage chemotherapy should be a negative PET scan; however, owing to the lack of randomized trials, the best strategy for patients not achieving a negative PET after the first salvage program is currently unclear. A second, non-cross-resistant salvage program or tandem ASCT (see Sect. 20.7) seem to be reasonable options. It must be stressed that patients with nodal only HL at this point can still achieve a negative PET with involved or extended field radiotherapy, a reasonable approach in this patient population. The treatment decision should be based on pretreatment, risk factors and comorbidities of the individual patient.

20.5 Salvage Radiotherapy

As stated above, SC followed by HDCT/ASCT is standard therapy for transplant-eligible patients with HL. The incorporation of radiotherapy (RT) to selected sites integrated into the salvage program either before or after transplantation can improve EFS for a subset of patients. An increasing number of patients who failed primary treatment are RT naïve, and this number will only increase since the evolving trend in many centers is to use short-course chemotherapy alone for early-stage HL. An important argument in support of incorporating RT into high-dose salvage programs is that the pattern of relapse after HDCT is similar to that after primary therapy, i.e., in sites of moderately bulky nodal involvement.

The issues of optimal timing of RT—pre- or post-HDCT/ASCT—is center dependent. At MSKCC, involved field RT (IFRT) is administered prior to HDCT as part of the salvage program for further tumor reduction, and interestingly, at times it is the IFRT that normalizes the pre-ASCT PET scan. From 1985 to 2008, it was MSKCC policy to employ both IFRT and total lymphoid irradiation (TLI) for RT-naïve patients without extranodal involvement. A cohort of 186 patients of which 53% had primary refractory disease to ABVD was recently updated. These patients received involved field RT (IFRT) at 18 Gy followed by total lymphoid radiation at 18 Gy as part of the conditioning regimen; the 5- and 10-year OS were 68% and 56%, and the 5- and 10-year EFS were 62% and 56%, respectively [47]. This data was confirmed by the group at Northwestern where TLI was found to be an independent predictor for improved EFS on multivariate analysis [48]. Within the GHSG, RT in case of residual disease after HDCT and ASCT is preferred aiming at a dose-dense salvage and high-dose chemotherapy.

Currently, the use of RT can help a substantial number of patients in the salvage setting. Since nodal only relapses are common, the avoidance of RT in this setting makes little sense in patients whose major cause of death will clearly be HL if HDCT/ASCT is not successful.

20.6 HDCT Regimens

Similar to SC regimen selection, the choice of the HDCT regimen before ASCT is not evidence-based: no randomized controlled trials comparing different regimens have been conducted, and the choice of regimen is mostly made on personal experience. Historical comparisons of different regimens are limited by high patient heterogeneity in terms of pretreatment, risk factors, and comorbidity [49]. Because BEAM (BCNU [=carmustine], etoposide, cytarabine, melphalan) was used in both of the randomized controlled trials that established ASCT in relapsed/progressive HL [1, 2] and yielded excellent results in the large HDR2 trial, this is the HDCT regimen of choice for most groups. CBV(−Mx) (cyclophosphamide, carmustine, etoposide, mitoxantrone) and (sub)total lymphoid irradiation ([S]TLI)-based conditioning regimens are frequently used alternatives [46, 50]. Phase I/II trials with modified HDCT regimens aiming at a reduced toxicity of BCNU using bendamustine [51] or

gemcitabine/vinorelbine [52] have been published, but owing to the lack of randomized trials, these approaches currently remain experimental.

The addition of sequential HDCT after SC was evaluated as a potential alternative to the commonly used multiagent HDCT regimens. Based on the challenging results of a phase II trial [53], sequential HDCT was tested in the prospective GHSG, EORTC, GEL/TAMO, and EBMT HDR2 trial. Patients with histologically confirmed early or late relapsed HL and patients in second relapse with no prior HDCT received two cycles of DHAP. Patients achieving at least SD after DHAP were randomized to receive either BEAM followed by ASCT (arm A of the study) or high-dose cyclophosphamide, followed by high-dose methotrexate plus vincristine, followed by high-dose etoposide, and a final myeloablative course with BEAM (arm B of the study). A total of 284 patients with relapsed HL were included in this largest randomized trial performed in this setting so far; 241 patients were randomized after DHAP. The intensified experimental arm showed significantly longer mean treatment duration and higher toxicity before BEAM. Mortality was nearly identical in both arms (20% and 18%) and there were no differences in terms of PFS and OS. The respective 3-year rates for the standard arm and the intensified arm were PFS 72% vs. 67% and OS 87% vs. 80%. In conclusion, both regimens tested showed equally favorable results in outcome and survival. Since further intensification did not improve results, two cycles of conventional SC followed by HDCT and ASCT remain the standard of care for patients with relapsed HL.

