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REVIEW

Salvage Therapy for Hodgkin's Lymphoma: A Review of Current Regimens and Outcomes

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Abstract: Relapse/refractory Hodgkin lymphoma patients are still a clinical concern. Indeed, despite more effective first-line chemotherapy regimens and better stratification of unresponsive patients by clinical factors and use of early PET, roughly one-third of such patients need salvage chemotherapy and consolidation with high-dose chemotherapy. In this paper, the authors review the different salvage treatments, with special emphasis on newer combinations with brentuximab vedotin or check point inhibitors. The overall response rate is constantly increasing, with a complete remission rate approaching 80%. Functional response evaluation by PET imaging is a strong predictive factor of longer survival, and more sophisticated tools, such as detection of circulating tumour DNA, are emerging to refine the disease-status assessment after treatment. Consolidation by high-dose chemotherapy is still considered the standard of care in chemosensitive patients, leading to a high fraction of patients towards long-term disease control. Maintenance therapy with BV is now approved, reducing disease relapse/progression. An increasing number of Hodgkin lymphoma patients will be cured after first- and second-line therapy, and long-term toxicity needs to be continuously assessed and avoided.

Keywords: Hodgkin lymphoma, refractory/relapsed disease, checkpoint inhibitors, brentuximab vedotin, high-dose chemotherapy

Introduction

The treatment of Hodgkin lymphoma (HL) is considered a paradigm of optimization of therapeutic resources and strategies to maximize responses while minimizing acute and mainly long-term toxicities.

The number of patients not cured by first-line therapy has changed over time due to the improvement of drug combinations employed in first-line treatment, either from the activity and safety profiles. An important point is to define the meaning of relapsed and refractory patients. In this review, patients were defined as refractory (Refr) when they did not show any response or progressed in the first 3 months after the end of first-line chemotherapy (CT); early relapsed (E-Rel) when relapse was diagnosed after 3 months and before 12 months after the end of first-line CT; late relapsed (L-Rel) when relapse occurred after 12 months.

Analysing data from several prospective, randomized studies, we can conclude that 2%-30% of HL patients (all stages together) required salvage chemotherapy (CT) because of a relapsed/refractory (R/R) status after first-line treatment. Two factors had an impact on the rate of R/R in patients: the disease or patient characteristics (early vs late stage, international prognostic score, age) and the intensity of initial treatment (BEACOPP vs ABVD). The prognosis of R/R HL patients varied based on both

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response and duration after first-line therapy. Indeed, in the era before the extensive use of PET to stage and evaluate the response, many papers identified some clinical factors affecting the prognosis of R/R patients, resulting in different clinical scores summarized in Table 1. The prognostic score from the German group (comprising stage IV, E-rel, and anaemia) was also validated in a prospective randomized trial.[1] However, the advent of PET for treatment evaluation of HL patients changed the paradigm (Table 2) because most of the prognostic clinical factors were cancelled out by the PET results. In a seminal paper from MSKCC, Moskowitz et al reported that PET positivity and the presence of extra-nodal disease (END) at the time of relapse were the only prognostic factors affecting the outcome. Three groups of patients were identified as having significantly different 3-y event-free survival (EFS: PET negative without END, PET negative with END, and PET positive.[2] In an international cooperative study, Brockelmann et al analysed more than 1000 patients, identifying 5 clinical risk factors and 4 prognostic groups (0 vs 1 vs 2 vs 3–5) with different survival after salvage treatment. Indeed, stage IV at relapse, bulky disease (>5 cm), time to relapse <3 months, inadequate response to salvage CT (defined as less than partial remission evaluated by CT scan or PET), and performance status >1 were significantly associated to survival after autologous stem cell transplantation.[3]

Table 1 Prognostic Factors Identified in the Pre-PET Era

Author	N	Prognostic Factors	End Points	
Lohri,[73] 1991	71	• B symptoms • Relapse < 12 m • Stage IV dg	5-y FF2F	0= 82% >0= 17%
Reece,[74] 1994	58	• B symptoms • Relapse < 12 m • Extranodal disease	3-y PFS	0= 97% 1= 87% 2= 47% 3=1%
Brice,[75] 1997	214	• Extra-nodal disease • Relapse < 12 m	4-y PFS	0= 93% 1= 59% 2= 43%
Horning,[76] 1997	119	• B symptoms • Stage IV (lung/BM) • > minimal pre-HDC disease	4-y FFP	0= 85% 1= 57% 2= 41% >3= <20%
Josting,[77] 2001	422	• Hb levels (< 10, < 12) • Stage III–IV • Relapse < 12 m	4-y FF2F	0= 100% 1= 70% 2= 55% 3= 50%
Moskowitz,[5] 2001	65	• B symptoms • Extranodal disease • Relapse < 12 m/refractory	EFS at 43 months	0–1= 83% 2= 27% 3= 10%

Abbreviations: FF2F, freedom from second failure; PFS, progression-free survival; FFP, freedom from progression; EFS, event-free survival.

Table 2 Studies Evaluating PET Predictive Significance in HL

Author	N	Study	PET+		PET-	
			OS	PFS	OS	PFS
Spaepen,[78] 2003	60	R	40%	23%	95%	100%
Jabbour,[79] 2007	211	R	58%	23%	87%	69%
Schot,[47] 2007	23	P	/	37–40%	/	73%
Filmont,[48] 2007	60	P	43%	25%	80%	81%
Moskowitz,[49] 2010	153	P	/	31%	/	75%

Notes: In Speapen, survival was reported at 2 y. In Jabbour, survival was reported at 3 y. In Schot, survival was reported at 2 y as failure-free survival. In Filmont, the median follow-up was 1510 days. In Moskowitz, survival was reported at 2 y as event-free survival.
Abbreviations: R, retrospective; P, prospective.

