bjh review

The role of transplantation in Hodgkin lymphoma

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Summary

Autologous stem cell transplantation is the standard salvage strategy for young and fit patients with Hodgkin lymphoma failing induction therapy, and is effective in nearly 50% of cases. The quality of response at transplantation is the most relevant prognostic aspect, as patients in complete response can obtain better outcomes. Therefore, first-line salvage treatments applied before transplantation need to produce high quality responses without excessive myelotoxicity and without affecting peripheral blood stem cell mobilisation. In this sense, the incorporation of new agents active in Hodgkin lymphoma, such as brentuximab vedotin and anti-programmed death 1 antibodies, in conventional regimens, may help to enhance complete remission rates. Working on conditioning regimen and applying a post-autologous consolidation treatment (for example with brentuximab vedotin) are two ways for improving transplant outcomes, particularly in patients displaying high-risk features for early relapse or progression. Allogeneic transplantation maintains its curative potential also in the era of new drugs, although its most correct timing and the most suitable sequence of post-autologous salvage treatments still remain to be determined.

Keywords: allogeneic stem cell transplantation, anti-PD1 antibodies, autologous stem cell transplantation, brentuximab vedotin, Hodgkin lymphoma.

Autologous stem cell transplantation (ASCT), preceded by non-cross resistant salvage chemotherapy, which allows both disease reduction and stem cell mobilisation in peripheral blood, is uniformly regarded as the current standard of care for young and fit patients affected by Hodgkin lymphoma (HL) who suffer disease relapse after a successful first-line treatment (roughly 20–30% of patients) or who experience treatment refractoriness (about 10% of cases). This has been established in two randomised clinical trials, which clearly identified the superiority of high-dose chemotherapy and ASCT over standard-dose chemotherapy and demonstrated that nearly 50% of patients with disease recurrence can be cured through this procedure (Linch *et al*, 1993; Schmitz *et al*, 2002).

Disease chemosensitivity at transplantation, which indicates the efficacy of the upfront treatment on lymphoma (i.e. primary refractory or early or late relapse) and disease status at transplantation, which accounts for the efficacy of the first-salvage strategy, are the most important clinical parameters that correlate with ASCT success and long-term prognosis. In particular, the positron emission tomography (PET) status at transplantation, which mirrors the efficacy of the salvage regimen, is fundamental in assessing patients' prognosis, as progression-free survival (PFS) rates are significantly better (i.e. more than doubled at 4 and 5 years) in patients who are transplanted with a negative PET scan, compared to those who still display PET positivity (Moskowitz *et al*, 2010a; Moskowitz *et al*, 2010b, 2012; Mocikova *et al*, 2011; Smeltzer *et al*, 2011; Devillier *et al*, 2012; Akhtar *et al*, 2013; Gentzler *et al*, 2014). Importantly, no differences in outcome have been reported for patients needing 2 salvage regimens instead of only one, provided the pre-autologous PET scan is negative (Moskowitz *et al*, 2012).

ASCT failures tend to occur within the first 2–3 years post-transplantation and are mostly related to clinical parameters indicative of high-risk disease, such as the presence of B-symptoms and Ann Arbor advanced stage at relapse (Josting *et al*, 2002a; von Tresckow *et al*, 2014). Historical data indicates that outcomes of patients who fail ASCT are very poor (Arai *et al*, 2013) and at least 80% of high-risk patients at relapse have died within 5 years: importantly, the shorter the duration of post-transplant remission, the lower the probability of remaining alive (Josting *et al*, 2002a). Although several histological and biological parameters that correlate with ASCT outcomes have been reported, there is a lack of clearly reproducible prognostic markers (Koreishi *et al*, 2010; Steidl *et al*, 2010; Casulo *et al*, 2013). A prognostic model to predict post-ASCT transplantation outcomes has been recently built on tissue specimens collected at the moment of disease relapse and validated in 2 independent cohorts of relapsed HL patients: this model establishes a correlation between post-ASCT failure-free survival (FFS) and the expression of genes related to B cells, macrophages, Hodgkin/Reed-Sternberg cells, neutrophils and natural killer

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First published online 8 November 2018
doi: 10.1111/bjh.15639

cells as well as drug resistance components, and stratifies patients into a low-risk group (with excellent FFS rates when treated with the current standard) and a sizable high-risk group clearly showing second-line treatment failure (Chan *et al*, 2017).

The purpose of this paper is to review the current ASCT standard in patients with recurrent HL, particularly focusing on possible new salvage schemes incorporating novel agents and on strategies aimed at preventing post-ASCT disease recurrence in high-risk patient populations. Indications for allogeneic stem cell transplantation (alloSCT) are also briefly reviewed.

The pre-autologous setting: boosting responses before transplantation

Given that disease status at transplantation is regarded as the most relevant indicator of ASCT efficacy in terms of durable disease control, salvage treatments play a role of utmost importance in this regard. Effective combinations should therefore be addressed at increasing the percentage of patients with complete PET-assessed metabolic responses. Moreover, in the era of new drugs proven effective in the treatment of HL, new salvage options – either chemotherapy-free or based on the combination of chemotherapy and novel agents – aimed at reducing myelosuppression and extra-haematological toxicity, at the same time allowing a successful mobilisation of fully functional $CD34^+$ cells, deserve attention. Brentuximab vedotin (BV) and anti-programmed cell death 1 (PD1, also termed PDCD1) antibodies are among the agents that warrant investigation in this regard.