20.7 Tandem HDCT/ASCT

The prognosis of high-risk patients with relapsed HL and especially the prognosis of refractory patients remain unsatisfactory despite HDCT and ASCT. Tandem autologous transplant is a potential strategy to improve the prognosis of these patients. In the French H96 prospective multicenter trial [50], 150 high-risk patients (primary refractory disease, $n = 77$, or two or more of the following risk factors at first relapse: time to relapse <12 months, stage III or IV at relapse, and relapse within previously irradiated sites, $n = 73$) were assigned to tandem ASCT. In the intent-to-treat analysis, the respective 5-year FF2F and OS estimates were 46% and 57%, with similar outcomes in primary refractory and high-risk relapsed patients. The 45% 5-year OS in patients with chemotherapy-resistant disease who completed tandem transplant compares favorably with previously reported 5-year OS rates of 30%. In the long-term follow-up analysis, these relatively favorable results were confirmed: 10-year FF2F and OS in the high-risk patients were 40% and 47%, respectively [54]. Additionally, two other analyses also suggested a benefit of tandem ASCT in high-risk relapsed/refractory HL patients [17, 55].

Moreover, a series of 111 consecutive patients who had relapsed or refractory HL achieving CR (PET negative) or PR (PET positive) after SC was reported; these patients underwent single or tandem ASCT [15]. In line with other analyses, outcomes were significantly better in patients with negative PET compared to patients who were PET positive after salvage with PFS and OS rates of 79% vs. 23% and 90% vs. 55%, respectively. In the PET-positive subgroup, tandem transplant improved 5-year PFS from 0% to 43% ($p = 0.034$) compared to single ASCT. In summary, tandem ASCT is an alternative for high-risk relapsed and primary refractory patients and for patients not sufficiently responding to SC.

20.8 Posttransplant Therapy

As stated above, single institution studies suggest nearly 2/3 of patients with a negative pre-ASCT pet scan are cured with ASCT, but registry and cooperative studies report that approximately 50% of patients can be cured after auto-HSCT, and most patients with unfavorable risk factors progress after transplant. Prior to the availability of checkpoint inhibitors, the median survival of ASCT failures was approximately 30 months. The AETHERA trial is a phase 3, randomized, double-blind, placebo-controlled, multicenter study initiated to

answer the question if there was benefit of giving post-ASCT therapy with BV to patients with an initial remission duration of <1 year or extranodal disease at the time of salvage therapy [56]. A total of 165 and 164 patients were randomized to receive either BV or placebo after high-dose therapy and stem cell infusion, respectively. At 5 years' follow-up, patients randomized to BV had a significantly longer PFS than patients who received placebo. Median 5-year PFS with BV was not reached and was 15.8 months with placebo. The 5-year PFS (95% CI) rate was 59% (51–66) with BV vs. 41% (33–49) with placebo (HR = 0.521; 95% CI, 0.379–0.717; Fig. 20.5). The data is very straightforward: one in five patients destined to be ASCT failures were now cured.

There were many lessons learned from this study: (1) A survival difference will not be achieved because of two main issues—crossover design where patients with progressive disease on the placebo arm were able to receive BV free of charge and more importantly checkpoint inhibitors became available and overall survival in patients where ASCT fails might be greater than 10 years as opposed to 30 months. (2) Five risk factors predicted outcome on the study: <CR pre-ASCT, extranodal disease, B symptoms at the time of salvage, the requirement of >1 salvage regimen to achieve ASCT eligibility and remission duration of less than 1 year. Only patients with at least two of these risk factors benefitted from maintenance. (3) PET imaging was not required and when done were not reviewed centrally; it is clear from other datasets however that patients with nodal only disease at the time of salvage in CR as defined by a negative pre-ASCT PET do extremely well with ASCT, and post-ASCT BV is likely of little benefit in the absence of other high-risk features. (4) At 5 years, BV-induced peripheral neuropathy resolved in 90% of patients. (5) All patients were BV naïve and the use of post-ASCT BV in this setting was not studied. The general recommendations in this situation requires common sense: if patients had a suboptimal response to BV prior to ASCT, defined as < partial response, administering BV again makes little sense.

