Current Treatment Options in Oncology (2014) 15:238–247
DOI 10.1007/s11864-014-0287-3

Lymphoma (A Engert, Section Editor)

The Role of Allogeneic Stem Cell Transplantation in Hodgkin's Lymphoma

Anna Sureda, MD, PhD[1,*]
E. Domenech, MD[1]
N. Schmitz, MD, PhD[2]
P. Dreger, MD, PhD[3] *on behalf of the Lymphoma Working Party of the European Group for Stem Cell Transplantation*

Address
[1,*]Hematology Department, Institut Català d'Oncologia – Hospital Duran I Reynals, Avda. Gran Via, 199 – 203, L'Hospitalet de Llobregat, 08908, Barcelona, Spain
Email: asureda@iconcologia.net
Email: edomingo@iconcologia.net
[2]Department of Haematology, Asklepios Klinik St. Georg, Lohmühlenstrasse 5, 20099, Hamburg, Germany
Email: n.schmitz@asklepios.com
[3]Medizinische Klinik u. Poliklinik V. Im Neuenheimer Feld 410, University of Heidelberg, 69120, Heidelberg, Germany
Email: Peter.Dreger@med.uni-heidelberg.de

Published online: 22 April 2014

Keywords Hodgkin's lymphoma · Refractory disease · Allogeneic stem cell transplantation · Reduced intensity conditioning regimen · Graft-versus-Hodgkin's lymphoma effect

Opinion statement

The treatment of patients with classical Hodgkin's lymphoma relapsing after autologous stem cell transplantation represents a clear unmet need. Overall long-term outcome is not the same in these patients and therapeutic options in this setting are very heterogeneous and include salvage CT and/or RT followed or not by a second stem cell transplantation, palliative care, new drugs, or biological agents. Despite the absence of prospective, randomized, clinical trials, allogeneic stem cell transplantation either from a HLA identical sibling or a matched, unrelated donor represents an attractive option for those young patients with chemosensitive disease after being treated with a salvage protocol. The use of reduced intensity conditioning regimens has been able to drastically decrease nonrelapse mortality, although relapse rate remains a significant issue in this setting. More intense conditioning protocols could eventually decrease the relapse rate after the allogeneic procedure and, as indicated by a recent retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation, nonrelapse mortality does not represent a major problem

nowadays for patients with multiply relapsed Hodgkin's lymphoma. Brentuximab vedotin is an antibody-drug conjugate that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells. Its use has been approved recently for patients with Hodgkin's lymphoma relapsing after autologous stem cell transplantation. As a single dose, brentuximab vedotin is able to achieve an objective response rate of 75 % with 34 % of the patients achieving a complete remission. Its widespread use will most certainly change the treatment paradigm of this subgroup of patients, either avoiding the allogeneic procedure in some patients or by increasing the group of potential candidates to an allogeneic transplant being used as a "bridge to allo." Additional information on long-term outcome of patients being treated with this drug or the development of prospective clinical trials in this setting will most probably give some light to this question we have nowadays.