Chemo-only regimens

Platinum-based and ifosfamide-containing regimens represent the standard schedules for patients who relapse or who do not show a response to first-line treatment. The ICE (ifosfamide, carboplatin, etoposide), DHAP (dexamethasone, cytarabine, cisplatin), IGeV (ifosfamide, gemcitabine, vinorelbine) and GDP (gemcitabine, dexamethasone, cisplatin) regimens are among the most widely used combinations (Table I).The choice of the salvage treatment largely depends on the experience of centres and treating physicians. All these regimens are able to induce a significant proportion of responses, as overall response rates (ORR) range between 70% to almost 90%, but complete response (CR) rates are much more variable, varying roughly between 20% and 75% (Moskowitz *et al*, 2001; Josting *et al*, 2002b; Baetz *et al*, 2003; Proctor *et al*, 2003; Bartlett *et al*, 2007; Santoro *et al*, 2007; Labrador *et al*, 2014). Of note, all these regimens yield significant myelosuppression, and an adequate supportive treatment (packed red cell or platelet transfusions, filgrastim prophylaxis) should always be planned. Moreover, standard treatments may also impair the ability to successfully mobilise and harvest peripheral blood stem cells (PBSC) required for ASCT.

Recently, the combination of bendamustine, gemcitabine and vinorelbine (BeGeV regimen) has been successfully tested in 59 patients with relapsed or refractory HL (46% with primary refractory disease and 37% with a CR lasting less than 1 year) in a phase 2 trial (Santoro *et al*, 2016). After 4 cycles of treatment, 43 patients (73%) achieved a CR and 6 patients (10%) a partial response (PR), with grade 3–4 thrombocytopenia and neutropenia experienced in 13·5% of patients each, thus enabling safe outpatient administration. Importantly, PBSC mobilisation and harvest could be accomplished in 96% of patients, and 88% of the responding patients proceeded to ASCT.

Single-agent brentuximab vedotin

BV was used as a single-agent for first salvage treatment in two published studies. In a trial from the Memorial Sloan Kettering Cancer Center (Moskowitz *et al*, 2015a), 45 patients with relapsed or refractory HL, 56% of whom were refractory to front-line therapy and 27% relapsed within 1 year of initial treatment, received BV at the dose of 1·2 mg/kg for 2 cycles on days 1, 8 and 15, then were reassessed by PET scan. Twelve patients (27%) achieved a PET-negative scan (defined as a Deauville score of 1–2) after this short BV trial and were considered eligible for stem cell mobilisation (with filgrastim alone or plus plerixafor) and immediate ASCT. Conversely, those displaying a Deauville score $\geq$3 (32 patients) received 2 cycles of augmented ifosfamide, carboplatin and etoposide (augICE) and underwent stem cell mobilisation: in this case, 22 patients (69%) converted their PET-positive status into a negative one, thus being able to proceed to transplantation. Overall survival (OS) at 2 years was 95% and event-free survival (EFS) was 80% for the entire population. Importantly, EFS for patients who were PET-negative after BV was 92% at 2 years, overlapping with the EFS of those who also received augICE (91%). A second study was a joint collaboration between City of Hope and Weill Cornell (Chen *et al*, 2015a), and involved 37 patients (65% were primary refractory to first-line therapy). All of the patients received BV at the dose of 1·8 mg/kg for up to 4 cycles; patients in CR or PR were allowed to mobilise PBSC and to proceed to ASCT, although PR patients could also receive an additional combination chemotherapy before ASCT. Sixty-eight percent of patients responded to BV, regardless of their stage at presentation (ORR was 68% for stage I/II patients and 67% for stage III/IV patients, respectively); 13 patients (35%) achieved a CR and proceeded to ASCT along with 4 PR patients; the remaining 8 PR patients (plus 9 patients with stable disease and 1 with progressive disease) received additional salvage chemotherapy (either ICE, IGeV or gemcitabine-based schemes). Overall, 32 patients received ASCT (75% in CR either with BV only or after BV + chemotherapy), without

Table I. Reported experiences with standard chemotherapy combinations before autologous transplantation.

