Published in final edited form as:

Curr Opin Oncol. 2011 November ; 23(6): 681–691. doi:10.1097/CCO.0b013e32834bb88e.

Current Status of Allogeneic transplantation for Aggressive Non-Hodgkin lymphoma

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Abstract

Purpose—To provide a succinct update on the role of allogeneic stem cell transplantation in the management of patients with aggressive lymphomas. To clarify the indications for allogeneic transplantation vis-à-vis autologous transplant and to discuss the rational and potential benefits of reduced intensity conditioning(RIC), non-myeloablative (NMA) transplant, T-cell depletion and variations in GVHD prophylaxis.

Recent findings—Considerable effort has been spent in developing transplant regimens with reduced toxicity and reduced GVHD. The role of allogeneic transplantation has also been redefined in light of advances in lymphoma classification, diagnostic methods, particularly PET scan and advances in transplant technology. Haplo and UCB SCT allow identification of a donor for nearly all patients.

Summary—RIC and NMA conditioning have reduced early toxicity but are associated with increased risk for disease recurrence. Promising data have been reported from a novel conditioning regimen combining NMA with ibritumomab tiuxetan. T-cell depletion reduces cGVHD but has some increase in rate of recurrence. Rapamycin may be associated with reduction in risk for disease recurrence. In diffuse large B cell lymphoma, the outcome of allo SCT depends on patient characteristics and chemosensitivity. It is useful after failure of autoSCT and in partial responses to salvage therapy. Allo SCT may be the treatment of choice for advanced T-cell and NK cell lymphoma and for ATLL. Prophylactic or preemptive DLI may be useful, but requires controlled studies.

Keywords

allogeneic transplant; Allogeneic; Lymphoma; PTCL; DLBCL; ATLL; GVL

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Conflict of Interest: none

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Introduction

The role of allogeneic transplantation for lymphoma is continually redefined as a result of advances in conventional treatments, in transplant technology, in diagnostic methods and in prognostic tools. Allogeneic transplantation for lymphoma is usually considered in the salvage setting, as an alternative to autologous stem cell transplantation or after failure of autologous transplantation. This review will focus on allogeneic transplantation for aggressive lymphoma, the largest subgroup of which is comprised of diffuse large B cell lymphoma. But numerous other subtypes exist some of which will be discussed.

Allogeneic transplantation – Comparison with autologous transplantation and graft vs lymphoma effects

It is generally and probably correctly assumed that allogeneic transplantation is both more effective and more toxic than autologous transplantation. Early retrospective observations^{1–5} were followed by a prospective study, where patients with matched siblings were assigned to allogeneic transplantation, all others to autologous.⁶ There was no complete balance between the groups since those undergoing allogeneic transplant more frequently had a history of bone marrow involvement and of chemotherapy resistant disease. Despite this, there was a significantly lower incidence of relapse after allogeneic transplant and a non-significant improvement in survival. (Figure 1A) Similarly, the transplant centers in Ontario, using allo transplant preferentially for those with bone marrow involvement or an inadequate bone marrow harvest, found a lower rate of disease recurrence after allogeneic transplantation.⁷ But the advantages of allogeneic transplant were at least partially offset by an increased rate of treatment related mortality.(Figure 1 B) The European Registry confirmed this in a large registry study.⁸ A recent CIBMTR study comparing allogeneic with autologous transplant in diffuse large B cell lymphoma was not able to show any benefit to allogeneic transplantation.⁹ In this study relapse rates after allogeneic and autologous transplantation were found to be similar after adjustment for various prognostic factors. Similarly, Gross et al studying pediatric patients did not find much advantage for allogeneic transplantation except in the subgroup with lymphoblastic lymphoma. There seems therefore a considerable discrepancy between the results of the few more or less prospective comparisons.^{6;7} and the registry analysis or retrospective comparisons. The reasons are multiple and include imbalances in patient characteristics, heterogeneity of disease histologies and differences in treatment protocols. Allo recipients tend to be younger, have more advanced disease, more frequent marrow involvement and receive TBI more commonly. Other important determinants of outcome such as serum LDH or PET scan results, measures of performance status or comorbidities are rarely included.^{10;11} Also, most studies report on patients accrued over long periods of time, during which improvements in supportive care and in HLA-typing have resulted in steady improvement in allogeneic transplant results.¹² So, the results may no longer be representative of current outcomes of allogeneic transplantation. By contrast, no major changes have occurred in autologous transplantation over the past decade.

2. Graft vs Lymphoma effects

The most definitive evidence of graft vs lymphoma effects remains the clinical observation of lymphoma regression after withdrawal of immunosuppression or after infusion of donor lymphocytes^{2;13;14}. In fact, one of the earliest observations of graft vs leukemia effects in man was made in a patient with Burkitt's disease, recurring after allogeneic bone marrow transplantation, whose disease responded to withdrawal of immuno-suppressive therapy². We also observed, responses to DLI or withdrawal of GHV-prohylaxis in six of nine patients recurring after transplantation.¹³ (Figure 2) In general though, responses to DLI or to withdrawal of immunosuppression appear more frequent in patients with indolent histologies than in those with aggressive histologies.^{15;16} GVL effects may also be more clinical important in certain disease histologies such as in peripheral T-cell lymphoma.

A second way in which GVL effects can be demonstrated is by the analysis of the relationship between GVHD and disease recurrence after allogeneic transplantation. In one retrospective study by the EBMTR, a lower recurrence rate was found for patients with chronic GVHD vs those without cGVHD (0% vs 35%, $p=0.02$).⁴ In other studies of intermediate grade lymphoma, no relation between the incidence of GVHD and disease recurrence could be demonstrated.¹⁷ Besides the presence of GVL effects, the lack of involvement by lymphoma cells in the graft, may also contribute to a decreased recurrence rate after allogeneic transplantation. There is considerable evidence that, in autologous transplantation, the infusion of occult lymphoma cells contributes in many cases to disease recurrence.¹⁸ CIBMTR and EBMTR several years ago conducted a joint study of syngeneic transplants, the recurrence rate of which was lower than that of autologous transplants and similar to that of allogeneic transplants, suggesting that GVL effects are less important in lymphoma.¹⁹

Conditioning Regimens

TBI, initially introduced for its antileukemic activity and immunosuppressive effects long constituted the backbone of allogeneic transplantation.²⁰ But TBI is toxic. Mucositis can be debilitating and is further exacerbated by post transplant methotrexate.²¹ Renal, hepatic and particularly pulmonary toxicity are life-threatening and TBI has been used rarely in older patients.^{3;22} Concerns over toxicity led to the development of novel conditioning regimens often labeled reduced intensity conditioning regimens (RIC) or non-myeloablative regimens (NMA). Numerous studies have been reported. But the terminology of RIC and NMA imply reduced toxicity, and are therefore somewhat self-fulfilling and potentially misleading.²³ They also mask the considerable heterogeneity of the various regimens, labeled as RIC or NMA by committee decision.^{24;25} GVHD related complications may be more common a cause of TRM than toxicities from conditioning, an issue not addressed by modifying the conditioning regimens.²⁶ After more than a decade of work, there is no definitive answer to the question of superiority of any regimen. The best evidence of advantages for RIC comes from Seattle studies demonstrating improved survival after non- myeloablative conditioning, but only in those with considerable comorbidities.²⁷ In most other reports, early TRM has been somewhat reduced, but late TRM due to GVHD and related complications may be higher. Relapse is similar or increased compared with myeloablative transplants.^{28;29} Overall, considerable questions linger over which transplant regimen is optimal. There may

be differences in outcome due to more or less intensive regimens, but overall outcome is affected considerably more by patient and disease related characteristics.

