

Syngeneic Transplant in Mantle Cell Lymphoma: A Rare Event and Review of the Literature

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Introduction

Mantle cell lymphoma (MCL) is an aggressive disease with historically poor long-term survival. Aggressive multi-agent chemotherapy followed by autologous stem cell transplant (ASCT) in first remission offers impressive disease-free survival (DFS) and prolonged overall survival (OS).^{1,2} To date, only 16 syngeneic transplants have been performed for patients with MCL.

Case Report

Our patient, a 66-year-old white male, presented with a white blood cell count (WBC) of 420,000/mL during routine surveillance. A WBC differential demonstrated 93% lymphocytes and 4% neutrophils with anemia (hemoglobin 10 g/dL) and a normal platelet count. A bone marrow biopsy showed extensive involvement with small lymphocytes that expressed CD5, CD19, CD20, and Cyclin D1, but were negative for the expression of CD23. Karyotype analysis demonstrated a t(11;14) within the lymphocytes. Computed tomography scans were significant only for massive splenomegaly. The patient was diagnosed with MCL, and R-CHOP (rituximab [Rituxan, Genentech], cyclophosphamide, doxorubicin, vincristine, prednisone) was administered and resulted in a partial remission (PR) after 4 cycles. The patient then received ICE (ifosfamide, carboplatin, etoposide) and, subsequently, bortezomib (Velcade, Millenium Pharmaceuticals). Neither regimen produced a response. After referral to our institution, the patient received high-dose etoposide (10 mg/kg/day continuous infusion for 4 days at 50% dose reduction) and cytarabine (2 g/m² every 12 hrs for 8 doses). After 2 cycles

of therapy, splenomegaly and bone marrow disease persisted, but a PR was achieved. Despite his age, the patient tolerated aggressive chemotherapy well and demonstrated an excellent performance status. He received a syngeneic stem cell transplant (SCT) from his identical twin brother following CBV chemotherapy (cyclophosphamide 100 mg/kg, carmustine 15 mg/kg, and etoposide 60 mg/kg), each at 75% dosing due to his age. His post-transplant clinical course was uncomplicated. Engraftment of neutrophils and platelets occurred on day 12, and he was discharged from the hospital on day 19. He showed no signs or symptoms of graft versus host disease. The patient demonstrated a pathologic complete remission (CR) at day 100 after transplant, with normal marrow by histology and molecular analysis. The patient remains in CR more than 5 years from the time of his transplant.

Discussion

MCL possesses characteristics of both aggressive and indolent lymphomas. The disease generally presents in older patients, is advanced at the time of presentation, and may have a rapidly progressive course. MCL is currently thought to be an incurable illness even with aggressive chemotherapy. At the present time, the National Comprehensive Cancer Network recommends that first-line treatment of newly diagnosed MCL in patients younger than 60 years of age include high-dose chemotherapy followed by a consolidative ASCT. There is debate addressing the optimal chemotherapeutic regimen, but no large trials have addressed this topic.

Chemotherapy

High-dose chemotherapy is one of the foundations of MCL treatment. Standard non-Hodgkin lymphoma therapies, such as R-CHOP, often induce CR but do not result in improved survival.³ Other studies, though, have shown lengthened OS rates of up to 82% at 3 years using more

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aggressive regimens like R-Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab, high-dose methotrexate and cytarabine).⁴ Hyper-CVAD, while promising in terms of yielding longer survival, possesses side effects that include a relatively high incidence of severe neutropenia, serious infections, secondary cancers (up to 11%, 5-year cumulative incidence), secondary myelodysplastic syndromes (MDS), and acute myelogenous leukemia (AML) leading to an overall treatment-related mortality as high as 8%.^{4,5} Because of these potential complications, more aggressive regimens are not recommended in the elderly.⁴ Despite a significant side effect profile, Hyper-CVAD has been shown to improve OS and is a reasonable regimen for initial therapy of MCL in younger patients with a good performance status.