Introduction

The majority of patients with advanced-stage Hodgkin's lymphoma (HL) can expect to be cured with conventional chemotherapy (CT) ± radiotherapy (RT) [1, 2]. Nevertheless, the prognosis of those patients who present with primary refractory disease or those patients who despite achieving a first complete remission (CR) eventually relapse at some point after combined modality treatments remains poor in many cases. Autologous stem cell transplantation (ASCT) is now considered the standard of care for relapsed HL patients on the basis of two randomized trials that showed significant benefit in terms of freedom from treatment failure (FFTF) for ASCT over conventional CT for relapsed disease [3–5]. Although sustained remissions after ASCT have been reported, between 40 % to 50 % of the patients will have recurrence of the disease. Patients relapsing following ASCT have an overall poor prognosis. There is currently little information on the predictors of outcome for patients whose disease recurs after ASCT. A retrospective analysis of the Lymphoma Working Party (LWP) of the European Group for Blood and Marrow Transplantation (EBMT) and Gruppo Italiano Trapianto di Midollo Osseo (GITMO) [6], including 511 adult patients with relapsed HL after ASCT, indicates that after a median follow-up of 49 months, overall survival (OS) of these patients was 32 % at 5 years; independent risk factors for OS were early relapse (<6 months) after ASCT, stage IV disease and bulky disease at the time of relapse, poor performance status, and age ≥50 years. For patients with no risk factors OS at 5 years was 62 % compared with 37 % and 12 % for those having 1 and ≥2 factors, respectively. Relapsed disease after ASCT represents a clear unmet need. Therapeutic options in this setting are very heterogeneous and include salvage CT and/or RT followed or not by a second stem cell transplantation, palliative care, new drugs, or biological agents. Within the "so-called" new drugs, it is worth mentioning brentuximab vedotin (BV), a highly effective antibody-drug-conjugate (ADC) directed against the CD30 antigen that recently received a fast tract approval by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The widespread introduction of BV is already changing the therapeutic landscape of those patients with HL relapsing or progressing after an ASCT.

Allogeneic stem cell transplantation

Compared with the number of autologous transplants, few patients with lymphoma have undergone allogeneic transplantation of hematopoietic stem cells (allo-SCT). In some histologies, this is probably due to the higher median age at diagnosis, the increasing effectiveness of conventional treatment options decrease the number of patients in a relapse situation, and the

success of high-dose therapy followed by ASCT. Most probably, one of the major obstacles for the wide use of an allogeneic procedure was the unfavorable long-term results reported in the earliest series. Nonrelapse mortality (NRM) had been devastatingly high and together with a high relapse rates (RR) had resulted in poor progression-free survival (PFS) and OS. Nonetheless and despite these caveats, some series indicated that RR was higher in ASCT than in the allogeneic setting, thus suggesting a potential role for a graft-vs.-lymphoma (GvLy) effect similar to what had been described as the graft-vs.-leukemia effect in the early 1980s [7, 8]. Reduced intensity-conditioning protocols (RIC), progressively introduced in the clinical practice in the second half of the last decade, demonstrated to be able to significantly reduce NRM, thus increasing the interest of allo-SCT in some diseases were myeloablative transplantation was associated to a high NRM and allowing the use of an allogeneic procedure in older patients with additional
comorbidities. RIC protocols were the main reason for the progressive increase in the number of patients with lymphoproliferative disorders being allografted.

In HL, the first registry-based analyses published in 1996 gave disappointing results regarding the role of myeloablative allo-SCT. The International Bone Marrow Donor Registry (IBMTR) reported the long term outcome of 100 consecutive HL patients treated with a myeloablative allo-SCT [9]. Three-year OS, disease-free survival (DFS), and the probability of relapse were only 21 %, 15 %, and 65 %, respectively. The most important clinical problems after transplantation were disease relapse or progression and infectious complications from the respiratory tract, which accounted for 35 % to 51 % of deaths. At the same time, the LWP of the EBMT published a paired-analysis comparing the four major outcomes after transplantation in 45 patients being treated with an ASCT and 45 with an allo-SCT [10]. There were no significant differences in terms of OS, progression-free survival (PFS), and RR between allo-SCT and ASCT (25 %, 15 %, 61 % vs. 37 %, 24 %, 61 %, respectively). NRM at 4 years was significantly higher for allografts than for autografts (48 % vs. 27 %) even when only considering the small subgroup of patients allografted with chemosensitive disease. A potential beneficial effect of the allogeneic procedure was not seen in any of these two studies due to an exceedingly high NRM.