Be it as it may, full dose TBI based regimens are rarely utilized, particularly in cases of lymphoma. The Seattle non-myeloablative conditioning regimen involving low doses of TBI are a common choice but associated with high rates of recurrence in patients with active disease. In a recent study the Seattle group combined their NMA conditioning with ibritumomab tiuxetan, a radio-labelled anti-CD20 and reported a 35% long term PFS in a group of patients with advanced and often bulky disease, though the results were superior in patients with indolent lymphomas.³⁰ Other commonly used conditioning regimens involve busulfan or melphalan in combination with other agents. In the 1990's we prospectively studied the tri-alkylator regimen consisting of thiotepa-busulfan and cyclophosphamide and found an approximately 30% long term remission rate in patients with refractory lymphoma.³¹ Others used busulfan-cyclophosphamide or busulfan cyclophosphamide-etoposide.³² More recently though, most studies have involved intravenous busulfan, often with AUC monitoring and encouraging results have been reported in lymphoma patients.^{33;34}

The BEAM regimen (BCNU, etoposide, cytarabine, melphalan) is commonly used in autologous transplantation and was developed by our group for use in allogeneic transplantation.³⁵ We found an approximately 40% long term survival including durable remissions in a large fraction of patients with refractory lymphoma and concluded that the BEAM regimen might be optimal for patients with lymphoma. Our encouraging results were subsequently confirmed by a British group who found an excellent long term survival with limited toxicity and by the Stanford group who used a variant, CBV.^{36;37} More commonly fludarabine melphalan is utilized. This regimen has resulted in favorable long term outcomes.^{38;39}

GVHD prophylaxis

GVHD can be beneficial by preventing relapse and detrimental by causing chronic morbidity and late deaths. The concept of reduced intensity conditioning is built on exploiting GVL effects. The Seattle group in particular has found that acute GVHD is to be avoided because it increases TRM; in their experience chronic GVHD prevents recurrence without increased TRM.⁴⁰ Such data do not take into account the serious morbidity associated with chronic GVHD and its impact on very long-term survival. Chronic GVHD and/or its treatment are the major risk factors for many late complications including infertility, early menopause, osteonecrosis, chronic pulmonary and cardiac problems and increased risk for skin cancer.^{41–44} Transplant patients in remission face an ongoing risk of death that well exceeds that of an age matched population and chronic GVHD is a major risk factor for late death after transplant.^{41;44} Avoidance of late chronic GVHD underlies our interest, and that of other groups in T-cell depleted transplant, usually using in vivo alemtuzumab or ATG.^{36;38;39;45} Many studies, usually non randomized have compared the outcomes of T-depleted transplant and, with few exceptions have shown a somewhat increased rate of disease recurrence but no effect on survival.^{46–48} Some studies, using profound in-vitro T-cell depletion have however shown a very high early recurrence rate.⁴⁹

It may therefore well be that outcomes depend on the T cell depletion technology utilized and on the lymphocyte subpopulations that are removed. Also, T-cell depletion increases the risk of early opportunistic infections and an effective strategy for CMV and EBV detection and treatment is essential.^{50–52} Others have used sirolimus, an immunosuppressant with antineoplastic activity in lymphoid malignancies. Sirolimus has reduced the incidence of acute, but not of chronic GVHD. In at least one study it was associated with a reduced incidence of disease recurrence.⁵³

Donor source

Most older studies of transplant for lymphoma are restricted to recipients of matched sibling transplant, which are available for fewer than half of the patients and which are increasingly problematic as we consider transplant for older individuals and knowledge of the genetic basis of disease increases. We currently estimate that we reject approximately 10 percent of our potential sibling donors because of comorbidities - Older recipients have older and sicker donors.⁵⁴ Interestingly, there are also increasingly frequent reports of clonal hemato-lymphopoiesis or genetic lesions in siblings of potential transplant recipients.^{55;56}

Advances in unrelated donor selection including high resolution HLA typing has resulted in major improvements in outcome of unrelated donor transplant.⁵⁷ Many recent large studies have a considerable number of unrelated donor recipients, who appear to have similar or even better outcomes than matched sibling transplants.^{26;39;58–61} As donor typing becomes more accurate, it is also clear that many patients, particularly those of minority descent, lack matching donors.⁶² Alternative donor transplant i.e. haplo-identical and/or cord blood transplantation is increasingly considered. Of interest reduced intensity haplo-identical transplantation as proposed by the Hopkin's group appears to have an excellent anti-tumoral effect with great rates of disease control, in contrast to the high rate of disease progression in myeloid diseases.⁶³ Umbilical cord blood transplantation appears reasonably effective as well.⁶⁴ Donor availability should therefore no longer constitute a major limitation for patients in need of allogeneic stem cell transplantation.

Allogeneic transplantation for recurrent or refractory intermediate grade lymphoma

Diffuse large B cell lymphoma is by far the most common subtype among the aggressive lymphomas. Several categories can be recognized based on molecular features. The most common categories include (1) GCB-like (2) non GCB-like and (3) those with primary mediastinal B cell lymphoma.⁶⁵ Furthermore, MYC translocations and in particular the double hit bcl2-Myc translocation are increasingly reported as having poor prognostic implications.^{66;67} The implications for allogeneic transplantation are unclear at present, though we have avoided allo transplant in PMBL which appears to be exquisitely susceptible to dose intensification.^{68–70}

Transplantation is commonly used in the management of patients with recurrent diffuse large B cell lymphoma. Comparisons between auto and allo have never convincingly demonstrated a survival benefit and often have also failed to show major differences in

recurrence rates.^{1;3;4;6;9;71;72} Autologous transplantation tends to be favored because of its feasibility, low TRM and proven track record.⁷³ But the results of the Coral study raise concern over the effectiveness of autologous transplantation in the rituximab era. Those failing rituximab-based first line chemotherapy had dismal outcomes with autologous transplantation.⁷⁴ This may raise interest in allogeneic transplantation anew.

