Review

How to Approach a Hodgkin Lymphoma Patient With Relapse After Autologous SCT: Allogeneic SCT

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Abstract

Hodgkin lymphoma (HL) is a highly curable B-cell lymphoma, and ~90% of patients who present with early-stage (stage I-II) disease and 70% of patients who present with late-stage disease will be cured with standard frontline treatment. For patients with relapsed or refractory (r/r) disease after initial therapy, the standard of care is salvage chemotherapy, followed by autologous transplantation (autoSCT). Although this approach will cure a significant proportion of patients, upto 50% of patients will experience disease progression after autoSCT, and this population has historically had a very poor prognosis. In the past, further salvage chemotherapy, followed by allogeneic transplantation (alloSCT), has been the only option associated with a significant probability of long-term survival, owing to a graft-versus-lymphoma effect. However, this approach has been complicated by high rates of treatment-related morbidity and mortality and a high risk of disease relapse. Furthermore, many patients have been unable to proceed to alloSCT because of disease refractoriness, poor performance status, or the lack of a donor. However, significant therapeutic advances in recent years have greatly expanded the options for patients with post-autoSCT r/r HL. These include the anti-CD30 antibody–drug conjugate brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab, as well as increasing experience with alternative donor alloSCT, especially from haploidentical donors. In the present review, we discuss the current role of alloSCT in the treatment of HL after autoSCT relapse.

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Introduction

Although Hodgkin lymphoma (HL) is often thought of as a disease that is easy to cure, upto 10% of patients with early-stage disease and 30% of patients who present with advanced-stage disease will experience disease progression at some point after receiving standard frontline therapy with ABVD (Adriamycin, bleomycin, vinblastine, doxorubicin).[1,2] For patients who are not cured with first-line treatment, ~50% can be cured with salvage chemotherapy, followed by autologous stem cell transplantation (autoSCT).[3] However, patients who experience disease recurrence after autoSCT have a far worse prognosis, with a median survival of only 29 months.[4] In this population, further chemotherapy, followed by allogeneic SCT (alloSCT) has been the traditional approach, given its superiority compared with chemotherapy alone.[5] However, many patients are unable to proceed to alloSCT at all owing to a lack of disease control with salvage therapy, declining performance status or organ function from the cumulative treatment, or lack of a suitable matched donor.[6] For patients who do proceed to allogeneic transplantation, the outcomes have been suboptimal. A recent meta-analysis showed that although transplantation outcomes have improved significantly over time, even in the more recent studies, only 40% of patients will be alive without disease relapse 3 years after alloSCT, with a 15% to 20% nonrelapse mortality (NRM) rate and cumulative incidence of relapse (CIR) of > 40%.[7]

Despite these sobering statistics, reason exists for optimism. Novel agents such as brentuximab vedotin (BV) and the checkpoint inhibitors (CPIs) nivolumab and pembrolizumab have resulted in much greater response rates as single agents compared with traditional cytotoxic chemotherapy when given as third-line treatment or beyond. Moreover, the responses realized with these agents can be quite durable and, as discussed in the present review, might potentially obviate the need for immediate alloSCT in select cases. Simultaneously, significant improvements in the field of alloSCT have also been made, including advances in supportive care, donor selection, and increasing familiarity and expertise in alternative

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donor transplantation, in particular, haploidentical alloSCT (haploSCT). In the present report, we review briefly the historical context of alloSCT for HL, followed by a discussion of the emerging role of haploidentical alloSCT. We then discuss the role of BV and CPIs for r/r HL, focusing on their role for patients who might potentially proceed to alloSCT. We also briefly address the difficult situation of post-alloSCT relapse. Finally, we conclude with a summary of our recommendations for the treatment of HL patients experiencing disease relapse after autoSCT.

AlloSCT for HL

Although alloSCT has been performed for r/r HL for > 30 years,[8] its applicability has always been limited by many factors. The high cure rate in the frontline setting and the reasonable cure rate and low morbidity afforded by autoSCT has meant that virtually all patients proceeding to alloSCT have been very heavily pretreated, with a large majority developing progression after previous autoSCT. In this population, a declining performance status, an inability to control the disease, and a lack of donor availability have been common barriers precluding consideration of alloSCT. Also, for patients who are able to undergo alloSCT, the morbidity and mortality of this procedure have been high. Despite these issues, alloSCT has continued to be a part of the treatment paradigm for r/r HL, because it offers curative potential for patients with progression after autoSCT, likely as a result of the graft-versus-lymphoma effect exerted by the donor immune cells and leading to a state of ongoing immune surveillance.[9] Furthermore, advances in transplantation medicine, especially with the ongoing development and refinement of haploSCT, have made alloSCT much more accessible. Finally, expansion of the therapeutic arsenal for HL to include BV and CPIs has also had a large effect on the management of r/r HL, because they confer relatively little toxicity, yet offer excellent disease control with or without subsequent alloSCT.

