Haematopoietic Stem Cell Transplantation in Mantle Cell Lymphoma

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Mantle cell lymphoma (MCL) is considered incurable; with a reported median survival of 3 years after conventional chemotherapy.1 Therapeutic options in MCL were very limited until the mid 1990s when autologous stem cell transplantation (ASCT) became available for this especially poor-risk subtype of lymphoma. The Omaha group was the first to show the potential efficacy of this intensive modality in MCL.2 Since then, numerous studies have been published documenting the feasibility and potent anti-lymphoma activity of ASCT in this entity, in particular if used as part of first-line treatment. However, almost all trials were uncontrolled and suffered from small patient numbers and limited observation times.3

Only recently Dreyling and co-workers were able to demonstrate the superiority of ASCT over standard CHOP chemotherapy with interferon maintenance in terms of progression-free survival (PFS) in a prospective randomized phase-III study. Nevertheless, with a median follow-up of 34 months, a plateau in the survival curve was not seen even in this trial, and a significant survival benefit could not be shown. In this trial patients 65 years of age or younger with advanced-stage MCL were assigned to ASCT or IFNα after achievement of complete or partial remission by a CHOP–like induction therapy. Sixty-two of 122 patients proceeded to ASCT and 60 received IFNα. Patients in the ASCT arm experienced a significantly longer PFS with a median of 39 months compared with 17 months for patients in the IFN arm (P = 0.0108). The 3-year overall survival (OS) was 83% after ASCT versus 77% in the IFNα group (P = 0.18). 4

Given the superiority of both ASCT and rituximab-supplemented therapy over conventional treatment in MCL, both modalities have been combined in a prospective phase II study. Thirty-four patients with newly diagnosed MCL were treated with a sequential dose-escalating therapy comprising standard chemotherapy for remission induction, intensive ara-C-containing chemotherapy for mobilization of stem cells, and myeloablative therapy followed by ASCT. The myeloablative regimen consisted of total body irradiation and high-dose cyclophosphamide supplemented with two doses (375 mg/m2) of rituximab. Outcome parameters (toxicity, clinical and molecular response as assessed by allele-specific IGH real-time quantitative polymerase chain reaction (RQ-PCR), EFS, and OS) were compared with those of 34 historical controls treated identically but without rituximab. Whereas engraftment, toxicity and clinical response were not different from those in controls, EFS was significantly increased with rituximab (4-year EFS 83% versus 47%, P =0.036). The difference in OS was not statistically significant (4-year OS 87% versus 77%). This was associated with a trend for a superior molecular response rate in 11 study versus 10 control patients with a marker available (73% vs. 30%, p=0.086) despite similar levels of lymphoma contamination of the stem cell inocula infused. It was concluded that incorporation of two standard doses of rituximab into the myeloablative regimen might improve outcome of upfront ASCT for MCL, allowing long-term disease control to an extent previously not reached in this disease.5

Based on series reporting a high efficacy in MCL of regimens containing cytarabine, both in terms of prolonged EFS and, in combination with rituximab, in terms of a high rate of clinical and molecular remission and tumor-cell free stem cell products, the second Nordic MCL protocol (NLG MCL-2) was launced in 2000, with the aim of increasing the rates EFS, PFS, and OS, and of molecular remission and PCR-negative stem cell products. In the 2nd Nordic MCL trial, 160 consecutive, untreated patients younger than 66 years were treated in a phase II protocol with dose-intensified induction immunochemotherapy with rituximab (R) + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP), alternating with R + high-dose cytarabine. Responders received high-dose chemotherapy with BEAM or BEAC (carmustine, etoposide, cytarabine, and melphalan/cyclophosphamide) with R-in vivo purged autologous stem cell support. Overall and complete response was achieved in 96% and 54%, respectively. The 6-year OS, EFS, and PFS were 70%, 56%, and 66%, respectively, with no relapses occurring after 5 years. Multivariate analysis showed Ki-67 to be the sole independent predictor of EFS. The non-relapse mortality was 5%. The majority of stem cell products and patients assessed with PCR after transplantation were negative. Compared with the historical control, the Nordic MCL-1 trial, the EFS, OS, PFS, the duration of molecular remission, and the proportion of PCR-negative stem cell products were significantly increased (P < .001). The emerging PFS plateau after 5 years could raise the hope that a proportion of younger MCL may be cured, but this will take longer follow-up to demonstrate than the median follow-up of only 3.4 years. 6

Few data are available on the results of myeloablative conditioning and allogeneic HCT for mantle cell lymphoma. The largest series from MDACC, EBMT, and Baltimore reported on 16, 22, and 19 patients with MCL, respectively. OS was > 50% at 2 or 3 years and indicated a potential role for allogeneic HCT in this disease. 7-9

The results of nonmyeloablative allogeneic HCT for relapsed or refractory MCL are promising. In one study, subjects with advanced recurrent mantle cell lymphoma, 89% of whom had chemosensitive disease, were treated with non-myeloablative allogeneic HCT. Complete remission was obtained in 17 of the 18 patients with a day-100 mortality of zero. At a median follow-up of 26 months, estimated three-year event-free survival was 82%. The high response and low relapse rates with this approach suggest that MCL is susceptible to graft-versus-tumor response 10

Aggressive MCL has a poor prognosis; however long-term disease free survival is possible after rituximab-containing autologous transplantation for patients in first remission, and after non-myeloablative allogeneic stem cell transplantation for patients with relapsed or refractory disease. 11

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