Until now though, we have limited allogeneic transplantation to patients who have adverse features for autologous transplantation, particularly those with refractory disease and/or multiple recurrences. A large number of reports show that allogeneic transplantation can be curative in a fraction of patients with otherwise refractory disease.^{2;3;17;22;26;31;34;35;37;58;75–83} Still the same rules that govern prognosis of autologous transplant are operative after allogeneic. Having refractory disease remains an adverse prognostic feature. Those who fail to respond to chemotherapy and come to transplant without radiologic response or with an elevated LDH are unlikely to do well; only a small fraction will be cured.^{26;32;39;58;83;84} By contrast, several investigators find that findings of PET positivity have no impact for response to allogeneic transplant.^{39;85} Patients with partial responses to salvage and normal LDH but residual PET positive areas may be good candidates for allogeneic transplant. (Figure 3) This needs to be confirmed in prospective studies, particularly since others continue to find prognostic value in PET scans.⁸⁶ At least one group found that patients with stable disease have a reasonable outcome after allogeneic transplant in contrast to those with progressive disease.^{87;88} When measured, performance status and comorbidity assessment also strongly correlate with long-term outcome.^{47;59;86} So, though allogeneic transplant may be effective in some patients who would be categorized as refractory based on lack of radiologic response (i.e. stable disease) or failure to resolve all PET positivity, it is unlikely to be effective in those with truly progressive disease and worsening radiologic findings or an increased LDH.

Allogeneic after failure of autologous transplantation

Allogeneic transplantation has also commonly been used after failure of autologous transplant, particularly in patients with diffuse large B cell lymphoma. An initial study by Freytes et al, found poor outcomes for such patients. The majority of patients relapsed again, but duration of response was largely dependent on whether the disease was still chemotherapy sensitive prior to transplant.⁸⁹ Subsequent studies, often using reduced intensity conditioning showed better outcomes, with durable remissions occurring in 20–40% of patients.^{90–94} In aggregate the data indicate that patient (performance status, albumin) – and disease related factors (duration of remission, extent of disease, chemotherapy sensitivity) predict outcome, more than any particular conditioning regimen utilized. Baron et al found that chronic GVHD was associated with decreased risk for disease recurrence.⁹⁴ While such data are often considered demonstrations of the power of GVL effects, durable remissions have also occurred after second autologous transplantation.⁹⁵

Allogeneic Transplantation for Burkitt's lymphoma

Very little has been reported on allogeneic transplantation for patients with recurrent Burkitt's lymphoma. It is a disease that is occasionally susceptible to graft vs lymphoma

effects and some of the earliest report on this phenomenon concerned patients with Burkitt's lymphoma.^{2;14} But Burkitt's lymphoma is also highly curable with intensive chemotherapy.⁹⁶ For those with recurrent Burkitt's lymphoma, the risk of recurrence after allogeneic transplant is extremely high. In an early series, we found among fourteen adults with refractory Burkitt's disease, only one long term remission. Very early relapse accounted for the majority of failures.⁹⁷ Similar outcomes were recently reported for pediatric patients.⁹⁸ Only about 30% were long-term survivors and the rate of early disease recurrence was 70%.

Peripheral T cell lymphoma, Mycosis Fungoides and NK cell Lymphoma

Approximately 10 to 20% of lymphomas are of T-or NK-cell lineage and constitute considerable challenges because of their complexity and in general their worse prognosis.⁹⁹ Emerging data suggest a considerable role for allogeneic transplantation in these disorders. Advanced mycosis fungoides can be an aggressive disease at times impossible to control with conventional chemotherapy. Several reports indicate that allogeneic transplantation, in contrast to autologous, can be curative, sometimes even in patients with very refractory disease.^{100–102} Molina et al, were among the first to document a high rate of durable responses in a series of 8 patients undergoing allogeneic transplantation.¹⁰⁰ Similar results were reported by the MD Anderson group.¹⁰² Wu et al in a meta-analysis find that remissions are more frequent and more prolonged after allogeneic than after autologous transplantation.¹⁰³ A registry study found prolonged survival in the majority of patients.¹⁰¹ Responses and response duration depended on the stage of disease. Relapse was more common after T-depleted transplant, but was not dependent on the conditioning regimen. After relapse, many patients responded to salvage therapy including donor lymphocyte infusions, suggesting a strong susceptibility to GVL effects of this disorder. Peripheral T cell lymphoma is highly heterogeneous and some subtypes are extremely aggressive. In some cases, allogeneic transplant offers the only chance for cure. For example, hepatosplenic T cell lymphoma an otherwise incurable disorder has occasionally been cured with allogeneic transplantation.¹⁰⁴ Similarly recurrent and refractory angioimmunoblastic T cell lymphoma can be cured by allogeneic transplant. Outcome correlates with chemotherapy sensitivity prior to transplant.¹⁰⁵ Woessman et al reported impressive outcomes in pediatric patients undergoing allogeneic transplant for relapsed and refractory anaplastic large cell lymphoma.¹⁰⁶ This may be of particular interest given the recent development of a brentuximab, a conjugated anti-CD30 with an impressive but transient rate of response in anaplastic large cell lymphoma.¹⁰⁷ Such patients may then be consolidated with allo transplant. The majority of patients with PTCL have lymphomas that cannot be further classified, so called PTCL NOS (not otherwise specified). Reports from several groups show high cure rates with allogeneic transplant in such patients often using reduced intensity conditioning.^{108–112} Many of these reports indicate responses to DLI or other immune manipulations or attribute the occurrence of response to GVL effects. Whether the results of allogeneic transplantation are truly superior to those of autologous transplantation or of conventional chemotherapy continues to be debated.¹¹³ Jacobsen from the Dana Farber group, in an interesting report, finds that allogeneic transplant is particularly successful for patients with nodal T-cell lymphoma and less so for extranodal disease.¹¹⁴

NK cell lymphoma is a devastating EBV –driven lymphoma that is quite common in the Far East and South America but also regularly encountered in Europe and the US. Many patients present with involvement of the sino-nasal area, but other presentations are also common. Until recently radiation therapy was the mainstay of treatment and was combined with chemotherapy. Emerging data suggest a major role for asparaginase in its treatment.¹¹⁵ Many patients still relapse, but allogeneic transplantation has been shown to be curative, particularly in younger patients with chemotherapy sensitive recurrences.^{116–118} The importance of GVL effects in this disorder is underscored by response to DLI.¹¹⁹

ATLL, caused by chronic infection with the HTLV-1 virus is common in Japan and in some Caribbean islands. The disease when aggressive, can only be cured by allogeneic transplantation. Many patients are elderly and have comorbidities and treatment related morbidity has been a concern.¹²⁰ After transplant responses to withdrawal of immunosuppression have been frequently observed.^{121;122} The prevalence of occult HTLV-I infection is high in endemic areas and many HLA-identical siblings are infected with the virus. Use of donors who are HTLV-1 positive is associated with an increased rate of complications.¹²²