Reference	Regimen	Patients (*n*)	Prior lines (*n*)	ORR (%)	CR (%)	Toxicity	Survival
Moskowitz *et al* (2001)	ICE	65	1–6	88	26	No toxic deaths. No haematological toxicity assessed.	82% EFS at 43 months for patients in CR.
Josting *et al* (2002b)	DHAP	102	1	89	21	No toxic deaths. Leucopenia (grade 4 in 43% of cycles) and thrombocytopenia (grade 4 in 48% of cycles).	NR
Labrador *et al* (2014)	ESHAP	82	1	67	50	No toxic deaths. Thrombocytopenia (grade 3–4, 24%), anaemia (grade 3–4, 18%), neutropenia (grade 4, 10%), febrile neutropenia (7%), liver toxicity (grade 3–4, 4%), gastrointestinal toxicity (grade 3–4, 3%), mucositis (grade 3–4, 3%).	52% PFS at 87 months.
Bartlett *et al* (2007)	GVD	88	1–3+	70	19	One toxic death (ARDS). Neutropenia (grade 4, 51%), anaemia (grade 3–4, 35%), thrombocytopenia (grade 3–4, 24%), mucositis (11%), febrile neutropenia (5%).	52% EFS at 4 years (for patients receiving autologous transplantation).
Baetz *et al* (2003)	GDP	23	1	70	17	No toxic deaths. Thrombocytopenia (grade 3, 13%), neutropenia (grade 3, 9%).	NR
Proctor *et al* (2003)	IVE	51	1–2	84	61	No toxic deaths. Haematological toxicity reported in all patients (grade 4). Infections (grade 3 in 10% of cycles).	26/51 patients in continuous complete response at 2 years.
Santoro *et al* (2007)	IGeV	91	1–4	81	54	No toxic deaths. Neutropenia (grade 3–4, 28%), thrombocytopenia (grade 3–4, 20%), anaemia (grade 3–4, 18%), nausea (grade 3–4, 3%), mucositis (grade 3–4, 2%).	53% failure-free survival at 3 years for all patients.
Santoro *et al* (2016)	BeGeV	59	1	83	73	Neutropenia (grade 3–4, 14%), thrombocytopenia (grade 3–4, 14%), febrile neutropenia (12%), nausea (grade 3–4, 7%), anaemia (grade 3–4, 3%), infections (grade 3–4, 3%).	62% PFS at 2 years for all patients; 81% PFS at 2 years for transplanted patients.

ARDS, acute respiratory distress syndrome; BeGeV, bendamustine, gemcitabine, vinorelbine; CR, complete response; DHAP, dexamethasone, high-dose cytarabine, cisplatin; EFS, event-free survival; ESHAP, etoposide, high-dose cytarabine, cisplatin, methylprednisolone; GDP, gemcitabine, dexamethasone, cisplatin; GVD, gemcitabine, vinorelbine, doxorubicin; ICE, ifosfamide, carboplatin, etoposide; IGeV, ifosfamide, gemcitabine, vinorelbine; IVE, ifosfamide, etoposide, epirubicin; NR, not reported; ORR, overall response rate; PFS, progression-free survival.

stem cell mobilisation failures (filgrastim alone or cyclophosphamide + filgrastim). The median cell dose collected was $6{\cdot}0 \times 10^6$ $CD34^+$/kg and the median number of days required for collection was 2.

Taken together, these experiences indicate that: (i) a proportion of patients may achieve PET-negative status with a short course of BV treatment, possibly avoiding myelotoxic chemotherapy; (ii) patients who do not attain a CR may be easily salvaged by conventional chemotherapy; (iii) long-term outcomes do not significantly differ between patients obtaining a CR with BV only and those who achieve a CR after further chemotherapy, thus confirming that a negative PET-scan before transplantation is the most reliable predictor of success; (iv) BV is an effective and safe agent for first-salvage treatment, without impairing autologous stem cell mobilisation.

Brentuximab vedotin-containing regimens

Given its activity in the salvage setting both as a single-agent and when applied sequentially with a standard chemotherapy, BV has been evaluated in combination with the ICE, DHAP and ESHAP (etoposide, prednisolone, cytarabine, cisplastin) regimens (Table II). Cassaday *et al* (2016) reported the initial data of a phase 1/2 trial combining BV with ICE in 16 patients with relapsed and refractory HL, with a median age of 32 years. BV was administered on days 1 and 8, along with ICE (etoposide on days 1–3; carboplatin and ifosfamide on day 2); BV starting dose was 1·2 mg/kg, to be escalated to 1·5 mg/kg or de-escalated to 1·2 mg/kg on day 1 only, depending on dose-limiting toxicity with ICE. Two 21-day cycles of BV-ICE were administered, with filgrastim support. Grade 3–4 neutropenia, lymphopenia and anaemia were seen in 12% of patients each; 6% of patients experienced grade 3 neuropathy. The dose of 1·5 mg/kg (days 1 and 8) was established as the maximum tolerated dose. The ORR was 94%, with a CR in 88% and 69% of cases (investigator-assessed and independent review, respectively). Fifteen patients (94% of cases) were able to mobilise PBSC (Cassaday *et al*, 2016). Garcia-Sanz *et al* (2016) conducted a phase 2 trial in which BV (1·8 mg/m^2 on day 1) was combined with ESHAP (BRESHAP) in 66 patients with primary refractory (61%) and relapsed (39%) HL, with a median age of 36 years. Pre-transplant ORR was 93%, with 71% and 22% CR and PR, respectively. At 3 years since initiation, FFS and PFS rates are 75% and 71%, respectively, with an OS rate of 91% at 1 year. Neutropenic fever, hypomagnesaemia and gastroenteric alterations were the most relevant severe adverse events; pneumonia, abdominal sepsis and pulmonary embolism were 3 severe adverse events terminating with death. Sixty-four (97%) patients were able to mobilise and collect $>2{\cdot}0 \times 10^6$ $CD34^+$/kg with subcutaneous filgrastim, and could proceed to ASCT in 61 instances (Garcia-Sanz *et al*, 2016). Another study applied BV-DHAP in HL patients refractory to first-line chemotherapy or at first relapse

Table II. Reported experiences with single agent brentuximab vedotin or brentuximab-containing regimens as pre-autologous stem cell transplantation salvage schedules.

