Classical Hodgkin's Lymphoma

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88.1 Definition and Epidemiology

HL is a malignancy arising from germinal centre or post-germinal centre B cells. The cancer cells form a minority of the tumour and are surrounded by a reactive inflammatory milieu comprising lymphocytes, eosinophils, neutrophils, histiocytes and plasma cells. These malignant cells can be pathognomonic, multinucleate giant cells or large mononuclear cells and, together, are referred to as Hodgkin and Reed-Sternberg (HRS) cells.

HL accounts for approximately 10% of cases of newly diagnosed lymphoma. The incidence of HL in Europe is 2.2 per 100,000 per year with a mortality rate of 0.7 cases/100,000 a year. The disease is more frequent in men than in women, and peaks in incidence are noted in young adults and in people older than 60 years. Incidence has remained mostly unchanged during the past two decades.

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88.2 Diagnosis

Pathological diagnosis should be made according to the WHO classification from a sufficiently large surgical specimen or excisional lymph node biopsy to provide enough material for fresh frozen and formalin-fixed samples (Eichenauer et al. 2018).

88.3 Classification

HL is classified as either classical (cHL, defined by the presence of HRS cells) or nodular lymphocyte-predominant (NLPHL). The immunophenotype of the malignant cells in cHL and NLPHL differs significantly and helps to establish the diagnosis. Four subtypes of cHL exist (nodular sclerosis, mixed cellularity, rich in lymphocytes, and lymphocyte depleted), which differ in presentation, sites of involvement, epidemiology and association with EBV. Management, however, is broadly similar in all subtypes. NLPHL has a distinct clinical course, and it only represents less than 5% of the cases of HL.

88.4 Risk Factors

The outlook for patients with early-stage disease (stages I–IIA) is excellent, with OS exceeding 90% in many trials. In advanced-stage disease (IIB, III–IV), OS is 75–90%. Risk factors for patients with early-stage disease are size of

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mediastinal mass, age, erythrocyte sedimentation rate, number of nodal areas, B symptoms and mixed cellularity or lymphocyte-depleted histology. Different risk stratification systems combining these factors are defined by the EORTC, GHSG, NCCN and National Cancer Institute of Canada and are currently used in clinical practice. Risk factors for advance stages consist of albumin <4 g/dL, haemoglobin <10.5 g/dL, male, age ≥45 years, stage IV disease, leucocytosis ≥15 x 10^9/L and lymphocytopenia (lymphocyte count less than 8% of white blood cell count and/or lymphocyte count less than 0.6 x 10^9/L) (International Prognosis Score, 1 point per factor) (Eichenauer et al. 2018).

88.5 First-Line Treatment

The treatment of patients with cHL is primarily guided by the clinical stage and prognostic factors of disease. Patients with early-stage disease are usually treated with a combination of chemotherapy (ABVD) plus RTx. The amount of chemotherapy and dose of radiation differ for patients with favourable and unfavourable prognosis of disease. Chemotherapy (ABVD, escalated BEACOPP or Stanford V) is the main treatment for patients with advanced stage, and RTx may be used for selected patients as consolidation (Eichenauer et al. 2018).

88.6 Second-Line Treatment Before Auto-HSCT

The principles of management of relapse or refractory cHL are shown in Table 88.1 (von Tresckow and Moskowitz 2016). All chemotherapy-based salvage regimens are associated with haematologic toxicity. Infection and neutropenic fever are reported in 10–24% of cases. Nephrotoxicity, hepatotoxicity, mucositis and gastrointestinal toxicity are observed in <10%. Haematopoietic stem cell mobilization appears adequate with all regimens. Efficacy of different salvage options is shown in Table 88.2.

Table 88.1 Principles of management of relapse or refractory cHL

New biopsy:
— Mandatory if relapse is ≥12 months after the end of primary treatment in order to exclude alternative diagnoses. Highly recommended for patients with suspected relapse <12 months
— If apparent primary refractory disease, histological confirmation of HL is only recommended if progression is suspected within new sites of disease. Biopsy may not be mandatory in patients with clear radiological progression in sites of primary disease during treatment
Radiological evaluation:
— A whole-body CT scan with contrast dye injection and a PET are recommended for further comparison
Therapy:
— Salvage therapy followed by high-dose chemotherapy and auto-HSCT is currently considered the standard of care for relapsed cHL patients
— No study has compared effectiveness of different salvage regimens
— Salvage strategy should be tailored on an individual basis taking into account the initial therapy given, the risk of adding cumulative non-haematologic toxicity and the possibility of harvesting stem cells
— Cardiac and pulmonary function should be evaluated prior to treatment
— If indicated, reproductive counselling should be proposed prior to treatment
— Objective of salvage chemotherapy: to produce a response (tumour remains chemosensitive), which has a major impact on post-auto-HSCT outcome. Achievement of PET negativity defines chemosensitivity and should be the goal of salvage chemotherapy