The LWP of the EBMT has performed the only comparative albeit retrospective analysis between reduced-intensity and myeloablative conditioning in patients with relapsed/refractory HL [11••]. NRM was significantly lower in the reduced-intensity group (23 % vs. 46 % at 1 year) [hazard ratio (HR) 2.43 (95 % CI 1.48–3.98), $p<0.001$]. PFS and OS also were better in the reduced-intensity group [HR 1.28 (95 % CI 0.92–1.78), $p=0.1$ and HR 1.62 (95 % CI 1.15–2.28), $p=0.005$, respectively] and the development of chronic graft-vs.-host disease (cGVHD) significantly decreased the incidence of relapse after transplantation, which translated into a better PFS and OS when considered the global population of patients.

The advent of RIC protocols renewed the enthusiasm of the scientific community on the use of allo-SCT in relapsed HL. This fact is clearly exemplified by the increasing numbers of patients with HL treated with an allo-SCT and being reported to the EBMT Lymphoma Database (Fig. 1a).

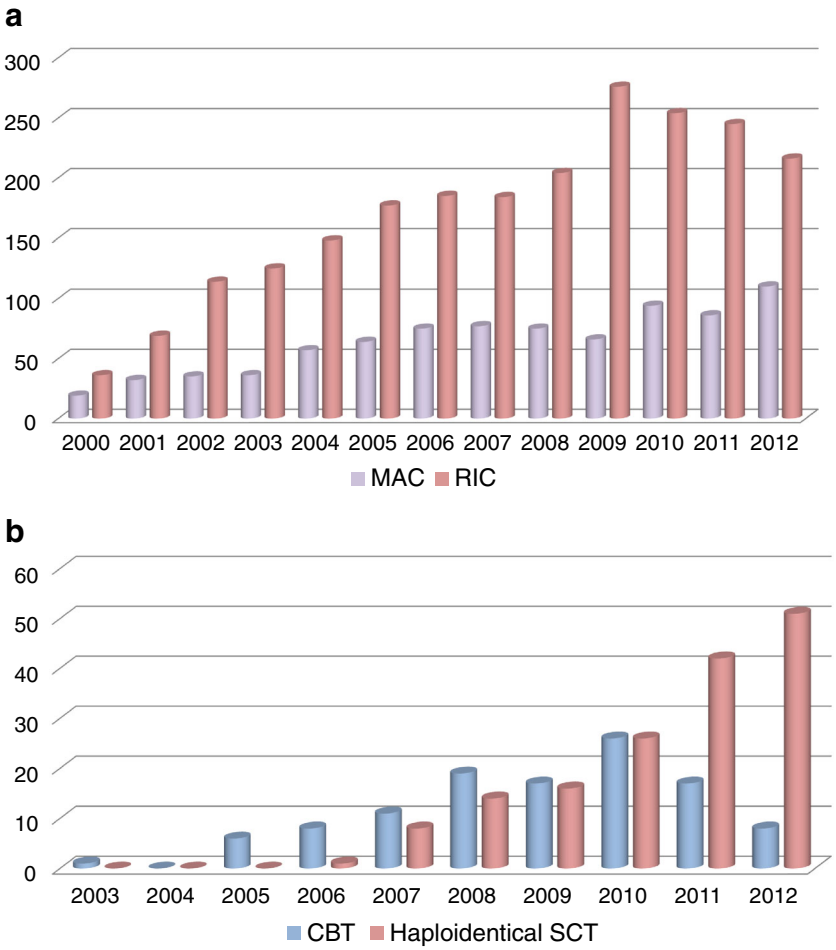

Fig. 1. Allogeneic stem cell transplantation for relapsed/refractory Hodgkin's lymphoma. Activity reported to the EBMT Database from 2000 to 2012 (data from the EBMT Lymphoma Database, with permission). **a** Comparison of myeloablative versus reduced-intensity conditioning protocols (2000–2010). **b** Comparison of cord blood and haploidentical donors in recent years (2003–2012).