Reference	Regimen	Patients (*n*)	Rel/Ref (*n*)	ORR (%)	CR (%)	PBSC ($\times 10^6$ $CD34^+$/kg)	ASCT (%)	PFS
Moskowitz *et al* (2015a)	BV	45	20/25	NR	27	6·2	95	80% at 2 years[†]
	BV + augICE	33*		NR	67			
Chen *et al* (2015a)	BV	37	13/24	68	35	6·0	89	NA
	BV + chemo	18*		83	61			
LaCasce *et al* (2018)	Benda-BV	55	27/28	93	74	4·2	74	70 at 2 years[‡] 63 at 2 years[§]
Cassaday *et al* (2016)	BV-ICE	16	5/11	94	69	11	75	NA
Garcia-Sanz *et al* (2016)	BRESHAP	66	26/40	93	71	5·8	92	71 at 3 years
Hagenbeek *et al* (2016)	BV-DHAP	12	10/2	100	100	5·3	100	NA
Herrera *et al* (2018)	Nivolumab-BV	62	34/28	82	61	4·7	46	NA

(aug)ICE, (augmented-dose) ifosfamide, carboplatin, etoposide; ASCT, proportion of patients receiving autologous transplantation; Benda, bendamustine; BRESHAP, BV, etoposide, high-dose cytarabine, cisplatin, methylprednisolone; BV, brentuximab vedotin; CR, complete response rate; DHAP, dexamethasone, high-dose cytarabine, cisplatin; NA, not assessed; NR, not reported; ORR, overall response rate; PBSC, harvested peripheral blood stem cells; PFS, progression-free survival; Rel/Ref, relapsed/refractory patients.

*Patients who proceeded to chemotherapy (ICE or others) after a suboptimal response to BV (see text for details).

[†]Event-free survival.

[‡]For patients receiving ASCT.

[§]For patients not receiving ASCT.

(Hagenbeek *et al* (2016). BV was given at the standard dose of 1·8 mg/kg on day 1, and the dose of cisplatin and cytarabine was modulated according to 3 dose levels in a classic 3 + 3 design. Twelve patients were enrolled, 2 with primary refractory disease, with a median age of 30·5 years. Grade 3–4 adverse events were observed in 7 patients (neutropenia and/or thrombocytopenia in 3 cases; thromboembolism, elevated transaminases, hypokalaemia and leucocytosis in 1 case each). No grade 3–4 peripheral neuropathy was documented. A CR was obtained in all patients, with a negative PET scan in 11 cases (1 PET positive patient showed no disease upon mediastinal biopsy). All patients mobilised and harvested PBSC (median yield of $5{\cdot}3 \times 10^6$ $CD34^+$/kg) and proceeded to subsequent ASCT (Hagenbeek *et al*, 2016).

Taken together, these trials indicate that BV may be favourably combined with conventional chemotherapy, producing significant CR rates without altering PBSC mobilisation or imparting significant toxicity.

Bendamustine-brentuximab vedotin

Bendamustine has clinical activity in patients with multitreated HL (Nieto *et al*, 2013) and may also overcome resistance to previous BV (Zinzani *et al*, 2015). Both BV and bendamustine are administered on an outpatient basis, they display no significant haematological adverse events and do not show an overlapping toxicity profile. Consequently, it appears that the two agents can be favourably combined in order to exploit a synergistic effect, with the purpose of improving the remission rates observed with either single agent in a pre-ASCT setting. O'Connor *et al* (2018) first tested the combination of both drugs in multiply relapsed HL patients: given the safety data obtained, with no more than 18% of the 65 patients treated reporting a grade 3–4 adverse event, they concluded that the combined regimen was not more toxic than the single agents alone. Moreover, they observed an ORR of 71%, which included 32% CR and 38% PR.

LaCasce *et al* (2018) combined the same two agents in a first-salvage regiment for patients with relapsed or refractory HL following induction. A total of 55 patients were recruited, with 53 deemed eligible for efficacy evaluation. Following an initial dose-finding phase 1, it was established that the recommended phase 2 doses for BV and bendamustine should be 1·8 mg/kg and 90 mg/m^2, respectively. The combination therapy consisted of 2–6 cycles every 21 days, with BV given on day 1 and bendamustine on days 1–2. Patients were allowed to go off-study to undergo ASCT at any time after cycle 2. Optionally, patients not receiving ASCT (or still meeting inclusion criteria after ASCT) could receive BV monotherapy, up to a maximum of 16 cycles (including those received in combination with bendamustine). A CR was observed in 73·6% of patients, with an ORR of 92·5%, including 85·7% among those with primary refractory disease and 100% in relapsed patients. Forty patients underwent ASCT after a median of 2 cycles of combination therapy; 34 of them were in CR at the time of transplantation. Thirty-nine patients underwent successful PBSC collection at the first attempt, either with filgrastim alone or after cyclophosphamide priming and plerixafor, with a median yield of $4{\cdot}2 \times 10^6$ $CD34^+$/kg. Estimated 2-year OS of 94·9% and PFS of 69·8% for those who received ASCT *versus* 94·2% and 62·6%, respectively, for those who did not receive ASCT were documented. Importantly, infusion-related reactions (IRR) occurred in 56·4% of patients as a consequence of the combination therapy: a mandatory premedication with steroids and antihistamines was introduced, which decreased the severity of the IRR, although not appreciably reducing their incidence.