More recently, a review and meta-analysis of studies investigating the role of pre-HDC PET stated that there was moderate evidence that PET was valuable for predicting the outcome.[4]

Even if relapsed and refractory patients are grouped as unique, refractory patients, those progressing during first therapy or relapsing shortly after (<3 months from the end of treatment) represent a homogenous cohort from the prognostic point of view since they historically have a dismal prognosis with conventional treatment strategy, as reported in Table 3.

Salvage Therapies

Conventional Salvage CT

To date, randomized studies have not been conducted to establish the best salvage regimen in R/R HL. In Table 4–6, we summarize the results of different salvage regimens. In Table 4, the main results of platinum-based salvage CT are reported. In all CT schemes but one, cis-platinum (CDDP) was used. Only one regimen included carboplatin instead of CDDP.[5] The total dose of CDDP was 100 mg/m^2 in all but one regimen, which used 75 mg/m^2.[6] Furthermore, in one study, DHAP was administered using a more intensive schedule every 16 days instead of every 21 days.[7] An important point is the number of included patients with refractory HL, consisting of a biologically less sensitive disease with a lower

Table 3 Clinical Results Obtained in Patients Refractory to First-Line CT

Author	N	Disease at HDC	OS	PFS	TRM	Stem cells
Andre,[80] 1999	86	CT S 62%	35% @ 5 y CR= 60% PD= 20%	25% @ 5 y	8%	BM
Sweetenham,[81] 1999	175	NS	36% @ 5 y	32% @ 5 y	14%	BM
Josting,[82] 2000	206	CT S 43%	43% @ 5 y 0= 55% 3= 0%	31% @ 5 y	10%	BM + PBSC
Constans,[83] 2003	62	NS	26% @ 5 y	15% @ 5 y	14%	BM + PBSC
Czyz,[84] 2004	76	NS	33% @ 5 y	NS	9%	BM + PBSC

Notes: In Josting et al risk factors were: PS <90%, age >50 y, and chemosensitive disease (CT S) to first-line CT.
Abbreviations: NS, not stated; BM, bone marrow; PBSC, peripheral blood stem cell.

Table 4 Platinum-Based Salvage CT Reported in the Literature

	Author	Regimen	N	Refractory	CT/PET Evaluation	ORR	CR	OS	PFS
Platinum-based	**Rodriguez,[8] 1999**	ASHAP	56	12%	CT+Gallium	70%	34%	41% @ 4 y	36% @ 4 y
	Aparicio,[85] 1999	ESHAP	22	22%	CT	68%	41%	/	/
	Moskowitz,[5] 2001	ICE	65	34%	CT	88%	26%	83% @ 43 m	68% @ 43 m
	Josting,[7] 2002	DHAP	102	16%	CT	89%	21%	/	/
	Baetz,[6] 2003	GDP	23	9%	CT	69%	17%	/	/
	Josting,[1] 2010	DHAP	279	/	CT	70%	24%	80% @ 3 y	62% @ 3 y
	Labrador,[14] 2014	ESHAP	82	50%	CT	67%	50%	74% @ 5 y	56 months

Note: OS and PFS are reported for patients receiving HDC.
Abbreviations: CT, CT scan; m, months; ASHAP, adriamycin, cytarabine, cisplatin, methylprednisolone; ESHAP, etoposide, cytarabine, cisplatin, methylprednisolone; ICE, ifosfamide, carboplatin, etoposide; DHAP, dexamethasone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin.

Table 5 Gemcitabine-Based Salvage CT

	Author	Regimen	N	Refractory	CT/PET Evaluation	ORR	CR	OS	PFS
Gemcitabine-based	**Bartlett,[9] 2007**	GVD	91	/	CT	70%	19%	70% @ 4 y	52% @ 4 y
	Santoro,[10] 2007	IGEV	91	39%	CT	81%	53%	/	/
	Santoro,[11] 2016	BeGEV	59	46%	PET	83%	73%	77% @ 2 y	62% @ 2 y
	Santoro,[12] 2020	BeGEV	59	46%	PET	83%	73%	78% @ 5 y	59% @ 5 y
	Cohen,[13] 2020	GB	22	/	PET	69%	46%	/	/

Note: In Bartlett et al, 51 patients were transplant naïve.
Abbreviations: IGEV, Ifosfamide, gemcitabine, vinorelbine; GVD, gemcitabine, vinorelbine, pegylated liposomal doxorubicin; BeGEV, Bendamustine, gemcitabine, vinorelbine; GB, gemcitabine, bendamustine.

response rate. Indeed, the included refractory patients ranged from 9% to 41%. Another point is the disease-response evaluation performed by CT scan, which can explain the quite low complete remission (CR) rate, namely, from 17% to 50%. Last, toxicity expressed as toxic death is not a concern with platinum-based regimens.

Table 6 Salvage CT Without Gemcitabine and Platine-Derived Compounds

Author	Regimen	N	Refractory	CT/PET Evaluation	ORR	CR	OS	PFS
Fermé,[86] 1995	MINE	100	41%	CT	73%	34%	71% @ 4 y	60% @ 4 y
Proctor,[87] 2003	IVE	51	/	CT	84%	61%	/	/

Abbreviations: MINE, mitoguazone, ifosfamide, vinorelbine, etoposide; IVE, ifosfamide, etoposide, epirubicin.