The LWP of the EBMT also has reported the largest retrospective analysis looking at 285 multiply relapsed HL being treated with a RIC/allo-SCT in HL [12]. Forty-seven patients (17 %) were in CR, 123 patients (43 %) had chemosensitive disease, and 115 patients (40 %) had chemoresistant disease. The 100-day NRM was 12 %, 20 % at 12 months, and to 22 % at 3 years; refractory disease was significantly associated with a higher NRM. Two-year PFS was 29 % and it also was significantly worse for patients with chemoresistant disease ($p<0.001$). A landmark analysis performed at 9 months after transplantation indicated that the development of either acute or cGVHD was associated to a lower RR.

Allo-SCT has basically been used in ASCT failures. Unfortunately, the information we have in this setting is based on phase II prospective clinical trials that include reduced number of patients with short follow. In addition, the transplantation procedure is so heterogenous amongst different studies that fair comparisons are impossible to perform. There is no single phase III randomized prospective clinical trial comparing the role of allo-SCT in front of other therapeutic strategies in this setting. A total of 40 patients with relapsed/refractory HL undergoing a RIC/allo-SCT from an HLA-identical

sibling ($n=20$) or a matched unrelated donor ($n=20$) was updated by Anderlini et al. [13]. Fourteen patients had refractory disease and 26 had sensitive disease at the time of allo-SCT. Two-year OS and PFS were of 64 % and 32 % respectively; the 2-year projected risk of disease progression was of 55 %. There was a trend for the response status before allo-SCT to favorably impact PFS ($p=0.07$) and disease progression ($p=0.049$), but not OS. Partial responders and patients with stable refractory disease did similarly with regards to OS and PFS. Response rate 3 months after the allo-SCT was 67 %. In the Spanish experience, forty patients with multiply relapsed disease and adverse prognostic factors were treated with iv fludarabine (150 mg/m^2) and melphalan (140 mg/m^2) and cyclosporine A and methotrexate as GVHD prophylaxis [14]. Eleven patients received donor lymphocyte infusions (DLIs) for relapse or persistent disease and six patients (54 %) responded. Two-year OS and PFS were 48 % and 32 %, respectively. Refractoriness to CT was the only adverse prognostic factor for both OS and PFS. The *in vivo* T-cell depletion with an anti-CD52 monoclonal antibody, alemtuzumab, was the basis of the RIC protocol used by the UK Cooperative Group [15]. The conditioning protocol also consisted on the combination of fludarabine (150 mg/m^2) and melphalan (140 mg/m^2). Engraftment was universal, grade II-IV aGVHD occurred in 16 % of patients, and 14 % developed cGvHD before DLIs. DLIs were given because of mixed chimerism ($n=3$) or disease progression ($n=16$). Fifty-six percent of the patients receiving DLIs responded, and this response was significantly associated with the development of GVHD after the infusion. NRM was 16 % at 2 years and projected 4-year OS and PFS were 56 % and 39 %, respectively.

The largest phase II trial, including 78 patients with multiply relapsed HL and with adverse prognostic factors, has been a joint effort of the Spanish Group for Lymphomas and Stem Cell Transplantation (GELTAMO) and the LWP of the EBMT [16••]. Median follow-up of the whole series was 4 years. NRM was 8 % at 100 days and 15 % at 1 year. Relapse was the major cause of failure. Patients allografted in CR had a significantly better outcome. PFS was 48 % at 1 year and 24 % at 4 years; OS was 71 % at 1 year and 43 % at 4 years, respectively. Chronic GVHD was associated with a lower relapse incidence and a better PFS.

Results of DLIs in patients with HL represent a source of indirect evidence of the existence of a clinically beneficial GvLy effect. The most extensive piece of evidence in this sense comes from the UK cooperative group [17••]. Forty-six consecutive patients with multiply relapsed or refractory disease who underwent allo-SCT that incorporated in vivo T-cell depletion received DLIs because of disease relapse ($n=24$) or mixed chimerism after allo-SCT ($n=22$). In a T-cell depleted setting, DLIs were able to reduce the RR of the disease as well as to induce durable antitumor responses. Outside the *in vivo* T-cell depletion situation, responses to DLIs are quite inconsistent and difficult to analyse. In most of the cases, lymphocytes are given because of disease progression and not with the objective to reverse a mixed chimera. Secondly, responses are usually short-lived and no patients achieved long-term disease control so far [13, 14].