Table 88.2 Salvage regimens

Conventional chemotherapy	
DHAP	ORR 89%, CR 21%
ESHAP	ORR 67%, CR 50%
ICE	ORR 88%, CR 67%
Gemcitabine-containing regimens	
• IGEV	ORR 81%, CR 54%
• GVD	ORR 70%, CR 19%
• GDP	ORR 62%, CR 1%
• BeGEV	ORR 83%, CR 73%
No chemotherapy strategies	
Brentuximab vedotin (BV)	Currently approved after failure of at least two prior multiagent chemotherapy regimens in patients who are not auto-HSCT candidates. ORR 50%, CR 12%
Pembrolizumab	Currently approved for the treatment of patients with refractory cHL or who have relapsed after three or more prior lines of therapy. ORR 69%, CR 22%
New drugs in association with chemotherapy[a,b]	
Sequential strategies	
• BV followed by ICE	77%
Combination strategies	
• BV plus bendamustine	74%
• BV plus ESHAP	70%
• BV plus ICE	69%
• BV plus DHAP	90%
• BV plus nivolumab	62%

[a]These combinations are not currently approved for this indication
[b]PET-negative response rate

88.7 Autologous HSCT

Auto-HSCT is currently considered the standard treatment for relapsed/refractory (R/R) cHL patients. Two landmark randomized clinical trials, the British National Lymphoma Investigation (BNLI) in 1993 and the joint German Hodgkin Study Group (GHSG)/EBMT HD-R1 trial in 2002, compared high-dose chemotherapy followed by auto-HSCT versus chemotherapy and showed significant a benefit of auto-HSCT in terms of EFS and FFTF in front of conventional salvage chemotherapy; however, there was no significant OS benefit. EBMT current indications for autologous HSCT in HL are shown in Table 88.3 (Sureda et al. 2015).

Table 88.3 EBMT current indications for autologous HSCT in cHL (Sureda et al. 2015)

Disease status	Recommendations
First complete remission	Generally not recommended Level of evidence I
Sensitive relapse/≥2nd complete response	Standard of care Level of evidence I
Refractory disease	Clinical option Level of evidence II

88.7.1 Stem Cell Source and Conditioning Regimen

Haematopoietic stem cells from mobilized PB are the preferred stem cell source for auto-HSCT.

Although the choice of preparative regimen varies and is typically based on institutional experience, BEAM is the preferred option. Standard BEAM consists of BCNU (300 mg/m^2 ×1, day -6), VP (200 mg/m^2, days -5 to -2), Ara-C (200 mg/m^2 bid, days -5 to -2) and MEL (140 mg/kg/day ×1, days -1). The CY, BCNU and VP (CBV) regimen is also commonly used in North America. The use of TBI-based regimens is not recommended due to the higher risk of developing secondary malignancies.

Late toxicities of BEAM include pulmonary complications (chronic interstitial fibrosis and decrease in lung diffusing capacity, 21%), infec-

tion (30%), metabolic syndrome (17%), cardiovascular complications (12%), secondary tumours (20%) and other toxicities (20%). The most frequent cause of NRM is subsequent malignancy (12-fold increased risk compared with the general population).

88.7.2 Prognostic Factors

Adverse prognostic factors for post-auto-HSCT outcome consistent across many reported trials included primary induction failure, initial remission duration of<3 months, relapse within 12 months of induction therapy, extranodal disease, B symptoms, advanced stage at relapse, resistance to salvage chemotherapy and persistent disease at the time of transplant.