Brentuximab vedotin and anti-PD1 agents

Given the efficacy of both BV and anti-PD1 agents in HL, their combination in a chemotherapy-free schedule for first-salvage treatment is sound, as these agents exploit complementary mechanisms of action on Reed-Sternberg cells. Moreover, anti-PD1 agents may enhance the response rates of pre-ASCT single-agent BV, as documented in earlier trials (Chen *et al*, 2015a; Moskowitz *et al*, 2015a). Herrera *et al* (2018) conducted a phase 1/2 trial of BV in combination with nivolumab (Nivo-BV) in patients with relapsed and refractory HL failing induction therapy. BV was delivered at the standard dose of 1·8 mg/kg on day 1 and nivolumab was given at the dose of 3·0 mg/kg (on day 8 on cycle 1, then on day 1); each cycle was repeated every 21 days, for up to 4 cycles. Sixty-two patients were enrolled, with a median age of 36 years, and 58 completed the scheduled 4 cycles. Primary refractory disease was documented in 45% of patients, and 31% had a disease relapse within 1 year. The ORR was 82% and the CR rate was 61%, higher than those observed with BV or nivolumab alone (Younes *et al*, 2012; Armand *et al*, 2018), and quite close to what was documented with sequential BV and chemotherapy (Moskowitz *et al*, 2015a; Cassaday *et al*, 2016; Garcia-Sanz *et al*, 2016; Hagenbeek *et al*, 2016).Stem cell mobilisation was possible in 44 patients within 9 days, with a median yield of $4{\cdot}7 \times 10^6$ $CD34^+$/kg. Importantly, this schedule was delivered on an outpatient basis, and the most relevant adverse events were nausea, fatigue and IRR. In particular, IRR were seen in 44% of cases, although being grade 1–2 in most of instances, and lead investigators to amend the protocol to institute mandatory premedication with steroids and antihistamines, nonetheless only minimally affecting the IRR rate. Another trial is taking into account the combination of BV with nivolumab or other immune checkpoint inhibitors (such as ipilimumab) (Diefenbach *et al*, 2017), confirming the synergistic approach of the combined treatment: nevertheless, this is not specifically designed for first-salvage purposes, as it also enrols patients failing more than one previous treatment.

Autologous stem cell transplantation

The conditioning regimen is the mainstay of treatment intensification, as it delivers highly cytotoxic myeloablative chemotherapy to residual lymphoma cells. The toxic effects on the bone marrow are mitigated by the infusion of previously collected PBSC, which restore a completely functional haemopoiesis within a few weeks. Strategies to improve ASCT outcomes – particularly for those patients presenting with high-risk factors, such as primary induction failure, initial response duration <3 months, relapse within 12 months since induction, extranodal disease, B-symptoms or advanced disease at relapse, resistance to salvage chemotherapy and persistent disease at the time of ASCT (Brice *et al*, 1996; Sureda *et al*, 2005) – rely on: (i) working on the conditioning regimen; (ii) boosting the response with a double autologous transplantation; (iii) refining prognosis with post-ASCT consolidation.

Working on conditioning

BEAM (carmustine, etoposide, cytarabine, melphalan) is regarded as the most widely applied regimen in patients with HL, at least in Europe and the United States, along with CBV (cyclophosphamide, carmustine, etoposide), busulfan and cyclophosphamide (BuCy) and total-body irradiation (TBI)-based regimens. A recently-conducted retrospective overview, which involved 1012 HL patients, analysed the impact of several conditioning regimens on outcomes, and showed that HL patients treated with BEAM displayed better OS and PFS rates than those who received a non-BEAM conditioning (Chen *et al*, 2015b). The same conclusion could not be drawn unequivocally for patients affected by non-Hodgkin lymphomas, thus suggesting that the impact of a certain conditioning regimen in terms of post-transplant survival could be different depending on histology. Similar findings by other institutions further support this evidence (William *et al*, 2013; Pasquini *et al*, 2014).

One group has developed the GemBuMel regimen (gemcitabine, busulfan, melphalan), which exploits the synergism of these drugs through DNA damage repair inhibition (Nieto *et al*, 2012 and Nieto *et al*, 2013). They have demonstrated its activity in patients with refractory and poor-risk HL, with possible superior outcomes when compared to BEAM (2-year PFS of 65% vs. 51% and 2-year OS of 89% vs. 73%, respectively), although tested in a non-randomised fashion against a concurrently treated and prognostic comparable cohort of BEAM-treated patients (Nieto *et al*, 2018).