Secondary malignancies occurred in six and three patients in the BV and placebo arms, respectively; they included myelodysplastic syndromes ($n = 2$), acute myelogenous leukemia,

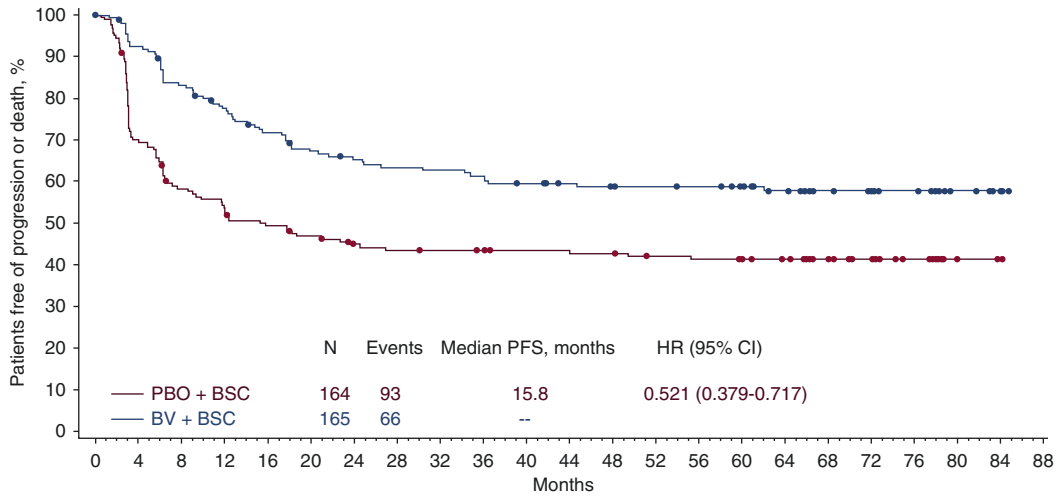

Fig. 20.5 AETHERA trial: Patients with increased risk of relapse after autologous stem cell transplantation received brentuximab vedotin (BV) or placebo as consolidation. All patients additionally had best supportive care (BSC). Progression-free survival (PFS) per investigator at 5 years [56, 57]

pancreatic, lung, and bladder cancer ($n = 1$ each) in the BV arm and mantle cell lymphoma, acute myelogenous leukemia, and myelodysplastic syndromes in the placebo arm ($n = 1$ each).

In summary, patients who received BV as early consolidation maintained a PFS benefit at 5 years and, despite a high rate of subsequent BV therapy in the placebo arm after relapse, also had a longer time to next salvage treatment [57]. Patients who received BV consolidation also required fewer therapies, including subsequent transplants. Lastly, PN continued to improve and/or resolve in 90% of patients. A final analysis of overall survival is expected in 2020.

20.9 Allogeneic Transplantation after Reduced Conditioning in Hodgkin Lymphoma

In most cases, allogeneic transplantation is not recommended for patients with HL. The reduced relapse rate associated with a potential graft-versus-tumor effect is offset by lethal graft-versus-host toxicity. Nevertheless, patients with first-line therapy failure or relapsed patients with additional risk factors such as insufficient response to SC face a poor prognosis after HDCT and ASCT. Therefore, the role of allogeneic transplant should be further evaluated within clinical trials in these patients. While allogeneic transplant after myeloablative conditioning led to poor results because of the exceedingly high non-relapse mortality, several retrospective analyses have suggested that dose-reduced allogeneic transplant (RIC-allo) could be an option for HL patients relapsing after ASCT. The largest multicenter phase 2 prospective clinical trial of RIC-allo in relapsed or refractory HL so far reported favorable results in a subset of patients [58]. The role of allogeneic transplant in HL is discussed in detail in Chap. 21.

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