

Therapeutic Vaccination for Lymphoma

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At the present there is no **Active immunotherapy** maneuver that has been proven effective in the clinic but there are intense efforts underway to develop such an approach. The immunoglobulin molecule on each lymphoma can be target for immunotherapy. When the **idiotype** is used as a vaccine, antibodies and T cells can be induced and each can cause rejection of the tumor by the host. This special opportunity for tumor specificity is accompanied by the challenge of constructing a different vaccine for each patient. It is important to define the **appropriate clinical setting** for vaccination against tumors. Patients can be induced to make anti idiotypic immune responses prior to initial chemotherapy as well as after chemotherapy both in remission and in relapse. A big question in the field is what type of immune response, antibodies or T cells will be most beneficial. Clearly, the question of the relationship of vaccination to antibody therapy with Rituximab, which depletes B cells and interferes with primary antibody responses, is important to address.

In the first clinical trial of Id vaccination for lymphoma 32 patients were vaccinated in first remission, roughly half (14/32) mounted anti-Id immune responses to the vaccine. These were principally humoral responses rather than cellular responses, and were more common in patients in complete remission than in those with residual tumor at the time of vaccination. The development of an immune response was strongly correlated with prolonged freedom from disease progression in comparison to non-responders. Overall survival has also been superior in immune responding patients. We have now found that the production of anti idiotypic antibodies and the genetic makeup of the patient (Fc receptor genotype) are correlated with clinical outcome in vaccinated patients. The clinical activity of Id-KLH vaccination was confirmed by investigators at the National Cancer Institute. Prospective, randomized trials are now underway to seek evidence of clinical benefit following Id vaccination. Early results from the first multicenter randomized trial will be available this Fall.

Dendritic cells (DCs) are rare, stellate-shaped leukocytes which are the most powerful antigen-presenting cells. These cells can be co-cultured ("pulsed") with antigen, and re-infused as a cellular vaccine. This treatment was first applied in a pilot study of ten patients with measurable, relapsed follicular lymphoma. There were the clinical responses in these patients. These included two complete tumor regressions, one lasting 44 months, and another ongoing at 37 months. There was also one partial response lasting 12 months, and one molecular response. Given these results, this treatment was then applied to patients with follicular lymphoma in first remission. In some cases, revaccination with Id-KLH after tumor recurrence has resulted in tumor regression.

Id vaccination has potential to improve clinical outcome, but how can this customized vaccine approach be applied to large numbers of patients? The ability to amplify and clone Id genes from B-cell tumor specimens using PCR has opened up a variety of new strategies which are streamlining the production of custom Id vaccines. Stevenson *et al.* have used naked DNA encoding Id proteins as the vaccine. Osterroth and colleagues in Germany have produced Id vaccines in bacteria. McCormick *et al* have exploited the tobacco mosaic virus to produce Id vaccines in tobacco plants. Swartz *et al.* have developed a completely in vitro protein production method for the manufacture of id. If Idiotype vaccine proves to efficacious then newer technologies such as these will certainly come to the fore.