NRM does not seem to be a relevant clinical issue anymore when discussing allo-SCT in HL patients; RR is the major cause of failure of the procedure. Disease status at the time of allo-SCT is as expected the most

important prognostic factor modifying long-term outcome. More effective salvage protocols need to be used in an otherwise heavily pretreated population of patients. Brentuximab vedotin is an antibody-drug conjugate (ADC) that selectively delivers monomethyl auristatin E, an antimicrotubule agent, into CD30-expressing cells. In phase I studies, BV demonstrated significant activity with a favorable safety profile in patients with relapsed/refractory CD30-positive lymphomas. The interesting results seen in the phase I trial led to a phase II one that evaluated the efficacy and safety of BV (1.8 mg/kg by intravenous infusion every 3 weeks up to a maximum number of 16 cycles) was evaluated in 102 patients with relapsed or refractory HL after ASCT [18••]. Overall response rate (ORR) was 75 % with a CR in 34 % of patients. The median PFS time for all patients was 5.6 months, and the median duration of response for those in CR was 20.5 months. After a median observation time of more than 1.5 years, 31 patients were alive and free of documented progressive disease. The drug was quite well tolerated: the most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. BV has been used in the pre-allo-SCT setting, as a "bridge to allo" and in the postallogeneic setting to treat patients with relapsed/progressive disease after the allogeneic procedure. Chen et al. [19•] have recently published their experience with 18 patients with multiply relapsed HL undergoing a RIC/allo-SCT after being treated with brentuximab vedotin as salvage therapy. NRM, acute, and cGVHD incidence after the allogeneic procedure were not significantly different from what had been previously described, and with a median follow-up of only 12 months, PFS was 100 %. In a retrospective analysis comparing patient characteristics before allo-SCT and outcomes after allo-SCT in relapsed/refractory HL, patients who received BV and underwent a RIC allo-SCT versus those who did not receive BV and still underwent a RIC-allo, Chen [20] also found that the administration of BV as a bridge to transplant significantly increased the percentage of patients achieving a CR before the procedure, thus improving the comorbidity index of the patients before the procedure, decreasing NRM, RR after the procedure, and finally improving the overall outcome of the patients. The broad spread use of BV in patients with HL relapsing after an ASCT will most probably change the therapeutic approach in this setting.

Accepting all the caveats inevitably associated with retrospective analyses, two studies, one from the UK Cooperative Group [21] and the most recent one from the Italian Group [22], indicate that for chemosensitive patients who have either a HLA identical sibling or a matched unrelated donor, allo-SCT offers better long-term outcome both in terms of PFS and OS. But this assumption was made in the "pre-BV era"; BV is able to offer a very effective and well-tolerated treatment option that will eventually lead to more patients reaching the allo-SCT procedure in better clinical conditions, thus improving at the end of the day the results of the procedure. On the other hand, relapsed patients would have the option to be treated with a less toxic treatment approach. For those achieving a metabolic CR, the question of whether to consolidate this response with an allotransplant is still a matter of huge debate in the scientific community. Moreover, there seems to be a plateau around 20 % in PFS for those patients being included in the phase II pivotal trial in the 3-year follow-up analysis [23], raising the possibility of

having a proportion of patients being cured with the drug alone and no further therapy. Additional studies and longer follow-up of the patients included in the pivotal trials will eventually solve all of these issues in the near future.