The frequency of haematological toxicity varies from 9%[6] to 100%.[8]

In Table 5 and 4 studies reported the outcomes using a gemcitabine-based CT regimen. In Bartlett's study,[9] liposomal doxorubicin was used in combination with gemcitabine and vinorelbine, while in the 2 other studies from the same group, ifosfamide[10] or bendamustine[11,12] were used in combination with the same 2 drugs. The overall response rate (ORR) was similar (from 69% to 83%), but the CR rate was higher with IGEV and BeGEV, even if only 51 patients were transplant-naïve in Bartlett's study. The BeGEV study is unique because PET was used to evaluate the response at the end of treatment, probably explaining the high CR rate (73%). Overall, these regimens are well tolerated, and the toxicity is mostly haematological, with grade 3–4 neutropenia observed in 24–51% and thrombopenia in 14–16% of patients. Gemcitabine (1000 mg/m^2) was used in combination with bendamustine (240 mg/m2 in 2 days) in a prospective Phase I/II study. Twenty-six heavily pretreated (46% relapsed after HDC, 69% after BV, and 15% after checkpoint inhibitors) patients were included, and the ORR and CR rate were 69% and 46%, respectively. Grade 3–4 adverse events comprised lymphopenia, thrombopenia, anaemia, and pneumonia.[13] In Table 6, we report salvage CT not containing gemcitabine or CDDP. The ORR was similar to other regimens as well as the CR rate, evaluated by CT scan. Overall, even if the comparison between all these studies should be taken with caution, the ORR of CDDP-based and gemcitabine-based studies was similar, ranging from 67%[14] to 89%.[7] On the other hand, the difference in terms of the CR rate was more pronounced, ranging from 17%[6] to 73%,[11] but not all studies used PET scans to evaluate the response. The toxicity of all these schemes was good because they were mainly haematological. All CT regimens were able to mobilize stem cells in peripheral blood.

Some CT-based salvage regimens have been used in combination with biological drugs to improve the ORR and the CR rate (Table 7). Anti-CD20 monoclonal antibodies have been used in combination with conventional salvage CT based on the expression of the target antigen on Reed Stenberg cells, on the putative B-lineage of stem cell origin and on the presence of B-cells in the microenvironment. In a prospective Phase 2 study, Martinez et al employed the combination of ofatumumab plus ESHAP in 62 R/R HL patients. One-third of patients had *Refr* disease. Disease evaluation was performed by PET scan. The ORR was 73%, and the CR rate was 44%. Tolerance was good as well as the capability of CD34-positive cell mobilization.[15]

BV Alone and BV-Based Regimens

One of the most relevant steps forward in the R/R HL treatment was the introduction of anti-CD30 monoclonal antibody conjugated to mono-methyl auristatin molecule (brentuximab vedotin, BV). Several studies have been published mostly in the setting of R/R patients (Table 7). BV was first used as a single drug and, more recently, in combination with conventional CT.

As a single drug, the ORR was encouraging, ranging from 60% to 75%, with CR rates of 17%-44%. It should be noted that in all these studies, most patients had relapsed after previous HDC (from 33% to 100%). Overall, the drug was well tolerated, with peripheral neuropathy as a peculiar side effect affecting 42% of patients (8% grade 3) and haematopoietic toxicity (mainly neutropenia 19%) as the second most frequent adverse event.[16] In one study, the activity of BV as a single agent was exclusively evaluated in patients not previously treated by HDC. In this investigation, 37 patients were included, 65% were refractory to first-line CT, and the ORR was 68% (CR rate 35%).[17] Non-responding patients were treated with conventional salvage CT, and overall, 86% proceeded to HDC. In a prospective Phase II study, Moskowitz et al treated 46 patients with BV alone, and the CR rate was 27%. The remaining patients, who were PET positive after BV, were treated with high-dose ICE, and the CR rate was 69%. Overall, 76% of the patients achieved CR.[18]

Table 7 Salvage CT Associating CT and BV and Salvage Therapy with BV Alone

	Author	N	Refr	Rel After HDC	CT/PET Evaluation	ORR	CR	ORR Refr	CR Refr	OS	PFS
BV alone	**Younes,[16] 2012 §Chen[17] 2015**	102	/	100%	PET	75%	34%	/	/	/	/
	Rothe,[88] 2012	45	64%	87%	PET	60%	22%	/	/	/	/
	Zinzani,[89] 2013	65	69%	92%	PET	70%	21%	/	/	/	/
	Gibb,[90] 2013	18	71%	33%	PET	72%	17%	/	/	/	/
	Chen,[17] 2015	37	65%	/	PET	68%	35%	67%	/	/	/
	¤Moskowitz,[18] 2015	47	56%	/	PET	76%	76%	/	/	95% @ 2 y	80% @ 2 y
	^Perrot,[91] 2016	240	56%	59%	CT or PET (78%)	64%	33%	58%	/	/	57% @ 2 y
	Eyre,[32] 2018	99	/	/	CT or PET	53%	29%	/	/	70% @ 2 y	68% @ 2 y
BV-Benda	**LaCasce,[19] 2018**	55	50%	/	PET	92%	73%	85%	64%	67% @ 3 y	60% @ 3 y
	O'Connor,[20] 2018	65	/	63%	PET	71%	32%	/	/	/	/
	Kalac,[21] 2018	10	100%	/	PET	100%	90%	/	/	/	/
	Picardi,[22] 2019	20	55%	25%	PET	100%	100%	/	/	/	/
	Broccoli,[23] 2019	40	50%	/	PET	80%	75%	75%	65%	88% @ 2 y	67% @ 2 y
	Iannitto,[24] 2020	47	51%	25%	PET	79%	49%	/	/	72% @ 2 y	60% @ 2 y
BV-CT	**Michallet,[28] 2015 GVD**	11	45%	/	PET	100%	73%	/	/	60% @ 1 y	/
	Abuelgasim,[25] 2019 IGEV	28	43%	/	PET	96%	71%	/	/	87% @2 y	73% @ 2 y
	Garcia-Sanz,[27] 2019 ESHAP	66	40%	/	PET	91%	70%	/	37%	91% @ 2.5 y	71% @ 2.5 y
	Hagenbeek,[26] 2019 DHAP	12	/	/	PET	92%	92%	/	/	/	/
O-CT	**Martinez,[15] 2016 ESHAP**	62	32%	/	PET	73%	44%	50%	/	88% @ 2 y	46% @ 2 y