Relapse

When relapse occurs in patients with aggressive lymphoma it often happens within the first six months after transplant and the prognosis for such early relapsing patients is poor. Few if any such patients obtain durable remissions to further chemotherapeutic or immunologic intervention.^{39;123–125} Occasional patients, particularly those with late relapses respond to further interventions and appear susceptible to GVL effects. Because of the poor progression of early relapsing patients, some have recommended pre-emptive therapy with DLI when mixed chimerism is observed.¹²⁶ This approach is controversial since DLI can induce GVHD and since others have not found mixed chimerism to be predictive of disease recurrence.^{58;127} Others have administered prophylactic DLI and rituximab to prevent relapse and report encouraging pilot data.¹²⁸ Any prophylactic or pre-emptive therapy should be carefully tested in prospective studies before being widely adopted, particularly since the toxicity profile of various medications can change dramatically when administered after allogeneic transplant.¹²⁹

Conclusion

Allogeneic Stem Cell Transplantation is a curative treatment for various subtypes of aggressive lymphoma. In Diffuse Large B cell lymphoma it is the treatment of choice for patients failing autologous transplantation and for patients with partial response to salvage therapy.¹³⁰ It may be used more in the future as autologous transplant has been found to be rather ineffective in patients failing rituximab based frontline therapy. Allogeneic transplantation is emerging as the treatment of choice in PTCL and NK cell lymphoma. Further study is needed to identify conditioning regimens with improved efficacy and reduced toxicity.

Acknowledgement

Support: Dr. van Besien is supported by Grant 5K24CA116471-05

Reference List

1. Jones RJ, Ambinder RF, Piantadosi S, Santos GW. Evidence of a graft-versus-lymphoma effect associated with allogeneic bone marrow transplantation. *Blood*. 1991; 77:649–653. [PubMed: 1991174]
 2. Petersen FB, Appelbaum FR, Bigelow CL, et al. high-dose cytosine arabinoside, total body irradiation and marrow transplantation for advanced malignant lymphoma. *Bone Marrow Transplant*. 1989; 4:483–488. [PubMed: 2676043]
 3. Appelbaum FR, Sullivan KM, Buckner CD, et al. Treatment of malignant lymphoma in 100 patients with chemotherapy, total body irradiation and marrow transplantation. *J.Clin.Oncol*. 1987; 5:1340–1347. [PubMed: 3305793]
 4. Chopra R, Goldstone AH, Pearce R, et al. Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group registry data. *J.Clin.Oncol*. 1992; 10:1690–1695. [PubMed: 1403052]
 5. Bureo E, Ortega JJ, Munoz A, et al. Bone marrow transplantation in 46 pediatric patients with non-Hodgkin's lymphoma. Spanish Working Party for Bone Marrow Transplantation in Children. *Bone Marrow Transplant*. 1995; 15:353–359. [PubMed: 7599558]
 6. Ratanatharathorn V, Uberti J, Karanes C, et al. Prospective comparative trial of autologous versus allogeneic bone marrow transplantation in patients with non-Hodgkin's lymphoma. *Blood*. 1994; 84:1050–1055. [PubMed: 8049425]
 7. Schimmer AD, Jamal S, Messner H, et al. Allogeneic or autologous bone marrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL): results of a provincial strategy. Ontario BMT Network, Canada. *Bone Marrow Transplant*. 2000; 26:859–864. [PubMed: 11081385]
 8. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplant*. 2003; 31:667–678. [PubMed: 12692607]
 - **9. Lazarus HM, Zhang MJ, Carreras J, et al. A comparison of HLA-identical sibling allogeneic versus autologous transplantation for diffuse large B cell lymphoma: a report from the CIBMTR. *Biol.Blood Marrow Transplant*. 2010; 16:35–45. [PubMed: 20053330]
- Shows no advantage for allo SCT in DLBCL
10. Artz A, Pollyea D, Kocherginsky M, et al. Performance Status and Comorbidity Predict Transplant Related Mortality After Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant*. 2006; 12:954–964. [PubMed: 16920562]
 11. Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. *Cancer*. 2008; 112:1992–2001. [PubMed: 18311781]
 12. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010; 363:2091–2101. [PubMed: 21105791]
 13. Van Besien KW, de Lima M, Giralta SA, et al. Management of lymphoma recurrence after allogeneic transplantation: the relevance of graft-versus-lymphoma effects. *Bone Marrow Transplant*. 1997; 19:977–982. [PubMed: 9169641]
 14. Grigg AP, Seymour JF. Graft versus Burkitt's lymphoma effect after allogeneic marrow transplantation. *Leuk.Lymphoma*. 2002; 43:889–892. [PubMed: 12153181]
 - **15. Porter DL, Alyea EP, Antin JH, et al. NCI First International Workshop on the Biology, Prevention and Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation: Report from the Committee on Treatment of Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol.Blood Marrow Transplant*. 2010
- Review of recurrence after allogeneic transplantation and its treatment.

16. Grigg A, Ritchie D. Graft-versus-lymphoma effects: clinical review, policy proposals, and immunobiology. *Biol Blood Marrow Transplant*. 2004; 9:579–590. [PubMed: 15319770]
17. Dhedin N, Giraudier S, Gaulard P, et al. Allogeneic bone marrow transplantation in aggressive non-Hodgkin's lymphoma (excluding Burkitt and lymphoblastic lymphoma): a series of 73 patients from the SFGM database. *Societ Francaise de Greffe de Moelle. Br.J.Haematol*. 1999; 107:154–161. [PubMed: 10520036]
18. Sharp JG, Kessinger A, Mann S, et al. Outcome of high-dose therapy and autologous transplantation in non-Hodgkin's lymphoma based on the presence of tumor in the marrow or infused hematopoietic harvest. *J.Clin Oncol*. 1996; 14:214–219. [PubMed: 8558200]
19. Bierman PJ, Sweetenham JW, Loberiza FM, et al. Syngeneic Hematopoietic Stem Cell Transplantation for Non-Hodgkin's Lymphoma: A Comparison with Allogeneic and Autologous Transplantation. *J.Clin.Oncol*. :20033744–3753.
20. Thomas ED. A history of haemopoietic cell transplantation. *Br J Haematol*. 1999; 105:330–339. [PubMed: 10233401]
21. Cutler C, Li S, Kim HT, et al. Mucositis after allogeneic hematopoietic stem cell transplantation: a cohort study of methotrexate- and non-methotrexate-containing graft-versus-host disease prophylaxis regimens. *Biol Blood Marrow Transplant*. 2005; 11:383–388. [PubMed: 15846292]
22. Phillips GL, Herzig RH, Lazarus HM, et al. High-dose chemotherapy, fractionated total-body irradiation, and allogeneic marrow transplantation for malignant lymphoma. *J.Clin.Oncol*. 1986; 4:480–488. [PubMed: 3514803]
23. Deeg HJ. Transplantation conditioning regimens: can we say it better? *Biol Blood Marrow Transplant*. 2009; 15:653–655. [PubMed: 19450748]
24. Giralt S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant*. 2009; 15:367–369. [PubMed: 19203728]
25. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009; 15:1628–1633. [PubMed: 19896087]
26. Kim SW, Tanimoto TE, Hirabayashi N, et al. Myeloablative allogeneic hematopoietic stem cell transplantation for non-Hodgkin lymphoma: a nationwide survey in Japan. *Blood*. 2006; 108:382–389. [PubMed: 16522821]
27. Sorror ML, Storer BE, Maloney DG, et al. Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia. *Blood*. 2008; 111:446–452. [PubMed: 17916744]
28. Tomblyn M, Brunstein C, Burns LJ, et al. Similar and promising outcomes in lymphoma patients treated with myeloablative or nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation. 2008; 14:538–545. [PubMed: 18410896]
29. Rodriguez R, Nademanee A, Ruel N, et al. Comparison of reduced-intensity and conventional myeloablative regimens for allogeneic transplantation in non-Hodgkin's lymphoma. *Biol.Blood Marrow Transplant*. 2006; 12:1326–1334. [PubMed: 17162215]
30. Gopal AK, Guthrie KA, Rajendran J, et al. 90Y-ibritumomab tiuxetan, fludarabine, and TBI based non-myeloablative allogeneic transplant conditioning for patients with persistent high-risk B-cell lymphoma. *Blood*. 2011
31. van Besien K, Thall P, Korbling M, et al. Allogeneic transplantation for recurrent or refractory non-Hodgkin's lymphoma with poor prognostic features after conditioning with thiotepa, busulfan, cyclophosphamide. Experience in 44 consecutive patients. *Biol Blood Marrow Transplant*. 1997; 3:150–156. [PubMed: 9310192]
32. Aksentjevich I, Jones RJ, Ambinder RF, Garrett-Mayer E, Flinn IW. Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin's lymphoma. *Biol Blood Marrow Transplant*. 2006; 12:965–972. [PubMed: 16920563]
33. Pidala J, Roman-Diaz J, Kim J, et al. Targeted IV busulfan and fludarabine followed by post-allogeneic hematopoietic cell transplantation rituximab demonstrate encouraging activity in CD20+ lymphoid malignancies without increased risk of infectious complications. *Int.J.Hematol*. 2011; 93:206–212. [PubMed: 21246311]