Autologous Stem Cell Transplant

ASCT is part of first-line therapy for MCL in many treatment regimens. In one study, patients receiving ASCT after CHOP chemotherapy had a 3-year OS rate of 83% versus 77% in those receiving interferon after CHOP.⁶ These findings were confirmed in another study, showing a 5-year OS rate of 75% in patients undergoing high-dose chemotherapy followed by consolidative ASCT.² While there is debate as to the initial chemotherapy after diagnosis, most authors agree that ASCT is a beneficial treatment for MCL and should be performed in first remission.²

Allogeneic Stem Cell Transplant

Several studies have demonstrated success with allogeneic transplant in first complete remission for MCL, however they had small numbers of patients.^{2,8} While possessing far fewer complications than allogeneic SCTs, ASCTs lack a graft versus tumor (GvT) effect, which some authors suggest is critical in the treatment of MCL.^{7,9} Nonmyeloablative allogeneic SCTs have been performed in patients with MCL, generally in patients with relapsed or refractory disease, and have demonstrated 45% OS at 3 years.^{9,10} Larger studies in patients in first CR are needed to further clarify the role of allogeneic SCT as part of first-line therapy for MCL.

Immunotherapy

The role of rituximab in the treatment of MCL is actively debated within the literature. For example, R-CHOP was significantly better than CHOP since it improved overall response rate from 75% to 94%, yet it had no effect on progression free survival.³ It has also been shown that the addition of rituximab to ASCT conditioning regimens improves OS.¹¹⁻¹³ While rituximab monotherapy does not produce durable remissions, it significantly improves complete remission and overall response rates when used in conjunction with conventional chemotherapy regi-

mens.¹⁴ The data suggest that rituximab is a useful agent in the treatment of MCL during initial chemotherapy and possibly in transplant conditioning regimens.¹¹⁻¹³

Conclusion

Our patient is one of only 16 individuals worldwide to receive a syngeneic stem cell transplant for MCL, indicating the uniqueness and the rarity of this setting. Further, he remains in CR more than 5 years following syngeneic stem cell transplant. Fifteen other patients who have received a syngeneic SCT for MCL have been reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).¹⁵ Per the CIBMTR, 11 of 16 are still alive at 3–84 months from the date of transplant. Eight of 11 patients with available disease information continue in CR, and the status of the remaining patients is unknown. Four patients receiving syngeneic transplant for MCL died; one patient was in CR at the time of death.

Commonly, age, refractory disease, and the lack of a donor prevent the pursuit of a syngeneic transplant for patients with MCL. For this elderly patient with active bone marrow disease, however, a healthy identical twin donor assured that the graft was not contaminated with lymphoma. Graft mobilization from the healthy donor was excellent, whereas the recipient had received many cycles of chemotherapy prior to transplant and never cleared his marrow of disease. Thus, he may not have had an optimal stem cell yield from mobilization if autologous transplant had been pursued. The persistence of this patient's remission is testament to the potential value of syngeneic transplant in MCL.

There is substantial evidence demonstrating that high-dose chemotherapy followed by ASCT is beneficial for younger MCL patients, with acceptable side effects. There remains a paucity of compelling data indicating a clearly optimal induction regimen, though the addition of rituximab appears to be universally beneficial. Further studies of allogeneic SCT are needed to elucidate its role in the management of MCL. Based on our patient's unusual success with syngeneic transplant for MCL, we believe there is strong justification for pursuing this modality in a subset of patients with this challenging malignancy.

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Review

Stem Cell Transplantation for Mantle Cell Lymphoma: Not Yet the Standard of Care

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Mantle cell lymphoma (MCL) is an uncommon disease comprising approximately 7% of all non-Hodgkin lymphoma (NHL) and characterized by a peak incidence in males in their 60s and 70s, advanced disease at presentation, and an aggressive natural history with reported median survival times of 3–4 years in most older published series.¹⁻³ Despite reported response rates of 70–85% after conventional dose chemotherapy regimens, most patients relapse and long-term survival is very poor. As a result, recent prospective clinical trials have investigated the use of dose-intensive induction therapies for MCL, the inclusion of rituximab (Rituxan, Genentech), and the addition of high-dose therapy and autologous or allogeneic stem cell transplantation (SCT) as a component of initial therapy.