Notes: §Long-term follow-up of Younes 2012. ^15% of the patients received allogeneic stem cell transplantation. ¤In this study, after BV alone, the CR rate was 27%. Seventy-three percent of non-responding patients received CT, and 73% obtained CR. Overall, after BV and CT, 76% obtained PET negativity.

Abbreviations: O, ofatumumab; Rel, relapse; Refr, refractory; CT, chemotherapy; IGEV, Ifosfamide, gemcitabine, vinorelbine; GVD, gemcitabine, vinorelbine, pegylated liposomal doxorubicin; DHAP, dexamethasone, cytarabine, cisplatin; ESHAP, etoposide, cytarabine, cisplatin, methylprednisolone.

In combination schemes, BV has been associated mainly with bendamustine (benda).[19–24] In all but one study, the doses of BV and bendamustine were the same (BV 1.8 mg/kg and bendamustine 180 mg/m^2 in 2 days). In a phase I/II trial, different doses of BV (1.2 and 1.8 mg/kg) and benda (70, 80, 90 mg/m^2) were tested, and the definitive dose level was associated with a regular dose of BV and 90 mg/m^2 of benda.[20] In only one study,[22] the dose of bendamustine was higher (240 mg/m^2 in 2 days). The tolerance was acceptable, and G3-4 toxicity consisted of

neutropenia (23%-35%), lung infections (4%-14%) and peripheral neuropathy (2%-11%). With a higher dose of bendamustine, an increased incidence of CMV reactivation (20%) was observed. The ORR, evaluated by PET in all studies, was interesting, ranging from 71% to 100%. This result is of particular value if we consider that a high proportion of the patients were refractory to previous CT lines (from 50% to 100%). The association of BV plus conventional polychemotherapy (poly-CT) was reported in 3 studies. In the first paper,[25] 28 patients (refractory 43%) were treated with BV-IGEV as first or subsequent salvage therapy. Grade 3–4 haematopoietic toxicity (neutropenia) was observed in 96% of patients, and febrile neutropenia was observed in 57%. Peripheral neuropathy was rare (4%). The ORR was 96% (CR rate 70%). The second trial was a Phase I study combining BV with DHAP.[26] Only 12 patients were included, and 3 dose levels of platinum and cytarabine were tested with a fixed dose of BV (1.8 mg/kg), and the full dose levels were considered feasible. The ORR was 92% (CR rate 92%). In the third phase I/II study, BV was used in combination with ESHAP.[27] Here, the authors tested 3 dose levels of BV (0.9, 1.2, and 1.8 mg/kg) with a standard dose of ESHAP. In the phase II part of the study, the BV dose was 1.8 mg/kg. Grade 3–4 haematological toxicity was observed in 50% of patients; febrile neutropenia in 8% and CMV reactivation in 3%. The ORR was 91% (CR rate 70%). Finally, Michallet et al reported on 11 patients treated with the combination of BV plus GVD. The ORR was 100% (CR rate 72%), and the 1-y OS was 60%.[28]

In some studies, the ORR or CR rates were separately reported for *Refr* patients. For the BV-benda association, the differences in terms of ORR and CR rate were not significant between *Refr* and other categories of disease (92% vs 85% and 73% vs 64%, respectively.[19,23,24] On the other hand, in the BV-ESHAP, the CR rate was lower for *Refr* patients than for the others (70% vs 37%, respectively).[25] We do not have an immediate explanation for why disease characteristics (*Refr* vs *Rel*) matter only after BV-polyCT and not after BV-benda, but a potential synergistic effect between benda and BV could be a possible explanation. Furthermore, the disease response criteria differed in the various studies, as follows: Cheson 2007[29] in the LaCasce,[19] O'Connor,[20] and Garcia-Sanz[27] studies; RECIL criteria[30] in the Lannitto[24] study; and Lugano criteria[31] in the Broccoli[23] and Abuelgasim[25] studies. In Moskowitz's study,[18] PET negative was defined as DS 1 and 2.