34. Malard F, Cahu X, Clavert A, et al. Fludarabine, Antithymocyte Globulin, and Very Low-Dose Busulfan for Reduced-Intensity Conditioning before Allogeneic Stem Cell Transplantation in Patients with Lymphoid Malignancies. *Biol.Blood Marrow Transplant.* 2011
 35. Przepiorka D, van Besien K, Khouri I, et al. Carmustine, etoposide, cytarabine and melphalan as a preparative regimen for allogeneic transplantation for high-risk malignant lymphoma. *Ann.Oncol.* 1999; 10:527–532. [PubMed: 10416001]
 36. Faulkner RD, Craddock C, Byrne JL, et al. BEAM-alemtuzumab reduced-intensity allogeneic stem cell transplantation for lymphoproliferative diseases: GVHD, toxicity, and survival in 65 patients. *Blood.* 2004; 103:428–434. [PubMed: 12969983]
 37. Law LY, Horning SJ, Wong RM, et al. High-dose carmustine, etoposide, and cyclophosphamide followed by allogeneic hematopoietic cell transplantation for non-Hodgkin lymphoma. *Biol Blood Marrow Transplant.* 2006; 12:703–711. [PubMed: 16785059]
 38. Thomson KJ, Morris EC, Bloor A, et al. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. *J.Clin.Oncol.* 2009; 27:426–432. [PubMed: 19064981]
 - *39. Kenkre VP, Horowitz S, Artz AS, et al. T-cell-depleted allogeneic transplant without donor leukocyte infusions results in excellent long-term survival in patients with multiply relapsed Lymphoma. Predictors for survival after transplant relapse. *Leuk.Lymphoma.* 2011; 52:214–222. [PubMed: 21142785]
- Outcomes of T-cell depleted transplant without prophylactic or preemptive DLI. Also describes outcome after relapse.
40. Baron F, Maris MB, Sandmaier BM, et al. Graft-Versus-Tumor Effects After Allogeneic Hematopoietic Cell Transplantation With Nonmyeloablative Conditioning. *J.Clin.Oncol.* 2005; 23:1993–2003. [PubMed: 15774790]
 41. Bhatia S, Francisco L, Carter A, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study. *Blood.* 2007; 110:3784–3792. [PubMed: 17671231]
 42. Baker KS, Ness KK, Weisdorf D, et al. Late effects in survivors of acute leukemia treated with hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Leukemia.* 2010; 24:2039–2047. [PubMed: 20861916]
 43. Bacigalupo A, Lamparelli T, Barisione G, et al. Thymoglobulin prevents chronic graft-versus-host disease, chronic lung dysfunction, and late transplant-related mortality: long-term follow-up of a randomized trial in patients undergoing unrelated donor transplantation. *Biol.Blood Marrow Transplant.* 2006; 12:560–565. [PubMed: 16635791]
 - **44. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J.Clin.Oncol.* 2011; 29:2230–2239. [PubMed: 21464398]
- Shows that cGVHD is a major cause of late death in alloSCT recipients.
45. Novitzky N, Thomas V. Allogeneic stem cell transplantation with T cell-depleted grafts for lymphoproliferative malignancies. *Biol.Blood Marrow Transplant.* 2007; 13:107–115. [PubMed: 17222759]
 46. Juckett M, Rowlings P, Hessner M, et al. T cell-depleted allogeneic bone marrow transplantation for high-risk non-Hodgkin's lymphoma: clinical and molecular follow-up. *Bone Marrow Transplant.* 1998; 21:893–899. [PubMed: 9613781]
 47. Perales MA, Jenq R, Goldberg JD, et al. Second-line age-adjusted International Prognostic Index in patients with advanced non-Hodgkin lymphoma after T-cell depleted allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2010; 45:1408–1416. [PubMed: 20062091]
 48. Perez-Simon JA, Kottaridis PD, Martino R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. *Blood.* 2002; 100:3121–3127. [PubMed: 12384408]
 49. Glass B, Nickelsen M, Dreger P, et al. Reduced-intensity conditioning prior to allogeneic transplantation of hematopoietic stem cells: the need for T cells early after transplantation to induce a graft-versus-lymphoma effect. *Bone Marrow Transplant.* 2004; 34:391–397. [PubMed: 15273707]

