Vaccination Strategies in Follicular Lymphoma

Shibichakravarthy Kannan, MBBS, PhD, and Sattva S. Neelapu, MD

Corresponding author
Sattva S. Neelapu, MD
Department of Lymphoma and Myeloma, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 903, Houston, TX 77030, USA.
E-mail: sneelapu@mdanderson.org

Current Hematologic Malignancy Reports 2009, 4:189–195
Current Medicine Group LLC ISSN 1558-8211
Copyright © 2009 by Current Medicine Group LLC

Follicular lymphoma is one of the most immune-responsive cancers. The clonal tumor immunoglobulin expressed on the surface of malignant B cells, termed idiotype, has been used as a tumor-specific antigen in therapeutic vaccination strategies for follicular lymphoma and other B-cell malignancies. A number of phase 1 and phase 2 clinical trials have established the safety and immunogenicity of idiotype vaccine in follicular lymphoma. Three randomized, double-blind, controlled phase 3 clinical trials have recently been completed to definitively evaluate the clinical benefit of idiotype vaccine in follicular lymphoma. This review focuses on the results of these idiotype vaccine trials and discusses potential strategies to enhance the efficacy of vaccines in the future.

Introduction
It is estimated that non-Hodgkin’s lymphoma (NHL) will be diagnosed in 65,980 patients in the United States in 2009, and an estimated 19,500 will die from NHL. Follicular lymphoma, the most common low-grade B-cell lymphoma, comprises 22% of all NHL cases worldwide. More than 85% of patients with follicular lymphoma have advanced-stage disease at the time of initial diagnosis. Advanced-stage follicular lymphoma has a generally indolent course with a median survival of 8 to 10 years. Although it is highly responsive to various therapies such as chemotherapy, radiation therapy, and/or biologic therapy, advanced disease is characterized by repeated remissions and relapses and is considered incurable with the available treatment options [1]. The recent use of rituximab in combination chemotherapy regimens has improved the response rates, progression-free survival (PFS), and overall survival of patients with follicular lymphoma. However, even these combinations do not appear to be curative, as no plateau in the survival curves has been demonstrated [2–4]. Therefore, novel treatment options are needed to improve clinical outcome in these lymphomas.

The natural history of follicular lymphoma, characterized by stable disease or spontaneous remissions lasting months to years in a significant proportion of patients observed [5], suggests that the immune system may play a major role in the control of this tumor. This notion is now supported by several recent studies. First, the survival of patients with follicular lymphoma appears to correlate with the gene expression signatures of infiltrating, nonmalignant immune cells in the tumor [6]. Second, high levels of CD8+ T-cell content in diagnostic lymph nodes correlates with better prognosis [7]. Third, the presence of an immunosurveillance pattern (CD8+ T cells) correlates with good prognosis, whereas an immune-escape pattern (CD57+ T cells) correlates with poor prognosis [8]. Finally, tumor-specific T cells can be easily isolated from the peripheral blood and tumor microenvironment in follicular lymphoma [9,10]. Together, these results suggest that follicular lymphoma is particularly immune-sensitive and they support the development of immunotherapeutic strategies for the treatment of this disease.

Idiotype as a Target for Active Immunotherapy
As opposed to passive immunotherapy with monoclonal antibodies, active immunotherapy with therapeutic vaccines has the potential to induce polyclonal humoral and cellular immune responses against one or more targets expressed by the tumor and therefore may minimize the emergence of tumor escape variants. Furthermore, active immunotherapy can generate immunologic memory, which in turn may lead to long-term control of the tumor.

A therapeutic cancer vaccine usually comprises tumor-specific or tumor-associated antigen, a carrier, and an adjuvant. Follicular lymphoma is characterized by clonal proliferation of B cells expressing an identical immunoglobulin (Ig) on the cell surface. The clonal tumor Ig has unique amino acid sequences, termed idiotype or Id, within the complementarity determining regions (CDRs) of the variable sections of the heavy and light chains. Because of the clonal nature of B-cell malignancies, the
Id expressed on tumor B cells of a patient is distinct from that of normal B cells and therefore can serve as a tumor-specific antigen for active immunotherapy. The tumor antigen can be formulated into a vaccine with the use of a carrier to facilitate presentation of the tumor antigen to professional antigen-presenting cells (eg, dendritic cells) to induce antitumor humoral and/or cellular immune responses. An adjuvant is usually included in the vaccine formulation to enhance the immune responses induced by the tumor antigen–carrier complex.