88.7.3 Results of Auto-HSCT

Disease status pre-auto-HSCT	NRM (%)	OS at 5 years (%)	PFS at 5 years (%)
Chemosensitive disease	0–18	75	50
Primary refractory disease	0–18	30–36	15–38

88.7.4 Consolidation Treatment After Auto-HSCT

Brentuximab vedotin (BV) is currently the only drug approved for consolidation treatment after auto-HSCT in patients at risk of relapse or progression. This approval was obtained after the results of the phase III AETHERA trial. In this multicentre randomized trial, 329 patients with relapsed or refractory HL were allocated to either consolidation therapy of up to 16 cycles of BV or placebo after auto-HSCT. PFS was significantly longer in patients in the BV group (median PFS 43 months vs. 24 months, $P = 0.0013$). When patients were grouped by the number of risk factors, a higher number led to more notable benefits in the consolidation arm (Moskowitz et al. 2015).

88.8 Tandem Auto-HSCT

Several groups have explored a tandem transplant approach to improve post-transplant outcomes of patients with poor risk factors. These studies showed that tandem auto-HSCT is feasible and associated with a NRM of 0–5%, 5-year OS of 54–84%, and 5-year PFS of 49–55% (Smith et al. 2018). According to these results, risk-adapted tandem auto-HSCT can be considered an option for poor-risk patients, but integration of PET findings and new drugs such as BV and checkpoint inhibitors may help to refine the need for a second auto-HSCT and possibly improve outcomes of these patients.

88.9 Disease Relapse After Auto-HSCT

Patients relapsing following auto-HSCT have an overall poor prognosis with an OS of 30% at 5 years. Early relapse, stage IV, bulky disease, poor performance status and age ≥50 years at auto-HSCT failure have been identified as predictors of poor outcome (Jethava et al. 2017; Kallam and Armitage 2018; Lapo and Blum 2016). Therapeutic options are very heterogeneous (Table 88.4) (Martínez et al. 2013; Hahn et al. 2013).

88.10 Allogeneic HSCT

Allo-HSCT is still considered a curative treatment strategy for patients with cHL who relapse or progress after auto-HSCT (Peggs et al. 2008). Our knowledge on the curative capacity of allo-HSCT relies on the results of several retrospective analyses, some of them registry-based, phase II prospective clinical trials Sureda et al. (2012) that included low number of patients and retrospective analyses that in a donor-versus-no-donor strategy demonstrate that allo-HSCT offers a significant benefit in terms of both PFS and OS. EBMT current indications for allo-HSCT in cHL are shown in Table 88.5.

Table 88.4 Therapeutic options after auto-HSCT relapse

Brentuximab vedotin (Chen et al. 2016)	Currently approved for the treatment of cHL relapsed after auto-HSCT ORR 75%, CR 34% PFS 5.6 months
Nivolumab	Currently approved for the treatment of cHL relapsed after auto-HSCT and BV ORR 69%, CR 16% 1-year OS 92%, median PFS 12–18 months
Pembrolizumab	Currently approved for the treatment of cHL relapsed after auto-HSCT ORR 69%, CR 22% PFS 72% at 6 months
Gemcitabine-based chemotherapy	ORR 69–86%, EFS 10%
Bendamustine	ORR 53–78%, CR 29–33%
Lenalidomide	ORR 19%
Histone deacetylase inhibitors	ORR 4–74%, CR 0–4% 1-year OS 78%
Everolimus	ORR 47%
Second auto-HSCT	NRM 15%, 5-year OS and PFS 30%
Allogeneic transplantation	See Sect. 88.10

Table 88.5 EBMT current indications for allogeneic HSCT in cHL (Sureda et al. 2015)

Disease risk	MSD	MUD	Alternative donors[a]
First remission	GNR Level of evidence III	GNR Level of evidence III	GNR Level of evidence III
CR > 1, previous auto-HSCT: no	Developmental Level of evidence III	Developmental Level of evidence III	GNR Level of evidence III
CRF > 1, previous auto-HSCT: yes	Standard Level of evidence II	Standard Level of evidence II	Clinical option Level of evidence III
Refractory disease	Developmental Level of evidence II	Developmental Level of evidence II	Developmental Level of evidence III

[a]*MMUD* haploidentical donors, CB, *GNR* generally not recommended

88.10.1 Stem Cell Source, Type of Donor and Conditioning Regimen

HSC from mobilized PB are the preferred stem cell source for allo-HSCT. The use of haploidentical donors has increased the use of BM in some of the series. Later studies have demonstrated no significant differences in terms of GVHD incidence with the use of PB in this setting.