50. Kline J, Pollyea DA, Stock W, et al. Pre-transplant ganciclovir and post transplant high-dose valacyclovir reduce CMV infections after alemtuzumab-based conditioning. *Bone Marrow Transplant.* 2006; 37:307–310. [PubMed: 16400339]
 51. Avivi I, Chakrabarti S, Milligan DW, et al. Incidence and outcome of adenovirus disease in transplant recipients after reduced-intensity conditioning with alemtuzumab. *Biol Blood Marrow Transplant.* 2004; 10:186–194. [PubMed: 14993884]
 52. Landgren O, Gilbert ES, Rizzo JD, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. *Blood.* 2009
 53. Armand P, Gannamaneni S, Kim HT, et al. Improved survival in lymphoma patients receiving sirolimus for graft-versus-host disease prophylaxis after allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning. *J.Clin.Oncol.* 2008; 26:5767–5774. [PubMed: 19001324]
 54. Estey E, de LM, Tibes R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood.* 2007; 109:1395–1400. [PubMed: 17038533]
 55. Hardy NM, Grady C, Pentz R, et al. Bioethical considerations of monoclonal B-cell lymphocytosis: donor transfer after haematopoietic stem cell transplantation. *Brit.J.Haematol.* 2007; 139:824–831. [PubMed: 18021093]
 56. Garcia JS, Madzo J, Cooper D, et al. Pre-Donor Evaluation of an HLA Matched Sibling Identifies a Novel Inherited RUNX1 Mutation Encoding a Missense Mutation Found Outside of the RUNT Domain in Familial Platelet Disorder. *Blood (ASH Annual Meeting Abstracts).* 2010; 116:2709.
 57. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. *Blood.* 2007
 58. Armand P, Kim HT, Ho VT, et al. Allogeneic transplantation with reduced-intensity conditioning for Hodgkin and non-Hodgkin lymphoma: importance of histology for outcome. *Biol.Blood Marrow Transplant.* 2008; 14:418–425. [PubMed: 18342784]
 59. Farina L, Bruno B, Patriarca F, et al. The hematopoietic cell transplantation comorbidity index (HCT-CI) predicts clinical outcomes in lymphoma and myeloma patients after reduced-intensity or non-myeloablative allogeneic stem cell transplantation. *Leukemia.* 2009; 23:1131–1138. [PubMed: 19194465]
 60. Rezvani AR, Norasetthada L, Gooley T, et al. Non-myeloablative allogeneic haematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: a multicentre experience. *Br J Haematol.* 2008; 143:395–403. [PubMed: 18759762]
 - *61. Ho VT, Kim HT, Aldridge J, et al. Use of matched unrelated donors compared with matched related donors is associated with lower relapse and superior progression-free survival after reduced-intensity conditioning hematopoietic stem cell transplantation. *Biol.Blood Marrow Transplant.* 2011; 17:1196–1204. [PubMed: 21193054]
- Improved outcomes after unrelated vs related donor transplant
62. Dew A, Collins D, Artz A, et al. Paucity of HLA-identical unrelated donors for African-Americans with hematologic malignancies: the need for new donor options. *Biol.Blood Marrow Transplant.* 2008; 14:938–941. [PubMed: 18640578]
 63. Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol.Blood Marrow Transplant.* 2008; 14:641–650. [PubMed: 18489989]
 64. Brunstein CG, Cantero S, Cao Q, et al. Promising progression-free survival for patients low and intermediate grade lymphoid malignancies after nonmyeloablative umbilical cord blood transplantation. *Biol.Blood Marrow Transplant.* 2009; 15:214–222. [PubMed: 19167681]
 65. Alizadeh A, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature.* 2000; 403:503–511. [PubMed: 10676951]
 66. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood.* 2009; 114:3533–3537. [PubMed: 19704118]

67. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood*. 2009; 114:2273–2279. [PubMed: 19597184]
 68. Smith SM, Levitan D, Welborne K, et al. TBC (Thiotepa, Busulfan, Cyclophosphamide) Conditioning for Second Autologous Transplants in Patients with Primary Mediastinal B Cell Lymphoma May Induce Durable Remissions. [abstract]. *Blood*. 2003; 102:5684.
 69. van Besien K, Kelta M, Bahaguna P. Primary mediastinal B-cell lymphoma: a review of pathology and management. *J.Clin Oncol*. 2001; 19:1855–1864. [PubMed: 11251018]
 70. Popat U, Przepiorka D, Champlin R, et al. High dose chemotherapy for relapsed and refractory diffuse large B-cell lymphoma; mediastinal localization predicts for a favorable outcome. *J.Clin.Oncol*. 1998; 16:63–69. [PubMed: 9440724]
 71. Bureo E, Ortega JJ, Muñoz A, et al. Bone marrow transplantation in 46 pediatric patients with non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 1995; 15:353–359. [PubMed: 7599558]
 72. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. *Bone Marrow Transplant*. 2003; 31:667–78. [PubMed: 12692607]
 73. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N.Engl.J.Med*. 1995; 333:1540–1545. [PubMed: 7477169]
 - **74. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J.Clin.Oncol*. 2010; 28:4184–4190. [PubMed: 20660832]
- Inferior outcome of autologous transplant in rituximab era.
75. Copelan EA, Kapoor N, Gibbins B, Tutschka PJ. Allogeneic marrow transplantation in non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 1990; 5:47–50. [PubMed: 2404530]
 76. Lundberg JH, Hansen RM, Chitambar CR, et al. Allogeneic bone marrow transplantation for relapsed and refractory lymphoma using genotypically HLA-identical and alternative donors. *J.Clin.Oncol*. 1991; 9:1848–1859. [PubMed: 1919635]
 77. Ernst P, Maraninchi D, Jacobsen N, et al. Marrow transplantation for non-Hodgkin's lymphoma: a multi-centre study from the European co-operative bone marrow transplant group. *Bone Marrow Transplant*. 1986; 1:81–86. [PubMed: 3332123]
 78. Shepherd JD, Barnett MJ, Connors JM, et al. Allogeneic bone marrow transplantation for poor-prognosis non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 1993; 12:591–596. [PubMed: 8136743]
 79. Mendoza E, Territo M, Schiller G, et al. Allogeneic bone marrow transplantation for Hodgkin's and non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 1995; 95:299–303. [PubMed: 7773222]
 80. Demirer T, Petersen FB, Appelbaum FR, et al. Allogeneic marrow transplantation following cyclophosphamide and escalating doses of hyperfractionated total body irradiation in patients with advanced lymphoid malignancies: a Phase I/II trial. *Int.J.Radiat.Oncol.Biol.Phys*. 1995; 95:1103–1109. [PubMed: 7607931]
 81. Demirer T, Weaver CH, Buckner CD, et al. High-dose cyclophosphamide, carmustine, and etoposide followed by allogeneic bone marrow transplantation in patients with lymphoid malignancies who had received prior dose-limiting radiation therapy. *J.Clin.Oncol*. 1995; 95:596–602. [PubMed: 7884421]
 82. Dann EJ, Daugherty CK, Larson RA. Allogeneic bone marrow transplantation for relapsed and refractory Hodgkin's disease and non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 1997; 20:369–374. [PubMed: 9339751]
 83. Sirvent A, Dhedin N, Michallet M, et al. Low non-relapse mortality and prolonged long-term survival after reduced-intensity allogeneic stem cell transplantation for relapsed or refractory diffuse large B-cell lymphoma: Report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *Biol Blood Marrow Transplant*. 2010; 16:78–85. [PubMed: 19744569]