Double ASCT

A tandem ASCT was adopted in the Lymphoma Study Association (LySA)-H96 trial for HL patients presenting with poor-risk recurrent disease (primary refractory disease or at least 2 risk factors among: relapse ≤12 months, stage III/IV at relapse, relapse in a previously irradiated site); patients with standard-risk HL (only one risk factor at relapse), instead, received a single ASCT (Morschhauser *et al*, 2008). At a median follow-up of 10·3 years, the 10-year freedom from second failure and OS were 64% and 70% for the intermediate-risk group and 41% and 47% for the high-risk group, which indicated a possible benefit of a double ASCT in overcoming the adverse prognostic impact of poor-risk factors at relapse, thus justifying this risk-adapted transplantation strategy (Sibon *et al*, 2016). The double ASCT policy did not seem to increase the risk of secondary malignancies or therapy-related cardiovascular events.

Similarly, the South West Oncology Group S0410 trial included high-risk HL patients with disease recurrence and treated them according to a double ASCT programme (Smith *et al*, 2018). Among 92 eligible patients, 89 started the treatment, but 82 received both ASCTs. The first ASCT was conditioned with melphalan, whereas the second was conditioned with TBI or carmustine, in either case combined with cyclophosphamide and etoposide. With a median follow-up of 6·2 years, the 2-year and 5-year PFS were 63% and 55%, and the 2-year and 5-year OS were 91% and 84%, respectively. For both survival figures, there were no significant differences for patients with either resistant or sensitive disease.

Although in both cases the double ASCT policy seemed to benefit patients with poor-risk disease, these trials lacked a PET-based response assessment (as it was not part of disease evaluation at the time of trial design), which may refine the real need for a second ASCT.

Consolidation after ASCT

Post-ASCT consolidation is intended as the delivery of an effective anti-lymphoma drug immediately after ASCT, when its therapeutic effect might be greater, in patients who bear adverse prognostic factors at transplantation or, in other terms, display high-risk disease (Brice *et al*, 1996; Sureda *et al*, 2005). The most challenging aspect of this procedure is the difficulty in administering many agents in this phase, as patients may have not achieved a complete haematological recovery or do not tolerate drugs because of cumulative toxic effects.

One study demonstrated how early consolidation with BV after ASCT improved PFS in patients with HL bearing one or more risk factors for relapse or progression after transplantation, namely primary refractory disease (i.e. failure to achieve a CR with induction therapy), relapsed disease with a duration of initial remission ≤12 months or extranodal disease manifestations at the moment of pre-transplantation salvage therapy (Moskowitz *et al*, 2015b). BV was considered a suitable agent for a pre-emptive therapy immediately after ASCT given the lower frequency of haematological toxic effects related to its administration and the effective

mechanism of action in HL patients. Investigators blindly randomised 329 patients either to BV (1·8 mg/kg) or placebo, to be given every 3 weeks for up to 16 cycles, provided they achieved at least a stable disease after pre-ASCT salvage chemotherapy. In case of disease progression, treatment assignment could be revealed and patients had the opportunity of switching to BV if receiving placebo. The primary endpoint of PFS was significantly improved in the BV arm, which displayed a 2-year PFS of 63% compared to 51% observed in the placebo group (hazard ratio 0·57, $P = 0·0013$). Importantly, this difference was consistent when all the high-risk factors were taken into account. No differences in OS were reported for the two groups, given that 85% of the patients in the placebo group received BV outside the study. This means that a survival benefit related to BV administration was evident also in patients who received this drug after an initial progression and not immediately after ASCT. Peripheral sensory neuropathy was the most common treatment-emergent adverse event, which involved 67% of patients in the BV arm and 19% in the placebo group. These data granted BV the approval for the post-ASCT consolidation of HL patients with increased risk of relapse or progression.

ASCT as early salvage treatment

ASCT, preceded by second-line chemotherapy, may be conceived as a salvage strategy for patients whose poor prognosis is determined by a persistently positive *interim* PET (PET2) during induction treatment (i.e. after 2 cycles): it is well known, that PET2 results after the initial cycles of chemotherapy have indeed a strong predictive value on long-term outcomes (Gallamini *et al*, 2007).

In light of this observation, a phase 2 study conducted by the Italian Lymphoma Foundation included patients with advanced-stage HL still displaying PET positivity after 2 cycles of induction with adriamycin, bleomycin, vinblastine and dacarbazine (ABVD), who were offered an IGeV chemotherapy salvage treatment followed by high-dose therapy and ASCT (Zinzani *et al*, 2016). Although not all patients with persistent PET2 positivity proceeded to ASCT (adherence to protocol was 79%, mainly because of minimally positive PET2 cases, i.e. Deauville 3), the 2-year PFS survival of those who actually received ASCT was comparable with the PFS of PET2-negative patients, who completed all 6 ABVD cycles without any ASCT (74% and 81%, respectively). More precisely, the results were the same if PET2 Deauville 4 and 5 patients were analysed separately. Such a policy may timely address high-risk patients, as demonstrated by a lack of response to the initial induction cycles, to ASCT intensification, thus reducing resistance to induction regimen and unnecessary toxic effects related to standard ABVD. Nevertheless, the major disadvantage is the possible overtreatment of patients with minimally positive PET2 (e.g. Deauville 3), who may benefit from ABVD continuation.

