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Idiotype Immunization Following High-Dose Therapy and Autologous Stem Cell Transplantation for Non-Hodgkin Lymphoma

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The treatment of low- and intermediate-grade subtypes of malignant lymphoma continues to evolve. Mantle cell lymphoma (MCL) accounts for 6% of all non-Hodgkin lymphoma (NHL) and is generally considered incurable. Although high response rates can be achieved with initial chemotherapy, median survival is only 3-4 years. Intensified consolidation with high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) has been reported to improve progression-free survival (PFS), but most patients eventually relapse. Indolent lymphoma accounts for 35% of all NHL and is associated with a median survival of 9 years. Similar to MCL, it is also generally considered incurable, and the PFS also appears to be improved following HDT/ASCT. We initiated a pilot study to evaluate idiotype (Id) vaccination following HDT and ASCT for patients with MCL, indolent, and transformed NHL to evaluate the ability of Id-keyhole limpet hemocyanin (KLH) to induce immune responses, and to evaluate overall survival (OS) and PFS. We treated 15 patients: 8 with MCL, 4 with follicular lymphoma, 1 with small lymphocytic lymphoma, and 2 with transformed lymphoma. After a median follow-up of approximately 6.3 years (range: 1-9), PFS and OS at 9.05 years from time of ASCT are 59% and 52%, respectively.

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INTRODUCTION

The treatment of low- and intermediate-grade subtypes of non-Hodgkin lymphomas (NHL) continues to evolve. The introduction of immunotherapeutic strategies has become an attractive means of treatment, particularly with the use of passive immunotherapy (eg, rituximab). High response rates can be achieved with chemotherapy, monoclonal antibodies, and radioimmunotherapy. However, progression of disease is frequent. Intensified consolidation with high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) has been reported to improve progression-free survival (PFS), but most patients ultimately relapse [1-4].

The use of idiotype (Id) immunization to develop an anti-Id antibody immune response has been demonstrated as a promising approach to the treatment of B cell lymphomas, and could result in more durable remissions and improved overall survival (OS) than with standard chemoimmunotherapeutic options [5-7]. Immunoglobulin (Ig) molecules on the surface of clonal B cells in NHL can be used as a tumor-specific target for immunotherapy. A unique Ig receptor expressed on the malignant B cell surface contains a specific antigen-recognition region, the Id, which can be targeted as a strong antigen for the induction of an anti-Id immune response. The coupling of the Id protein to keyhole limpet hemocyanin (KLH) and simultaneous local administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) produces an augmented immune response targeted at malignant B cells while sparing normal B cells [5,8]. Studies in animals and humans have shown the effectiveness of the immune system to target Id and kill lymphoma cells [9-12]. Treatment with monoclonal anti-Id antibodies can cause tumor

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regression and possibly induce long-term clinical remissions [12,13].

Invariably, early clinical trials in patients with B cell lymphomas have shown that Id vaccination is effective in eliciting specific anti-Id responses, accompanied by clinical benefit [14,15]. Long-term follow-up of these patients has shown improved clinical outcomes with prolonged PFS and OS [5]. Recent trials have evaluated the use of Id vaccination in patients with follicular non-Hodgkin lymphoma (NHL[FL]). Early trials showed tumor regression and durable objective responses to vaccination in pretreated patients with relapsed/refractory NHL used as a single agent, or following rituximab immunotherapy [16-19].

Prior studies have demonstrated a strong inverse correlation between the presence of detectable malignancy and the laboratory detection of a cellular or humoral Id-specific immune response [5,20]. Enhanced immune responsiveness to vaccination that was seen in patients in complete remission (CR) at the time of vaccination prompted the hypothesis that a vaccine was most effective in patients with minimal or no detectable residual disease. This suggested the consideration of HDT followed by ASCT as a means to achieve a maximal response to therapy while providing an ideal opportunity to mount an effective immune response via Id vaccination. Davis et al. [21] demonstrated the feasibility of this concept in 12 pretreated patients with refractory or relapsed B cell lymphomas, producing prolonged remissions particularly in patients with FL. The applicability of Id vaccination after ASCT in other subtypes of B-cell lymphoma has not yet been evaluated.

Mantle cell lymphoma (MCL) was originally described more than 30 years ago but was finally accepted as a separate entity when it became evident that the t(11;14)(q12;q32) translocation was consistently present [22,23]. MCL accounts for 6% of all NHL and is often indolent or moderately aggressive at diagnosis, but with time the disease invariably becomes clinically aggressive and chemotherapy refractory. It has shown the worst long-term survival among all B cell lymphoma subtypes, and is generally thought to be incurable [24]. Although high response rates can be achieved with initial chemotherapy for MCL, median survival is only 3-4 years [25]. Data of cohorts following HDT and ASCT suggest a higher event-free survival (EFS) and OS compared with historic controls [2,26-32]; however, no randomized trial has reached conclusive results [2]. All data suggest that there is no disease-free plateau, and therefore relapse is likely in most patients with MCL. Data from the Nordic Lymphoma Group MCL2 study and the M. D. Anderson Cancer Center, however, have recently shown that intensified consolidation with HDT and ASCT could provide long-term disease control in chemotherapy-naïve patients in first CR [28,33]. Although recent data has been promising, relapse rates after HDT and ASCT remain high [26,28,33-36].

With this background, we initiated a pilot study evaluating Id vaccination following HDT and ASCT for patients with MCL, indolent NHL, and transformed NHL (TL) to explore the feasibility and efficacy of this post-ASCT immunotherapeutic strategy to induce and maintain complete clinical or molecular remissions.

METHODS

Patient Population

Between April 2001 and September 2006, 32 patients with NHL were enrolled in a pilot study to evaluate the feasibility, safety, and potential efficacy of Id immunization following HDT and ASCT. Eligible patients were between the ages of 18 and 75, had a Karnofsky Performance Status of $\geq$70%, and had received any number of prior chemotherapy regimens. Patients may not have undergone prior HDT and ASCT. Histologic confirmation of lymphoma was required and included patients with small lymphocytic lymphoma (SLL), follicular small cleaved cell, follicular mixed small and large cell, MCL, or TL. Patients were required to have a left ventricular ejection fraction >40%, diffusion lung capacity of carbon monoxide >40% of predicted, creatinine <1.8 mg/dL, and be a candidate for ASCT. Patients were excluded for known central nervous system lymphoma or meningeal lymphomatosis, human immunodeficiency virus, or chronic inflammatory disorders requiring the continued use of glucocorticoids or other immunosuppressive medications. The population included 16 patients with FL, 10 with MCL, 3 with TL, 2 with SLL, and 1 with marginal zone lymphoma (MZL). The institutional review boards of the participating centers approved the study. Written informed consent was obtained from all participants before enrollment.

Treatment Design

A lymph node biopsy, peripheral blood draw, or bone marrow biopsy was performed on eligible patients to provide material for the generation of tumor-specific Id. Patients whose lymphoma cells expressed surface Ig were then eligible to continue on the study. All patients had measurable disease after obtaining tissue for vaccine production. Following tissue collection, patients proceeded to undergo a standard cytoreductive chemotherapy regimen before stem cell mobilization, and HDT followed by ASCT. Cytoreductive chemotherapy was chosen and administered at the discretion of the treating physician, although fludarabine and rituximab were