The efficacy of BV alone was tested in patients not responding to first salvage therapy. The response rate in these poor prognosis patients was low, and the outcome was dismal. In the first study, Eyre et al treated 99 patients in a multicentre retrospective study, and the ORR and CR rate were 56% and 29%, respectively; 61% of patients received a transplant (15% HDC), achieving a much longer overall survival than those not transplanted.[32] Picardi et al treated 20 patients with BV in combination with bendamustine in a small prospective study. The CR rate was 80%, and 70% of patients were consolidated by HDC, reaching a 2-y PFS of 97%.[22] Several years ago, Villa et al treated 19 patients who were chemorefractory to first salvage CT (GDP) by mini-BEAM. The CR rate was 32%, but the 2-y OS and PFS rates were only 20% and 11%, respectively.[33]

Check-Point Inhibitors (CPIs)

The introduction of monoclonal antibodies against check-point molecules such as PD1 in the armamentarium of treatments for poor-prognosis HL has been a major step forward. HL cells are intrinsically susceptible to the inhibition of PD1 because all of them carry out a copy gain of chromosome 9p24.1, leading to overexpression of PD1 ligands (PDL1 and 2) on tumoural cells. The CPI sensitizes Reed Stenberg cells to the immunological attack masking PD1 and blocking the inhibitory effect on T-cells. In Table 8, we report the results published to date, using 2 different CPIs, nivolumab and pembrolizumab, as single agents in advanced HL patients. In the first group, 23 patients[34] relapsing after HDC (78%) or BV

Table 8 Results from Clinical Trials Using CPIs in R/R HL

	N	Study	CPI	ORR	CR Rate
Ansell,[34] 2014	23	P	Nivo	87%	17%
*Younes,[35] 2016	80	P	Nivo	66%	9%
Beköz,[39] 2017	82	R	Nivo	64%	21%
Armand,[36] 2018	243	P	Nivo	69%	16%
Chen,[42] 2019	210	P	Pembro	69%	22%
Manson,[38] 2109	78	R	Nivo	65%	38%
Bair,[37] 2019	53	R	Nivo	68%	45%
Shi,[43] 2019	96	P	Sintilimab	80%	

Notes: *In this study, there was an important difference in terms of ORR and CR rate between investigators and independent reviewers (66% vs 78% and 9% vs 28%, respectively).
Abbreviations: P, prospective; R, retrospective.

(78%) and nivolumab (3 mg/m^2, every 15 days) showed a high ORR, but the CR rate was low (17%). The toxicity profile of the drug was linked to the overreactivity of the immune system with autoimmune complications. In a second prospective phase II trial, 80 patients were treated with nivolumab, the ORR was 66%, and the CR rate was 9%. All patients had relapsed after HDC, and 54% were not responsive to BV. The median time to detect an objective response was 2.1 months (meaning 4 doses of drug), and the median duration of response was almost 8 months. The higher the expression of PDL1 on PAX5-positive cells (Reed Sternberg cells), the higher was the probability of achieving an objective response. Adverse events were recorded in 41% of patients, and the most frequent events were neutropenia and lipase increase.[35] Armand et al published the results of a previous study after an extended follow-up with more patients. Three cohorts of patients (n= 243) were indeed included, and the results were analysed in these different patient types: relapsing after HDC, relapsing after HDC and BV, and BV-naïve. For the whole cohort, the ORR and CR rate were 69% and 16%, respectively. The ORR and CR rate were similar in the 3 cohorts of patients.[36] The authors outlined that atypical patterns of response could explain why the time to next treatment was longer than progression-free survival. In a real-world analysis from the US, 53 patients were included; the ORR was 68%, and the CR rate was 45%. The patient characteristics were similar to those in prospective studies because the median number of previous CT lines was 4; 53% of patients had relapsed after HDC, and 19% had relapsed after allogeneic stem cell transplantation. An interesting point addressed in this analysis was the high efficacy of conventional therapy (ORR 70%) when patients failed CPI.[37] In a French retrospective study comprising 78 patients and with a long follow-up (median 34 months), the ORR was 68% and the CR rate was 38%.[38] Another retrospective study from Turkey reported on 82 heavily pretreated patients (5 median CT lines, 70% relapsed after HDC). The ORR was 64%, and the CR rate was 21%.[39] Nivolumab was associated with BV in a prospective phase I/II study, and the interim results were recently published. Sixty-two patients were included; the ORR was 83%, and the CR rate was 61%. Moreover, 87%[33] of patients proceeded to consolidation by HDC, and of these, 77% proceeded directly after BV-nivolumab. Patients not responding to BV-nivo were sensitive to conventional chemotherapy, and in these patients, the ORR was 80% and the CR rate was 40%. The tolerance was good, and grade 3–4 adverse events occurred in 31% of patients.[40] Forty-two patients out of 60 received HDC after stem cell mobilization by growth factor (G-CSF) alone or by G-CSF plus chemotherapy or plerixafor at a median time from the end of the BV/nivo treatment period of 9 days. No significant toxicities were recorded after the HDC course.[40]

It is quite evident that the CR rate was higher in retrospective than in prospective studies. This difference was probably due to PET interpretation, which is particularly troublesome after CPI. Indeed, these difficulties have been taken into account in the adapted Lugano response criteria,[31] where the definition of progressive disease was modified by introducing 3 different scenarios: immune response (IR) 1 (defined as a ≥ 50% increase in the sum of the products of the diameter in the first 12 weeks); IR2: <50% increase in the sum of the products of the diameter in the first 12 weeks with new lesions or ≥50% increase in the product of the perpendicular diameters of a lesion or set of lesions at any time during treatment; IR3: increase in FDG uptake without a concomitant increase in lesion size meeting the criteria for PD). In a Cochrane review, the data on the efficacy of nivolumab, which were derived from a few studies, were considered too sparse and limited to make a strong recommendation on its use in R/R HL.[41] Chen et al used pembrolizumab (200 mg every 3 weeks) as CPI in 210 patients, subdivided into 3 cohorts: relapsing after HDC and BV; relapsing after CT and BV; relapsing after HDC. The ORR and CR rate were 69% and 22%, respectively. The response rate did not seem different between the 3 cohorts.[42] The toxicity profile was also similar to that reported with nivolumab. In both prospective studies with nivolumab[36] and pembrolizumab,[42] one of the 3 cohorts included patients not eligible for HDC. In Armand's study, the ORR in this cohort of patients (cohort A) was similar to that in the others, while the CR rate was higher (29% vs 13% and 12%). The 1-year OS was in line with that of the whole population. In this study, 9 patients in this cohort underwent allogeneic stem cell transplantation, but it was not reported if any patients received consolidation by HDC.[36] In the second study, cohort 2 included patients ineligible for HDC and failing BV. The ORR and CR rate were superimposable on the other cohorts, as well as survival. In this study, only 4 patients, out of 210, received HDC.[42] However, in Herrera's study, R/R HL received the combination of BV plus nivolumab as first salvage therapy.