The intensity of the conditioning regimen also seems to play a major role in the final outcome of the allogeneic procedure. Retrospective analyses show that low-dose total body irradiation containing protocols is specifically associated with a very high RR after transplantation [11••, 12]. In addition to that, another EBMT retrospective analysis performed in children and adolescents [24] indicates that RIC protocols give at the end a poorer outcome because the decreased NRM seen in this setting is not able to counterbalance the higher RR after the transplant. Recently, the LWP of the EBMT has undertaken a second retrospective analysis comparing long-term outcome of patients with HL undergoing a myeloablative allo-SCT (MAC) ($n=99$) versus those receiving a RIC-allo-SCT ($n=215$) in recent years, from January 2006 to December 2010 (S. Stavrik, personal communication). With a median follow-up of 34 months, NRM did not show significant differences between both groups of patients (11 % at 36 months). RR was significantly higher in the RIC group (55 % vs. 40 % at 36 months, $p=0.05$) giving a significant advantage in terms of PFS for the MAC group (50 % vs. 33 % at 36 months, $p=0.02$) with no differences in OS (53 % for MAC vs. 50 % for RIC at 36 months). Multivariate analyses did not show any adverse prognostic factor for NRM; the use of RIC was an adverse prognostic factor for RR [HR 0.57, 95 % CI (0.36–0.9), $p=0.01$]. PFS was adversely affected by the use of total body irradiation [HR 1.5, 95 % CI (0.99–2.26), $p=0.05$] and the use of RIC [HR 0.6, 95 % CI (0.4–0.9), $p=0.01$]. The most important prognostic factor for OS was having chemosensitive disease at allo-SCT [HR 1.75, 95 % CI (1.21–2.54), $p=0.002$]. In this sense, efforts should be made to try to personalize the conditioning regimen taking into consideration clinical characteristics of the patients. Of note, and after a sharp decrease in numbers of MAC protocols favoring the reduced intensity ones, data coming from the Lymphoma database of the EBMT indicate that the number of MAC transplants have steadily been increasing from 2004 and onwards (Fig. 1a).

The more recent investigation of a response-adjusted transplantation algorithm identifies a further potential strategy for evaluation of allo-SCT in those deemed to be at high risk of failure of ASCT, targeting the intensification to those who have residual FDG-avid disease following salvage therapy [25•]. The 3-year PFS of 68 % in this high-risk group was encouraging, with 80 % of "current" PFS following DLIs. Such approaches may require refinement according to delineation of number of lines of salvage, and according to the outcome of prospective studies evaluating maintenance strategies following ASCT (e.g., the AETHERA trial), and it is recommended that they be evaluated within the context of prospective national studies. In fact, these results have constituted the basis for a phase II prospective clinical trial (CRUK-PAIReD, EUDRACT-2008-004956-60) already closed for recruitment that analyzes long-term outcome of relapsed/refractory HL patients who do not achieve a metabolic CR with first-line salvage chemotherapy and undergo an allo-SCT with BEAM protocol as conditioning regimen and the use of Campath 1H as GVHD prophylaxis. Final results of this trial are eagerly awaited by the transplant community.

Finally, the number of potential candidates for an allogeneic procedure could be increased with the use of haploidentical donors. Raiola et al. [26] recently published the results of a group of 26 multiply relapsed HL patients treated with a related HLA haploidentical allo-SCT, following a nonmyeloablative conditioning with low-dose total body irradiation, as proposed by the Baltimore group. GVHD prophylaxis consisted of high-dose posttransplantation cyclophosphamide, mycophenolate, and a calcineurin inhibitor. All patients failed a previous ASCT, and 65 % had active disease at the time of the allogeneic procedure. The incidence of grade II-IV aGVHD and of cGVHD was 24 % and 8 %, respectively. With a median follow-up of 24 months, 21 patients were alive and 20 were disease-free. Cumulative incidences of NRM and relapse were 4 % and 31 %, respectively, and the actuarial 3-year OS and PFS were 77 % and 63 %, respectively. These appealing but still preliminary results have significantly increased the interest in performing haploidentical allo-SCT in this subpopulation of patients as indicated by the raising numbers of this procedure being reported to the EBMT Database (Fig. 1b).

