Original Study

Hematopoietic Cell Transplantation for Mantle Cell Lymphoma: Predictive Value of Pretransplant Positron Emission Tomography/Computed Tomography and Bone Marrow Evaluations for Outcomes

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Abstract

We examined the predictive value of pretransplant positron emission tomography/computed tomography and marrow involvement evaluation on outcomes of 66 patients with mantle cell lymphoma treated with hematopoietic cell transplantation (HCT). Residual disease detected by either method prior to autograft was associated with increased relapse rates at 2 years and worse 5-year disease-free survival. Allograft recipients had favorable long-term outcomes despite the presence of residual disease pre-HCT.

Background: The prognostic roles of 18F-fludeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging and marrow involvement evaluation on outcomes following autologous and allogeneic hematopoietic cell transplantation (HCT) for mantle cell lymphoma (MCL) are uncertain and require more data. **Patients and Methods:** We categorized 66 patients with MCL who received HCT (38 autologous and 28 allogeneic) on the basis of pre-HCT residual disease (RD) status as assessed by marrow MCL morphology and flow/molecular analysis and PET/CT imaging to RD positive (RD^+) (either or both measures positive) and RD^- (both negative). We analyzed the predictive value of these RD detection methods on transplant outcomes. **Results:** The 2-year relapse rate after autograft was significantly higher in pre-HCT RD^+ patients (46% [95% CI 16-77%]) than in patients who were RD^- (19% [95% CI 0-42%]; $P = .02$), leading to worse 5-year disease-free survival (DFS) in RD^+ patients (46% [95% CI 14%-73%] vs. 68% [95% CI 33-87%], $P = .04$). In multivariate analysis, RD^+ status was associated with a reduction in DFS (hazard ratio, 5.6; $P = .02$). Most allogeneic HCT recipients had advanced disease and most were RD^+ (12 PET/CT^+; 5 marrow-positive). The 5-year DFS and relapse rates after allogeneic HCT were 34% and 25% for all patients and 40% and 33% for RD^+ recipients, suggesting that active disease at the time of allograft does not preclude long-term remissions in advanced MCL. **Conclusion:** Both autologous and allogeneic HCT lead to promising long-term survival. RD detected prior to autograft was associated with increased relapse and worse 5 year DFS. Allograft recipients had favorable long-term outcomes even in presence of pre-HCT detectable disease.

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Introduction

Mantle cell lymphoma (MCL) comprises 5%-10% of all of non-Hodgkin lymphomas (NHL). It predominately affects older male patients and commonly presents in advanced stage with extranodal involvement and marrow infiltration.[1] The median survival in patients with MCL ranges from 3 to 7 years.[2] Although the disease is incurable with chemotherapy alone, complete responses can be achieved in 90% of patients with rituximab and intensive chemotherapies containing high-dose cytarabine.[3] These

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remissions are often consolidated with hematopoietic cell transplantation (HCT); however, there is wide variation in reported outcomes.[4-9]

Recent advances in the understanding of the clinical, molecular, and genetic characteristics of MCL have identified prognostic factors useful to develop risk-adapted therapies. The Mantle Cell International Prognostic Index (MIPI) comprises 4 nonmodifiable factors (age, white cell count at diagnosis, lactate dehydrogenase level, and performance status) and was developed to predict overall survival (OS) from diagnosis.[10] The discriminatory power of MIPI has been validated in the era of rituximab and intensive immunochemotherapy. Previous studies have shown that a high-risk MIPI score indicates worse disease-free survival (DFS) after autologous HCT or rituximab plus hyper-CVAD/MA (cyclophosphamide, vincristine, Adriamycin [doxorubicin], dexamethasone/methotrexate, cytarabine) chemotherapy.[11,12] In addition to the MIPI, the presence of residual MCL in marrow as assessed by polymerase chain reaction (PCR) for the immunoglobulin heavy chain (IgH) has been correlated with an increased risk of relapse and progression after autologous HCT.[13] A unique MCL flow cytometric phenotype defined by surface expression of CD20, CD5, surface light chain, and FMC7 or CD79b and the absence of CD23 has also been validated for pretransplant bone marrow evaluation.[14]

Recently, positron emission tomography/computed tomography (PET/CT) imaging has become an important advance in noninvasive lymphoma assessment. PET/CT has been applied for assessing disease burden and response to therapy in Hodgkin lymphoma and diffuse large B-cell lymphoma; however, its utility as a stratification tool in MCL is debated.[15-19] Particularly, there is little data on prognostic utility of pre-HCT PET/CT imaging on transplant outcomes in MCL. For the past decade we have used PET/CT imaging and PCR/flow cytometric bone marrow assessment prior to HCT to restage MCL patients enrolled on transplant protocols at the University of Minnesota. In this single-institution analysis, we investigated the impact of residual disease (RD) as detected by either pretransplant PET/CT scan or MCL marrow assessment on transplant outcomes in 66 patients with MCL who received consolidation autologous or allogeneic HCT.