Finally, a third fully humanized CPI, sintilimab, was tested in China in a multicentre phase II study including 96

R/R HL patients. The ORR was 80%, and the CR rate was 31%. The drug was well tolerated. It should be noted that in this cohort, few patients were previously treated with BV and HDC.[43]

Predictive and Prognostic Factors of Response

Other than the clinical factors (Table 1), interim PET evaluation of the response during salvage therapy is considered to be a surrogate marker of chemosensitive disease and survival. This assumption is supported by the results of prospective randomized studies during first-line therapy in advanced disease, leading to an improvement in survival and a reduction in toxicity.[44–46] In the context of R/R HL, the value of interim PET is well established as a strong factor predicting survival, usually after consolidation of the response by HDC.[47–49] Less clear was the role of interim PET as a predictor of response. Our group evaluated R/R HL treated by conventional salvage CT (IGEV), where PET was performed after 2 courses (PET2). PET2-positive patients achieved less CR after 2 supplemental courses, and survival was significantly reduced.[50] The prognostic value of interim PET during CPI therapy was analysed in 45 patients in a multicentre retrospective study. The first interim PET was performed after a median of 2 months. Responses were classified following the Lugano and LYRIC criteria, and complete metabolic response (CMR) was observed in 29% of the patients; partial MR, in 36%; no MR, in 9%; and progressive MR, in 27%. The survival of patients was correlated and significantly different based on the response obtained. It is interesting to note that there was a direct correlation between progressive disease defined by the Lugano criteria and the 3 categories of progression defined according to the LYRIC criteria. In other words, all patients classified as having immunological responses 1, 2, and 3 were progressive following PET evaluation.[51] If these results will be confirmed in a large prospective study, early interim PET during CPI could be used as a prognostic marker of response and survival, helping to stratify patients for different treatments.

Recently, a more sophisticated and appealing molecular method was introduced to evaluate the sensitivity to treatment based on the tracking of circulating tumour DNA (ctDNA). Spina et al elegantly showed that ctDNA is representative of native tumoural DNA and contains different mutations. The most frequent mutation is located on the STAT6 gene (40%). In the setting of R/R HL, ctDNA contains either original mutations or other mutations not presented at diagnosis, confirming clonal evolution. In classical HL, the researchers identified a high number of mutations similar to that found in solid tumours. The performance of ctDNA to identify resistant clones was coupled to interim PET response, and a high log reduction of ctDNA was predictive of cure even in PET-positive patients.[52]

Serum biomarkers such as thymus and activation-regulated chemokine (TARC) and galectin-1, both highly expressed on Reed Sternberg cells, can be useful to monitor the response during first-line treatment.[53–55] However, TARC was prospectively proven to be predictive of response in only one study where 109 R/R HL patients were treated with panobinostat.[56]

Outcome After HDC and Maintenance Therapy

HDC followed by autologous stem cell support is considered the standard for R/R HL patients responding to first salvage chemotherapy. This was well established by 2 randomized studies,[57,58] where OS was almost 80% and 71%, event-free survival was 53%[57] and freedom from treatment failure was 55%.[58] In these studies, the conventional arm was represented by mini-BEAM and dexa-BEAM. A third randomized study compared the standard arm (salvage CT plus HDC) to an experimental intensified arm (salvage CT, cyclophosphamide, methotrexate, and etoposide). The OS and PFS were not different (87% vs 80% and 72% vs 67%, respectively), while the PFS was influenced by the factors included in the German score (stage IV, anaemia, and early or multiple relapse).[1] In Table 4–7, we report the survival obtained in patients treated with salvage CT and HDC.

Recently, a supposed improvement in survival by adding a maintenance treatment after HDC has been reported. The AETHERA study randomized patients at high risk of relapse after HDC (relapsed or progressive less than 12 months from the end of frontline therapy; refractory HL or extranodal involvement at the time of relapse) to receive BV (up to 16 cycles) or placebo. This study showed that PFS was significantly enhanced with BV, with tolerable neurological toxicity. The five-year PFS in the BV arm was 59% compared to 41% in the placebo arm, and fewer patients in the BV arm required additional therapy (32% vs 54%).[59] Recently, a prospective phase 2 study reported

on 30 patients treated with HDC. Among the included patients, 87% had at least 1 criterion corresponding to the inclusion criteria of the AETHERA study. They received 8 courses of pembrolizumab starting from day +21. The 19-month PFS was 85%, and the tolerance was good, with grade 3–4 toxic complications of 30%.[60]

Allogeneic Stem Cell Transplantation in R/R HL

Although many patients can be cured by conventional chemoradiotherapy or autologous transplantation, some of them remain refractory or relapse. These refractory patients can finally receive allogeneic stem cell transplantation (allo-SCT). Historically, HL cells are not considered to be sensitive to immunocompetent cells, and this was well explained by an array of cellular abnormalities that transform HL cells in ghost cells to the immune system.[61,62] The most interesting of this aberrant phenotype is the overexpression of PDL1 and PDL2 molecules, due to recurrent chromosome 9p24.1 amplification, which are targeted by CPI. The activity of CPI against HL cells changed the paradigm of resistance of HL to immune cells.