Matched Sibling Donor and Matched Unrelated Donor Transplantation

The earliest studies of alloSCT for HL demonstrated poor outcomes, primarily owing to the prohibitive rates of NRM.[10,11] Refinements in transplant medicine such as the development of reduced-intensity conditioning (RIC), with disease control provided by the graft-versus-lymphoma effect, resulted in a significant improvements in NRM. An analysis from 2008 by the European Society for Blood and Marrow Transplantation (EBMT) of patients who had undergone transplantation from 1997 to 2001 showed improved survival without an increase in relapse for patients who had undergone RIC alloSCT compared with myeloablative (MAC) alloSCT.[12] However, more recent data from the EBMT have suggested that MAC alloSCT might not be more toxic than RIC alloSCT, possibly owing to better patient and donor selection and improvements in supportive care.[13] A meta-analysis from 2016 of alloSCT for r/r HL found that patients who had undergone transplantation after 2000 had a 3-year overall survival (OS) and relapse-free survival (RFS) of ~60% and ~40%, respectively, and fared significantly better than patients treated before 2000. Regarding other prognostic factors, chemosensitivity and previous autoSCT both were associated with improved OS and RFS, and previous autoSCT was also associated with decreased NRM.[7]

The EBMT conducted a large retrospective registry analysis of 312 patients who had undergone alloSCT for r/r HL from 2006 to 2010 with the goal of comparing the outcomes between patients treated with MAC (n = 63) versus RIC (n = 249). The primary outcomes were OS and event-free survival (EFS). OS was not significantly different between the 2 cohorts and was 73%, 64%, and 45% at 1, 2, and 5 years, respectively. EFS was nonsignificantly improved in the MAC cohort, with a hazard ratio of 0.7 ($P = .07$). In addition, NRM was not different between the 2 groups, with a 1-year NRM rate of 5% and 10%, respectively, in the MAC and RIC cohorts. The 2 groups were significantly different with respect to a number of clinical parameters, especially previous autoSCT (62% in the RIC cohort and 27% in the MAC cohort) and the interval from diagnosis to alloSCT (35.6 months in the RIC cohort and 21 months in the MAC cohort). Chemosensitivity, or disease status, was the only factor significantly predictive of relapse, OS, and EFS.[13] However, although chemosensitivity has been consistently associated with improved post-alloSCT outcomes in multiple series, achievement of a metabolic complete response (CR) before transplantation, a crucial prognostic factor with autoSCT,[14,15] might not be crucial. Reyal et al[16] analyzed 116 patients with r/r HL who had undergone T-cell–depleted alloSCT, none of whom had had progressive disease before alloSCT. The final pretreatment positron emission tomography/computed tomography scan findings, stratified by the Deauville score, did not correlate significantly with either OS or progression-free survival (PFS).[16] Similarly, in a report from Giaccone et al[17] of 69 patients with r/r HL who had undergone alloSCT, with a median follow-up of 7.2 years, the 5-year OS and RFS was 51% and 39%, respectively. Also, chemosensitivity was associated with improved RFS; no difference was found in RFS between patients with a CR versus a partial response (PR).[17]

An analysis from the MD Anderson Cancer Center by Anderlini et al[18] examined the results for 58 patients undergoing RIC alloSCT for r/r HL (matched sibling donor [MSD], n = 25; mismatched unrelated donor [MUD], n = 33) conditioned with fludarabine and melphalan. Graft-versus-host disease (GVHD) prophylaxis consisted of a calcineurin inhibitor with methotrexate (MTX). Some of the MUD recipients received antithymocyte globulin (ATG; n = 14). The 2-year OS, PFS, and CIR was 64%, 32%, and 55%, respectively, with no differences seen between the MUD and MSD groups. However, chronic GVHD (cGVHD) developed more often in the MUD recipients (85% vs. 57%). A trend toward improved PFS was seen in patients with a CR or unconfirmed CR compared with all other disease states. However, no difference in OS was seen.[18] Kako et al[19] performed a retrospective analysis of data from the Japanese Society for Hematopoietic Cell Transplantation. Of 122 patients with r/r HL who had undergone alloSCT from 2002 to 2009, the 3-year PFS, OS, and NRM was 31%, 42%, and 32%, respectively. Female recipient gender and performance status were significantly associated with improved OS, and a mismatched donor and umbilical cord blood (UCB) predicted for worse OS. In their series, disease status before alloSCT was only associated with a trend toward improved OS and PFS.[19] Peggs et al[20] reported on 67 patients from Spain and the United Kingdom who had undergone MSD RIC alloSCT from 1997 to 2004. The 36 patients from Spain received cyclosporine (CsA) and alemtuzumab for GVHD prophylaxis. The 31 patients from the United Kingdom received CsA