Many preclinical studies suggested that immunization with idiotype alone can induce antitumor immune responses [11–13]. However, Kaminski et al. [14] demonstrated that conjugation of the idiotype to a carrier protein such as keyhole limpet hemocyanin (KLH) significantly improved the immunogenicity of idiotype protein in a 38C13 mouse lymphoma model. In this study, the antitumor effects of the Id-KLH vaccination were found to depend on induction of anti-Id antibody responses. Subsequently, Kwak et al. [15], using the same 38C13 lymphoma model, showed that low doses of free granulocyte-macrophage colony-stimulating factor (GM-CSF) delivered intraperitoneally or subcutaneously daily for 4 days could significantly enhance the protective antitumor immunity induced by Id-KLH immunization. This effect was critically dependent upon effector CD4+ and CD8+ T cells and was not associated with any increased production of anti-idiotype antibody. This study suggested that the primary antitumor immune response was T-cell mediated and GM-CSF had a major role in boosting this response [15].

Phase 1 and Phase 2 Idiotype Vaccine Trials
The first clinical study using idiotype vaccine was conducted by Kwak et al. [16] with autologous tumor-derived Id protein conjugated with KLH (Id-KLH) and Syntex adjuvant formulation-1 (SAF-1). In this trial, follicular lymphoma patients were treated into clinical remission with standard chemotherapy to reduce tumor burden prior to vaccination. The long-term results of the phase 1 trial published by Hsu et al. [17] reported adequate immune response and tumor regression in two patients. Importantly, only the subset of patients with anti-idiotype immune response showed significant improvement in PFS and overall survival, suggesting a positive role for vaccination.

Based on the preclinical observation that GM-CSF can enhance the potency of the Id-KLH vaccine, Bendandi et al. [18] tested Id-KLH+GM-CSF vaccine in 20 previously untreated follicular lymphoma patients after induction of clinical remission with prednisone, doxorubicin, cyclophosphamide, and etoposide (PACE) chemotherapy. This study demonstrated that Id vaccination induced both humoral (75%) and T-cell–mediated immune responses (95%) and provided the first convincing evidence of an in vivo antitumor effect of Id vaccination, with induction of molecular remissions in 8 of 11 patients with minimal residual disease. Although this study was not randomized, the improved disease-free survival (DFS) [19] compared with historical controls using ProMACE chemotherapy alone [20] suggested potential clinical benefit with this vaccine.

In a study by Inoges and colleagues [21••], the effects of Id-KLH+GM-CSF vaccine was evaluated in 25 patients with follicular lymphoma after induction of a second complete clinical response with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-like chemotherapy. Overall, 20 (80%) of 25 patients had either humoral or cellular anti-Id immune responses. The median duration of the second complete response (CR) among the 20 immune responders was significantly longer than the median duration of their first CR or the CHOP-induced second CR.

It is important to note that rituximab was not used in the induction therapy in these clinical trials. Because rituximab causes B-cell depletion for several months and therefore can impair the induction of humoral responses, the immunogenicity and clinical efficacy of the Id-KLH+GM-CSF vaccine following induction therapy containing rituximab was evaluated in two clinical trials [22,23]. These studies suggested that vaccine-induced antitumor T-cell responses were not impaired following rituximab administration. However, anti-idiotype antibody responses were observed in only a minority of the patients. The humoral responses were delayed and correlated with B-cell recovery in the peripheral blood. Nevertheless, an improvement in overall response rate to 63% was observed after combined treatment with rituximab and Id-KLH+GM-CSF, compared with 47% at 3-month follow-up after rituximab therapy in patients with follicular lymphoma [23]. Moreover, this single-arm, phase 2 trial also demonstrated an improvement in time to progression (TTP) as compared with historical controls using rituximab alone, suggesting potential clinical benefit induced by the idiotype vaccine after rituximab-based induction therapy [23].

Phase 3 Idiotype Vaccine Trials
The demonstration of the safety and immunogenicity of the Id-KLH+GM-CSF vaccine in multiple phase 1 and phase 2 trials, together with the induction of molecular remissions and the apparent improvement in PFS and DFS, prompted the initiation of three randomized, double-blind, placebo-controlled, multicenter clinical trials to definitively test the clinical benefit of idiotype vaccination in follicular lymphoma (Table 1). The results of these three clinical trials were released within the past year and are discussed below.

Biovest trial
This trial was initiated by the National Cancer Institute, National Institutes of Health (Bethesda, MD) and later sponsored by Biovest International, Inc. (Worcester, MA) [24••]. The study design was very similar to that of the