Allogeneic stem cell transplantation

AlloSCT is reserved for HL patients who relapse or do not adequately respond to ASCT. As with ASCT, disease status at transplantation or, in other terms, disease chemosensitivity, plays the most important role in terms of relapse rates and survival functions. Historical experiences with myeloablative conditioning (MAC) in patients with HL showed high mortality rates, with survival outcomes at 3 years roughly reaching 20% as a consequence of both disease relapse and unacceptably high (30–50%) non-relapse mortality (NRM), mostly related to infections (Gajevski *et al*, 1996). Reduced-intensity conditioning (RIC) regimens accounted for a significant reduction in NRM. In a retrospective review involving 168 HL patients undergoing either MAC or RIC, Sureda *et al* (2008) demonstrated a higher transplant-related mortality in those receiving MAC (46% vs. 23% for those receiving a RIC, at 1 year), which translated into a statistically significant lower OS (22% vs. 28%, $P = 0·003$), given that MAC and presence of refractory disease were both detrimental for survival. Disease relapse still remains the major concern with RIC, as 57% of patients in the RIC group displayed relapse versus 30% in the MAC group. The development of a chronic graft-versus-host disease (GVHD) was correlated with a decreased incidence of relapse and, consequently, to a trend for better PFS (Sureda *et al*, 2008). Similar outcomes with RIC have been confirmed in independent clinical trials and registry studies (Robinson *et al*, 2009; Sureda *et al*, 2012). With the use of more advanced transplantation practices [e.g. advances in human leucocyte antigen (HLA) typing, better selection of donors and transplant candidates, better supportive measures and highly-trained clinical teams], differences in NRM between MAC and RIC groups have decreased strikingly. In a more recent population, more representative of current clinical practices, MAC-treated patients displayed comparable survival functions with RIC-treated patients (who were, in general, older and more treated), with NRM rates comparable for both groups (Chen *et al*, 2016). This data, although retrospective and insufficient to completely determine the best conditioning regimen to be used, suggest that the intensity of conditioning still matters in HL patients, and that it should be finely tuned depending on the patient and on the desired graft-versus-lymphoma effect, whose existence is confirmed (Peggs *et al*, 2011), although it seems of limited clinical efficacy.

Haploidentical alloSCT with post-transplant cyclophosphamide (PT-Cy) is now regarded as a standard procedure in multi-treated HL patients, as it reduces the incidence of GVHD, is able to prevent graft rejection and does not ablate the graft-versus-lymphoma effect. This procedure has yielded low NRM rates (4–20%) and 3-year OS rates of 63%, with relapse rates ranging from 21% to 31% (Raiola *et al*, 2014; Castagna *et al*, 2017). Pellegrini *et al* (2017)

reported their experience with 98 haploidentical alloSCT patients with PT-Cy and compared their outcomes with 338 patients receiving matched-related donor (HLA-matched sibling, SIB) alloSCT and 273 patients receiving matched-unrelated donor (MUD) alloSCT, receiving standard GVHD prophylaxis with calcineurin inhibitors/methotrexate. The incidence of GVHD was lower in the haploidentical group (26%) compared with MUD (41%), with comparable 2-year OS (67%, 71% and 62% for haploidentical, SIB and MUD, respectively) and PFS (43%, 38% and 45% for haploidentical, SIB and MUD, respectively). Based on these data, alloSCT using a haploidentical donor and PT-Cy should be considered as feasible as using an HLA-matched donor; moreover, it emerges as a good option when no conventional donor is available.

At present, BV and anti-PD1 agents used before alloSCT are able to induce deeper clinical response after ASCT (Younes *et al*, 2012; Chen *et al*, 2017; Armand *et al*, 2018), thus allowing a larger proportion of patients to be transplanted in CR or, at least, with chemosensitive disease. In this sense, newer agents may permit better transplant outcomes. Nonetheless, given the efficacy of these drugs, the timing of alloSCT is nowadays an important issue to be solved, as it tends to be progressively postponed as newer agents become available. It is demonstrated, in fact, that some (selected?) patients may enjoy significantly long disease-free periods using BV or anti-PD1 agents without the need of any alloSCT (Chen *et al*, 2016; Martinez *et al*, 2017).

Tandem ASCT-alloSCT

This procedure exploits the combination of a high-dose cytoreduction and an immune aggression on lymphoma cells as a consequence of a graft-versus-lymphoma effect. This seems sound for the treatment of high-risk patients (as defined above), especially those for whom ASCT by itself yields unsatisfactory results.

Data in this regard are indeed rather scarce. Carella *et al* (2000) reported their experience in 15 patients with resistant lymphoma (10 with high-risk HL and 5 with non-Hodgkin lymphoma): they stated that a CR could be obtained in those who only achieved a PR after ASCT, and that a relevant proportion of continuous CR (33%) was attained at the end of the procedure. Importantly, acute GVHD was observed in 47% of patients and extensive chronic GVHD in 13% of cases (Carella *et al*, 2000). More recently, a LySA study reported the results on 73 patients with high-risk HL who received a double transplant procedure: this was a tandem ASCT-alloSCT in 37% of cases (44 patients) and a double ASCT in 24% of cases (29 patients). Thirteen (30%) deaths occurred in the ASCT-alloSCT cohort, with a NRM rate of 14% (6 patients), including GVHD in 2 cases. A median PFS of 54 months was obtained in the ASCT-alloSCT group, while it was not reached in the ASCT-ASCT one, although this difference was not statistically significant. A high occurrence of early disease progression between the first ASCT procedure and the subsequent one was the major concern of this study (Deau *et al*, 2018).