Table 9 Clinical Results After Allo-SCT from MRD and MUD

Author	N	CTX	MRD/ MUD	Disease Status CR/ PR	Grade 2–4 aGVHD	cGVHD Overall	OS	PFS	Relapse Rate	NRM
Robinson[72] 2002	52	RIC	NR	67%	27%	16%	56% @ 2 yr	42% @ 2 yr	45% @ 2 yr	17% @ 2 yr
Peggs[92] 2005	49	RIC	63%/37%	67%	16%	14%	55% @ 4 yr	39% @ 4 yr	33% @ 4 yr	15% @ 2 yr
Alvarez[93] 2006	40	RIC	93%/5%	50%	45%	45%	48% @ 2 yr	32% @ 2 yr	NR	25% @ 1 yr
Corradini[94] 2007	32	RIC	NR	62%	35%	49%	32% @ 3 yr	NR	81% @ 3 yr	3% @ 3 yr
Anderlini[95] 2008	58	RIC	43%/57%	52%	28%	73%	48% @ 2 yr	20% @ 2 yr	61% @ 2 yr	15% @ 2 yr
Devetten[96] 2009	143	RIC	MUD 100%	44%	60%	66%	37% @ 2 yr	20% @ 2 yr	47% @ 2 yr	33% @ 2 yr
Robinson[97] 2009	285	RIC	63%/37%	59%	30%	42%	25% @ 4 yr	29% @ 4 yr	53% @ 4 yr	19% @ 1 yr
Sureda[98] 2012	92	RIC	70%/30%	67%	32%	44%	43% @ 4 yr	24% @ 4 yr	59% @ 4 yr	15% @ 1 yr
Kanate[99] 2016	236	RIC-ATG	MUD 100%	81%	49%	37%	50% @ 3 yr	38%@ 3 yr	36% @ 3 yr	26% @ 2 yr
Ghosh[100] 2016	807	RIC	MRD 100%	86%	25%	52%	62% @ 3 yr	48%@ 3 yr	40% @ 3 yr	13% @ 2 yr
Anderlini[101] 2016	40	RIC	52%/48%	92%	26%	36%	75% @ 3 yr	54% @ 3 yr	28% @ 3 yr	17% @ 3 yr
Martinez[102] 2017	338	RIC	MRD 100%	78%	18%	25%	71% @ 2 yr	38% @ 2 yr	49% @ 2 yr	13% @ 1 yr
Martinez[102] 2017	273	RIC	MUD 100%	84%	30%	41%	62% @ 2 yr	45% @ 2 yr	32% @ 2 yr	21% @ 1 yr
Gauthier[103] 2018	90	RIC	MRD 100%	86%	22%	37%	82% @ 2 yr	NR	15% @ 2 yr	12% @ 2 yr

Abbreviations: NR, not reported; CTX, conditioning regimens; RIC, reduced intensity conditioning; ATG, anti-thymocyte globulin.

Table 10 Clinical Results After Allo-SCT from Haploidentical Donors

Author	N	CTX	Disease Status CR/ PR	Grade 2–4 aGVHD	cGVHD Overall	OS	PFS	Relapse Rate	NRM
Burroughs[104] 2008	28	NMAC	75%	43%	35%	58% @ 2 yr	51%@2 yr	40% @ 2 y	9% @2 yr
Raiola[105] 2014	26	NMAC	92%	24%	9%	77% @ 4 yr	63% @ 4 yr	31% @ 4 y	4% @ 3 yr
Kanate[99] 2016	199	NMAC	93%	27%	13%	68% @ 3 yr	42% @ 3 yr	36% @ 3 y	11% @ 1 yr
Gayoso[106] 2016	43	RIC	32%/NR	39%	19%	58% @ 2 yr	48% @ 2 yr	24% @ 2 y	21% @ 2 yr
Martinez[102] 2017	98	RIC/NMAC	85%	33%	26%	67% @ 2 yr	43% @ 2 yr	39% @ 2 yr	17% @ 1 yr
Castagna[107] 2017	62	RIC/NMAC	55%/32%	24%	16%	63% @ 3 yr	59% @ 3 yr	21% @ 3 y	20% @ 1 yr
Gauthier[108] 2017	34	RIC/NMAC	44%/38%	28%	15%	75% @ 3 yr	66% @ 3 yr	25% @ 3 y	9% @ 1 yr
Gauthier[103] 2018	61	RIC/NMAC	70%	29%	15%	81% @ 3 yr	NR	15%	12% @ 1 yr
Marani[109] 2018	41	RIC	47%	20%	11%	75% @ 3 yr	43% @ 3 yr	55% @ 3 yr	7% @ 3 yr

Abbreviations: NR, not reported; CTX, conditioning regimens; RIC, reduced intensity conditioning; ATG, anti-thymocyte globulin; NMAC, nonmyeloablative conditioning regimen.