In recent years, there has been a significant increase in the use of haploidentical donors with the introduction of the PT-CY approach. The interesting results observed with this type of transplant have already decreased the use of MUD and MRD in the EBMT reporting centres (Gayoso et al. 2016). Retrospectively, registry-based studies from both EBMT and CIBMTR indicate that outcomes of PT-CY-based haplo-HSCT are similar to those of MRD and MUD; cumulative incidence of GVHD seems to be lower with the haploidentical approach and translates into a better PFS-cGVHD in some of the series (Martínez et al. 2017).

More than 50% of the patients with HL treated with allo-HSCT receive a RIC protocol. RIC regimens have demonstrated to significantly reduce NRM after transplantation but also to increase RI after transplant (Sureda et al. 2008). There are no formal prospective clinical trials demonstrating the superiority of a given conditioning protocol in front of the others. Retrospective analysis indicates that low-dose TBI-containing regimens are associated with a higher RI and lower survival than non-TBI-containing protocols.

88.10.2 Prognostic Factors

The most important adverse prognostic factor associated with long-term outcome after allo-HSCT is the disease status before transplant. However, the impact of a PET-negative CR before the procedure is not as straightforward as in the auto-HSCT setting.

88.10.3 The Use of Allo-HSCT in the Era of New Drugs

The role and positioning of allo-HSCT in patient's relapsing/progressing after auto-HSCT are less clear with the introduction of new drugs. Numbers of allo-HSCT for this indication seem to have decreased over the last 2 years.

BV has been used as a bridge to allo-HSCT. There is no evidence of a need of a washout period between the last dose of BV and day 0 of HSCT. The number of BV cycles being given before allo-HSCT is usually between four and six. The use of BV before transplant does not modify post-transplant-related toxicities and might improve results by improving performance status and disease status before allo-HSCT. It might also allow more patients to successfully go through the transplant.

Checkpoint inhibitors (nivolumab, pembrolizumab) before allo-HSCT seem very effective with promising survival results (Dada 2018). However, follow-up is still too short, and it has been suggested that their use could be associated with increase in transplant-related toxicity (SOS/VOD, post-transplant hyperacute febrile syndrome). A retrospective study does not indicate a higher NRM and higher incidence of acute GVHD in patients pretreated with checkpoint inhibitors. There is no clear information on the need of a washout period when using this combined strategy although it seems that nivolumab levels on day 0 do not correlate with incidence of GVHD and NRM.

The final decision of whether to allograft a patient that relapses after auto-HSCT might rely on the risk profile of the underlying disease as well as the transplant-related risk.

88.10.4 Results of Allo-HSCT

Disease status pre-allo-HSCT	NRM (%)	OS at 3 years (%)	PFS at 3 years (%)
Chemosensitive disease	15–20	60–70	40–50
Chemorefractory disease	20–30	40–50	20–30