84. Doocey RT, Toze CI, Connors JM, et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. *Br.J Haematol.* 2005; 131:223–230. [PubMed: 16197454]
- *85. Lambert JR, Bomanji JB, Peggs KS, et al. Prognostic role of PET scanning before and after reduced-intensity allogeneic stem cell transplantation for lymphoma. *Blood.* 2010; 115:2763–2768. [PubMed: 20124510]
- No prognostic impact of PET before allo-SCT
- *86. Doderio A, Crocchiolo R, Patriarca F, et al. Pretransplantation [18-F]fluorodeoxyglucose positron emission tomography scan predicts outcome in patients with recurrent Hodgkin lymphoma or aggressive non-Hodgkin lymphoma undergoing reduced-intensity conditioning followed by allogeneic stem cell transplantation. *Cancer.* 2010; 116:5001–5011. [PubMed: 20665491]
- PET still matters before allo-SCT
87. Bishop MR, Dean RM, Steinberg SM, et al. Correlation of pretransplant and early post-transplant response assessment with outcomes after reduced-intensity allogeneic hematopoietic stem cell transplantation for non-Hodgkin's lymphoma. *Cancer.* 2010; 116:852–862. [PubMed: 20041482]
88. Dean RM, Fowler DH, Wilson WH, et al. Efficacy of reduced-intensity allogeneic stem cell transplantation in chemotherapy-refractory non-hodgkin lymphoma. *Biol.Blood Marrow Transplant.* 2005; 11:593–599. [PubMed: 16041309]
89. Freytes CO, Loberiza FR, Rizzo JD, et al. Myeloablative allogeneic hematopoietic stem cell transplantation in patients who relapse after autologous stem cell transplantation for lymphoma: a report of the international bone marrow transplant registry. *Blood.* 2004; 104:3797–2803. [PubMed: 15280203]
90. Bashey A, Owzar K, Johnson JL, et al. Reduced-intensity conditioning allogeneic hematopoietic cell transplantation for patients with hematologic malignancies who relapse following autologous transplantation: a multi-institutional prospective study from the Cancer and Leukemia Group B (CALGB trial 100002). *Biol.Blood Marrow Transplant.* 2011; 17:558–565. [PubMed: 20674758]
- *91. Kim JW, Kim BS, Bang SM, et al. Allogeneic stem cell transplantation in patients with non-Hodgkin lymphoma who experienced relapse or progression after autologous stem cell transplantation. *Ann.Hematol.* 2011
- Outcome of patients undergoing allogeneic after failing autologous SCT
92. Escalon MP, Champlin RE, Saliba RM, et al. Nonmyeloablative allogeneic hematopoietic transplantation: a promising salvage therapy for patients with non-Hodgkin's lymphoma whose disease has failed a prior autologous transplantation. *J.Clin.Oncol.* 2004; 22:2419–2423. [PubMed: 15197204]
- **93. van Kampen RJ, Canals C, Schouten HC, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. *J.Clin.Oncol.* 2011; 29:1342–1348. [PubMed: 21321299]
- Outcome of patients undergoing allogeneic after failing autologous SCT
94. Baron F, Storb R, Storer BE, et al. Factors Associated With Outcomes in Allogeneic Hematopoietic Cell Transplantation With Nonmyeloablative Conditioning After Failed Myeloablative Hematopoietic Cell Transplantation. *J.Clin.Oncol.* 2006; 24:4150–4157. [PubMed: 16896000]
95. Smith SM, van Besien K, Carreras J, et al. Second autologous stem cell transplantation for relapsed lymphoma after a prior autologous transplant. *Biol Blood Marrow Transplant.* 2008; 14:904–12. [PubMed: 18640574]
96. Thomas DA, Faderl S, O'Brien S, et al. Chemotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer.* 2006; 106:1569–1580. [PubMed: 16502413]
97. Van Besien KW, Mehra RC, Giralt SA, et al. Allogeneic bone marrow transplantation for poor-prognosis lymphoma: response, toxicity and survival depend on disease histology. *Am J Med.* 1996; 100:299–307. [PubMed: 8629675]

- *98. Gross TG, Hale GA, He W, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. *Biol.Blood Marrow Transplant.* 2010; 16:223–230. [PubMed: 19800015]
- Outcome of Allo SCT for lymphoma in children and adolescents.
99. Armitage JO, Hsi ED, Foss FM. Clinical roundtable monograph. T-cell lymphoma: therapeutic overview and disease state awareness. *Clin.Adv.Hematol.Oncol.* 2010; 8:1–15. [PubMed: 21491667]
100. Molina A, Zain J, Arber DA, et al. Durable clinical, cytogenetic, and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. *J Clin Oncol.* 2005; 23:6163–6171. [PubMed: 16135483]
- **101. Duarte RF, Canals C, Onida F, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sezary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J.Clin.Oncol.* 2010; 28:4492–4499. [PubMed: 20697072]
- Largest series on allo SCT in Mycosis Fungoides.
102. Duvic M, Donato M, Dabaja B, et al. Total skin electron beam and non-myeloablative allogeneic hematopoietic stem-cell transplantation in advanced mycosis fungoides and Sezary syndrome. *J.Clin.Oncol.* 2010; 28:2365–2372. [PubMed: 20351328]
103. Wu PA, Kim YH, Lavori PW, Hoppe RT, Stockerl-Goldstein KE. A meta-analysis of patients receiving allogeneic or autologous hematopoietic stem cell transplant in mycosis fungoides and Sezary syndrome. *Biol.Blood Marrow Transplant.* 2009; 15:982–990. [PubMed: 19589488]
104. Mansour MR, Dogan A, Morris EC, et al. Allogeneic transplantation for hepatosplenic alphabeta T-cell lymphoma. *Bone Marrow Transplant.* 2005; 35:931–934. [PubMed: 15778731]
105. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. 2009; 27:3951–3958.
106. Woessmann W, Peters C, Lenhard M, et al. Allogeneic haematopoietic stem cell transplantation in relapsed or refractory anaplastic large cell lymphoma of children and adolescents--a Berlin-Frankfurt-Munster group report. *Br.J.Haematol.* 2006; 133:176–182. [PubMed: 16611309]
107. Shustov AR, Advani R, Brice P, et al. Complete Remissions with Brentuximab Vedotin (SGN-35) in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma. *ASH Annual Meeting Abstracts.* 2010; 116:961.
108. Corradini P, Doderio A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. *J Clin Oncol.* 2004; 22:2172–2176. [PubMed: 15169805]
109. Zain J, Palmer JM, Delioukina M, et al. Allogeneic hematopoietic cell transplant for peripheral T-cell non-Hodgkin lymphoma results in long-term disease control. *Leuk.Lymphoma.* 2011; 52:1463–1473. [PubMed: 21699453]
110. Shustov AR, Gooley TA, Sandmaier BM, et al. Allogeneic haematopoietic cell transplantation after nonmyeloablative conditioning in patients with T-cell and natural killer-cell lymphomas. *Br.J.Haematol.* 2010; 150:170–178. [PubMed: 20507311]
111. Wulf GG, Hasenkamp J, Jung W, et al. Reduced intensity conditioning and allogeneic stem cell transplantation after salvage therapy integrating alemtuzumab for patients with relapsed peripheral T-cell non-Hodgkin's lymphoma. *Bone Marrow Transplant.* 2005; 36:271–273. [PubMed: 15937499]
112. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. *J.Clin.Oncol.* 2008; 26:2264–2271. [PubMed: 18390969]
113. Dreger P, Laport GG. Controversies in lymphoma: the role of hematopoietic cell transplantation for mantle cell lymphoma and peripheral T cell lymphoma. *Biol.Blood Marrow Transplant.* 2008; 14:100–107. [PubMed: 18162229]