Conclusions

Allo-SCT is probably the most frequently used treatment strategy in ASCT failures if the patient is young, has chemosensitive disease, and an appropriate donor is available. Its role is with no doubt going to be extensively analyzed in the future at earlier stages of the disease and might be challenged in the post-ASCT setting by BV or other new out comers.

Compliance with Ethics Guidelines

Conflict of Interest
A. Sureda, E. Domingo, N. Schmitz, and P. Dreger declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. J Clin Oncol. 2002;20:630–7.
2. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med. 2003;348:2386–95.
3. Ljungman P, Bregni M, Brune M, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. Bone Marrow Transplant. 2010;45:219–34.

4. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341:1051–4.

5. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease. Lancet. 2002;359:2065–71.

6. Martínez C, Canals C, Sarina B, et al. Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. Ann Oncol. 2013;24:2430–4.

7. Weiden PL, Flournoy N, Thomas ED, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts. N Engl J Med. 1979;300:1068–73.

8. Weiden PL, Sullivan KM, Flournoy N, et al. Antileukemic effect of chronic graft-versus-host disease: contribution to improved survival after allogeneic marrow transplantation. N Engl J Med. 1981;304:1529–33.

9. Gajewski JL, Philips GL, Sobocinski KA, et al. Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. J Clin Oncol. 1996;14:572–8.

10. Milpied N, Fielding AK, Pearce RM, Erns P, Goldstone AH. Allogeneic bone marrow transplant is not better than autologous transplant for patients with relapsed Hodgkin's disease. J Clin Oncol. 1996;14:1291–6.

11.•• Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2008;26:455–62.

A total of 168 patients with Hodgkin's lymphoma undergoing a first allogeneic stem cell transplantation [reduced intensity conditioning (RIC), n=89; myeloablative conditioning, n=79] between January 1997 and December 2001 were compared. Nonrelapse mortality was significantly decreased in the RIC group, overall survival was better in the RIC group, and there was a trend for better progression-free survival in the RIC group. The development of chronic graft-versus-host disease significantly decreased the incidence of relapse, which translated into a trend for a better progression-free survival.

12. Robinson SP, Sureda A, Canals C, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome. Haematologica. 2009;94:230–8.

13. Anderlini P, Saliba R, Acholonu S, et al. Reduced-intensity allogeneic stem cell transplantation in relapsed and refractory Hodgkin's disease: low transplant-related mortality and impact of intensity of conditioning regimen. Bone Marrow Transplant. 2005;35:943–51.

14. Alvarez I, Sureda A, Caballero MD, et al. Nonmyeloablative stem cell transplantation is an effective therapy for refractory or relapsed Hodgkin lymphoma: results of a Spanish prospective cooperative protocol. Biol Blood Marrow Transplant. 2006;12:172–83.

15. Peggs KS, Hunter A, Chopra R, et al. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. Lancet. 2005;365:1934–41.

16.•• Sureda A, Canals C, Arranz R, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Español de Linfomas/Trasplante de Médula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica. 2012;97:310–7.

In this phase II study, 92 patients with relapsed Hodgkin's lymphoma were treated with salvage chemotherapy followed by reduced-intensity allogeneic transplantation. Seventy-eight patients proceeded to allograft. Fludarabine (150 mg/m(2) iv) and melphalan (140 mg/m(2) iv) were used as the conditioning regimen. The nonrelapse mortality rate was 8 % at 100 days and 15 % at 1 year. Relapse was the major cause of failure. The progression-free survival rate was 47 % at 1 year and 18 % at 4 years from trial entry. The overall survival rate was 71 % at 1 year and 43 % at 4 years. Chronic graft-versus-host disease was associated with a lower incidence of relapse. Patients allografted in complete remission had a significantly better outcome.