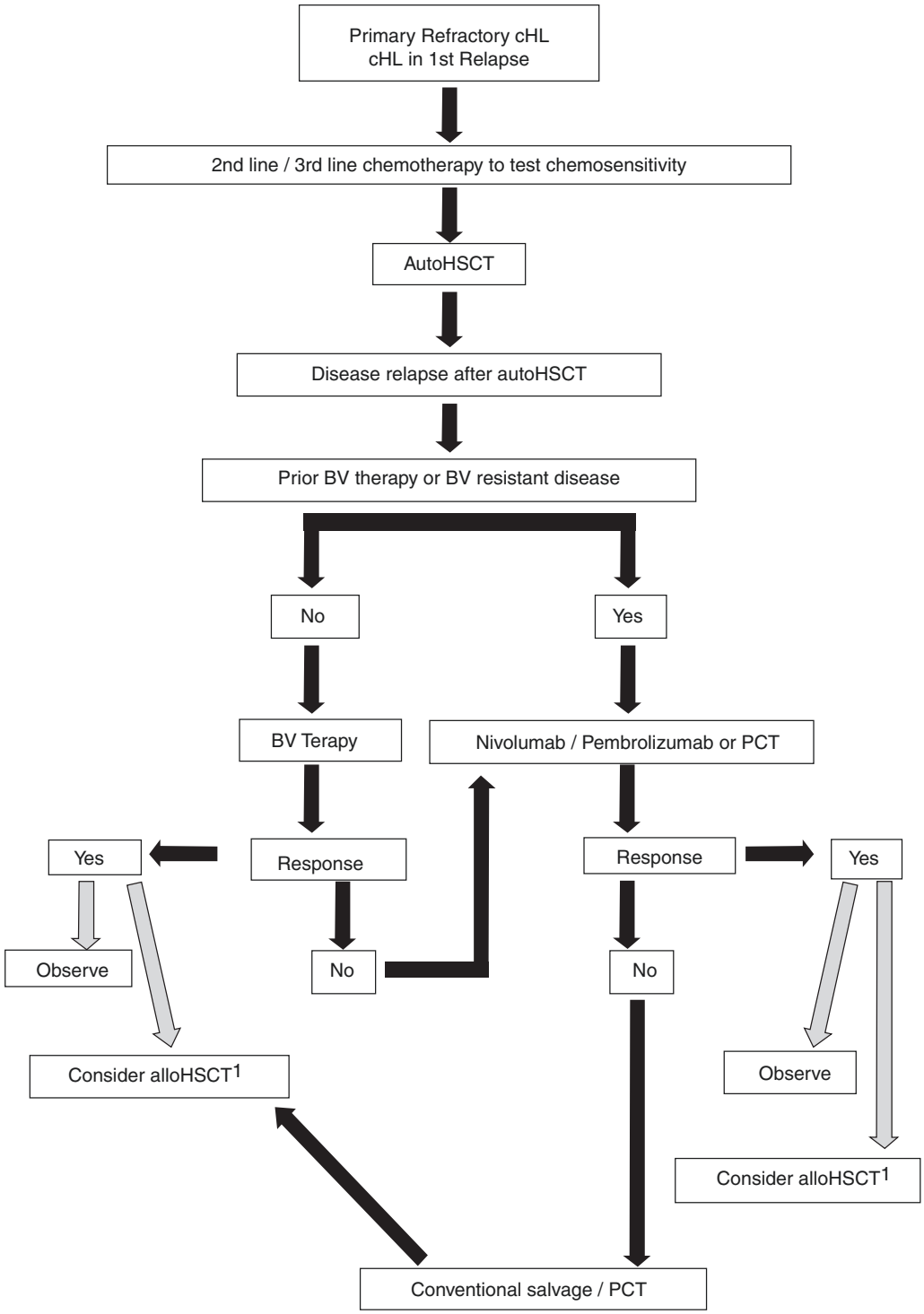
88.10.5 Disease Relapse After Allo-HSCT

Disease relapse carries out a dim prognosis. Therapeutic options are variable and heterogeneous (Table 88.6), and in some cases, palliative care is the only feasible one.

Table 88.6 Therapeutic options after allo-HSCT relapse

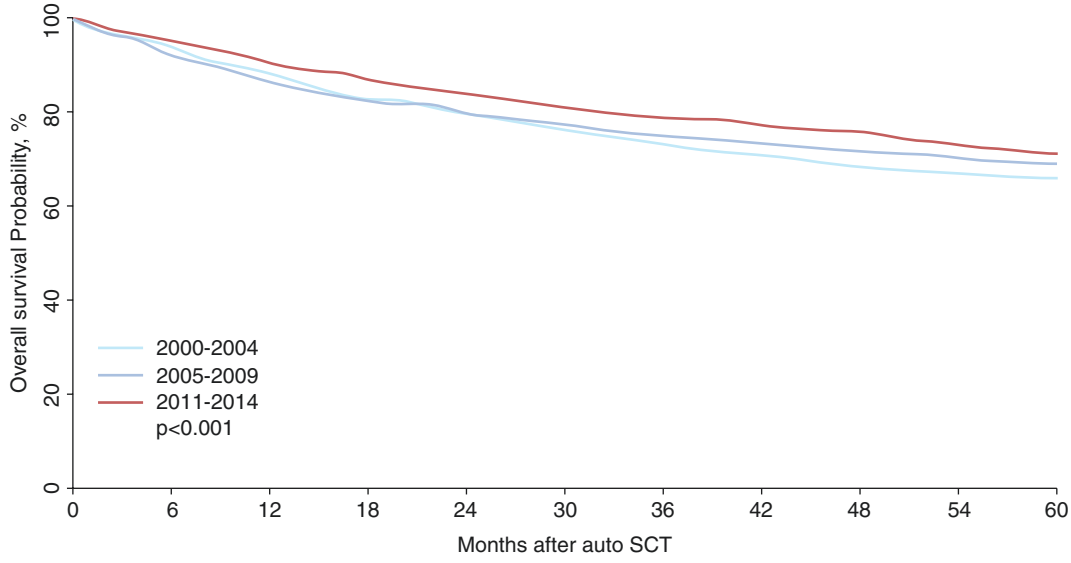
DLI alone	ORR 33–54%
DLI + brentuximab vedotin DLI + bendamustine	ORR 69% (CR 54%/PR 15%), PFS 5.5 months ORR 55% (CR 16%/39%), PFS 6 months
Brentuximab vedotin (Gopal et al. 2012)	ORR 50–69% CR 31–38%/PR 37% Median PFS 7–8 months
Nivolumab (Herbaux et al. 2017)	ORR 77–95% CR 42–55%/PR 40–52% 1-year PFS 58%