Patients and Methods

Study Design

We analyzed outcomes of all consecutive patients $\geq$ 18 years of age with a diagnosis of MCL who underwent autologous or allogeneic HCT at the University of Minnesota from 1999 to 2010. A diagnosis of MCL was confirmed according to the World Health Organization criteria. Patient data prospectively collected in the University of Minnesota Transplant Database were supplemented with data from individual medical records, imaging files, and pathology reports. Treatment responses were evaluated according to criteria described by Cheson et al.[20] The MIPI score was calculated as previously described.[10] Outcomes included DFS, OS, treatment-related mortality (TRM), and relapse rates. Pretransplant disease burden was determined by PET/CT scan or bone marrow MCL assessment. Transplantation protocols were approved by the institutional review board (IRB), and informed consent for clinical data collection was obtained prior to treatment. We also obtained IRB approval to retrospectively review imaging studies and pathologic materials of transplanted patients.

RD Definitions

Patients were defined as RD negative (RD^-) if both the PET/CT scan and marrow were negative for disease prior to HCT. Patients were defined as RD positive (RD^+) if the results of either 1 (PET/CT or marrow) or both methods were positive prior to HCT.

RD Measurement by PET/CT Scan

Patients underwent imaging by PET/CT $\leq$ 4weeks before HCT, and all PET/CT scans were reviewed by a nuclear medicine radiologist (JF) who was blinded to clinical outcomes. We used a Siemens Biograph 16 PET scanner with HD detector system for all patients. Criteria proposed by the Imaging Subcommittee for International Harmonization Project for lymphoma were used.[15] PET/CT scans were positive if focal or diffuse 18F-fludeoxyglucose (FDG) uptake above the surrounding background in a location incompatible with normal anatomy and physiology was identified. The standardized uptake value (SUV), representing the ratio of the tumoral tracer concentration to the average tracer concentration in the entire body, was used. PET/CT-negative patients had no evidence of metabolically active MCL.

RD Measurement by Bone Marrow Examination

A hematopathologist (MAL) performed a central review of data from bone marrow trephine biopsies and aspirates collected 10 to 30 days prior to HCT. As this retrospective study spanned 11 years, the methods used to evaluate RD varied. Morphology was interpreted from core biopsies. If lymphoid aggregates were absent on multiple hematoxylin-eosin–stained levels, the core biopsies were interpreted as negative. Any lymphoid aggregates with atypical morphologic features were immunostained and deemed positive if stains were diagnostic of MCL independent of percentage involvement. A molecular assay to detect common breakpoints comprising t(11;14) translocations was employed during the early years, as previously described.[21] A subset of cases had aspirate material evaluated for a t(11;14) by fluorescence in situ hybridization (FISH) or conventional G-banding karyotypic analysis. We performed 4- or 8-color flow cytometry using antibodies to the following antigens: CD5, CD10, CD14, CD19, CD20, CD23, CD45, CD79b, polyclonal kappa, and lambda light chains. Analysis was performed on BD FACSCalibur or BD FACSCanto II, and flow cytometry data were analyzed by FACSDiva, FCS Express, or Kaluza. For marrow analysis, a minimum of 100,000 events was collected to identify B-cell clones aberrantly coexpressing CD5 and light chain restriction. Small $CD5^+$ B-cell populations with monotypic light chains were tested for CD79b expression and absence of CD23 to confirm the MCL immunophenotype. In a few cases, clonality studies by PCR amplification of VDJ rearrangements were performed as previously described.[21,22] RD positivity was defined as any evidence of disease by morphology, molecular assays, or flow cytometry; for a patient to be RD^-, all test results had to be negative.

Conditioning Regimens

Myeloablative conditioning (MAC) for allogeneic HCT recipients consisted of cyclophosphamide (CY) 60 mg/m^2/day intravenously

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