17.•• Peggs KS, Kayani I, Edwards N, et al. Donor lymphocyte infusions modulate relapse risk in mixed chimeras and induce durable salvage in relapsed patients after T-cell-depleted allogeneic transplantation for Hodgkin's lymphoma. J Clin Oncol. 2011;29:971–8.

Forty-nine patients with multiply relapsed Hodgkin's lymphoma were allografted using in vivo T-cell depletion as graft-versus-host disease prophylaxis. Eight of 49 (16 %) had grade II-IV acute GVHD and 7 (14 %) had chronic GVHD before donor-lymphocyte infusion. Sixteen (33 %) patients received donor-lymphocyte infusion from 3 months after transplantation for residual disease or progression. Nonrelapse-related mortality was 16.3 % at 730 days. Projected 4-year overall and progression-free survival were 55.7 % and 39 %, respectively.

18.•• Younes A, Gopal AK, Smith SE, et al. Results of a pivotal Phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30:2183–9.

The efficacy and safety of brentuximab vedotin were evaluated in patients with relapsed or refractory Hodgkin's lymphoma after autologous stem-cell transplantation. A total of 102 patients were treated with brentuximab vedotin 1.8 mg/

kg by intravenous infusion every 3 weeks. In the absence of disease progression or prohibitive toxicity, patients received a maximum of 16 cycles. The overall response rate was 75 % with complete remission in 34 % of patients. The median progression-free survival time for all patients was 5.6 months, and the median duration of response for those in CR was 20.5 months. The most common treatment-related adverse events were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea.

19.• Chen R, Palmer JM, Thomas SH, et al. Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2012;119:6379–81.

Eighteen patients with refractory Hodgkin's lymphoma, candidates for allogeneic stem cell transplantation and having received brentuximab vedotin before the allogeneic procedure, were analyzed. The 1-year overall survival was 100 %, progression-free survival was 92.3 %, and nonrelapse mortality was 0 %. The incidence of acute graft-versus-host disease was 27.8 % and chronic graft-versus-host disease was 56.3 %. Brentuximab vedotin before reduced-intensity allogeneic stem cell transplantation did not adversely affect engraftment, GVHD, or survival and provided sufficient disease control to enable the transplantation procedure.

20. Chen R, Palmer J, Tsai NC, et al. Brentuximab vedotin improves HCT-CI, CR status, and peritransplant toxicity in patients with relapsed/refractory Hodgkin lymphoma heading to RIC Allo-HCT. Blood. 2013;122:3374.

21. Thomson KJ, Peggs KS, Smith P, et al. Superiority of reduced-intensity allogeneic transplantation over conventional treatment for relapse of Hodgkin's lymphoma following autologous stem cell transplantation. Bone Marrow Transplant. 2008;41:765–70.

22. Sarina B, Castagna L, Farina L, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. Blood. 2010;115:3671–7.

23. Gopal AK, Chen R, Smith SE, et al. Three-year follow-up data and characterization of long-term remissions from an ongoing Phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2013;122:4382.

24. Claviez A, Canals C, Dierickx D, et al. Allogeneic hematopoietic stem cell transplantation in children and adolescents with recurrent and refractory Hodgkin lymphoma: an analysis of the European Group for Blood and Marrow Transplantation. Blood. 2009;114:2060–7.

25.• Thomson K, Kayani I, Ardeshna KM, et al. A response-adjusted PET-based transplantation strategy in primary resistant and relapsed Hodgkin lymphoma. Leukemia. 2013;27:1419–22.

A response-adjusted transplantation algorithm using allogeneic stem cell transplantation with a BEAM-Campath conditioning protocol for those patients deemed to be at high risk of failure of autologous stem cell transplantation because of a metabolically active disease after first-line salvage chemotherapy is analyzed.

26. Raiola A, Dominietto A, Varaldo R, et al. Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. Bone Marrow Transpant. 2014;49:190–4.