Allo-SCT is considered the prototype of adoptive immunotherapy, but at least in Europe, only 2–3% of HL patients received allo-SCT,[63] probably because of supposed immunoresistance and high toxicity. In recent years, many advances have been made in the allo-SCT field, such as the introduction of reduced intensity or nonmyeloablative conditioning regimens (RIC and NMAC), improvement of infectious complication control, HLA typing resolution, graft-versus-host disease therapy and prophylaxis. Altogether, these improvements lead to lower nonrelapse mortality and better survival.[64]

Moving to the results obtained with allo-SCT in HL, we summarized the clinical results in Tables 9 and 10. In Table 9, we report the results obtained using so-called conventional donors, namely, matched related (MRD) and unrelated donors (MUD). It is evident that survival and toxicities were heterogeneous due to selection bias. Chemosensitive disease before allo-SCT ranged from 44% to 92%, the incidence of grade 2–4 acute GVHD ranged from 16% to 60%, chronic GVHD ranged from 14% to 73%, and OS and PFS ranged from 25% to 82% and from 20% to 54%, respectively. The relapse rate ranged from 15% to 81%, and the NRM ranged from 3% to 33%. Only 1 prospective study had been published to date,[65] where 67% of patients were in CR or PR before allo-SCT from MRD or MUD. The incidence of acute and chronic GVHD was 32% and 44%, respectively, and the survival was disappointing (OS 43%, PFS 24%) due to the high relapse rate (59%). In recent years, an increasing number of patients have received allo-SCT from haploidentical donors. Different platforms have been developed, and most of them use unmanipulated stem cell sources. The most popular platform, at least in Europe and the US, was based on the use of post-transplantation cyclophosphamide (PT-Cy), as pioneered by the Baltimore group.[66] In Table 10, we summarized the results obtained using unmanipulated stem cell support and PT-Cy. Disease before allo-SCT was considered chemosensitive in 46% to 93% of patients, the incidence of grade 2–4 acute GVHD was detected in 24% to 43% of patients, and chronic GVHD was detected in 9% to 35% of patients. The OS and PFS ranged from 58% to

81% and from 42% to 66%, respectively. The relapse rate ranged from 15% to 55%, and the NRM ranged from 4% to 21%. Even if it is difficult to compare the results after allo-SCT from conventional donors to those with haploidentical donors, it seems that haploidentical transplantation leads to a low relapse rate without a high NRM. This tendency was also reported in 2 recent papers.[67,68]

Considering that most, if not all R/R HL patients will receive CPI, it was important to look to the outcome in this special cohort of patients. Indeed, exposure to CPI was considered potentially dangerous, as initially reported, leading the FDA to release warning notes on the use of allo-SCT after CPI. Other authors reported a higher incidence of acute and chronic GVHD and NRM in this situation,[69,70] in part due to a persistent high Tcons/Treg ratio after allo-SCT.[69] However, this immune hyperreactivity induced by CPI could be better controlled using a different GVH prophylaxis. McCurdy et al reported that the use of PT-Cy could overcome the negative impact of CPI on GVHD, also outside the haploidentical context.[71] Finally, our group retrospectively compared the impact of CPI before haploidentical transplantation using PT-Cy, suggesting that the incidence of GVHD was not different, but the relapse rate was lower with CPI.[72] The efficacy of allo-SCT after CPI was reported by Armand et al analysing the data of the Check-Mate 205 study, in which 44 patients underwent allo-SCT after CPI. The survival rate was extremely promising, even if after a short follow-up, the 6-month PFS was 82% and the OS was 87%; the cumulative incidence of TRM and relapse was 7% and 13%, respectively.[36] Overall, these data suggest that allo-SCT is feasible after CPI, in particular using PT-Cy prophylaxis, and that at least in patients not achieving complete remission, allo-SCT is effective. For patients achieving a CR, the indication to perform an allo-SCT should be carefully discussed with the patient, considering the consistent risk of relapse.

Conclusions

R/R HL patients still represent a clinical concern. Salvage CT in combination with BV or treatment with BV plus CPI is highly effective in inducing a PET-negative disease status. Almost 2/3 of patients can indeed achieve this status, which is predictive of survival after consolidation by high-dose chemotherapy plus autologous stem cell support (HDC). HDC remains the gold standard for these patients, even if this could be challenged by CPI. PET remains the most useful technique to evaluate the disease status before HDC, with strong predictive significance. However, new methods such as the detection of ctDNA could help to further define the disease status. Maintenance therapy after HDC has been approved for BV, while the use of CPI after HDC has begun to be evaluated with encouraging results.

Allo-SCT remains, in our opinion, an important therapeutic tool in the most advanced cohort of patients not responding to BV and CPI.

Disclosure

Armando Santoro reports advisory board for BMS, SERVIER, GILEAD, PFIZER, EISAI, BAYER, and MSD, consultancy for ARQULE and SANOFI, speaker's bureau for TAKEDA, BMS, ROCHE, ABB-VIE, AMGEN, CELGENE, SERVIER, GILEAD, ASTRAZENECA, PFIZER, ARQULE, LILLY, SANDOZ, EISAI, NOVARTIS, BAYER, and MSD, during the conduct of the study. C. Carlo-Stella has received research support from ADC Therapeutics and Rhizen Pharmaceuticals; has served as consultant or advisor for Servier, Novartis, Genenta Science srl, ADC Therapeutics, Roche, Sanofi, Karyopharm; and has received honoraria for speaker engagements from Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen Oncology, Astra-ZenecaLuca Castagna. The authors report no other potential conflicts of interest in this work.

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