88.11 Therapeutic Algorithm Recommended by the Authors (Modified from Yethava et al.)



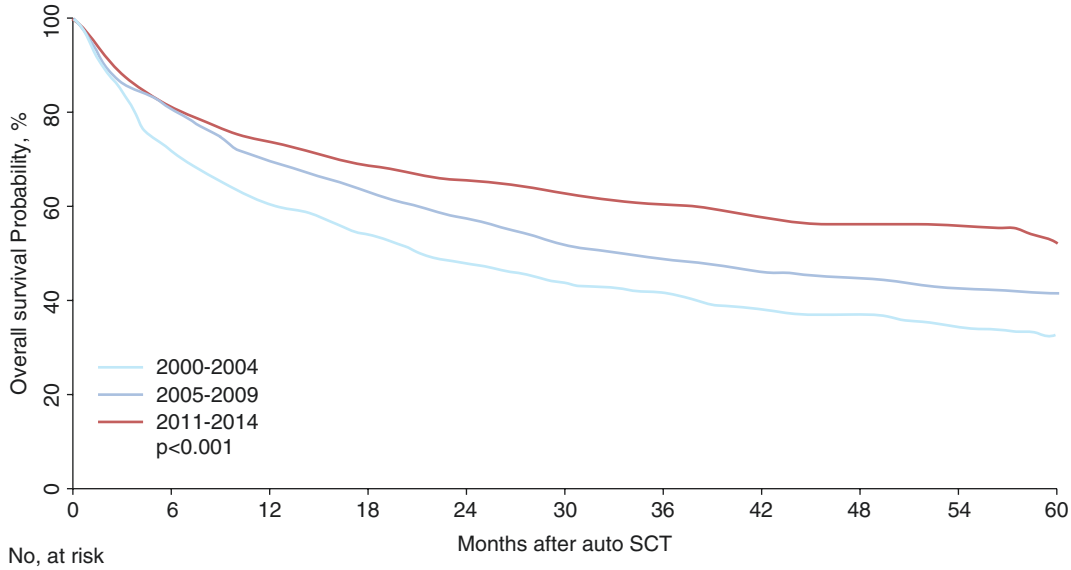
PCT, prospective clinical trials. [1]In young and fit patients with responding disease and an adequate donor available. Grey arrows. Both options can eventually be considered acceptable after a careful balance of adverse prognostic factors of the patient/transplant-related comorbidities/ careful discussion with the patient

88.12 Long-term outcomes of Auto-HSCT and Allo-HSCT in Patients with Relapsed/Refractory cHL (EBMT Database, with Permission)



No, at risk										
2000-2004	1699	1469	1322	1217	1118	1047	960	914	857	816
2005-2009	2560	2189	1912	1756	1631	1507	1386	1291	1211	1124
2011-2014	2571	2095	1819	1603	1382	1161	933	763	570	418

OS of auto-HSCT in relapsed/refractory cHL over time



No, at risk										
2000-2004	242	196	175	153	136	127	115	105	94	87
2005-2009	550	447	386	344	297	281	260	238	224	211
2011-2014	729	631	550	477	417	343	271	211	162	104

OS of allo-HSCT in relapsed/refractory cHL over time

Key Points

- Auto-HSCT is still the standard of care for those patients with primary refractory/chemosensitive first relapse. Results of auto-HSCT might improve in the future with better selection of patients, improved results of salvage strategies and consolidation treatment in those patients with high risk of relapse after auto-HSCT.
- Allo-HSCT is the only curative treatment options for those patients relapsing after auto-HSCT. The use of allo-HSCT is being modified by the introduction of haploidentical donors as well as targeted therapies in this setting.

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