Encouraging results have been reported for many phase II trials of these intensive approaches. For example,

the rituximab-Hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose cytarabine and methotrexate) produces complete remission rates of up to 90% with 5-year failure free survival in 60% of selected younger patients with MCL.⁴ The use of high dose therapy and autologous SCT as post-induction therapy after CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), R-CHOP (rituximab + CHOP), or similar regimens produces 3-year progression-free survival rates in excess of 50%.⁵ Recent reports of the use of allogeneic SCT using either myeloablative or nonablative conditioning regimens have shown over 40% progression-free survival at 5 years, even for patients with relapsed or refractory disease.^{4,6}

A recent report from the German Low Grade Lymphoma Study Group (GLSG) has suggested that there has been a marked improvement in the outcome for patients with MCL in the last 30 years, during which 5-year overall survival rates have increased from 22% to 47%.⁷ This improvement has been attributed to many factors including improved diagnostic and staging techniques, improved supportive care, the introduction of anthracycline-based chemotherapy for induction, the inclusion of rituximab, and the widespread use of SCT.

Despite these encouraging data, the overall impact of intensive treatment strategies on outcome for patients with MCL is unclear. Martin and colleagues have recently published their single center experience of the use of nonintensive strategies for unselected patients with MCL. They found a median overall survival of 7.1 years in their series of 111 patients.⁸ Their report suggests that patient selection may be a major factor in the apparent superiority of intensive approaches to MCL.

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The favorable outcome reported by Engman and coworkers after syngeneic transplantation in a 66-year-old man with MCL, and their review of the transplant literature in this disease must, therefore, be interpreted in the context of the available evidence.⁹ This patient underwent a syngeneic transplant after several lines of initial therapy, although it is not clear from the case report whether the patient had relapsed between these regimens or was in first partial remission at the time of SCT. In either case, the patient is now in continuing complete remission 5 years after SCT. Based on current data regarding the role of SCT, it may be premature to consider this patient cured.

A previous retrospective study has reported remarkable long-term disease-free survival in indolent lymphoma after syngeneic SCT, suggesting that the use of high-dose chemotherapy with an uncontaminated source of stem cells is a particularly effective treatment in these diseases.¹⁰ However, although the observation of efficacy of syngeneic transplantation is interesting, this can never be a widely applied strategy.

Autologous SCT remains the most widely used transplant approach in MCL as consolidation of first remission or at the time of relapse. The European MCL Network has reported results from a randomized study in which all patients underwent induction therapy with CHOP, R-CHOP, or a similar regimen, with subsequent randomization to autologous SCT or maintenance interferon in responding patients.⁵ Although this study shows superior progression-free survival in the autologous SCT arm, no overall survival advantage has been shown to date. Successive phase II studies from M.D. Anderson Cancer Center have demonstrated 5-year progression-free survival rates in excess of 60% in patients undergoing autologous SCT after achieving a CR to R-Hyper-CVAD therapy—an observation confirmed at other centers.⁴ The Nordic Lymphoma Group has recently published similar results from a phase II study of an intensive induction chemo-immunotherapy regimen followed by immediate high-dose therapy and autologous SCT.¹¹ Although these results are impressive, they must be interpreted cautiously, since most do not include an intent-to-treat (ITT) analysis and are therefore subject to the potential for major selection bias. For example, the median age for patients in the MD Anderson series was 57 years, which is much lower than the general population of patients with MCL. Other groups have been unable to reproduce the high reported response rates achieved with the R-Hyper-CVAD regimen, and mobilization of adequate numbers of hematopoietic stem cells can be problematic after this regimen with some patients being unable to proceed to SCT. ITT analyses in unselected patients are therefore unlikely to reproduce the excellent results reported to date for this intensive first-line strategy.

Reported results for allogeneic SCT in the frontline and salvage settings are equally impressive, but subject to even greater potential for selection bias in view of the high regimen-related toxicity and mortality associated with these approaches, especially in older patients.

In summary, Engman and coworkers describe a rare case of syngeneic SCT in mantle cell lymphoma, which serves as an intriguing model to explore the benefit of high-dose strategies in this disease. Although these therapies have gained widespread use, their applicability is limited to a relatively small proportion of patients with MCL, and their effect on outcome is unclear. Continued prospective studies of these approaches are needed.

The identification of new rational therapeutic targets in MCL has resulted in the recent introduction of many new agents including proteasome and mammalian target of rapamycin inhibitors.^{12,13} Early clinical trials of these agents have been promising and some are now being assessed as components of first-line therapy in this disease. If results in early phase studies are confirmed, the use of dose-intensive therapy may be more limited in patients with MCL in the future.

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