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Autologous Stem Cell Transplant: Still the Standard for Fit Patients With Mantle Cell Lymphoma

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Abstract

Mantle cell lymphoma is a relatively rare malignancy, comprising fewer than 10% of all non-Hodgkin lymphomas. It is a heterogeneous disease, and although most patients experience an aggressive clinical course, some have a more indolent disease and may not require immediate therapy. There are currently few reliable prognostic markers, making it difficult to accurately predict which patients require early intensive treatment. We argue that consolidative autologous stem cell transplantation in first remission remains the standard of care for the young and fit patient population, based on long-term data from phase II and III trials demonstrating that early transplantation extends both progression-free and overall survival. Novel targeted agents are currently being investigated in both the upfront and relapse settings, but to date there are few data to suggest durable treatment responses that compare favorably with results of transplantation.

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Introduction

In 1994, the REAL (Revised European-American Lymphoma) classification system first defined mantle cell lymphoma (MCL) as a distinct entity within the broad category of B-cell non-Hodgkin lymphomas. Almost immediately, it was noted that MCL generally followed a more aggressive clinical course than most of the other B-cell lymphomas, with early and aggressive relapses after standard CHOP (cyclophosphamide, doxorubicin, vincristine [Oncovin], prednisone) chemotherapy. Median age at diagnosis is approximately 65 years, with a male predominance of nearly 3 to 1 over women, and median overall survival (OS) among early patient cohorts was approximately 3 years.[1] More than 95% of cases are associated with the characteristic translocation t(11;14), which induces cyclin D1 overexpression. Nevertheless, MCL does not carry a uniform prognosis, with a spectrum of clinical scenarios ranging from relatively indolent initial presentations in a small subset of patients, to most cases, which display an aggressive clinical course.[2] The most durable survival times have been reported with induction chemotherapy followed by consolidative high-dose chemotherapy and autologous stem cell transplantation (ASCT), and this treatment scheme remains the standard of care at most institutions for young and fit patients. Our own data from a retrospective multicenter analysis also suggests that early transplantation provides optimal benefit for younger fit patients with MCL.

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Discussion

Soon after the initial classification of MCL, the European MCL Network launched a randomized comparison of CHOP followed by myeloablative radio-chemotherapy followed by ASCT versus maintenance interferon-α (IFN-α).[1] In a long-term follow-up analysis, the progression-free survival (PFS) and median OS were superior in the ASCT arm. The OS for the ASCT arm was 90 months versus 54 months in the INF-α arm.[3] Subsequent studies incorporating high-dose cytarabine into the treatment regimen showed even more promising outcomes. In a small phase II study, a sequential CHOP-DHAP (dexamethasone, high-dose cytarabine, and cisplatin) regimen led to a complete response (CR) rate of greater than 80%. Responders went on to intensified consolidation, with total body irradiation, high-dose cytarabine (Ara-C), melphalan, and ASCT, yielding impressive 3-year event-free survival

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(EFS) of 83% and OS of 90%.[4] The Nordic Lymphoma Group went on to conduct a larger multicenter phase II trial of 160 patients with MCL who received an induction with R-maxi-CHOP alternating with R-high-dose cytarabine, followed by a high-dose consolidation (BEAM [carmustine, etoposide, cytarabine, and melphalan]) with ASCT. Molecular remission was achieved in 92% of the 79 evaluable patients, and overall responses and CRs were achieved in 96% and 54%, respectively. The 6-year EFS, PFS, and OS were 56%, 66%, and 70%, respectively, with no relapses observed after 5 years.[5]

In addition to phase II trials, there have been several large retrospective population-based analyses that show similar patterns of favorable clinical results of high-dose cytarabine-containing schedules followed by ASCT, with overall response rates (ORR) ranging from 70% to 100% and 5-year OS ranging from 64% to 75%.[6-8]