- **114. Jacobsen ED, Kim HT, Ho VT, et al. A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. *Ann.Oncol.* 2011; 22:1608–1613. [PubMed: 21252059]
Large single institution study on allo SCT for T cell lymphoma. Shows marked difference in outcome between nodal and non-nodal based lymphoma.
115. Kwong YL. Hematopoietic stem cell transplantation in natural killer cell lymphoma and leukemia. *Int.J.Hematol.* 2010; 92:702–707. [PubMed: 21107769]
116. Yokoyama H, Yamamoto J, Tohmiya Y, et al. Allogeneic hematopoietic stem cell transplant following chemotherapy containing l-asparaginase as a promising treatment for patients with relapsed or refractory extranodal natural killer/T cell lymphoma, nasal type. *Leuk.Lymphoma.* 2010; 51:1509–1512. [PubMed: 20496989]
117. Murashige N, Kami M, Kishi Y, et al. Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. *Br.J.Haematol.* 2005; 130:561–567. [PubMed: 16098071]
- *118. Ennishi D, Maeda Y, Fujii N, et al. Allogeneic hematopoietic stem cell transplantation for advanced extranodal natural killer/T-cell lymphoma, nasal type. *Leuk.Lymphoma.* 2011; 52:1255–1261. [PubMed: 21599584]
Large series on allo SCT for NK cell lymphoma.
119. Ito T, Makishima H, Nakazawa H, et al. Donor lymphocyte infusion for extranodal NK/T cell lymphoma, nasal type, relapsed after allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2010
120. Kato K, Kanda Y, Eto T, et al. Allogeneic bone marrow transplantation from unrelated human T-cell leukemia virus-I-negative donors for adult T-cell leukemia/lymphoma: retrospective analysis of data from the Japan Marrow Donor Program. *Biol Blood Marrow Transplant.* 2007; 13:90–99. [PubMed: 17222757]
121. Shiratori S, Yasumoto A, Tanaka J, et al. A retrospective analysis of allogeneic hematopoietic stem cell transplantation for adult T cell leukemia/lymphoma (ATL): clinical impact of graft-versus-leukemia/lymphoma effect. *Biol Blood Marrow Transplant.* 2008; 14:817–823. [PubMed: 18541202]
- **122. Hishizawa M, Kanda J, Utsunomiya A, et al. Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study. *Blood.* 2010; 116:1369–1376. [PubMed: 20479287]
Largest series on allo SCT for ATLL
- *123. Ram R, Gooley TA, Maloney DG, et al. Histology and Time to Progression Predict Survival for Lymphoma Recurring after Reduced-Intensity Conditioning and Allogeneic Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant.* 2011
Describes outcome of lymphoma after relapse from allo SCT.
124. Wudhikarn K, Brunstein CG, Bachanova V, et al. Relapse of Lymphoma after Allogeneic Hematopoietic Cell Transplantation: Management Strategies and Outcome. *Biol.Blood Marrow Transplant.* 2011
125. Russell NH, Byrne JL, Faulkner RD, et al. Donor lymphocyte infusions can result in sustained remissions in patients with residual or relapsed lymphoid malignancy following allogeneic haemopoietic stem cell transplantation. *Bone Marrow Transplant.* 2005; 36:437–441. [PubMed: 15980879]
126. Morris E, ackinnon S. Outcome following alemtuzumab (CAMPATH-1H)-containing reduced intensity allogeneic transplant regimen for relapsed and refractory non-Hodgkin's lymphoma (NHL). *Blood.* 2004; 104:3865–71. [PubMed: 15304395]
127. van Besien, K.; Dew, A.; Lin, S., et al. Leukemia & Lymphoma. Patterns and kinetics of T-cell chimerism after allo transplant with alemtuzumab based conditioning: mixed chimerism protects from gvhd, but does not portend disease recurrence. In press
128. Cavattoni I, Zabelina T, Ayuk F, et al. Pilot study of rituximab plus donor-lymphocyte infusion to prevent or treat relapse in B-cell lymphoma after allogeneic stem cell transplantation. *Leuk.Lymphoma.* 2010; 51:146–148. [PubMed: 19860607]

- *129. McIver Z, Stephens N, Grim A, Barrett AJ. Rituximab administration within 6 months of T cell-depleted allogeneic SCT is associated with prolonged life-threatening cytopenias. *Biol.Blood Marrow Transplant.* 2010; 16:1549–1556. [PubMed: 20580848]
Toxicity of Rituximab when administered after allo SCT.
- **130. Oliansky DM, Czuczman M, Fisher RI, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B cell lymphoma: update of the 2001 evidence-based review. *Biol.Blood Marrow Transplant.* 2011; 17:20–47. [PubMed: 20656046]
Consensus statement on the current role of Stem cell Transplant in large cell lymphoma.

Bullet Points

- AlloSCT is the treatment of choice for DLBCL relapsing after auto SCT of with PR to salvage.
- Outcome of AlloSCT is dependent more on patient characteristics and chemosensitivity than on conditioning regimens.
- AlloSCT is the treatment of choice for advanced PTCL and NK cell lymphoma.
- RIC and NMA conditioning have reduced early toxicity at the expense of more cGVHD and recurrence rate.
- In some studies, outcomes are better with mismatched or unrelated donors. One should therefore be able to identify suitable donors for all patients.

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Figure 1 A.

Allogeneic vs Autologous transplantation for lymphoma. Prospective randomized study (A) Progression Free Survival (B) Relapse rate

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Figure 1B.
 Allogeneic or autologous bone marrow transplantation (BMT) for non-Hodgkin's lymphoma (NHL): results of a provincial strategy (A) Relapse Free Survival (B) Relapse Rate

Figure 2.

Regression of diffuse large B cell lymphoma upon withdrawal of tacrolimus.

A: 30 days after allogeneic transplant: progressive lymphoma. Tacrolimus was held.

B: 70 days after transplant. Regression of adenopathy.

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3B. Reproduced with permission from [39]

3C: Reproduced with permission from [86]

Figure 3.
Progression Free Survival after Allo SCT depending on PET scan results