Given that a significant death rate has been observed following this highly intensive approach, tandem ASCT-alloSCT should be used with caution and probably only in selected cases. Importantly, its effectiveness and feasibility are clearly challenged by the use of BV applied as a consolidation after ASCT (Moskowitz *et al*, 2015b).

Indications to alloSCT in the era of new drugs

At present, it is highly unlikely that a patient with HL who relapses after ASCT and requires alloSCT is BV-naïve, as the main indication of this agent is the immediate post-ASCT salvage treatment. Given its high efficacy, BV is now considered a suitable drug to "bridge" patients to alloSCT. Chen *et al* (2014) showed that BV-treated patients had better 2-year PFS compared to a matched group of HL patients who were re-induced with standard chemotherapy (mainly gemcitabine-based) before RIC-alloSCT (59·3% vs. 26·1%), and also displayed a reduced cumulative incidence of relapse or progression (23·8% vs. 56·5%). This was mainly due to a better disease control prior to alloSCT obtained with BV, which allowed a pre-transplant ORR of 71% against 43% obtained with conventional treatment (Chen *et al*, 2014). Long-term survival data of the pivotal phase 2 study of BV in relapsed and refractory HL (Chen *et al*, 2016) clearly show, however, that 38% of complete responders may maintain a sustained response over time, sometimes without any alloSCT consolidation or further anticancer treatment. This may indicate that some patients, albeit with multiply relapsed disease, may be considered cured without transplant consolidation.

For this reason, some authors suggest that it may be reasonable to delay an alloSCT to the time when disease progression is documented (while receiving BV or after treatment with BV), provided a salvage treatment with an anti-PD1 agent is available (Chen *et al*, 2017; Armand *et al*, 2018). On the contrary, patients who are in CR after 3–4 cycles of BV may continue their treatment up to 16 cycles and, if still in CR, they can only be monitored.

Anti-PD1 agents can, in this sense, be considered the most suitable drugs to "bridge" patients to alloSCT. However, the correct timing for an alloSCT in patients receiving anti-PD1 agents is not yet clearly determined. Should alloSCT be performed (i) only in patients achieving a CR? (ii) in all patients with at least stable disease? (iii) only in patients progressing while on anti-PD1 agents, provided an alternative regimen or a clinical trial is available before transplantation?

Importantly, the efficacy and the safety of alloSCT can be altered in patients receiving anti-PD1 agents, as a consequence of their immunomodulatory effect and their prolonged clinical activity. More precisely, residual PD1 inhibition may enhance allogeneic T-cell response, which in

turn translates into both an augmented graft-versus-lymphoma effect and an enhanced incidence of GVHD, along with other immune-mediated complications. Merryman *et al* (2017) described the post-alloSCT effects of anti-PD1 antibodies (nivolumab in 72% of cases, pembrolizumab in 28%) in patients with lymphoma (79% of the cases were HL). They observed a 1-year cumulative incidence of grade 2–4 and 3–4 acute GVHD of 44% and 23%, respectively, and an incidence of chronic GVHD of 41%. Four patients died because of acute GVHD (3 cases) and hepatic sinusoidal obstruction syndrome; in addition, 7 patients developed a non-infectious febrile syndrome after alloSCT, which only responded to high-dose corticosteroids (Merryman *et al*, 2017).

Taken together, these data suggest that: (i) BV is a suitable post-ASCT treatment to "bridge" patients to alloSCT, as it is able to establish higher CR rates than conventional chemotherapy; (ii) some patients receiving 16 cycles of BV can maintain a sustained CR, without any alloSCT consolidation, thus putatively being considered cured; (iii) anti-PD1 agents are used as further salvage treatment in order to induce a response before alloSCT in patients who have failed BV; (iv) the immunomodulatory properties of anti-PD1 agents may increase the risk of alloSCT immune-mediated complications, above all acute and chronic GVHD.

Conclusions

ASCT is the salvage strategy of choice for young and fit HL patients who progress or relapse after induction, as it is able to rescue roughly 50% of cases. Disease status at ASCT is regarded as the most relevant prognostic factor, as patients transplanted in CR are more likely to attain better outcomes. At present, efforts are underway to improve pre-ASCT salvage regimens, possibly incorporating new agents active in HL within chemotherapy-free regimens, in order to increase CR rates. Post-ASCT BV consolidation also provides survival benefit in patients with poor prognostic factors before transplantation who are at risk of relapse or progression. AlloSCT still maintains its curative role in patients who progress after ASCT, and haploidentical transplantation with PT-Cy seems to be a valid alternative in those who do not have a conventional donor. Nevertheless, the optimal timing of alloSCT is not clearly determined in the era of new drugs, as some patients may potentially be cured with post-ASCT salvage BV only, without needing alloSCT. Whether anti-PD1 agents represent a suitable and safe tool for disease control before alloSCT remains to be assessed.

Author contribution

AB and PLZ reviewed the literature and wrote the paper.

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