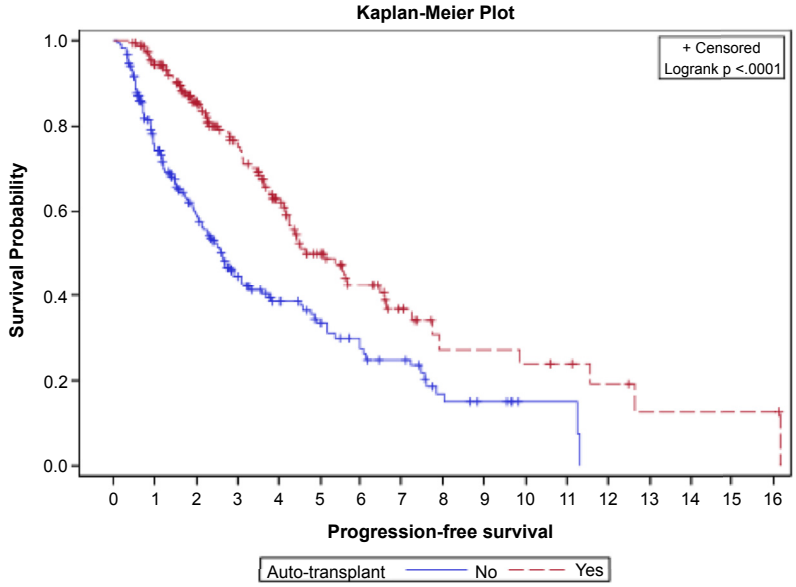
The introduction of rituximab coupled with high-dose cytarabine-containing regimens have improved the median OS from 3 years in the CHOP era to more than 10 years in the updated Nordic Lymphoma Group experience. Unfortunately, late relapses continue to occur in this population, suggesting that ASCT-based approaches alone may not be sufficient to permanently eradicate MCL.[9]

High response rates of greater than 90% also have been reported in the MD Anderson experience in which 25 patients received an alternating regimen of hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) with high-dose cytarabine and methotrexate (MA), and it may be that some patients treated with such aggressive regimens do not benefit further from consolidative ASCT, but we do not currently have validated methods for identifying such patients, so the issue remains under study.[10,11]

In our own multicenter analysis of data from 5 academic institutions, we have long-term data on 389 patients with MCL showing a PFS advantage of 5.1 years versus 2.6 years ($P < .001$) for patients who underwent ASCT, as shown in Figure 1. There was also an OS benefit of 11.6 years versus 9.8 years for patients receiving ASCT ($P = .035$), as shown in Figure 2. Of the 185 patients who had an ASCT, mean age at diagnosis was 57.1 years, 96.5% had an Eastern Cooperative Oncology Group score of 0 or 1, and 88.8% were Ann Arbor Stage IV. There was most certainly a selection bias due to the retrospective nature of this analysis, and it appears that those who were treated with intensive induction followed by ASCT had higher-risk disease, and good performance status with younger age. Nevertheless, this select group of patients may have benefited from this high-dose schedule containing cytarabine and rituximab, followed by an ASCT.[12-14]

Despite optimization of induction and consolidation methods, late relapses continue to occur, raising the question of whether maintenance therapy should play a role following ASCT.[15,16] Rituximab maintenance is considered the current standard for elderly patients after chemotherapy induction,[17] and several studies

Figure 1 The Progression-free Survival From the Emory Experience: 185 (47.5%) of the 389 Patients Underwent an Autologous Stem Cell Transplant in CR1. The Patients Who Received an ASCT Median Survival Was 5.1 Years Versus 2.6 Years for Those Who Did Not Undergo ASCT ($P < .0001$)



Auto-transplant	No. of Subject	Event	Censored	Median Survival (95% CI)	1 Yr Survival	2 Yr Survival
No	204	124 (61%)	80 (39%)	2.6 (2.1, 3.2)	74.8% (68.0%, 80.3%)	59.4% (51.8%, 66.1%)
Yes	185	79 (43%)	106 (57%)	5.1 (4.2, 6.6)	94.4% (89.9%, 97.0%)	85.7% (79.4%, 90.2%)